UNIVERSITE DE LILLE
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Ecole Doctorale Biologie-Santé

FILMS D'ENROBAGE POLYMERIQUE POUR DES FORMES GALENIQUES SOLIDES A LIBERATION CONTROLEE

POLYMERIC CONTROLLED RELEASE FILM COATINGS

THESE

pour l'obtention du grade de
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LIST OF ABBREVIATIONS

AFM: Atomic force microscopy

API: Active pharmaceutical ingredient

DBS: Dibutyl sebacate

DSC: Differential scanning calorimetry

DMA: Dynamic mechanical analysis

e.g.: exempli gratia

HPLC: High performance liquid chromatography

MCC: Microcrystalline cellulose

MEB: Microscopie électronique à balayage

mDSC: Modulated differential scanning calorimetry

MFT: Minimum film formation temperature

Mw: Molecular weight

NaCl: Sodium chloride

PVA: Poly(vinyl acetate)

PVP: Poly(vinyl pyrrolidone)

rpm: rotation par minute / revolution per minute

SA: Substance active

SEM: Scanning electron microscopy

TEC: Triethylcitrate

Temp: Temperature

Tg: Température de transition vitreuse / Glass transition temperature

TGI: Tractus gastro-intestinal

TMA: Thermal mechanical analysis

TPI: Terahertz pulsed imaging

USP: United States pharmacopeia

UV: Ultra-violet

w/w: Weight/weight

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RÉSUMÉ DÉTAILLÉ

L'administration d'une substance active (SA) par voie orale est la plus fréquente pour soigner une pathologie de par ses avantages tels que son acceptabilité, son confort pour le patient, ainsi que son faible coût de fabrication. Les formes orales sèches occupent la majeure partie du marché pharmaceutique de ville (68.3% en 2013) (ANSM, 2014).

La réussite thérapeutique dépend essentiellement des concentrations en SA au site d'action et du temps d'action. Des concentrations trop faibles (< concentration minimale efficace) conduisent à un échec du traitement tandis que des concentrations trop élevées (> concentration toxique) peuvent engendrer des effets indésirables nécessitant l'arrêt du traitement. Il faut être toutefois vigilant lorsqu'il s'agit de SA avec une fenêtre thérapeutique étroite (c'est-à-dire que la dose minimale efficace est très proche de la dose maximale tolérable par l'organisme). Si cette SA est incorporée dans une forme galénique conventionnelle, la dose totale est rapidement libérée dans le tractus gastro-intestinal (TGI), atteint son site d'action et peut provoquer des effets secondaires plus ou moins importants selon la SA. Cependant, l'effet thérapeutique s'avère court du fait que l'organisme élimine continuellement le médicament, donc le traitement est peu efficace et surtout récurrent. C'est pourquoi, des nouvelles formes galéniques sont nécessaires pour améliorer l'efficacité thérapeutique.

De plus, la découverte de nouvelles molécules actives est de plus en plus difficile due à sa complexité et au manque de financement. Par conséquent, les industries pharmaceutiques développent de nouvelles technologies pour des molécules déjà existantes afin de perfectionner le système de délivrance, d'améliorer la pharmacocinétique d'un médicament et de créer de nouvelles entités. Parmi ces dernières, les formes orales sèches à libération contrôlée sont les plus répandues sur le marché pharmaceutique.

La libération contrôlée a pour objectif de maîtriser dans le temps la vitesse à laquelle la SA est libérée de sa forme galénique et donc de contrôler son absorption tout au long du TGI afin de pouvoir adapter l'activité thérapeutique en fonction de la pathologie (figure 1).

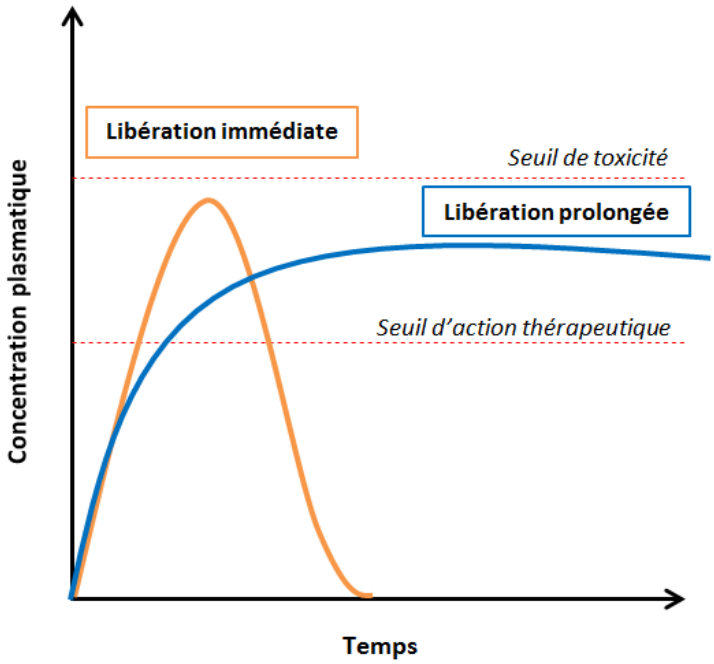


Figure 1 : Profils de libération immédiate versus contrôlée d'une substance active.

Ainsi, la vitesse à laquelle la molécule active est résorbée dans le système sanguin et donc la vitesse à laquelle elle parvient au site d'action peut être influencée. Par exemple, il est possible d'assurer un taux constant en principe actif dans le temps, afin de compenser son élimination du corps humain. Il en résulte une activité médicamenteuse au site d'action sur du long terme.

En parvenant à contrôler la libération d'une SA à partir de sa forme galénique, d'autres bénéfices s'ajoutent tels que (Hong Wen and Kinam Park, 2010) :

- ✓ Diminution des effets indésirables
- ✓ Diminution des fréquences d'administration
- ✓ Augmentation de l'efficacité du traitement
- ✓ Amélioration de l'observance des patients

Plusieurs médicaments à libération contrôlée existent déjà sur le marché et d'ailleurs plus de 10 % des 200 principaux traitements vendus en 2007 en étaient et ont rapporté plus de 12.6 milliards de dollars. Par exemple, le top 10 des meilleures ventes concernent Effexor XR, Adderall XR, Oxycontin, Concerta, Wellbrutin XL, Torpol XL, Ambien CR, Detro LA, Depakote ER et Allegra-D (P.I. Lee and J-X Li, 2010) (Jayanthi *et al.*, 2011).

Pour pouvoir maîtriser la vitesse de libération d'une SA au cours du temps, on utilise des systèmes composés d'une matrice polymérique dans laquelle la SA est

dispersée appelé **système matriciel**, ou alors d'un noyau inerte autour duquel est la SA, l'ensemble enrobé d'un film de polymère, appelé **système réservoir** (figure 2) (Dashevsky, Kolter, and Bodmeier, 2004).

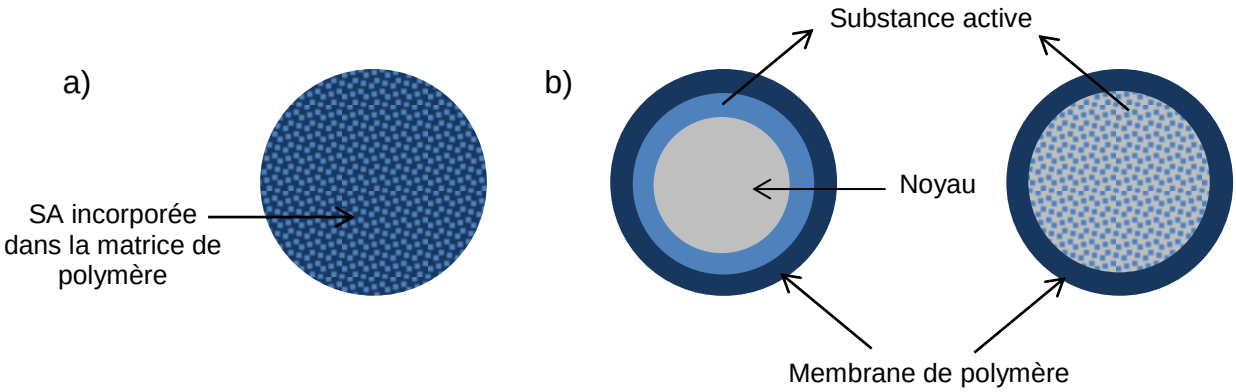


Figure 2 : Représentation schématique d'un système matriciel (a) et de systèmes réservoirs (b).

- Les systèmes matriciels

Dans les systèmes matriciels tels que microcapsules, comprimés et mini-granules, la molécule active est dissoute ou dispersée dans un réseau polymérique formant la matrice. Cette dernière est composée d'excipients physiologiquement tolérés et résistants à toute dissolution lors du passage gastro-intestinal afin d'obtenir une libération contrôlée. La libération du principe actif peut s'effectuer soit par diffusion, gonflement et/ou érosion selon la matrice. Il existe différents systèmes matriciels selon leurs structures et les propriétés physico-chimiques des polymères. On peut distinguer les matrices homogènes, formées d'une phase continue non poreuse où la SA sortira par diffusion, des matrices hétérogènes où des pores sont présents et participent à la libération de la molécule active.

En résumé, la libération de la SA implique l'entrée du liquide environnant, la dissolution de la molécule active et le relargage de celle-ci par diffusion à travers la membrane de polymère intact et/ou par des pores et/ou par gonflement et érosion de la matrice.

Pour conclure, les systèmes matriciels sont très utilisés pour leurs faibles coûts et leur facilité de fabrication, ainsi que le faible risque de libération massive du médicament. Ils ont également l'avantage de pouvoir contenir une forte dose en SA (P.I. Lee and J-X Li, 2010).

- Les systèmes réservoirs

Les systèmes réservoirs consistent en un film de polymère enrobant la SA qui peut se trouver soit autour d'un noyau inerte ou soit à l'état solide dans une matrice (figure 2, b). Selon les caractéristiques de la membrane, les mécanismes de libération et donc le profil de libération de la SA seront différents.

Deux cas de figures peuvent se présenter :

- Les systèmes réservoirs à activité constante où la molécule active se trouve en excès et donc une partie est sous forme solide dans le réservoir : la concentration en molécules dissoutes et donc diffusantes reste égale à la concentration en saturation au cours du temps.
- Les systèmes réservoirs à activité non constante où la SA est déjà entièrement dissoute : la concentration en molécule active va décroître au cours du temps.

Une fois ces systèmes en contact avec les fluides du TGI, l'eau pénètre à l'intérieur et dissout la SA. Dans les cas de systèmes réservoirs à activité constante, une partie des molécules seulement est dissoute due à leur faible solubilité. Dans l'autre cas, toutes sont rapidement dissoutes. Puis, elles diffusent à travers la membrane perméable de polymère par gradient de concentration. Différents phénomènes se succèdent, la diffusion de l'eau, la dissolution de la SA, la diffusion de celle-ci, le gonflement des chaines de polymères, leur dissolution et/ ou leur dégradation. L'étape de diffusion de la SA est généralement la plus lente donc contrôle la vitesse de libération et elle peut être caractérisée via la loi de Fick et des modèles mathématiques. Toutefois, il est important de porter l'attention sur le fait que des « cracks » peuvent se former. En effet, la pénétration de l'eau à l'intérieur de ce système amène une pression hydrostatique interne agissant contre la membrane. Si cette dernière est trop fragile pour résister à cette pression, des fissures peuvent se produire et la libération de la substance médicamenteuse se fera à la fois par diffusion à travers la membrane restée intacte et par les fentes créées. De plus, cette pression hydrostatique peut aussi générer un transport de la SA par convection à travers ces canaux (Siepmann *et al.* 2012).

En résumé, les mécanismes de libération impliqués à partir de systèmes réservoirs sont la diffusion de la SA à travers la membrane intacte, la diffusion à travers des pores ou « cracks », la diffusion à travers des pores due au relargage du plastifiant, et/ou par effet osmotique. Ces mécanismes peuvent être modulés en variant l'épaisseur de la membrane de polymère, mais aussi en modifiant la perméabilité de cette dernière par ajout d'additifs solubles en milieu aqueux ou des agents formant des pores (Ozturk *et al.*, 1990).

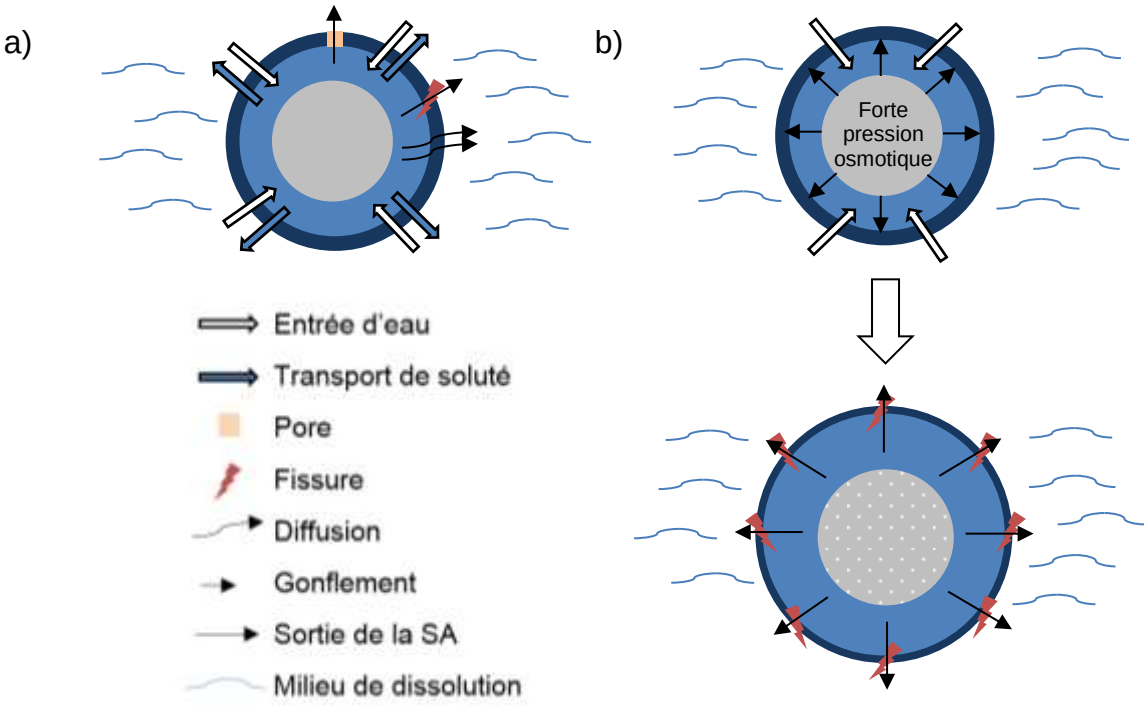


Figure 3 : Représentation schématique des différents mécanismes de libération à partir d'un système réservoir (a : par diffusion, b : par effet osmotique).

Pour conclure, les systèmes réservoirs ont les avantages de pouvoir contenir de haut taux de chargement en SA (dans le cas où la SA est incorporée dans une matrice d'excipients) et différentes vitesses de libération peuvent être obtenues en adaptant la nature et la composition de l'enveloppe polymérique.

Dans ce projet de thèse, l'étude porte sur un type de système réservoir, les **mini-granules enrobés**.

D'après Ghebre-Sellassie, les mini-granules sont définis comme étant des particules solides et sphériques avec une distribution de taille allant de 500 à 1500 µm destinés à des applications pharmaceutiques par voie orale (Ghebre-Sellassie I., 1989). Ces derniers sont pelliculés et agissent comme des systèmes réservoirs où la SA se libère de façon contrôlée et sur des sites d'action spécifiques selon l'activité thérapeutique souhaitée. Les mini-granules peuvent être administrés sous forme de

gélules dans lesquelles ils sont disposés ou alors compactés en comprimés (figure 4), tout en conservant leurs avantages d'unités multiples.

Figure 4 : Exemple de formes galéniques obtenues à partir de mini-granules (Catalent, 2016).

D'une part, ils fournissent une très grande flexibilité en termes de design et de développement de formes orales. En effet, ils peuvent être divisés en dose unitaire sans devoir modifier la formulation ou le procédé, être mélangés à des produits bioactifs incompatibles et fournir différents profils de libération au même ou à divers sites d'action dans le TGI. D'autre part, ils présentent également des avantages thérapeutiques. Une fois administrés par voie orale, les mini-granules se dispersent librement dans le TGI, et par conséquence la SA a une absorption maximale et ainsi minimise les irritations locales de la muqueuse ; du fait aussi que la SA est répartie sous forme de petite dose unitaire. De plus, les variabilités inter et intra-patients sont réduites. Enfin, ils possèdent des bénéfices techniques. Les sphères ont généralement un bon écoulement ce qui facilite l'automatisation et les procédés de fabrication ; leur enrobage leur confère, mis à part une libération contrôlée, une protection du système et surtout de la SA ; ils ont une densité convenable pour le procédé et le packaging et une uniformité de dose**.**

Afin que les mini-granules soient efficaces et atteignent leur objectif thérapeutique, ils doivent respecter certaines exigences (tableau 1) (Jawahar and Hardik Anilbhai, 2012) (Ratul and Abdul Baqee, 2013)**.**

Tableau 1 : Propriétés requises pour des mini-granules enrobés.

Propriétés	Prérequis
Forme	Sphérique, uniforme
Taille	0.5 – 1.5 mm Distribution de taille uniforme
Ecoulement	Bon
Friabilité	Faible, avec peu d'émission de particules fines

Surface	Lisse
Porosité	Faible
Densité	Haute
Résistance aux forces	Haute

Une fois enrobés, ils conservent les mêmes caractéristiques et ont en plus le profil de libération désiré.

Il existe plusieurs techniques applicables à la production de mini-granules utilisées en industrie pharmaceutique, les plus communes sont schématisées en figure 5.

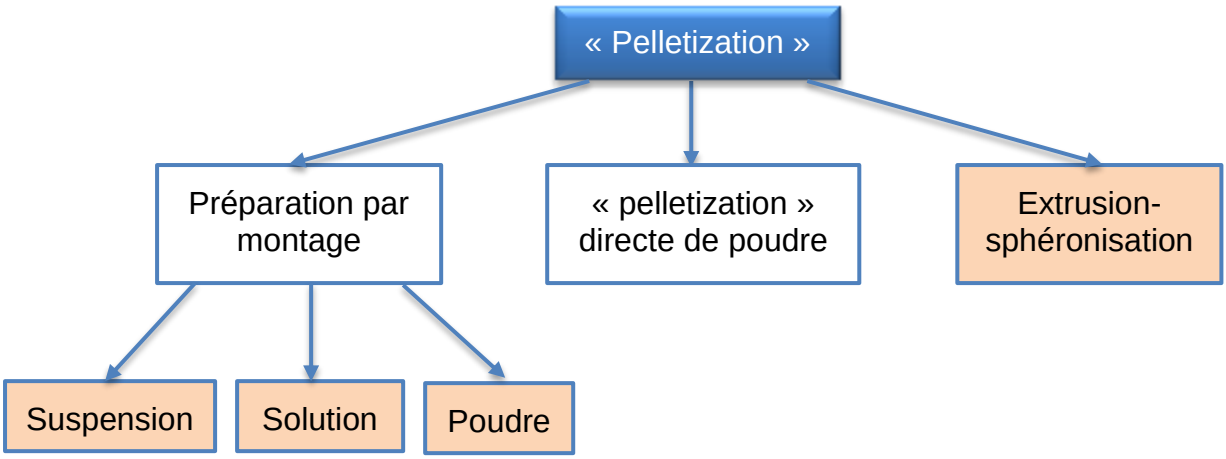


Figure 5 : Représentation schématique des différentes techniques de « pelletization ».

Seules les préparations par montage et l'extrusion-sphéronisation seront développées car elles ont été utilisées lors de ce projet de thèse.

- Préparations par montage (ou « layering ») à partir de solution, suspension ou de poudre

Cette méthode implique un dépôt de couche(s) à partir de solution, suspension ou de poudre contenant la SA sur des noyaux inertes (à base de cellulose microcristalline, de sucre ou de cire par exemple).

Dans les cas de solution ou suspension, la substance médicamenteuse est dissoute (solution) ou dispersée (dispersion) dans un milieu aqueux ou organique (selon la solubilité de la SA) pouvant contenir un liant et d'autres excipients. Ensuite, cette formulation est pulvérisée à l'aide d'un lit d'air fluidisé (figure 6), les gouttelettes formées se déposent à la surface des noyaux, s'étalent puis coalescent entre elles.

Enfin, l'eau s'évapore grâce au séchage. Ainsi, il en résulte une couche homogène et uniforme à la surface des sphères inertes (figure 7, a).

Figure 6 : Lit d'air fluidisé (Aeromatic Strea 1) (Unité Inserm and Université de Lille 2, 2015).

Pour obtenir une libération contrôlée, le même procédé est appliqué sur ces dernières sphères à partir de solution organique ou de dispersion aqueuse de polymère. Cependant, de nos jours les dispersions aqueuses sont préférées d'un point de vue environnemental et sécuritaire (figure 7, b).

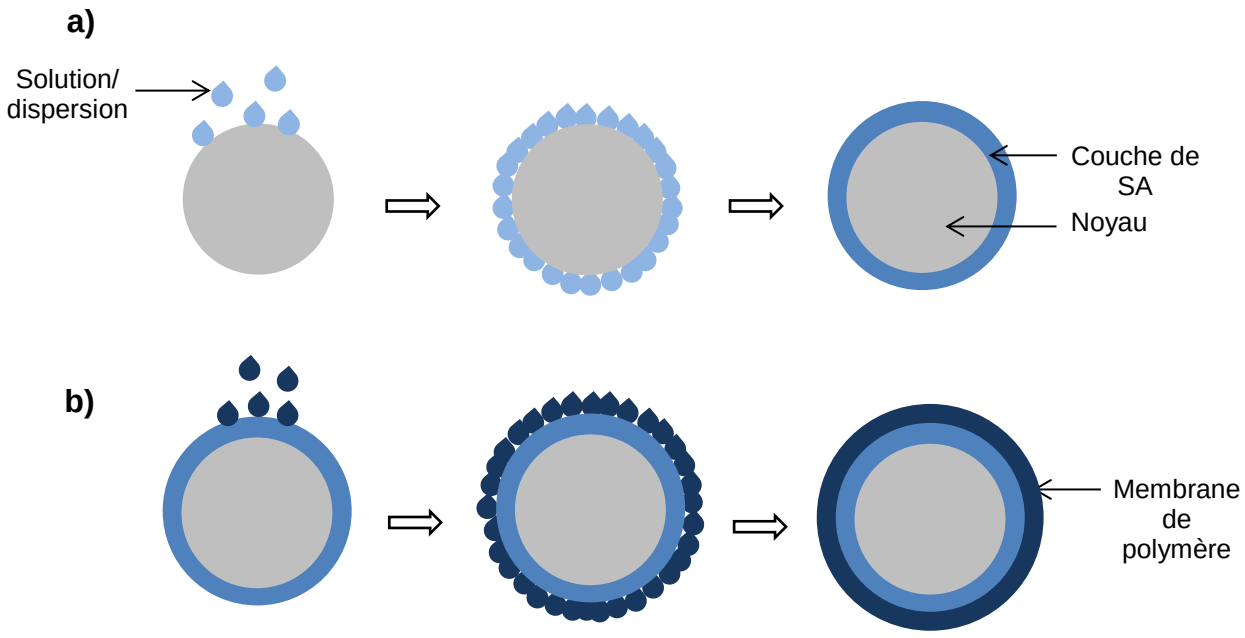


Figure 7 : Schéma des étapes de « pelletization » par montage ; a) pulvérisation d'une couche de SA et b) pulvérisation de la couche de polymère.

Concernant le montage à partir de poudre, le procédé est identique au précédent. En revanche, à la place d'une solution ou suspension, la SA se présente sous forme de poudre sèche. En amont, une solution liante est pulvérisée afin de mouiller la surface des noyaux, puis la poudre est ajoutée. Ainsi, la poudre adhère à

la surface et après séchage une couche de SA est formée. Ces étapes se déroulent dans une turbine rotative conventionnelle (Sauer *et al*., 2013).

- Extrusion-sphéronisation

L'extrusion-sphéronisation est une des techniques les plus employées qui offre l'avantage de pouvoir incorporer de grande quantité de SA sans devoir augmenter la taille des granules. Cette méthode de préparation comporte plusieurs étapes dont quelques-unes illustrées en figure 8.

1. **Mélange** des poudres à sec dans un mélangeur (mélangeur à haut cisaillement, à vis ou encore horizontaux) dans le but d'obtenir une dispersion de poudre homogène.
2. **Granulation** : mouillage des poudres par un ajout d'une solution/solvant et mélange jusqu'à l'obtention d'une masse humide homogène. C'est une étape fondamentale car elle va influencer la qualité des extrudats et donc des sphéroïdes selon le taux d'humidité du mélange.
3. **Extrusion** : compaction et transformation de la masse humide en bâtonnets appelés extrudats uniformes lors du passage dans un cylindre contenant des orifices calibrés placé dans un extrudeur.
4. **Sphéronisation** : les extrudats se cassent et s'arrondissent pour former des sphéroïdes grâce au plateau rotatif du sphéroniseur. Une force centrifuge est créée par le mouvement rotatif du plateau, qui envoie les extrudats contre les parois de l'appareil pour les casser en petits bâtonnets, ensuite les frictions interparticulaires et le contact avec la surface striée du plateau vont permettre de les rendre sphériques.
5. **Séchage** des sphères dans une étuve ou dans un lit d'air fluidisé jusqu'à obtention d'une teneur en humidité résiduelle suffisante pour assurer la stabilité du produit fini (Mohan Kandukuri *et al.*, 2009)**.**

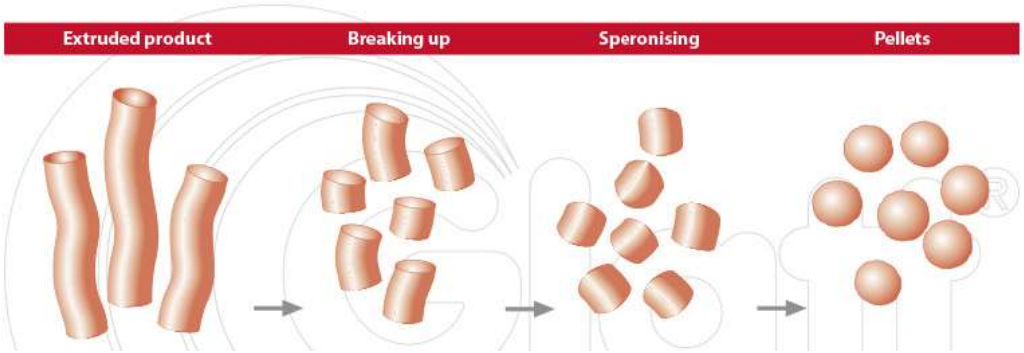


Figure 8 : Schéma des étapes de « pelletization » par extrusion-sphéronisation (Glatt GmbH, 2016).

Une fois les mini-granules secs, ils peuvent être enrobés avec un ou des polymères soit pour des raisons esthétiques soit pour leur conférer une fonctionnalité supplémentaire comme une libération contrôlée, masquage du goût ou encore une protection contre les conditions environnementales.

Le pelliculage est de plus en plus réalisé à partir de dispersions aqueuses de polymère, moins toxiques et moins dangereuses que des solutions organiques. Les polymères insolubles sont les plus adaptés pour formuler une forme orale à libération contrôlée. On les trouve dans des dispersions aqueuses où une forte concentration de polymère est présente soit sous forme de particules colloïdales de latex si la préparation est faite à partir de monomères, ou soit de pseudo-latex si une émulsification de polymère a été réalisée. Les polymères les plus utilisés pour l'enrobage de mini-granules sont les suivants :

- Les dérivés vinyliques : poly(vinyl acétate) (Kollicoat® SR 30 D)
- Les dérivés cellulosiques : éthylcellulose (Aquacoat®, Surelease®)
- Les polyméthacrylates : Eudragit® NM 30 D, Eudragit® RL, Eudragit® RS

- <u>Les dérivés vinyliques</u>

Le Kollicoat® SR 30 D est une dispersion aqueuse colloïdale récente sur le marché, composée de 27 % de poly(vinyl acétate) (figure 9), polymère insoluble dans l'eau, de 2.7 % de poly(vinyl pyrrolidone) (ou povidone), polymère soluble dans l'eau, porogène et améliorant la perméabilité du film par absorption d'eau, et de 0.3 % de sodium lauryl sulfate, stabilisant.

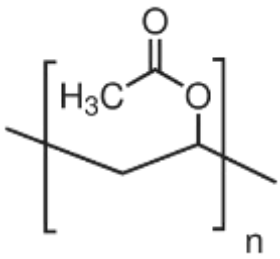


Figure 9 : Structure chimique du poly(vinyl acétate).

Cette dispersion est commercialisée avec une teneur en matière sèche de 30 % (m/m). Le Kollicoat® SR possède beaucoup de qualité. Tout d'abord, il est adapté à la formulation de formes solides à libération contrôlée ou prolongée et il permet une libération de la SA indépendamment du pH du milieu. Ensuite, il est très résistant face au stress mécanique et est très flexible. Enfin, ses propriétés physico-chimiques répertoriées dans le tableau 2 sont intéressantes et tendent vers un procédé d'enrobage réussi (Kolter *et al.*, 2013).

Tableau 2 : Propriétés physico-chimiques du Kollicoat® SR 30 D.

Propriétés	Spécifications
Taille des particules moyenne	160 nm
Distribution de taille	Etroite
pH	~ 4.5
Viscosité	< 5 cPs
Masse moléculaire	~ 450 000 Da
MFT	18 °C
Tg	~ 40 °C

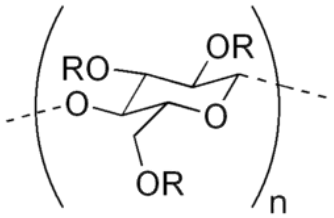
La faible taille des particules confère une rapide et complète coalescence des particules de polymère entre elles permettant la formation homogène du film pendant le procédé d'enrobage. Cette dispersion ne nécessite pas particulièrement de plastifiant car la température minimale de formation de film (MFT) est suffisamment faible. Cependant, l'ajout d'un plastifiant peut améliorer l'uniformité et la flexibilité du film. Généralement, des petites quantités suffisent, la concentration recommandée est d'environ 5 à 10 % (m/m, basée sur la masse sèche du polymère), et les plastifiants les plus efficaces sont le triéthylcitrate (TEC), la triacétine ou encore le propylène glycol (Dashevsky *et al.*, 2005) (Kolter *et al.*, 2013) (Bordaweka *et al.*, 2006) (Shao *et al.*, 2002).

Dans le premier projet de cette thèse, le Kollicoat® SR 30 D est employé à 10 % de matière sèche de polymère et plastifié avec 10 % de TEC, plastifiant soluble

dans l'eau afin de diminuer la Tg (environ 26 °C). Le plastifiant est ajouté à la dispersion 24 h avant pour une efficacité optimale.

- Les dérivés cellulosiques

L'éthylcellulose (figure 10) est un dérivé de la cellulose insoluble dans l'eau et hydrophobe fréquemment utilisé pour la libération contrôlée, le masquage de goût et la protection du système contre les conditions environnementales. Néanmoins, il est rarement utilisé seul de par sa faible perméabilité. La dispersion aqueuse d'éthylcellulose utilisée ici est commercialisée sous le nom d'Aquacoat® ECD 30.



R = H or CH_2CH_3

Figure 10 : Structure chimique de l'éthylcellulose.

L'Aquacoat® ECD 30 est composé d'éthylcellulose, d'un surfactant le sodium lauryl sulfate et d'un stabilisant le cetyl alcool (tableau 3) (Harris and Ghebre-Sellassie, 2008).

Tableau 3 : Spécifications et propriétés de l'Aquacoat® ECD.

Propriétés	Spécifications
Solide total	29-32 %
Ethylcellulose	24.5-29.5 %
Sodium lauryl sulfate	0.9-1.7 %
Cetyl alcool	1.7-3.3 %
pH	4-7
Viscosité	< 150 cPs
MFT	81 °C
Tg	90 °C

Cette dispersion aqueuse contient 30 % de matière sèche. Elle présente plusieurs avantages :

- Pas de solvant nécessaire
- Profil de libération modulable

- Faible viscosité, non collant
- Facile d'application et de nettoyage
- Pas de talc nécessaire
- Large choix de plastifiant compatible

L'Aquacoat® ECD 30 offre une libération contrôlée stable, reproductible et pH-indépendant. Cependant, un plastifiant doit être ajouté à la dispersion pour améliorer la flexibilité du polymère et donc du film d'enrobage. Un large choix de plastifiant peut être utilisé avec ce polymère selon les caractéristiques souhaitées. Les plastifiants recommandés avec l'Aquacoat® sont : Dibutyl Sebacate (DBS), Myvacet® (monoglycérides acétylés), triacétine, triéthylcitrate (TEC). Selon le pourcentage de plastifiant ajouté, la température de transition vitreuse (Tg) et donc la MFT seront plus ou moins faibles et la vitesse de libération plus ou moins rapide. La MFT de l'Aquacoat® est de 81 °C (Lippold *et al.*, 1999). Par exemple, pour atteindre une MFT entre 30 et 40 °C, il faut ajouter 20 à 25 % de plastifiant (FMC Biopolymer, 1996).

Dans le deuxième projet de cette thèse, l'Aquacoat® est utilisé à 10 % de matière sèche et plastifié avec 20 % de dibutyl sebacate, plastifiant insoluble dans l'eau afin de diminuer la MFT (environ 30 °C). En effet, il faut que la MFT ne soit pas trop élevée, pour pouvoir régler le lit d'air fluidisé à une température atteignable par l'appareil. Le plastifiant est ajouté à la dispersion 24 h avant afin que l'interaction polymère-plastifiant soit optimale, et que la coalescence des particules de polymère soit complète pour avoir un film d'enrobage uniforme.

- <u>Les polymethacrylates</u>

Les polymethacrylates sont commercialisés sous le nom d'Eudragit®. Il en existe toute une variété se différenciant par leur structure chimique et donc leur propriété physico-chimique et leur application. Les polymères intéressants pour l'enrobage de formes solides et la libération contrôlée sont insolubles, bien qu'il en existe des solubles pour d'autres applications. Selon les groupements fonctionnels ioniques ou non présents sur la chaine de polymère, ils peuvent être classés ainsi :

- Neutre : Eudragit® NM, Eudragit® NE
- Cationique : Eudragit® E
- Anionique : Eudragit® L, Eudragit® S
- Zwittérionique : Eudragit® RS, Eudragit® RL

Les copolymères ioniques absorbent l'eau et gonflent en contact du milieu de dissolution. Toutefois, leur fonction ionique peut être influencée par d'autres ions, ou par une pression osmotique.

La taille moyenne des particules des Eudragit® est d'environ 100 nm, donc très fines, permettant une fusion complète des particules entre elles et donc l'obtention d'un film uniforme. Les propriétés physico-chimiques de quelques copolymères méthacrylates sont référencées dans le tableau 4 (Evonik industries, 2009).

Tableau 4 : Propriétés physico-chimiques de quelques copolymères méthacrylates.

Type	**Propriétés**		
	Masse moléculaire (g/mol)	*Tg (°C)*	*MFT (°C)*
Eudragit® NM	~ 600 000	~ 11	5
Eudragit® NE	~ 800 000	~ 9	5
Eudragit® E	~ 47 000	~ 48	
Eudragit® L	~ 123 000	~ 110	~ 25
Eudragit® RS	~ 30 000	~ 65	~ 45

Seul l'Eudragit® NM 30 D sera décrit dans cette partie, car il est le sujet de la seconde partie. L'Eudragit® NM 30 D (figure 11) est une dispersion aqueuse d'un copolymère neutre l'acrylate d'éthyle et le méthacrylate de méthyl. Comme les précédentes, cette dispersion contient 30 % de matière sèche.

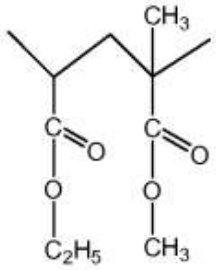


Figure 11 : Structure chimique de l'Eudragit® NM 30 D.

L'Eudragit® NM est insoluble et non chargé. La libération de la SA est pH-indépendant. Il est doté d'une grande flexibilité et peut gonfler une fois en contact avec le milieu physiologique. De plus, il possède une faible perméabilité et donc peut être mélangé avec d'autres polymères afin d'adapter le profil de libération à l'application thérapeutique souhaitée. Vu sa faible Tg et MFT, aucun plastifiant n'est requis.

Enfin, l'Eudragit® NM peut être utilisé dans les procédés de granulation humide comme liant pour obtenir une libération contrôlée de la molécule active de comprimé matriciel. Sa flexibilité unique permet la compression des particules enrobées en

comprimés sans aucune influence sur le résultat de cinétique de libération (Evonik industries, 2009) (Skalsky and Petereit, 2008).

Dans les dispersions aqueuses de polymère, des additifs peuvent être ajoutés pour modifier les propriétés physico-chimiques, mécaniques et thermiques du film d'enrobage. Comme déjà annoncé précédemment, un plastifiant peut être incorporé pour diminuer la Tg et la MFT, dépendant de la quantité et de la compatibilité de ce dernier avec le polymère. Il est important de diminuer la Tg et la MFT si nécessaire pour faciliter le procédé d'enrobage. Le plastifiant permet la diminution des forces intermoléculaires entre les chaines de polymère augmentant ainsi leur mobilité. C'est pourquoi, il augmente la flexibilité et diminue la résistance à la traction du film. Cependant, il ne faut pas négliger que cet ajout influence la cinétique de libération de la SA en modifiant les propriétés du film.

Pour assurer l'efficacité du plastifiant, il doit être miscible avec le polymère, et non volatile pour un effet permanent. S'il tend à s'échapper, le film deviendra fragile. Afin de plastifier le polymère, cet agent doit bien diffuser à travers les chaines de polymère pour interrompre les interactions intermoléculaires. Cette étape dépend de la solubilité du plastifiant dans l'eau et de son affinité pour le polymère (Carlin *et al.*, 2008) (Felton, 2010). Les plastifiants solubles dans l'eau interagissent plus rapidement que ceux insolubles dans l'eau. Généralement, ils sont mélangés plusieurs heures (et jusqu'à 24 heures dans le cas des polymères insolubles) avant le procédé d'enrobage. Siepmann *et al.* ont développé un modèle mathématique pour prédire le temps minimum de mélange (Siepmann *et al.*, 1998).

Les plastifiants les plus courants sont les suivants (Carlin *et al.*, 2008) :

- Triéthylcitrate (TEC)
- Triacétine
- Polyéthylène glycol
- Propylène glycol

Polymères solubles

- Dibutylsébacate (DBS)
- Dibutyl phtalate
- Monoglycéride acétylé

Polymères insolubles

Ensuite, d'autres excipients peuvent être additionnés. Tout d'abord, un agent anti-adhérent est nécessaire pour diminuer l'aspect collant de certaines dispersions aqueuses de polymère (par exemple Eudragit NM®) et donc d'éviter toute agglomération des mini-granules entre eux durant le procédé d'enrobage, de

séchage et de stockage. Par exemple, ces produits (talc, silice pyrogénée Aerosil®) peuvent être saupoudrés sur les mini-granules enrobés pour résoudre le problème de collage lors du stockage. Sinon, ces excipients (généralement talc, monostéarate de glycérol) sont ajoutés dans la dispersion aqueuse de polymère directement avant la pulvérisation. Le talc est utilisé entre 25 à 100 %, basé sur la masse sèche de polymère. Cependant, il peut créer des instabilités dans le film, diminuer la flexibilité et influencer la cinétique de libération de la SA. Avec une grande quantité de talc la perméabilité du film diminue due aux particules du talc insolubles dans l'eau et le film devient opaque. Le monostéarate de glycérol est une alternative au talc. Il est également insoluble dans l'eau et seulement 5 à 20 % (basé sur la masse sèche de polymère) est suffisant dû à son efficacité. Cependant, il est contraignant au niveau de la préparation, et peut diminuer la cinétique de libération de la SA.
Ensuite, des pigments sont généralement employés pour fournir une meilleure identification et améliorer l'aspect esthétique du produit. Le dioxyde de titane est un pigment blanc commun, incorporé dans la formulation en tant qu'opacifiant pour améliorer la stabilité des molécules actives sensibles à la lumière. Sinon, des pigments de couleur peuvent être ajoutés à la dispersion aqueuse de polymère ou en couche de finition.

Puis, des émulsifiants et stabilisants sont requis pour des dispersions de latex qui contiennent des électrolytes pouvant changer le zeta-potentiel et causer une coagulation après mélange. Selon la quantité d'excipients instables dans la formulation, entre 2.5 et 10 % (calculé sur la masse sèche du polymère) de stabilisant est nécessaire tel que le polysorbate, poly(vinyl pyrrolidone) ou le sodium dodecyl sulfate.
Enfin, l'addition d'édulcorants ou d'agents de saveur est limitée due à leur complexité chimique et à leur faible stabilité. Toutefois, de faibles quantités (2-10 % basé sur la masse sèche de polymère) peuvent être utilisées selon l'application souhaitée (Skalsky and Petereit, 2008).

Une fois les mini-granules enrobés, des **tests de dissolution** sont réalisés afin de connaître la cinétique de libération de la SA. Dans la pharmacopée européenne, différentes méthodes sont décrites selon la forme galénique et l'application pharmaceutique. Dans le cas des mini-granules enrobés à libération contrôlée, les libérations de la SA se font dans des appareils de dissolution tels que le Sotax (figure 12). Les conditions utilisées sont les suivantes : les mini-granules

sont placés dans 900 mL de tampon phosphate pH 7.4 (selon l'USP 35) à 37 °C, agités à l'aide de pâle à 100 rpm.

Figure 12 : Exemple d'un appareil à dissolution, le Sotax® (Sotax, n.d.).

Selon la forme galénique, la SA et le type d'enrobage, la cinétique de libération de la SA sera différente, et donc les mécanismes de libération de la SA aussi. Pour comprendre et justifier le profil, il est nécessaire de les élucider. Plusieurs paramètres influencent le relargage de la substance médicamenteuse dans le milieu de dissolution. En revanche, les mécanismes qui contrôlent la libération de la SA à partir des mini-granules enrobés sont souvent complexes et dépendent principalement de la molécule active, du type de noyau, de la composition de la dispersion aqueuse de polymère et de l'épaisseur de la couche de polymère.

Tout d'abord, les propriétés physico-chimiques de la SA sont importantes à considérer, comme sa nature (acide ou base), sa solubilité dans l'eau et son affinité pour le polymère (Sousa *et al.*, 2002). Une molécule active très soluble dans l'eau diffusera plus rapidement à travers le film de polymère. En effet, cette substance va attirer plus d'eau dans le système, se dissoudre rapidement et se libérer dans le milieu extérieur (Porter and Ghebre-Sellassie, 1994). Dans ce cas, une épaisse couche de polymère est recommandée pour atteindre la libération contrôlée. Il est donc important d'étudier la solubilité de la SA dans le milieu désiré, surtout si la SA a une solubilité pH-dépendante ou une solubilité variant avec la nature du milieu (exemple en présence de NaCl ou de sucre) (Porter and Ghebre-Sellassie, 1994).

Ensuite, les propriétés physico-chimiques du noyau constituant le cœur de la mini-granule ont un impact sur les mécanismes de libération de la SA. Premièrement, les caractéristiques physiques du substrat concernent : (i) l'aire de surface qui influence la taille des particules, et cette dernière ajoutée à la densité sont deux facteurs impliqués dans le mouvement des sphères lors de la fluidisation, paramètre

important pour une bonne formation de film homogène. De plus, l'aspect de la surface des noyaux (lisse, irrégulière, rugueuse) a des conséquences sur le résultat du film d'enrobage et donc sur la cinétique de libération de la SA ; les plus lisses fournissent une cinétique plus lente. (ii) La morphologie et la porosité dépendent de la méthode de préparation. La présence de pores interfère le mécanisme de formation du film car l'eau de la dispersion pénètre dans le noyau selon la taille des pores. Il y a peu de risque si la taille des particules de la dispersion est inférieure à celle des pores. (iii) Des mini-granules friables produisent des profils de libération plus rapides que des non friables. En effet, des particules fines peuvent être générées dues aux frictions entre elles et contre la paroi de l'appareil, et celles-ci vont être soient retenues par le filtre ou bien s'intégrer aux sphéroïdes et créer des défauts lors du procédé d'enrobage (Porter and Ghebre-Sellassie, 1994). Deuxièmement, quelques propriétés chimiques sont à prendre en compte : (i) la solubilité des excipients constituant le noyau ; un noyau soluble (à base de sucre par exemple ou une matrice contenant une SA très soluble dans l'eau) attire beaucoup d'eau, et cet influx d'eau a deux conséquences majeures : il présente un frein à la diffusion de la SA vers le milieu extérieur (influx d'eau par convection versus diffusion de la SA en contre-courant) et génère une pression hydrostatique à l'intérieur du système et stresse le film de polymère. Par conséquent, des fissures peuvent être causées si la stabilité mécanique du film est insuffisante pour supporter cette pression. Ainsi, la cinétique de libération de la SA sera rapide et se fera à travers ces pores (Muschert *et al.*, 2009a) (Lecomte *et al.*, 2005).

Par ailleurs, le choix du polymère et les excipients ajoutés dans la dispersion ont bien entendu une influence sur la cinétique de libération de la SA (tableau 5).

Tableau 5 : Exemples d'impacts sur le film d'enrobage en fonction de la formulation d'enrobage (Porter and Ghebre-Sellassie, 1994).

Composition de la formulation d'enrobage	Conséquences
Type de polymère	- Tg - Formation du film - Perméabilité de la membrane
Masse moléculaire	- Elasticité et résistance du film
Plastifiant	- Tg - Coalescence des particules colloïdales de polymère - Flexibilité
Additifs insolubles	- Perméabilité de la membrane - Elasticité et résistance du film - Viscosité de la dispersion
Additifs solubles	- Perméabilité de la membrane - Changement de la membrane avec le temps et le pH
Propriétés physico-chimiques du solvant	- Temps de séchage - Relargage de la SA - Porosité de la membrane

Les dispersions aqueuses de polymère se diffèrent par leur nature chimique, leur masse moléculaire, la méthode de préparation, la présence d'additifs, la stabilité physique, leur Tg, la taille des particules du polymère, le pH et leur charge. En fonction de ces critères, la dispersion requiert ou non des additifs supplémentaires tels que : un second polymère, un agent porogène, un plastifiant, un agent anti-adhérent ou bien un pigment. Comme énoncé précédemment, tous ces produits ont un impact sur le mécanisme de formation du film (et ses propriétés mécaniques) et finalement sur le profil de libération de la SA. Pour éviter tous défauts et problèmes, il est primordial de s'assurer de la compatibilité des substances entre elles, de leur efficacité et de leur permanence (Porter and Ghebre-Sellassie, 1994).

En outre, l'épaisseur de la membrane de polymère a toute son importance puisque si elle s'élargit, la SA mettra plus de temps pour diffuser à travers et donc la cinétique de libération diminuera. Une faible épaisseur favorise l'existence de pores tandis qu'avec une bonne épaisseur, les pores deviennent suffisamment recouverts pour

que la SA diffuse à travers une membrane de polymère intacte (Muschert *et al.*, 2009b).

Enfin, les conditions du procédé d'enrobage (tableau 6) déterminent la qualité et l'uniformité du film de polymère. Par exemple, la porosité dans la membrane est causée par un excès de séchage et une incomplète coalescence des particules de polymère (Porter and Ghebre-Sellassie, 1994).

Tableau 6 : Exemples d'influences des conditions du procédé d'enrobage.

Variable	Influence
Equipement	- Qualité et fonctionnalité de l'enrobage
Contenu en masse sèche de polymère	- Structure et uniformité de la membrane
Débit de pulvérisation	- Structure de la membrane - Uniformité de distribution de l'enrobage - Relargage de la SA
Pression d'air atomisé	- Structure de la membrane - Uniformité de distribution de l'enrobage
Conditions de séchage	- Coalescence des particules de polymère - Relargage de la SA - Agglomération - Cinétique de libération de la SA

Pour conclure, des études complètes sont réalisées sur certains polymères, par exemple Siepmann *et al.* ont considéré les facteurs de la formulation et du procédé d'enrobage affectant la cinétique de libération de la SA à partir de mini-granules enrobés avec de l'Aquacoat® (J. Siepmann *et al.*, 2008).

Après avoir pris connaissance de tous les paramètres affectant la cinétique de libération de la molécule active, les formes orales solides à libération contrôlée peuvent rester complexes et tous les mécanismes de libération ne sont pas complètement compris. Il est parfois indispensable et judicieux de faire appel à des méthodes analytiques et d'imagerie pour élucider la structure du système (tableau 7).

Tableau 7 : Méthodes de caractérisation d'une forme orale solide à libération contrôlée.

Méthodes analytiques	Méthodes d'imagerie
- Calorimétrie différentielle à balayage (DSC) / Analyse thermomécanique (et dynamique) - Propriétés mécaniques des films - Test de dissolution d'un mini-granule et étude de son gonflement - Spectroscopie Raman	- Microscopie dont microscope à force atomique - Microscopie électronique à balayage (ou SEM) - Imagerie Terahertz - Microtomographie à rayons X

En premier lieu, la calorimétrie différentielle à balayage est utilisée pour déterminer la température de transition vitreuse (Tg) de film d'enrobage car généralement les polymères sont amorphes. Elle est définie par le passage d'un état vitreux et rigide, caractérisé par une faible mobilité des chaines polymériques à un état caoutchouteux, où la mobilité des chaines et l'élasticité du polymère sont augmentées. Il est indispensable de connaître la Tg du ou des polymères constituant l'enrobage afin de régler le lit d'air fluidisé à la température optimale c'est-à-dire 10 à 20 °C au-dessus de la MFT (température minimale de formation du film inférieure ou égale à la Tg). La calorimétrie différentielle à balayage permet aussi de déterminer le point de fusion, de détecter un polymorphisme, d'étudier la miscibilité d'un mélange de polymères (Bley *et al.*, 2008). Toutefois, il existe d'autres méthodes déterminant la Tg, comme l'analyse thermomécanique, l'analyse mécanique dynamique ou encore la thermo analyse dynamique et mécanique (Lafferty *et al.*, 2002). Elles sont plus complexes et plus précises et donc adaptées à des échantillons compliqués (mélange de polymères). Par exemple, l'analyse mécanique dynamique est environ 1000 fois plus sensible qu'une DSC, elle est capable de mesurer la Tg d'un film de polymère immergé dans le milieu de dissolution (Fadda *et al.*, 2010).

En deuxième lieu, les propriétés mécaniques de chaque film de polymère doivent être connues pour comprendre les mécanismes de libération de la SA, d'autant plus que les additifs dans les dispersions les affectent. Pour obtenir une libération contrôlée, le film d'enrobage doit conserver son intégralité physique sans être cassant, ni trop élastique. Les propriétés mécaniques comprennent entre autres la résistance à la rupture, l'élongation à la rupture et l'énergie nécessaire pour perforer le film. Elles sont mesurées à l'aide d'un analyseur de texture (figure 13).

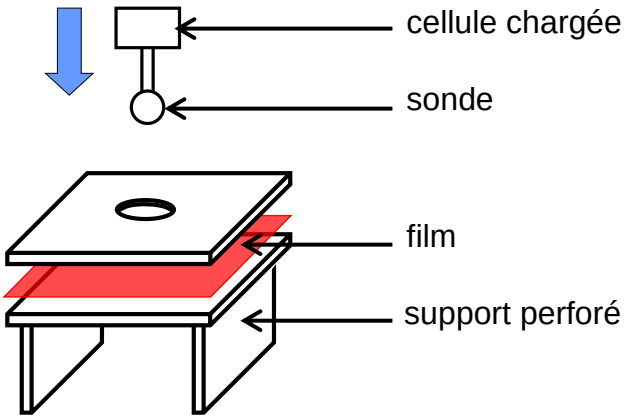


Figure 13 : Schéma d'un analyseur de texture.

D'un point de vue pratique, les mesures sont faites avant et après exposition dans le milieu de dissolution (tampon phosphate pH 7.4). A des temps prédéterminés, le film est placé sur un support perforé, une sonde descend à vitesse constante et applique une force continue jusqu'à rupture du film ; un graphique (figure 14) est ainsi obtenu.

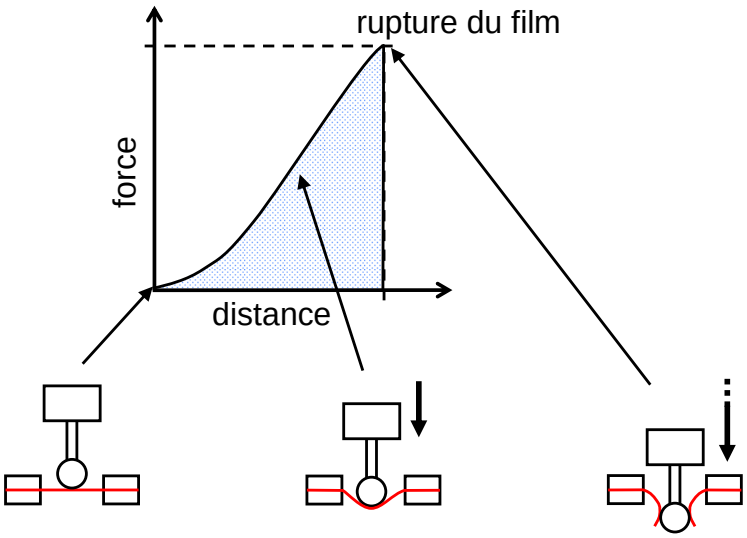


Figure 14 : Représentation schématique des étapes d'une analyse de film et du graphique obtenu.

Etudier les propriétés mécaniques à l'état sec comme à l'état mouillé a toute son importance. En effet, une fois le film d'enrobage en contact avec le milieu environnant, il va s'hydrater et donc contenir une certaine quantité d'eau, pouvant entrainer le relargage de certains additifs, tels que les plastifiants solubles dans l'eau (Bodmeier and Paeratakul, 1994). De ce fait, les propriétés mécaniques du film peuvent changer au cours du temps de transit, perdre sa flexibilité, se rompre et libérer massivement la SA.

En troisième lieu, pour compléter les études sur les films de polymère, des tests de dissolution sur des mini-granules individuels peuvent être testés avec en parallèle une étude comportementale afin de savoir si le lot est homogène et surtout si le diamètre change au cours du temps. Ces expériences révèlent souvent des aspects importants, comme un gonflement suivi d'un « crack » visualisé par une augmentation de taille suivie d'une diminution brutale. De plus, ils sont faciles à mettre en œuvre, et nécessite peu de matériels.

En dernier lieu pour les méthodes analytiques, la spectroscopie Raman donne des informations relativement étendues :

- Identification des composés organiques et chimiques
- Caractérisation des matériaux
- Détermination de la structure moléculaire
- Etude des systèmes amorphes et cristallins

Cette technique est performante et sensible, dotée d'une excellente résolution de l'ordre du micromètre. De plus, elle est non destructive et facile à mettre en œuvre : le temps de préparation est négligeable et ne requiert qu'une très faible quantité de matière (de l'ordre du microgramme). La nature de l'échantillon n'intervient pas dans la mesure qu'il soit liquide, solide ou gazeux et les conditions opératoires peuvent être adaptées (étude à air ambiant ou sous atmosphère contrôlée). Dans le cas des mini-granules enrobés, la spectroscopie Raman permet par exemple l'observation de la surface d'un film de polymère renseignant la distribution des composants dans la membrane et son homogénéité ; la visualisation de la distribution d'une SA dans un film d'enrobage (Ringqvist *et al.*, 2003) etc.

Concernant les méthodes d'imagerie, le microscope classique est bien entendu utilisé pour toute visualisation succincte d'une surface tandis que le microscope à force atomique fournit plus de détails et d'informations. En effet, on peut obtenir des images tridimensionnelles, visualiser les hétérogénéités et la topographie des surfaces à l'état sec comme en milieu aqueux sans destruction de l'échantillon. Dans le cas de formes solides enrobées, cette technique s'avère intéressante pour étudier le système une fois en contact avec le milieu de dissolution pour suivre son comportement (Ringqvist *et al.*, 2003). Dans la même catégorie, on trouve la microscopie électronique à balayage (SEM) qui permet d'étudier la forme générale et l'aspect de la surface (lisse, rugueuse, poreuse) d'un comprimé ou d'un mini-granule (Strübing *et al.*, 2007) ; de même, l'épaisseur d'une membrane peut être

mesurée via une coupe de l'échantillon (Gryczová *et al.*, 2008) (Xu *et al.*, 2015) . En revanche, une des limites de cette méthode est que l'échantillon doit être sec, donc aucune mesure ne peut être faite sur échantillon humide ou en milieu aqueux.

Ensuite, l'imagerie Terahertz est devenue une technique répandue dans l'industrie pharmaceutique pour mesurer directement l'épaisseur d'un film d'enrobage et l'uniformité tridimensionnelle des formes solides enrobées. Vu que cette analyse ne détruit pas l'échantillon et ne demande pas de calibration particulière, elle est attractive dans ce genre d'application pharmaceutique. Pour des comprimés enrobés, il est possible de visualiser l'épaisseur de l'enrobage sur toute la surface afin de déterminer l'homogénéité et de détecter d'éventuelles ruptures de la membrane (Müller *et al.*, 2012).

Enfin, une dernière technique récente, performante et révolutionnaire : la micro tomographie à rayons X. Landis et Keane ont publié une revue expliquant en détail le principe et quelques applications de ce procédé (Landis and Keane, 2010). Elle permet de visualiser la structure interne d'un médicament, d'avoir une reconstruction tridimensionnelle sans détruire l'échantillon. Ainsi, plusieurs caractéristiques sont obtenues : l'uniformité, l'épaisseur, la porosité, la densité, le volume et la surface. Analyser en profondeur un mini-granule enrobé porte toute son importance. En effet, nous avons pratiqué cette technique et observé la structure interne de mini-granules enrobés et son évolution une fois en contact avec le milieu de dissolution. Cela a révélé le rôle du noyau dans les mécanismes de libération d'une SA et élucider ceux impliqués dans notre système. Pour finir, la micro tomographie à rayons X à divers avantages : elle est non destructive, l'acquisition d'image est rapide, l'échantillon peut se présenter à l'état sec comme en milieu aqueux, et a une définition allant jusqu'au nanomètre (Perfetti *et al.*, 2010) (Yang *et al.*, 2014) (Gendre *et al.*, 2013).

Cette thèse est scindée en deux projets. Le premier a été effectué en partenariat avec l'industrie pharmaceutique MSD. Les principaux objectifs incluent :

(i) La préparation et la caractérisation physico-chimique de mini-granules pelliculés et de films polymériques libres de composition identique au pelliculage.

(ii) L'étude de l'impact des paramètres de formulation et de procédé (ex: type de polymère, nature et taille du noyau, du principe actif, etc sur les cinétiques de libération résultantes).

(iii) L'élucidation des mécanismes de libération sous-jacents en se basant sur les propriétés physico-chimiques des mini-granules pelliculés et des films polymériques libres, s'aidant de techniques analytiques et d'imagerie.

(iv) La modélisation mathématique du système.

Les cinétiques de libération du principe actif à partir de mini-granules enrobés et de films polymériques sont étudiées. Différentes SA modèles telles que le chlorydrate de propranolol et la théophylline sont déposées sur les mini-granules. Ces derniers sont préparés par succession de couches, une contenant la SA et l'autre constituée de polymère, le Kollicoat® SR 30 D. En parallèle, des films de polymères libres chargés ou non en principe actif sont préparés et servent de référence aussi bien pour les caractéristiques physico-chimiques que pour les corrélations quantitatives avec les cinétiques de libération in-vitro des enrobés. Différents paramètres de préparation et de formulation sont testés (ex : variation de la composition et taille du noyau, utilisation de deux SA modèles de solubilités différentes, changement de l'épaisseur de la membrane de polymère).

Les cinétiques de libération du principe actif à partir des mini-granules sont réalisées dans un appareil à pales tournantes (USP 35) sous des conditions standards (Pharmacopée européenne) comme décrites auparavant. Le dosage de la molécule active est fait par spectrophotométrie UV. Ensuite, l'étude des cinétiques à partir des films de polymère chargés en principe actif est réalisée par la prise d'échantillons de volumes définis sous agitation et à 37 °C, tandis que les films non-chargés en SA sont analysés avec des cellules de diffusion pour caractériser la diffusion du principe actif à travers le film. Les caractéristiques physico-chimiques des films de polymère sont étudiées grâce à : (i) la capacité d'absorption d'eau et le gonflement du polymère, (ii) la perte de poids due à la libération du polymère et/ou plastifiant dans le milieu environnant, (iii) les propriétés mécaniques du film, (iv) la température de transition vitreuse par DSC. De plus, les films d'enrobage et les mini-granules

enrobés sont caractérisés morphologiquement (SEM, microtomographie à rayons X), afin d'étudier la surface, la porosité et la structure interne.
Lors de la modélisation mathématique, différents processus de transport sont pris en compte : (i) la diffusion à travers le polymère, (ii) la diffusion à travers des pores remplis d'eau (formation de films poreux par la méthode de préparation, par contact du film polymérique avec le milieu de libération) et (iii) la convection du principe actif à travers des pores remplis d'eau du fait de la pression hydrostatique en présence de substances osmotiquement actives. Enfin, les cinétiques de libération de la SA sont prédites via les modèles mathématiques et validées ou non via les expériences.

Le second projet concerne la mise au point d'une forme orale solide à libération contrôlée de même type que le premier projet, c'est-à-dire des mini-granules enrobés où le mécanisme de libération impliquée est la diffusion à travers la membrane intacte. Les principaux objectifs sont :

(i) Le screening de polymères, et la sélection d'un mélange de deux polymères.
(ii) La préparation des mini-granules et la mise au point de la formulation d'enrobage.
(iii) Le réglage des paramètres du procédé d'enrobage.
(iv) L'étude des profils de libération de la molécule active, et l'ajustement de la formulation d'enrobage.
(v) L'élucidation des mécanismes de libération de la SA en se basant sur les propriétés physico-chimiques des mini-granules pelliculés et des films polymériques libres.
(vi) La modélisation mathématique et sa validation expérimentale.
(vii) Comparaison avec des comprimés pelliculés de même composition que les mini-granules, et étude de l'impact de la forme galénique sur la cinétique de libération de la SA.

Les méthodes utilisées sur la conception des mini-granules sont quasi identiques au premier projet. Une des différences est le procédé de fabrication des noyaux, où la SA, ici la diprophylline utilisée comme modèle, est incorporée dans une matrice constituée de cellulose microcristalline et de lactose par extrusion-sphéronisation. Ensuite, une dispersion aqueuse comprenant un mélange de deux polymères, l'Aquacoat® ECD 30 et l'Eudragit® NM 30 D est pulvérisée autour de ces noyaux

dans un lit d'air fluidisé. Différents ratios de ces deux polymères ont été testés afin d'obtenir une libération de la SA par diffusion à travers la membrane de polymères. Un travail de réflexion sur la mise au point des paramètres du lit d'air fluidisé et sur leur compatibilité selon les caractéristiques physico-chimiques des polymères a été investi. L'étude des cinétiques de libération à partir des mini-granules et des films de polymères reste identique au précédent projet. Enfin, des modélisations mathématiques de ce système sont prédites et validées expérimentalement.

CHAPTER I:
INTRODUCTION

I. Coated pellets as oral drug delivery systems

I.1. Introduction

Nowadays, the discovery of new Active Pharmaceutical Ingredients (API) is more and more difficult due to the complexity and the lack of financing. So, the pharmaceutical companies develop new pharmaceutical technologies for existing molecules to improve the bioavailability and the delivery system. That is why, **controlled release dosage forms** have gained much attention and on the pharmaceutical market their number has increased these last years due to their temporal and spatial control of drug release. Indeed, compared to the conventional dosage forms, they offer many therapeutic benefits:

- ✓ The increase of therapeutic effect
- ✓ Improvement of treatment efficiency
- ✓ Minimization of side effects
- ✓ The reduction of administration
- ✓ The increase patient convenience and compliance

Controlled release systems aim to control the kinetic of the API released from the dosage form in time. Moreover, they are capable of achieving different therapeutic effects and they can include mainly delayed release (*e.g.* enteric coated tablet) and sustained release (coated pellets) compared to an immediate release (figure 1) (Hong and Kinam, 2010).

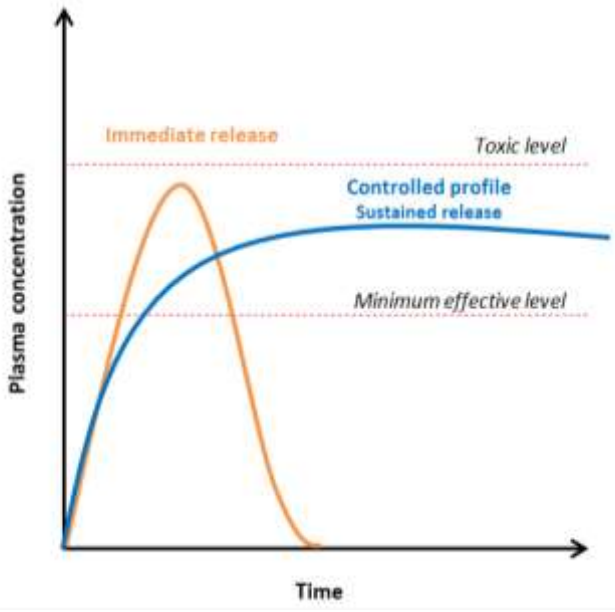


Figure 1: Representation of plasma concentrations of an immediate versus controlled release dosage form.

To obtain a controlled release rate over time, drug delivery systems based on polymers are usually used and their functionalities are determined by the polymer properties. They can be separated in two groups: (i) **matrix systems** where the API is dispersed within the polymeric matrix (figure 2 a); (ii) **reservoir systems** where the drug is surrounded by a polymeric film controlling the drug release. The drug can be included into the core or surrounded on the inert core (figure 2 b).

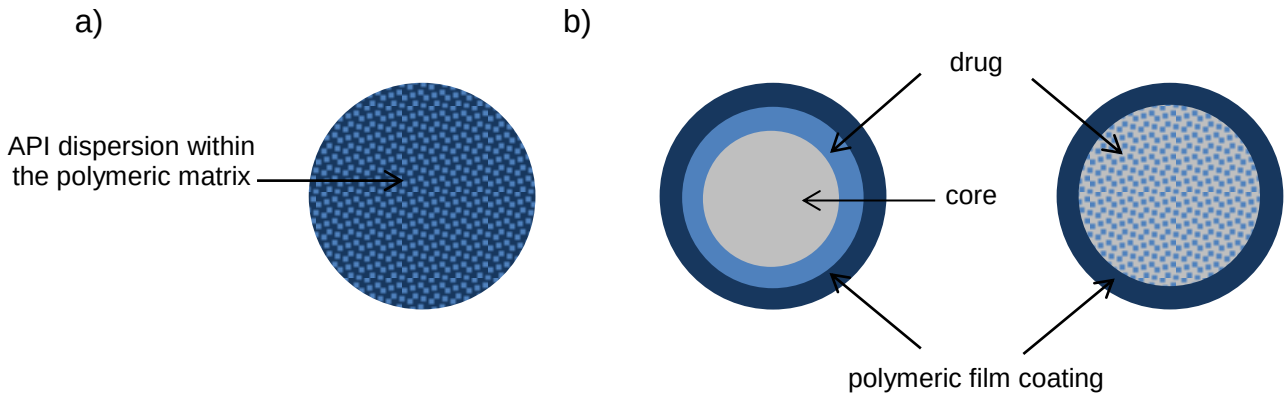


Figure 2: Schematic presentation of a matrix system (a) and reservoir systems (b).

- Matrix systems

A drug is dissolved or dispersed in a polymeric network to obtain a matrix system with a controlled drug release. These devices provide several advantages such as the easy-manufacture, the low cost and the capacity for incorporating a high amount of API. Various types of matrix systems can be achieved and thus the drug release mechanisms will be different. The drug release will occur due to diffusion from homogeneous matrix, or diffusion through the pores and/or by swelling and/or erosion from heterogeneous matrix.

- Reservoir systems

In this case, the API is layered around an inert core or incorporated into a water-soluble excipient matrix, the whole surrounded by a coating layer. According to the polymer properties, the drug release mechanisms and so release profiles will be different. Reservoir systems can be divided as having either:

- A non-constant activity source where the API concentration in the reservoir is below its solubility, so all the drug is dissolved and drug molecules that are released through the membrane are not replaced and so the concentration will decrease with time (*first order* in vitro drug release profiles).

- A constant activity source where an excess of API is present and drug molecules released are quickly replaced by dissolution of the remaining non-dissolved drug. Therefore, the drug release remains constant as long as enough excess of drug is available (*zero order* in vitro drug release profiles).

Once in contact with aqueous gastro-intestinal fluids, water penetrates into these systems and dissolves the drug. In the case of constant activity sources, only a part of the API is dissolved due to its low solubility. In the other case, all drugs are rapidly dissolved. Then, the drug molecules diffuse through the polymeric film by concentration gradient. Different mass transport processes occur: water diffusion, drug dissolution, its diffusion, the swelling of the polymer chains, their dissolution and/or degradation. Frequently, drug diffusion is the slowest step and therefore rate controlling, so the drug release can be characterized by mathematical models. This simplification is not always acceptable depending of the system. Certainly, an attention must be paid to potential crack formation that might occur during dissolution test. The penetration of water into the device leads to an internal hydrostatic pressure acting against the membrane. If this latter is too fragile to resist, some cracks can occur and the drug will be released by diffusion both, through the intact film and through the cracks. In addition, this created pressure might also generate a convective drug transport through the pores. The crack formation is more common when the API is highly water-soluble and the mechanical stability of the film is poor (Siepmann *et al.*, 2012) (Lee and Li, 2010).

In this project, the studies are based on a reservoir system, the coated pellets. As defined by Ghebre-Sellassie, pellets are solid and spherical particles with a size distribution between 500 and 1500 µm reserved for oral applications (Ghebre-Sellassie I., 1989). They have generally a smooth surface, a high density and an excellent flowability (Palugan *et al.*, 2015). The latter are coated to act as a reservoir system where the drug release is controlled on specific site according to the therapeutic activity desired. Coated pellets can be administrated in the form of hard gelatin capsules or compacted in tablets (Dashevsky *et al.*, 2004b) while retaining their advantages of multiple-unit dosage forms (figure 3). Indeed, one of the advantageous of pellets is due to the subdivision of the total amount in several units. Its allows a distribution of the delivered dose on an extended surface area, thus decreasing the risk of dose dumping and some irritations of the mucosa (Palugan *et al.*, 2015).

- Capsules
- Tablets
- Caplets
- Melt tablets

Figure 3: Examples of drug delivery systems using coated pellets (Catalent, 2016).

I.2. Excipients for controlled release pellets

I.2.1. Active pharmaceutical ingredients

During this research project, different active substances have been used as model drugs to investigate the release characteristics and to compare the influence of the API properties on the drug release profiles. So, the physicochemical properties of the drugs have an impact on the kinetics and mechanisms of the drug release.

- *Propranolol hydrochloride*

Propranolol hydrochloride (figure 4) is a non-selective beta adrenergic blocking agent used for the treatment of hypertension, angina pectoris, arrhythmias and many cardiovascular diseases.

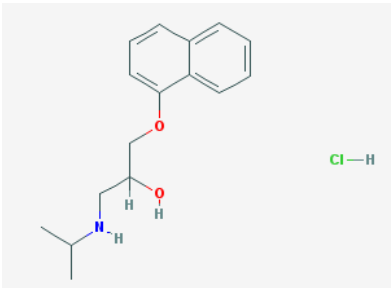


Figure 4: Structural formula of propranolol hydrochloride (Pubchem, 2016a).

Propranolol hydrochloride belongs to the class 1, drugs with high solubility and high permeability in agreement with the biopharmaceutical classification system (BCS) (Eddington *et al.*, 1998). The chemical and physical properties are mentioned in the table 1 (Pubchem, 2016a) (Vogelpoel *et al.*, 2004) (Huang *et al.*, 2004).

Table 1: Physicochemical properties of propranolol hydrochloride.

Molecular weight	~ 295.8 g/mol
Melting point	~ 163-164 °C
pKa	~ 9.45
Solubility	Freely soluble in water Insoluble in ether, benzene, ethyl acetate
Half-life	2-6 h

In addition, propranolol hydrochloride is a weakly basic drug with a solubility modified by the pH of the release medium. Therefore, propranolol hydrochloride is chosen as a model drug for our reservoir system and it is an appropriate candidate for formulating controlled release dosage forms due to its short half-life (Bolourchian and Dadashzadeh, 2008).

- *Theophylline*

Theophylline (figure 5) is a xanthine derivative mainly used as a bronchodilator for the treatment of asthma, bronchitis and emphysema.

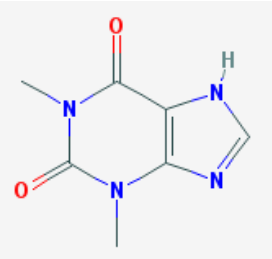


Figure 5: Structural formula of theophylline (Pubchem, 2016b).

Theophylline has a high solubility and high permeability (BCS - class 1) (Amidon *et al.*, 1995). Some chemical and physical properties are summarized in table 2 (Pubchem, 2016b) (Dashevsky *et al.*, 2010).

Table 2: Physicochemical properties of theophylline.

Molecular weight	~ 180.2 g/mol
Melting point	~ 270-274 °C
Pka	8.8
Solubility	Sparingly soluble in ethanol Slightly soluble in water
Half-life	7-9 h

Furthermore, theophylline has a constant solubility in a wide range of pH values. An attention must be paid with this molecule as it has a narrow therapeutic range. Theophylline is selected as a model drug for the preparation of coated pellets to be compared to propranolol HCl as the water solubilities of the two molecules differ significantly.

- *Dipropylline*

Diprophylline (or dyphylline) (figure 6) is a derivative of theophylline and so of xanthine also. Diprophylline has an action similar to theophylline as bronchodilator for the treatment of bronchial asthma, chronic bronchitis and emphysema (BASF, 2010).

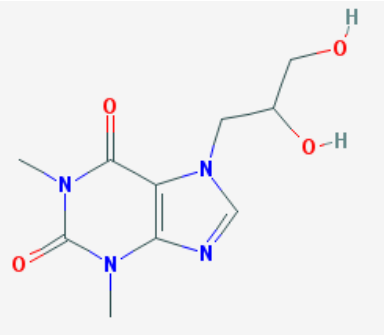


Figure 6: Structural formula of diprophylline (Pubchem, 2016c).

The physicochemical properties of diprophylline are described in table 3 (Pubchem, 2016c) (BASF, 2010).

Table 3: Physicochemical properties of diprophylline.

Molecular weight	~ 254.2 g/mol
Melting point	~ 158 °C
Pka	13.91
Solubility	Slightly soluble in ethanol Freely soluble in water
Half-life	2 h
Stability	Stable

I.2.2. Polymers

In controlled release oral dosage forms, coating layer is required to modulate the drug release. Nowadays, aqueous-based systems are preferred over organic one for safety and environmental points of view. The majority of polymers used for controlled drug delivery are water insoluble. They are presented as aqueous dispersion prepared by emulsion polymerization of a monomer (latex) or by emulsification of a polymer (pseudolatex). Generally, it results into contents of around 30 % of solid dispersion in water (Carlin *et al.*, 2008). Some common polymers are:

- Vinyl derivatives: polyvinyl acetate (Kollicoat® SR 30 D)
- Cellulose derivatives: ethylcellulose (Aquacoat®, Surelease®)
- Acrylate derivatives: Eudragit® NM 30 D, Eudragit® RL, Eudragit® RS

- Vinyl derivatives

Kollicoat® SR 30 D (figure 7) is an aqueous dispersion of 27 % polyvinyl acetate, water-insoluble polymer, containing also 2.7 % of polyvinylpyrrolidone, water-soluble polymer allowing its dissolution and thus the creation of pores once in contact with gastrointestinal fluids, and stabilized with 0.3 % of sodium lauryl sulfate (Kolter *et al.*, 2013). In addition, the excipients prevent particles sedimentation during storage.

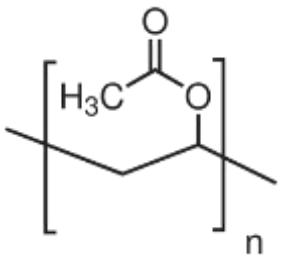


Figure 7: Structure of polyvinyl acetate.

Kollicoat® SR owns a wide range of applications: (i) it has been investigated for extended drug release; (ii) also used for compression of polymer-coated granules and (iii) to achieve taste masking (Kolter *et al.*, 2013) (Bordaweka *et al.*, 2006) (Shao *et al.*, 2002). Moreover, it has particular mechanical and physicochemical properties including a high flexibility rendering the film-coated pellets compressible without rupture (Dashevsky *et al.*, 2004b) and a pH independent release. Then, the physicochemical properties are noticed in table 4 (Dashevsky *et al.*, 2005) (Kolter *et al.*, 2013).

Table 4: Physicochemical properties of Kollicoat® SR 30 D.

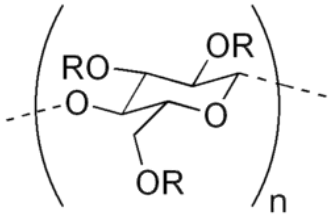
Property	Specification
Average particle size Size distribution	160 nm Narrow
pH	~ 4.5
Viscosity	< 5 cPs
Molecular mass	~ 450 000 Da
MFT	18 °C
Tg	~ 40 °C

The small particle size of this dispersion is favorable to a rapid and complete coalescence of the colloidal particles and thus to obtain a homogeneous film. In addition, the viscosity is very low allowing the atomization into fine droplets during the

coating process, and an easy manufacturing of coated pellets. Afterwards, Kollicoat® doesn't need a plasticizer because of its low MFT. Nevertheless, the latter can be optionally added to improve the uniformity, flexibility of the polymeric film and to prevent crack formation. Usually, small quantities are enough, the recommended concentration of plasticizer (*e.g.* triethyl citrate, propylene glycol) is 5 to 10 % (w/w, based on the dry polymer mass) (Kolter *et al.*, 2013).

- Cellulose derivatives

Ethylcellulose (figure 8) is a cellulose derivative water-insoluble and hydrophobic usually used for film coating of solid dosage forms to extend drug release, masking of bad taste and/or to protect against environmental conditions (Carlin *et al.*, 2008).



R = H or CH_2CH_3

Figure 8: Ethylcellulose polymer.

The aqueous dispersion Aquacoat® ECD 30 contains ethylcellulose, a surfactant - sodium lauryl sulfate and a stabilizer - cetyl alcohol, as shown in table 5 (Harris and Ghebre-Sellassie, 2008) .

Table 5: Specifications of Aquacoat® ECD.

Component / property	Specification
Total solid	29-32 %
Ethylcellulose	24.5-29.5 %
Sodium lauryl sulfate	0.9-1.7 %
Cetyl alcohol	1.7-3.3 %
pH	4-7
Viscosity	< 150 cPs
MFT	81 °C
Tg	90 °C

Aquacoat® is widely used in pharmaceutical area (Mohamad and Dashevsky, 2006) because of its safety and its various advantages: (i) no solvent required, (ii) adjustable drug release profile, (iii) easy manufacturing and cleaning, (iv) no talc

needed, (v) choice of compatible plasticizers, (vi) Stable and reproducible release rates, (vii) pH independent release profiles. However, the Aquacoat® dispersion forms tough and breakable film and its MFT is quite high, around 81 °C and the Tg is 90 °C (Lippold *et al.*, 1999) (Harris and Ghebre-Sellassie, 2008). That is why, this product needs a plasticizer to improve the flexibility of the film and to decrease the MFT in order to reach an appropriate product temperature during the coating process. Many plasticizers are compatible such as dibutyl sebacate (DBS), dibutyl phthalate, diethyl phtalate, triethyl citrate (TEC). For example, it is necessary to add 20 to 25 % of plasticizer in order to reach a MFT between 30 and 40 °C (Harris and Ghebre-Sellassie, 2008) (Lippold *et al.*, 1990).

- Acrylate derivatives

Most polymethacrylate polymers are commercialized under the trade name Eudragit®. This product includes many copolymers from esters of acrylic and/or methacrylic acid with different physicochemical properties according to the functional groups (table 6) (Skalsky and Petereit, 2008).

Table 6: Physicochemical properties of polymethacrylate polymers.

Type	**Properties**		
	Molecular mass (g/mol)	*Tg (°C)*	*MFT (°C)*
Eudragit® NM	~ 600 000	~ 11	5
Eudragit® NE	~ 800 000	~ 9	5
Eudragit® E	~ 47 000	~ 48	
Eudragit® L	~ 123 000	~ 110	~ 25
Eudragit® RS	~ 30 000	~ 65	~ 45

The size of colloidal particles is about 100 nm, sufficiently small to assure a complete fusion between particles and so to guarantee a uniform and homogeneous film.

Eudragit® NM 30 D (figure 9) is an aqueous dispersion of a neutral copolymer based on ethyl acrylate and methyl methacrylate. It is a water-insoluble, uncharged copolymer with pH-independent release.

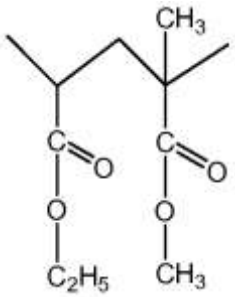


Figure 9: Chemical structure of Eudragit® NM 30 D.

Eudragit® NM provides a high flexibility, a low permeability to films, which can swell upon contact with release medium. Due its benefits, Eudragit® NM can be used in wet granulation as a binder for controlled release matrix tablets. Also, the unique flexibility allows the compression of coated pellets into tablets without influence on the drug release profile. Finally, the MFT of Eudragit® NM is very low, around 5 °C, so no plasticizer is required (Skalsky and Petereit, 2008).

I.2.3. Additives

Frequently, some additives are added in the aqueous dispersion of polymer to improve the physicochemical, mechanical and thermal properties of the film coating (Felton, 2010). As mentioned previously, **plasticizers** can be mixed with certain polymers to lower their MFT and prevent from fragility. Indeed, plasticizers can reduce the intermolecular attractions between polymer chains, thus increase the mobility of these latter and so the elongation and flexibility of the formed film. In consequence, the glass transition temperature, the minimum film formation temperature and process temperature are decreased. To be efficient, plasticizers must be: (i) compatible and miscible with the polymer, (ii) show sufficient partition behavior from the solvent phase into the polymer phase and diffuse throughout the polymer to disorder the intermolecular interactions, (iii) nonvolatile during coating, release and storage (J. Siepmann *et al.*, 2008) (Felton, 2010). In addition, the efficiency depends on the quantity, the interaction plasticizer-polymer and the solubility of the plasticizer in water (Carlin *et al.*, 2008). The study of the change in glass transition temperature of the polymer and the determination of the mechanical properties are the most common techniques to evaluate plasticizer efficacy.

Plasticizers are classified into water-soluble: triethyl citrate, triacetin, propylene glycol, polyethylene glycol; and water-insoluble: dibutyl sebacate, dibutyl phthalate, acetyltriethyl citrate, tributyl citrate. According to their solubility, the mixing time in the presence of the polymer need to be adjusted. Generally, water-soluble plasticizers

need fewer plasticization time compared to water-insoluble ones due to the dissolution in both aqueous and the polymer phase (Siepmann *et al*., 1998) (J. Siepmann *et al.*, 2008). Siepmann *et al.* showed that 85-90 % of water-insoluble plasticizer is incorporated into the colloidal polymer particles after 24 hours, the rest is not dissolved but still sprayed onto solid dosage forms. The curing step will help to give a homogeneous distribution of this latter. Also, these authors developed a mathematical model for predicting the minimum mixing time between polymer and plasticizer (Siepmann *et al.*, 1998). Nevertheless, it has to be kept in mind that incorporating plasticizer into aqueous dispersion influences on the drug release.
Several studies concerning the effectiveness of plasticizers and their influence on the drug release have been published (Porter and Ghebre-Sellassie, 1994) (Fukumori, 1994) (Shao *et al.*, 2002) (Lecomte *et al.*, 2004) (F. Siepmann *et al.*, 2008) (Felton and McGinity, 2008) (Felton, 2013).

Next to that, **antiadherents** can be useful to reduce the tackiness and to prevent agglomeration of the pellets during the coating process and the storage. Talc is one of the most common used in aqueous film coating. High levels of talc are indispensable like 25 to 100 % based on the dry polymer mass for efficiency. Nonetheless, this high amount can induce in clogging of the spray nozzle during the process, and opaque and rough coatings are obtained (Skalsky and Petereit, 2008) (Felton, 2010). In addition, it has been shown that talc may decrease the dissolution rate of drugs by decreasing the permeability of the film due to its hydrophobic nature (Maejima and McGinity, 2001). On the contrary, another study exhibits that the film in presence of talc becomes more brittle and thus the lag time decreases and the drug release becomes faster (Mohamad and Dashevsky, 2006) (Palugan *et al.*, 2015). The optimum quantity should be determined to obtain a continuous film coat being stable upon long-term storage (Kucera *et al.*, 2013). Glycerol monostearate, also a water-insoluble component, presents an alternative with concentrations of 2-15 % (based on the dry polymer mass) due to its efficacy; but it needs a preparation time and heating before using (Nollenberger and Albers, 2013). Finally, talc or fumed silica (Aerosil®) can be just sprinkled on the coated pellets to resolve tacking problems during curing or storage.

Pigments are also potential additives used for a better appearance and protection of the solid dosage forms. For example, titanium dioxide is an opacifying agent added in the coating formulation to improve the stability and the protection against environmental conditions (*e.g.* light, moisture). The water-insoluble lakes and

the iron oxides are the most commonly employed pigments (Felton, 2010). An attention must be paid concerning the influence of these components on the mechanical properties and the permeability of the films as well as the drug release kinetics. Many studies are referenced in the literature by Rowe *et al.* and by Bruce and McGinity for example on the consequences of excipients especially pigments on the coated systems (Gibson *et al.*, 1988) (Bruce and McGinity, 2008).

At last, **emulsifiers, stabilizers, flavors and sweeteners** can be mixed with the coating formulation but it is better to limit their use in favor for a greater stability of the system.

I.3. Formulation of coated pellets

I.3.1. Preparation of starter core

In pharmaceutical industry, several techniques of **pelletization** are available for pellet production (figure 10). Pelletization is a general term to define the agglomeration of fine powders (drugs and excipients) into spherical beads (Ghebre-Sellassie I., 1989).

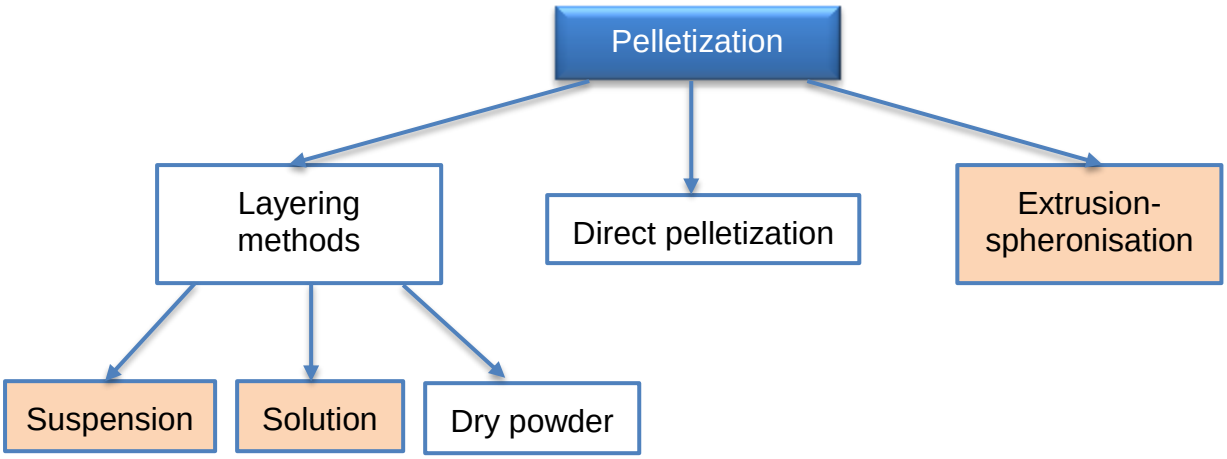


Figure 10: Main techniques for pellet manufacturing.

Only techniques by **solution or suspension layering** and **extrusion-spheronisation** are described in this section.

- Pelletization by layering

This manner consists of layering a drug onto an inert core consisting of microcrystalline cellulose or sugar from a solution or a suspension in a fluid bed coater which will be described within the next section. Actually, the drug is dissolved or dispersed in an aqueous or organic solution containing also binder and other excipients (Suhrenbrock *et al.*, 2011). Then, this medium is sprayed in a fluid bed coater; the droplets spread out on the substrates surface and the drying step allows

for their re-crystallization and the formation of solid bridges between the cores and the drug layer (Gryczová *et al.*, 2008) (Mohan Kandukuri *et al.*, 2009). In the end, a uniform and homogeneous layer is obtained (figure 11).

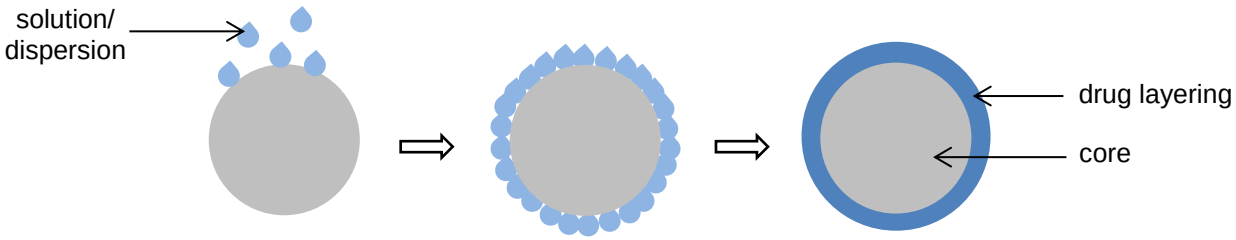


Figure 11: Drug layering steps.

One of the disadvantages is only low drug loading can be achieved.

- Extrusion-spheronisation

Manufacturing pellets by extrusion-spheronisation is a well-established method to obtain pellets with good properties such as high density, narrow size distribution and high drug loading despite processing time (Erkoboni, 2010). This preparation includes many steps (Mohan Kandukuri *et al.*, 2009) (Kranz *et al.*, 2009) (Koester and Thommes, 2010) :

1. **Dry mixing**: The drug and excipients are mixed together to get homogeneous powder dispersion using planetary mixer, high shear mixer or tumbler mixer.
2. **Wet granulation:** The powders are wet by a solution until the obtaining of wet plastic mass. This step is fundamental and will influence the quality of extrudates and so final spheroids.
3. **Extrusion:** The wet mass is shaped into cylindrical dies with uniform and defined diameters to collect extrudates.
4. **Spheronisation:** This step includes three stages: (i) breaking the extrudates due to the contact between them and with the device, (ii) agglomeration of the broken segments and (iii) formation of spherical particles due to the rotation of the friction plate.
5. **Drying:** Spheroids are dried at room temperature, in a fluid bed coater or oven until achieving the desired final moisture content.

Extrusion-spheronisation is illustrated in figure 12.

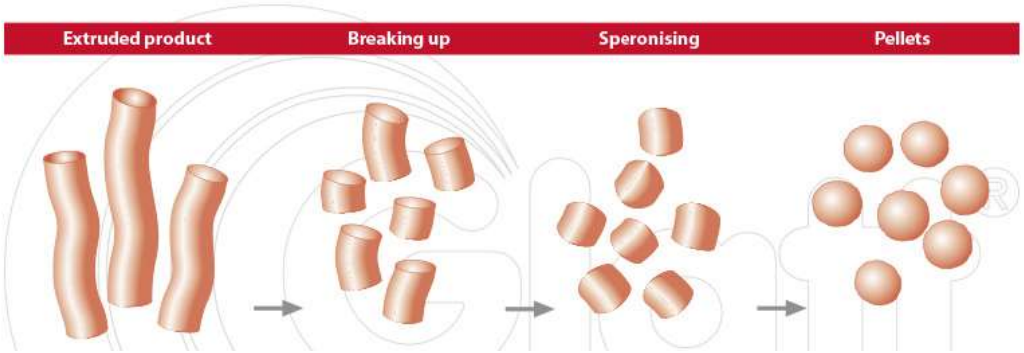


Figure 12: Extrusion-spheronisation steps (Glatt GmbH, 2016).

I.3.2. Polymer coating

The drug loaded pellets can be coated with polymer materials for esthetic, protective and/or functional purposes or taste-masking. Indeed, the film coat of solid dosage forms can (i) help to identify the medicine; (ii) provide a physical barrier against environmental storage conditions; (iii) improve the physical strength and resistance, (iv) mask unpleasant tastes and odors; (v) achieve desired drug release kinetics and modify drug release mechanisms (Felton, 2010).

Coating consists to apply solid substrates onto starter cores using a spray atomization technique. Firstly, the cores, which contain the drug (either incorporated or layered) are pre-heated in the fluid bed coat prior to the actual process. Secondly, the coating dispersion is atomized into small droplets by means of compressed air and spread out on the substrate's surface. Then, the solvent evaporates and the film is forming due to the suitable temperature for drying. The film formation from aqueous dispersion is different and more complex than organic solution. As already mentioned aqueous polymer dispersions are preferred and offer many benefits such as low viscosity, high solid loading, high spray rate, no solvent environmental and toxicity and safety. The major steps are represented in figure 13.

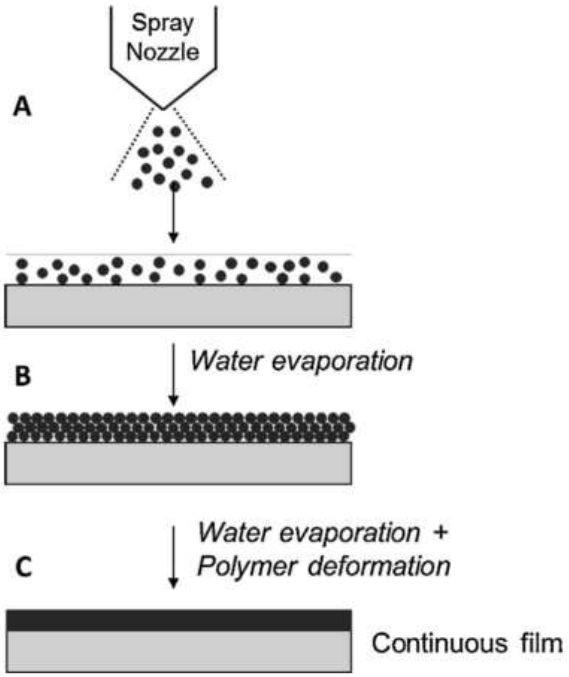


Figure 13: Film formation from an aqueous polymeric dispersion. Briefly, (A) atomization of droplets on the substrate surface; (B) evaporation of water; (C) coalescence of the polymeric chains (Felton, 2013).

Firstly, the polymer particles are deposited on the cores surface. Secondly, due to the temperature, water begins to evaporate which will bring the particles closer together with water filled voids. They start deformation and fuse due to the removal of water which fills the remaining voids. Lastly, the spheres coalesce and form a continuous polymeric film (Carlin *et al.*, 2008). The time required for a complete fusion depends on the process temperature and the nature and concentration of a plasticizer added to the coating formulation and the curing step (Felton, 2010).

I.3.3. Equipment and process parameters for coated pellets manufacturing

- Equipment

The equipment used to apply coatings onto pharmaceutical solids can be classified into three major categories: conventional pans, perforated pans and fluidized bed coaters. They all have in common the following steps: (i) atomization of the coating dispersion, (ii) motion of the particles, (iii) heating for solvent evaporation (Felton, 2010).

Only the fluid bed processor will be presented in detail within this section. The **fluid bed device** is well known for many years for drying and granulating steps. But more and more, this equipment is preferred for aqueous coating because of the enhanced drying efficiency, choice of techniques and various applications. Indeed, the fluid bed

technology can achieve fast and uniform coatings using air to mix, coat and dry the substrate at the same time. The principle is illustrated in figure 14.

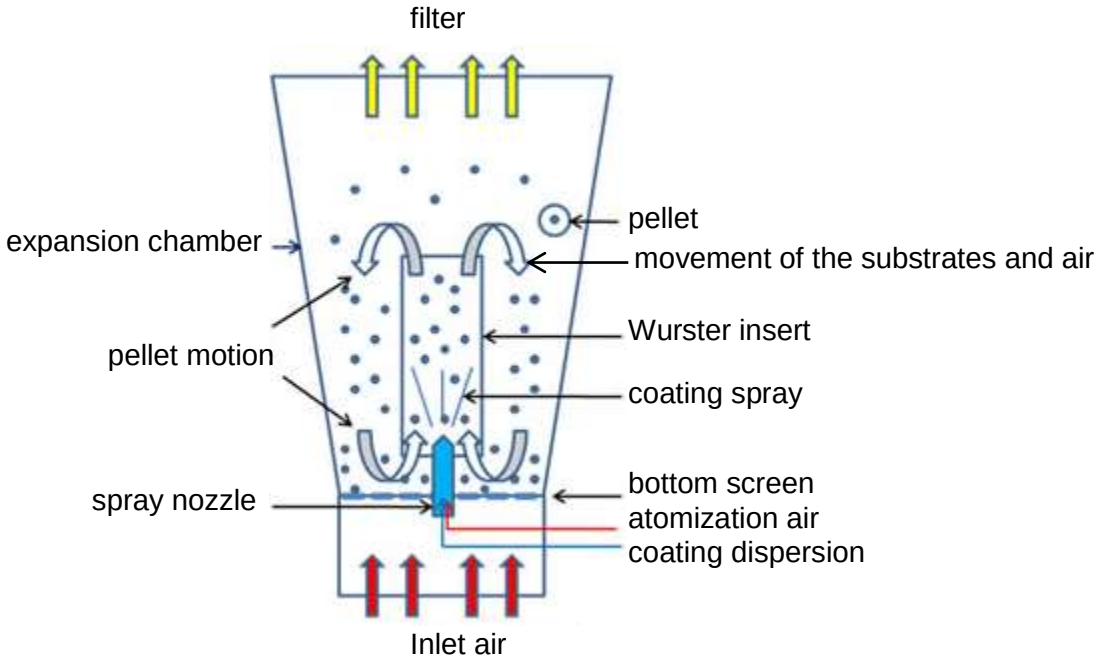


Figure 14: Schematic representation of fluid bed coater equipped with a bottom-spray and Wurster insert (adapted from Colorcon, n.d.).

Fluid bed apparatus is adapted for small particles such as powder, beads, and pellets. Different techniques (represented in figure 15) are available such as (i) top-spray processing for taste/odor masking, granulation and coating, (ii) bottom-spray processing (Wurster) for granulation and coating, (iii) tangential-spray processing for granulation and coating.

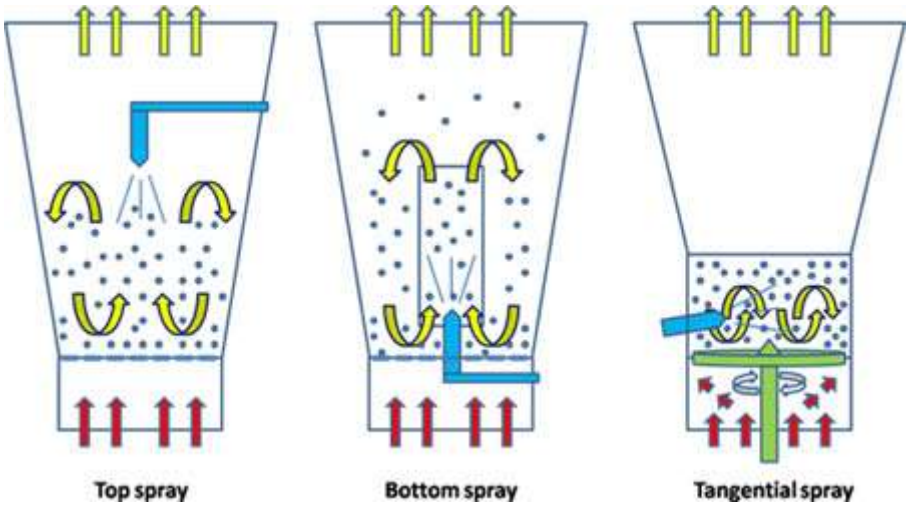


Figure 15: Schematic illustration of the three techniques used in fluid bed equipment (Colorcon, n.d.).

The top-spray granulator is applied to coat small particles. However, it is a simple and fast approach but the resultant film will not be completely uniform. The aim of this coating is for esthetic appearance or taste masking, so the drug release is not dependent on the thickness of the film layer. The coating dispersion/solution is sprayed counter-currently above the particle bed on the cores surface.

The bottom-spray equipment is the most common type in coating process for multiparticulate dosage forms. The flow pattern is created by a partition and a perforated base plate which controls the air and causes acceleration of the substrates through the cylindrical chamber called Wurster insert. The polymeric dispersions or solutions are atomized due to the air, creating a fine mist for a better deposition of the droplets on the core's surface. The particles are kept in movement by using a high air flow for a better efficiency and water removal. In summary, particles move up in the chamber, meet fine coating droplets and pass through the Wurster column to enter in an expansion chamber. Then, the particles fall to the bottom of the apparatus due to the gravitational forces and the process will be repeated until the coating dispersion is applied. The Wurster insert offers many advantages: it allows the application of droplets to the core before much evaporation occurs and a fast evaporation of water to prevent from core penetration; the high air velocity provides fine droplets; uniform and reproducible films are so obtained and dead zones are avoided.

The tangential-spray technique uses further centrifugational forces for a better solvent evaporation resulting into higher spray rates. Thus, this method offers rapid mixing and uniform film-formation with low processing time (Mehta, 2008) (Felton, 2010).

- Process parameters

The drug release kinetic depends not only on the coating formulation but also on the coating process parameters. This latter is complex due to a large number of involved variables. The main challenge is to apply fine droplets uniformly on the surface cores and to dry them at the optimum rate to avoid undesirable results. The process parameters are summarized in figure 16 (Srivastava and Mishra, 2010) (Albanez *et al.*, 2013).

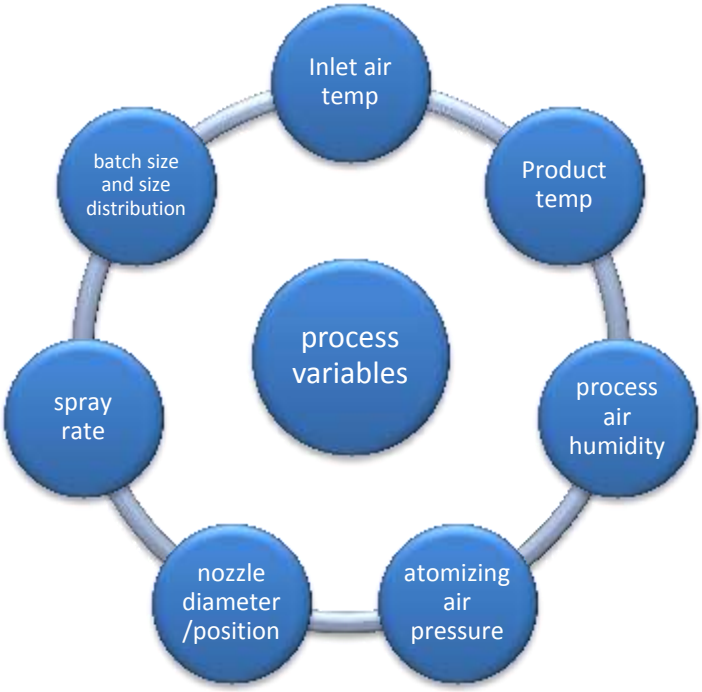


Figure 16: Process parameters for fluid bed equipment.

The spray rate is one of the most important considerations especially in the aqueous film coating process responsible for the uniform deposition of the coating dispersion on the cores (Mehta, 2008). A higher dispersion flow rate leads to a better coating efficiencies but also can generate agglomeration of the substrates depending on the drying rate (Albanez *et al.*, 2013). However, the spray rate should be decreased if the level of stickiness is too high in order to avoid agglomeration between particles, or another solution is to increase the drying air capacity and intensify the particle movement. Another option can be to dilute the coating dispersion. Moreover, the spray rate is determined by nozzle diameter and spray pressure (Lehmann, 1994).

The product temperature is also a key parameter for the success of a uniform film coating. It has to be high enough for the polymer particles' coalescence, which is 10-20 °C above the MFT of the dispersion (Lorck *et al.*, 1997).

The drying conditions have an important influence on the quality of the final product. Different variables such as drying air volume, drying air temperature, drying air humidity are involved. The drying rate is defined by the rate of heat transfer from the air to the water and the rate of mass transfer of the water to the coating surface (Mehta, 2008). A too high drying temperature can lead to a drug leaching, and agglomeration due to the tackiness of the film. Some variables are presented in table 7 (Porter and Ghebre-Sellassie, 1994) (Wlosnewski *et al.*, 2010).

Table 7: Influence examples of coating process in fluid bed coater.

Variable	Influence
Equipment	- Quality and functionality of coating
Coating dispersion solids content	- Membrane structure - Uniformity of coating distribution
Spray rate	- Membrane structure - Uniformity of coating distribution - Drug leaching
Atomizing air pressure	- Membrane structure - Uniformity of coating distribution
Drying conditions	- Coalescence of film - Drug leaching - Agglomeration - Drug release rate

Finally, the **atomizing air pressure** is a part of the main parameters. Aqueous dispersions have a low viscosity, so a high atomizing air pressure is not necessary to obtain fine droplets. The optimum level is 1 to 2 bar (Skalsky and Petereit, 2008).
In summary, all parameters are inter-connected which renders the process complex. Some examples of problems and the related parameters are illustrated in figure 17 (Porter and Ghebre-Sellassie, 1994).

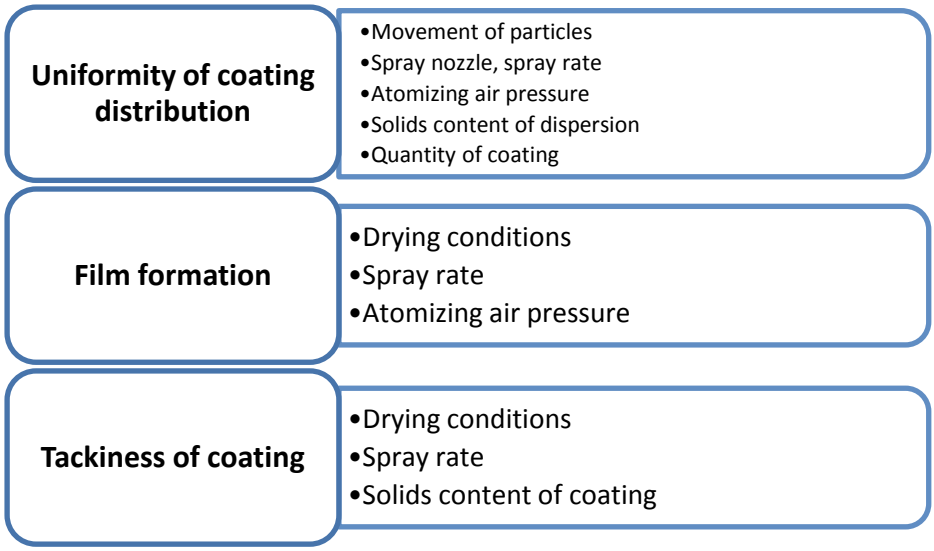


Figure 17: Examples of key parameters involved in coating process.

In the recent years, new tools have been developed such as in-line measurement in pellet coating process using Near Infrared Spectroscopy (NIR) to monitor in real-time the process. The coating thickness, particle size and undesirable defaults can be detected with this device, which is new within the development of pharmaceutical products (Quality by design) described in quality guidelines (Hudovornik *et al.*, 2015).

II. The underlying drug release mechanisms with coated pellets

The mechanisms involved in the drug release from reservoir system (*e.g.* coated pellets) can be complex and are not fully understood. They mainly depend on the polymer properties, coating thickness, properties of API, and the nature of the core.

II.1. Diffusion

A conventional dosage form will release rapidly the drug following by a subsequent decreasing release kinetics, requiring frequent dose administration to maintain the plasma-concentration within the therapeutic range. Thus, constant rate release of drug or zero order is desired to decrease the number of the dose, the side effects and to optimize the efficiency of the treatment. Zero order kinetic from controlled release dosage forms guarantee a best control of the plasma concentration. With reservoir systems, this kinetic can be achieved. Generally, diffusion and/or dissolution mechanisms are involved (Siegel and Rathbone, 2012) (Teng and Giu, 2010).

Diffusion is the most important drug release mechanism for controlled release devices and occurs in systems in which a water-insoluble polymer controls the flow of release medium and so the drug release. The diffusion is driven by the concentration difference between reservoir and environment and it influences by the solubility of the API or by a channeling agent in the film.

It seems easy to obtain diffusion mechanism but actually it is more complex. Some defects can occur during the film-formation and disturb the drug release (*e.g.* dose dumping). So, attention must be paid in this case.

Diffusion mass transport can be the major mechanism when the others don't interfere or become negligible in the control of drug release. The slowest step becomes dominant and the rate-limiting step and thus can simplify the mathematical model for a quantitative description. Theoretically, diffusional mass transport is described by Fick's first law (equation 1) where the flux of API diffuses from regions of higher concentrations to regions of lower concentrations.

$$J = D\frac{dC}{dx} \quad (1)$$

Where J is the flux of diffusion, D is the diffusion coefficient in a given medium, and $\frac{dC}{dx}$ is the concentration gradient of a drug across the diffusion path.

There are different ways to formulate diffusion dependent systems (matrix systems, porous or non-porous systems, monolithic systems). Nevertheless, Fick's law can be used under condition that these following assumptions are taken into account (Teng and Giu, 2010) (Siepmann and Siepmann, 2012):

- The diffusion through the membrane or dissolution of the coating (or matrix) is the rate-limiting step.
- The diffusion coefficient is constant.
- The drug particles are spherical with a smooth surface.
- Both core and coating film are homogeneous.
- The dissolution medium is well mixed and in sink condition.
- The system is not significantly swelling neither eroding during drug release.

➢ <u>Non-porous reservoir system</u>

For a pellet coated with a water-insoluble polymer, water penetrates to the core, dissolves the drug and this latter partitions into the film-coating from the reservoir and then diffuses across the polymeric membrane to the surrounding fluid following the gradient concentration (figure 18).

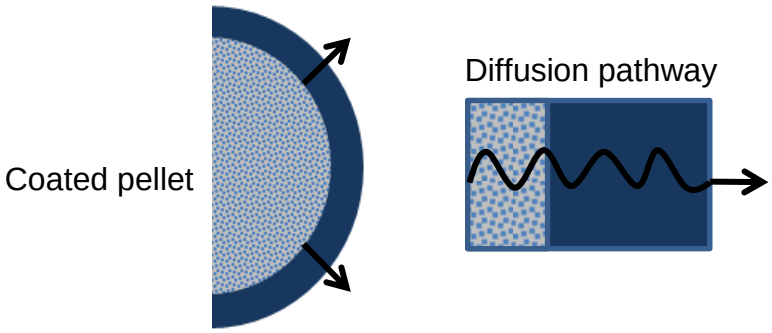


Figure 18: Schematic representation of drug release from pellet coated with a water-insoluble polymer (adapted from (Teng and Giu, 2010)).

The release rate is defined (equation 2):

$$\frac{dM}{dt} = \frac{ADK\Delta C}{l} \quad (2)$$

Where dM is the amount of drug released, dt is a period of time, A is the area, D is the diffusion coefficient, K is the partition coefficient of drug between the membrane and the core, l is the diffusion length and ΔC is the concentration difference across the membrane.

- Porous reservoir system

If some pore formers like water-soluble polymers or plasticizers are present in the coating layer, they will dissolve or leach to the release medium and create pores or channels once in contact to the gastro-intestinal fluids (figure 19).

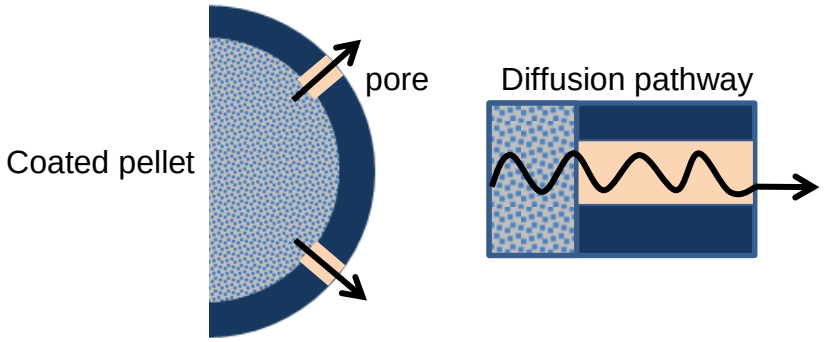


Figure 19: Schematic representation of drug release from pellet coated with a water-insoluble polymer containing pore former (adapted from (Teng and Giu, 2010)).

Thus, the release rate is described by the equation 3:

$$\frac{dM}{dt} = \frac{AD\Delta C}{l} \quad (3)$$

Where dM is the amount of drug released, dt is a period of time, A is the area, D is the diffusion coefficient, l is the diffusion length and ΔC is the concentration difference across the membrane (Teng and Giu, 2010).

Actually, the prediction by mathematical model is more complex and according to the geometry of the system, the mathematical equations have to be adapted. The appropriate equations for each type of system is presented in the literature (Siepmann and Siepmann, 2012).

Many articles in the literature offer mathematical approaches to describe diffusional mass transport (Kaunisto *et al.*, 2011) (Siepmann *et al.*, 2012) (Siepmann and Siepmann, 2012) (Cuppok *et al.*, 2011) (Kranz *et al.*, 2009) (Lecomte *et al.*, 2003) (Muschert *et al.*, 2009a) (Lippold *et al.*, 1999).

II.2. Osmotic effects

On the other hand, **osmotic effects** occur when the system is surrounded by a semi-permeable polymeric membrane, accentuated with an osmotically active core

and when a difference in the osmotic pressure between the inner and outer side of the coating membrane is present. The drug release rate is driven by the osmotic pressure in different cases: (i) with porous membrane when the core generates sufficient osmotic pressure; (ii) with a coated system containing a drug with a low molecular weight and water-soluble (± combined with an osmotically active core) (Ozturk *et al.*, 1990). Mainly, the process of drug release driven by osmotic pressure (figure 20) includes the following steps:

- The water penetration driven by the difference in osmotic pressure and inducing a hydrostatic pressure
- The dissolution of the drug
- Release of dissolved drug by diffusion countered by the convective flow of water
- Swelling of the pellet
- Crack formation

Cracks are created when the hydrostatic pressure inside the pellet is higher than the pressure supported by the coating layer.

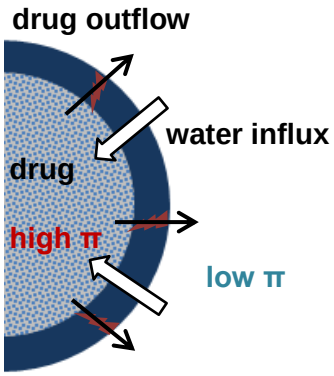


Figure 20: Drug release by osmotic effect from coated pellet (adapted from (Ozturk et al., 1990).

With this type of system, a lag phase is observed before cracks formation and the latter relies on the geometry of the system, the coating thickness, the mechanical properties of the film, the fluid permeability of the coating and the osmotic pressure. In addition, the osmotic effect depends on the porosity of the membrane, the type of core and the API. Indeed, the coating can have some leachable substances or pores inducing the release of the drug (Marucci *et al.*, 2007) (Kaunisto *et al.*, 2011).

The rate of drug delivery may be described by the equation 4:

$$J = k\sigma\,\Delta\pi\,(Ci - Cb) \qquad (4)$$

Where kσ is the osmotic force driving parameter (k is the filtration coefficient and σ is the reflection coefficient), Δπ is osmotic pressure difference across the polymeric membrane, Ci and Cb are core and bulk concentrations of the drug respectively (Ozturk *et al.*, 1990). However, many mathematical models have been published and summarized in this article (Kaunisto *et al.*, 2011).

To determine if the system is controlled by osmotic effects, some experiments can be performed. Salts like urea can be added in the release medium to increase the osmolality. Sodium chloride is less preferable due to the ionic strength effects that can contribute to changes in the drug kinetics (Dressman and Palsson, 1994). The changes in the osmolality can arrive in the GI fluid; in the stomach the osmotic pressure will vary due to the ingestion of foods contrary to the small intestine in which the osmotic pressure is low and decreases and delays the drug release. These conditions can modify the underlying drug release mechanism and the drug release rate.

At low osmolality of the bulk fluid, the water penetration into the system increases, resulting in increasing dissolved active substances and a rise of hydrostatic pressure acting against the polymeric membrane (figure 21 a). Consequently, crack formation can be induced if the film is not sufficiently flexible. Thus, the drug is released by diffusion through these water filled channels. However, when the osmolality of the medium increases, the drug release rate decreases. Indeed, less water penetrates into the system, water is required to dissolve the drug because only dissolved drug is able to diffuse through the membrane (figure 21 b) (Schultz and Kleinebudde, 1997) (Marucci *et al.*, 2007) (Rekhi *et al.*, 1995).

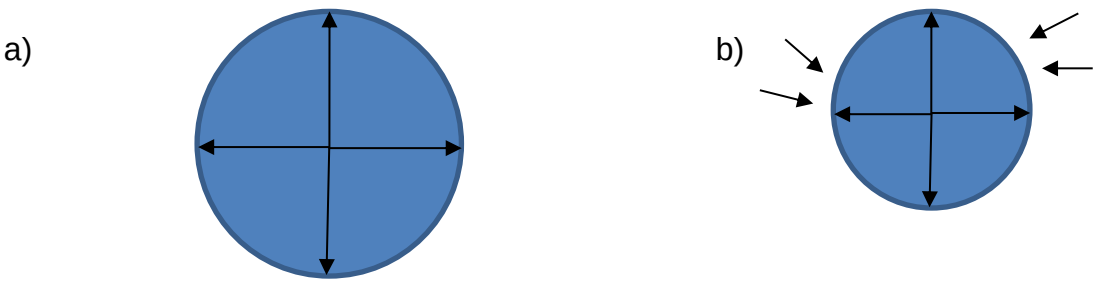


Figure 21: Illustrating schema of osmotic driven release mechanism; a: in phosphate buffer, b: in osmotic medium.

II.3. Parameters influencing the drug release

The drug release kinetic can be affecting by several parameters such as the starter core, the coating thickness, the properties of the API and the polymer.

The nature and the properties of the core can significantly alter the drug release rate. For example, sugar core, which consists of crystalline sucrose (*e.g.* ~ 84 % for suglets®) and starch (*e.g.* ~ 16 % for suglets®), is a water-soluble core and an osmotically active core. So, it attracts more water into the system and thus the drug molecules can be dissolved and released faster. Moreover, a water-soluble core can generate a hydrostatic pressure within the system (see section II.2), leading to an increase in diameter of the pellet until the rupture of the film coating. Indeed, after dissolution, sucrose is released, and causes an increase in the volume of the pellet, resulting into a higher water uptake and thus a faster drug release rate. From a physical point of view, sugar cores are more fragile and friable, and can become sticky due to the water drug solution sprayed onto their surface. Consequently during layering, they could partially dissolve sucrose on the surface become sticky and agglomerate. A particular attention must be paid on the fact that sucrose can change the drug solubility and the coating hydration (Gryczová *et al.*, 2008) (Muschert *et al.*, 2009b) (Sousa *et al.*, 2002).

On the other hand, the microcrystalline cellulose (MCC) core is a water-insoluble core, designed as an inert core (osmotically inactive). It doesn't induce significant water influx into the system compared to the sugar core. MCC core can swell in the presence of the release medium. In this case, a difference of osmotic pressure between outer and inner part of the membrane cannot be awaited, and it is this difference which leads to accelerate drug release. Consequently, the drug release rate from MCC coated pellet is slower than sugar core (Kállai *et al.*, 2010). In addition, MCC cores are harder, and have a high resistance against friction in contrast to sugar cores (Gryczová *et al.*, 2008).

There are also wax cores and isomalt cores used as starter core for drug layering but the data are limited and still unused (Singh *et al.*, 2007) (Kállai *et al.*, 2010).

Then, the size distribution, the surface area, shape and others properties of the cores have an influence on the drug release kinetics and on the coating thickness (Schultz and Kleinebudde, 1997) (Porter and Ghebre-Sellassie, 1994).

The **coating thickness** allows adjusting the drug release rate in function of pharmacokinetic goals and the desired therapeutic activity. An increase in coating level results into a decrease of the drug release rates by lengthening the diffusion pathway (Shao *et al.*, 2002).

The **physicochemical properties of the drug** have an impact on the drug release profile. The drug can interact with the coating and can generate osmotic

effects dependent on the chemical properties of the drug. Also, the drug solubility is a very important parameter which influences the drug release rate and the potential migration and leaching of the drug into the polymeric membrane. The more soluble the drug, the more rapid is the drug release rate (Ragnarsson *et al.*, 1992) (Porter and Ghebre-Sellassie, 1994).

The **composition of the coating formulation** defines partly the drug release mechanism, and thus affects the kinetic. Dependent on the properties of the polymer, different drug release profiles can be obtained and the underlying drug release mechanisms can be modulated by adding some additives. Some examples of characteristics and their influence are summarized in table 8 (Porter and Ghebre-Sellassie, 1994).

Table 8: Examples of coating formulation variables.

Variable	Influence
Polymer type	Permeability of the membrane Film formation Process parameters
Molecular weight of polymer	Mechanical properties of film
Plasticizers	Tg and MFT of the film Flexibility of film Film formation
Additives	Permeability of the membrane Drug release rate

III. Characterization methods of solid dosage forms

Taking into account all these parameters influencing the drug release kinetics, formulating solid dosage forms based on coated pellets can be complicated. The underlying drug release mechanisms are still not fully understood. That is why, it is essential to use some analytical and imaging methods to elucidate the structure of the system and understand the drug release profiles from reservoir systems.

III.1. Analytical method

First of all, thermal analytical techniques can be used to characterize pharmaceutical products such as API and excipients. **Differential Scanning Calorimetry** (DSC) is the most commonly used method allowing to study the thermal transitions of the heated sample such as the solid-state of API (crystalline or amorphous), polymorphism, melting point, glass transition temperature (Tg) etc. The principle is to heat the sample and the reference (empty pan) at a constant rate and

to measure the additional heat quantity to be supplied for sample compared to the reference pan. Thus, thermograms are obtained: for example, heat is produced when the sample recrystallizes and it's represented by an exothermic peak; and in contrast, heat is absorbed when the material melts, showing an endothermic peak (Munson, 2009). Glass transition temperature is the temperature range where the polymer changes from a rigid and glassy state, characterized by low mobility of the polymeric chains to a rubbery state, in which the mobility and the elasticity of polymeric chains increase. The interpretation of DSC data is easy for pure materials but becomes difficult for multicomponent systems such as aqueous dispersions of polymers or coated pellets. Indeed, some transitions can overlap in standard DSC. That is why, modulated Differential Scanning Calorimetry (mDSC) is more suitable. The total heat flow can be divided into a reversing heat flow and nonreversing heat flow signals (Dereymaker and Van Den Mooter, 2015). In the literature, Hsiu-O *et al.* and Zhang *et al.* performed DSC analysis with solid dispersions and coated pellets to validate their formulation process with solid dispersions using a fluid-bed system (Hsiu-O *et al.*, 1996) (Zhang *et al.*, 2008). Nikowitz *et al.* performed DSC analysis and other complementary techniques to evaluate the possible interactions between the drug and excipients and they found some interactions and migration of the drug into the film coating (Nikowitz *et al.*, 2013). Recently, Dereymaker and Van den Mooter developed an appropriate DSC method for coated pellets. They discovered that with whole coated pellets, no signals are obtained (except the melting point of sucrose) due to the insufficient area contact between sample and pan. They tried to crush them and sieve to have a narrow particle size distribution, and thus to have more coating than sucrose. Finally, they concluded that a shift and a large peak of Tg appears with increasing particle size, confirmed with free films. A complete study of this phenomena is referred to in their article (Dereymaker and Van Den Mooter, 2015).

It exists other reliable techniques called **thermal mechanical analysis** (TMA) and **dynamic mechanical analysis** (DMA), where a probe is applied in the film with a known force and the depth of penetration is calculated as the temperature is increased. This method determines the glass transition temperature, the miscibility of blend polymers and the efficacy of plasticizer on the polymer (Lafferty *et al.*, 2002). DMA is more sensitive compared to DSC and more suitable for heterogeneous samples. One of the advantages is the possibility to work in the dry and wet state (Fadda *et al.*, 2010).

Secondly, the **mechanical properties of polymeric film** need to be known in order to elucidate the drug release mechanism, especially when additives are incorporated in the formulation. For controlled release, the coating membrane should be neither breakable nor too elastic. The mechanical properties include among other things the puncture strength, the percent elongation and the energy at break and are measured using a texture analyzer (figure 22).

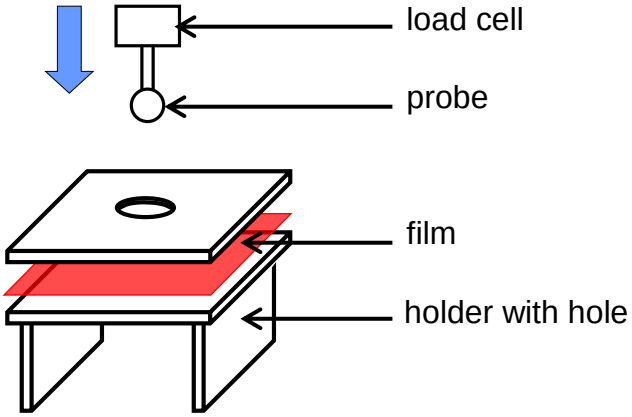


Figure 22: Schematic representation of texture analyzer.

From a practical point of view, the measurements are obtained before and after exposure to the release medium. At pre-determined time points, samples are withdrawn and mounted on the perforated holder; a spherical probe is fixed on the load cell (1 kg, 5 kg or more) and driven downward with a determined cross-head speed to the center of the film holder's hole. Load versus displacement curves are recorded until rupture of the film; thus a graph is acquired (figure 23).

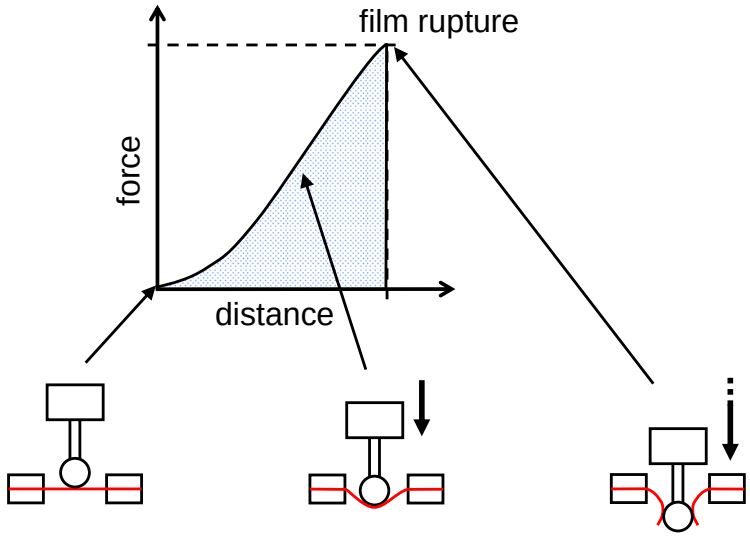


Figure 23: Steps and graph representations obtained with a texture analyzer.

This technique studies the effect of process formulation on properties of the film and also the performance of coated dosage forms once in contact with the biological

fluids by analyzing the physical stability of the film. Upon contact with the release medium, the polymeric film is hydrated and contains a significant amount of water. Also, plasticizers and/or some additives can leach into the aqueous environment. So, the mechanical properties can change during the dissolution time and affect the performance of the drug delivery system (Bodmeier and Paeratakul, 1994) (Cuppok *et al.*, 2011). It will be worthwhile therefore to study the properties of the film during several hours in the dissolution medium to overcome these defects.

Thirdly, **single pellet release and swelling behavior** can be performed to complete the study on the polymeric film. This method allows the evaluation of the coating quality, the potential swelling and crack formation of the coated pellet. Indeed, the uniform thickness and the entirety of the film are the keys to obtain the functionality of controlled release. Generally, *in vitro* dissolution test is realized from ensembles of pellets and aren't often representative for the individual units (Heinicke and Schwartz, 2007); single pellets result in a wide distribution of release profiles due to the heterogeneity within the batch (Borgquist *et al*., 2004). Investigating the single pellet release can identify the uniformity of the coating membrane. The dissolution apparatus can be the United States Pharmacopeia (USP) apparatus 7 which requires small volume dissolution testing (Xu e*t al*., 2015) or can be performed manually using micro cuvettes for example.

Finally, **Raman spectroscopy** provides various information: (i) identification and characterization of materials, (ii) determination of the molecular structure, (iii) identify the polymorphic forms, (iv) distribution of a compound in a free film, or in a complex mixture of components (Ensslin *et al*., 2009). Raman spectroscopy is an analyzing technique and non-destructive, based on the detection of diffused photon further to the interaction between the sample and the light source. This method has many advantages:

- Non-destructive
- Rapid process analytical technology tool
- Robust and reliable
- High quality with low detection
- Can be coupled with microscope
- Analyze the surface and the depth (few micrometers)
- Negligible preparation time
- Less amount of sample required

- Different process parameters: room temperature or controlled atmosphere

In the case of coated pellets, Raman spectroscopy allows an observation of the chemical composition of the coating, the surface and a penetration depth of around 3 µm (Ringqvist *et al*., 2003). Müller *et al.* tried to use Raman spectroscopy as a rapid process analytical tool to measure the coating thickness during the coating process (Müller *et al*., 2012). Gendre *et al*. used Raman spectroscopy coupled with different methods for a better insight into film coating structure. They studied the influence of curing conditions on film coating tablets. A densification and an improved organization of the coating layer were visible (Gendre *et al.*, 2013).

III.2. Imaging methods

Often, more efficient methods for the characterization of the pharmaceutical dosage forms are desirable for a better understanding of the drug release behavior.

Optical microscopy is a common technique to observe the structure of the solid dosage form. For example, it can be combined to cross polarizers to identify crystalline particles from amorphous ones. In addition, the sample can be followed upon heating (Munson, 2009). A more efficient and non-destructive technique is the **Atomic Force Microscopy** (AFM). This process allows the visualization of the three-dimensional morphology of the material surface at a nanoscale. The principle is based on the measurement of interaction forces between surface atoms of the sample and atoms from the probe containing a laser. Ringqvist *et al*. studied the surface of coated pellets in dry state and after immersion in aqueous environment. Thus, they can follow the behavior of the pellet during the dissolution test and they observed that the surface became wavy due to the swelling of the system. In conclusion, this is a powerful tool for the characterization of the surface of coated pellets in dry state as well as in liquid medium and very useful for a better understanding of the drug release mechanisms (Ringqvist *et al*., 2003).

About electronic microscopy, **Scanning Electron Microscopy** (SEM) is an imaging technique supplying high-resolution images of the surface of materials. The rule is based on interactions between electrons and a sample. Briefly, a high-energy electron beams sweeps the outer side of the material, which will produce signals required to reveal information about the morphology of the sample. Then, received signals are analyzed by detectors and a three-dimensional image is build-up. With this method, the morphology of the surface (rough or smooth) can be determined, the presence of pores (Häbel *et al*., 2016), and the thickness of the coating membrane

for example. This information may be important to understand the drug release profile and mechanisms (Strübing *et al*., 2007) (Heinicke and Schwartz, 2007) (Sheng-Feng *et al*., 2014) (Kovacevic *et al*., 2016). The disadvantages of SEM technique are that the sample must be solid and dry. So, it is impossible to usually follow a changes occurring within a product during a dissolution test. Also, the sample must be cut to visualize the intern structure.

Few years ago, the **terahertz technology** became a new and attractive tool for analyzing pharmaceutical products. Indeed, Terahertz Pulsed Imaging (TPI) is an established non-destructive technique used in the pharmaceutical industry to achieve deeper understanding on controlled drug delivery systems such as coating thickness and uniformity. In fact, it is a mapping method that operates in the far-infrared region of the electromagnetic spectrum (2 cm^{-1} – 120 cm^{-1}) called terahertz radiation. Terahertz pulses are propagated through the material and reflections created by the interfaces inside the sample are measured (Zeitler *et al.*, 2007). The analysis of the sample in depth is obtained and also the coating quality and thickness, which are significant parameters for understanding the drug release behavior. For example, Haaser *et al*. studied the coating thickness, the film-coat quality and the inter- and intra-variability between batches of coated pellets. They observed interfaces between the coating layer, the drug layer and the starter core (Haaser *et al*., 2013). Müller *et al*. used TPI as a tool to measure the coating thickness of tablets and obtained a map in which every colored pixel corresponds to a coating thickness. Thus, they map the coating thickness distribution of the tablet surface and they can observe the coating defects (Müller *et al.*, 2012). TPI is a promising technique used as process analytical tool to study the coating process (Ho *et al.*, 2010). In conclusion, Terahertz Pulsed Imaging provides three-dimensional imaging of the internal structure of the material without any destruction but little resolution.

The last technique presented in this section is one of the most powerful tools for morphological and internal characterization, called **X-ray micro tomography**. It is a new non-destructive technique (in the late 1970s) supplying two- and three-dimensional images with high resolution (up to the nanoscale) high contrast. Evaluating the properties of the coating system is essential for process controls and for ensuring the performance of the final product. This technique reveals in details the internal and external structure of a sample such as micro-cracks, air bubbles and coating defects. In addition, different parameters can be calculated like density, porosity and coating thickness. X-ray micro tomography is based on the interaction of

X-rays with the solid matter. X-rays are propagated through a material, then they are attenuated in a way depending on the atomic number and the density of the sample. A reconstruction in the three-dimensional can be made using the cross-sectional images of the structure from different angles. Perfetti *et al*. used X-ray micro tomography to demonstrate that it is a suitable tool to characterize coated particles. They analyzed the adhesion between starter core and coating layer, and observed some detachments between them (Perfetti *et al.*, 2010). The disadvantages are the high costs and that it is not applicable for a rapid process and thus not suitable for in-line daily control. Gendre *et al*. compared static curing and dynamic curing efficiency on the film coating. X-ray microtomography supplied deeper aspects of coating layers required to determine the influence of curing conditions and revealed characterization in details (Gendre *et al*., 2013). Yang *et al.* analyzed the external and internal structure of different individual pellets to investigate the drug release behavior of single pellet and also to correlate with ensembles of pellets in a dose capsule (Yang *et al*., 2014).

IV. Objectives of this work

This work is divided in two parts. The first one has been achieved in collaboration with the pharmaceutical company Merk Sharp & Dohme (MSD). The main objectives are:

(i) The formulation and the physicochemical characterization of coated pellets and free polymeric films with the same composition.

(ii) The study of the influence of different process parameters (type of polymer, nature and size of starter core, API etc.) on the resulting drug release kinetics.

(iii) The elucidation of the underlying drug release mechanisms based on the physicochemical properties of the coated pellets and the free films by using analytical and imaging techniques.

(iv) The mathematical modelling of the solid dosage forms.

The second part relates on the development of a controlled release solid dosage form. It is about coated pellets in which the drug is released only by diffusion through the intact polymeric film coating. The main goals are:

(i) Identification of a suitable polymer blend.

(ii) The formulation and design of coated pellets and the adjustment of coating formulation.

(iii) The establishment of suitable process parameters.

(iv) The study of drug release kinetics and the elucidation of drug release mechanisms.

(v) The mathematical modelling of the system.

(vi) Comparison with coated tablets of same composition as the coated pellets and the study of the influence of the dosage form on the drug release kinetics.

CHAPTER II:

MATERIALS AND METHODS

I. Materials

In this thesis, different **Active Pharmaceutical Ingredients** are used as model drugs:

- Propranolol hydrochloride (Salfic-Alcan, Puteaux, France)
- Theophylline anhydrous powder 200 (BASF, Ludwigshafen, Germany)

Within the first part, the following materials are used:
Sugar cores (sugar spheres, Suglets, 850-1250 µm in diameter) and hydroxypropyl methylcellulose (HPMC, Methocel E5) (Colorcon, Dartford, UK); microcrystalline cellulose cores (MCC cores, Cellets 700, 700-1000 µm in diameter; Pharmatrans Sanaq, Basel, Switzerland) and (MCC cores, Celphere 708, 710-850 µm in diameter; Seppic, Puteaux, France), MCC cores 1000-1250 µm in diameter were produced in-house by extrusion-spheronization ((Avicel PH-101; FMC BioPolymer, Brussels, Belgium); lactose monohydrate (Lactochem fine powder; DFE pharma, Goch, Germany)); an aqueous dispersion of poly(vinyl acetate) also containing small amounts of poly(vinyl pyrrolidone) and sodium lauryl sulfate (Kollicoat SR 30 D; BASF, Ludwigshafen, Germany); triethyl citrate (TEC; Alfa Aesar, Karlsruhe, Germany); polyethylene glycol 4000 (PEG; Cooper, Melun, France); ethanol 95 % (Charbonneaux-Brabant, Tressin, France); sucrose (Tereos, Thumeries, France); sodium chloride (NaCl; Fisher Bioblock Scientific, Illkirch, France); urea (Fluka analytical, Steinheim, Germany).

Finally, *in the second part*, the materials include:

- For coated pellets: Microcrystalline cellulose (Avicel PH-101; FMC BioPolymer, Brussels, Belgium); lactose monohydrate (Lactochem fine powder; DFE pharma, Goch, Germany); an aqueous dispersion of ethycellulose polymer (Aquacoat ECD 30; FMC BioPolymer, Brussels, Belgium); Stelliesters dibutyl sebacate (DBS; stéarinerie Dubois, Boulogne-Billancourt, France); an aqueous dispersion of neutral copolymer based on ethylacrylate and methylmethacrylate (Eudragit NM 30 D; Evonik industries, Darmstadt, Germany); fumed silica (Aerosil R972; Degussa, Frankfurt, Germany).
- For coated tablets: Lactose monohydrate (Pharmatose 350 M; DMV International, Veghel, Neetherlands); microcrystalline cellulose (Avicel PH-101; FMC BioPolymer, Brussels, Belgium); corn starch (Roquette, Lestrem,

France); polyvinylpyrrolidone (PVP) (Kollidon 30; BASF, Ludwigshafen, Germany); magnesium stearate (Fagron, Colombes, France); an aqueous dispersion of ethycellulose polymer (Aquacoat ECD 30; FMC BioPolymer, Brussels, Belgium); Stelliesters dibutyl sebacate (DBS; stéarinerie Dubois, Boulogne-Billancourt, France); an aqueous dispersion of neutral copolymer based on ethylacrylate and methylmethacrylate (Eudragit NM 30 D; Evonik industries, Darmstadt, Germany); fumed silica (Aerosil R972; Degussa, Frankfurt, Germany).

Concerning to the release medium, phosphate buffer pH 7.4 was prepared by using potassium dihydrogen orthophosphate and sodium hydroxide following the USP 35.

II. Methods

II.1. Pellets coated with Kollicoat SR 30 D

II.1.1. Free polymeric films

a) Preparation of drug-free films

Thin polymeric films were elaborated by spraying an aqueous Kollicoat SR dispersion (plasticized with 10 % w/w TEC, based on the dry polymer mass). The polymer blend was stirred during 24 h for the plasticization prior to spraying onto 20 x 20 cm teflon plates using a spraying gun (LacAir SW gravity spray gun; Lacme, La Fleche, France), and subsequent controlled drying for 24 h at 60 °C in an oven. The polymer content of the Kollicoat SR dispersion was adjusted to 10 % w/w. Optionally, films containing sucrose (10 and 30 %) were prepared in the same conditions.

b) Characterization of free films

The *thickness* of the films was measured using a thickness gauge (Minitest 600; Erichsen, Hemer, Germany).

The *mechanical properties* (percent elongation and energy at break in the dry and wet state) of the films were measured using a texture analyzer (TA.XT Plus, Stable Micro Systems, Surrey, UK) in the dry state (at room temperature) and after exposure to phosphate buffer pH 7.4 (at 37 °C) and optionally with 50 % of sucrose. Film specimens of 8 x 8 cm were placed into 250 mL plastic flasks filled with 200 mL pre-heated medium and agitated in a horizontal shaker (80 rpm, 37 °C; GFL 3033, Gesellschaft fuer Labortechnik, Burgwedel, Germany). At predetermined time points, samples were withdrawn and mounted on a film holder. The puncture probe

(spherical end: 5 mm diameter) was fixed on the load cell (1 kg or 5 kg) and driven downward with a cross-head speed of 0.1 mm/s to the center of the film holder's hole (diameter: 10 mm). Load versus displacement curves were recorded until rupture of the film and used to determine the mechanical properties as follows:

$$\%\, elongation\ at\ break = \frac{\sqrt{R^2+d^2}-R}{R}.100\,\% \qquad (5)$$

Here, *R* denotes the radius of the film exposed in the cylindrical hole of the holder and *d* the displacement to puncture.

$$energy\ at\ break\ = \frac{AUC}{V} \qquad (6)$$

Where *AUC* is the area under the load versus displacement curve and *V* the volume of the film located in the cylindrical cavity of the film holder (the energy at break is normalized to the film's volume).

Water uptake and dry mass loss studies were carried out by placing 5 x 5 cm film pieces into plastic flaks filled with 100 mL pre-heated phosphate buffer pH 7.4 (USP 35), followed by horizontal shaking (37 °C, 80 rpm; GFL 3033; n = 3). At predetermined time points, film samples were withdrawn, excess surface water carefully removed, the films accurately weighed [wet mass (*t*)], and then dried to constant mass at 60 °C [dry mass (*t*)]. The water content (%) and dry film mass (%) at time *t* were calculated as follows:

$$water\ content\ (\%)\ (t) = \frac{wet\ mass\ (t) - dry\ mass\ (t)}{wet\ mass\ (t)} \cdot 100\,\% \qquad (7)$$

$$dry\ film\ mass\ (\%)\ (t) = \frac{dry\ mass\ (t)}{dry\ mass\ (t0)}.\ 100\,\% \qquad (8)$$

Where *dry mass (t0)* denotes the dry mass of the film before exposure to the release medium.

Drug transport through initially drug-free films was measured using *side-by-side diffusion cells:* The films (8 x 8 cm, thickness = 38 µm) were placed into horizontal side-by-side diffusion cells (2 x 100 mL; Permegear, Hellertown, PA, USA). The donor compartment was filled with a propranolol HCl solution (70 mg/mL) in phosphate buffer pH 7.4. The acceptor compartment was filled with phosphate buffer pH 7.4 only. The system was placed in a horizontal shaker at 37 °C (80 rpm, GFL

3033). At predetermined time points, 3 mL samples were withdrawn from the acceptor compartment and replaced with fresh medium. The propranolol HCl contents in the samples were determined by UV-spectrophotometry (λ = 289 nm, UV 1650 PC; Shimadzu, Champs-sur-Marne, France).

Thermal analysis of free films was performed on film pieces using a modulated differential scanning calorimeter (DSC Q1000; TA Instruments, Guyancourt, France). During all the measurements the calorimeter head was flushed with highly pure nitrogen gas. Temperature and enthalpy readings were calibrated using pure indium at the same scan rates used in the experiments. Film samples were accurately weighed and placed into aluminum pans hermetically sealed. Initially the samples were cooled to -30 °C, then they were heated up to 100 °C at 5 °C/min using a modulation amplitude of ± 0.663 °C and a modulation period of 50 s. Two heating cycles were run, and the reported data were obtained from the second cycle. Thermograms were analyzed using TA Universal Analysis 2000 software (TA instrument Co., New castle, DE). The glass transition temperature (Tg) was defined as the midpoint of the transition that appeared in the reversible heat flow.

II.1.2. Coated pellets

a) Preparation of drug layered starter cores

MCC and sugar cores (850-1250 µm in diameter) were coated with a solution consisting of 21.7 % (w/w) **propranolol HCl**, 1 % (w/w) HPMC, 0.1 % (w/w) PEG in 36.4 % (w/w) demineralized water and 40.8 % (w/w) ethanol in a fluidized bed equipped with a Wurster insert (Strea 1, Niro; Aeromatic-Fielder, Bubendorf, Switzerland). The process parameters were as follows: product temperature = 42 ± 2 °C, spray rate = 1-3 g/min, atomization pressure = 1.2 bar, nozzle diameter = 0.8 mm. The final drug loadings were 2.5 %, 3.9 %, 5.8 %, 10 % and 25 %.

MCC and sugar cores (850-1000 µm in diameter) were coated with an aqueous ethanol suspension of **theophylline** (2.5, 5, 10 % w/w), containing 20 % (w/w) HPMC in a fluidized bed coater (Strea 1, Wurster insert). The process parameters were as follows: product temperature = 42 ± 2 °C, spray rate = 1-3 g/min, atomization pressure = 1.2 bar, nozzle diameter = 1.2 mm. The final drug loadings were 2.1 %, 4.4 % and 7.5 %.

b) Coated controlled release pellets

The drug layered starter cores were coated with a plasticized Kollicoat SR dispersion in a fluidized bed coater (Strea 1, Wurster insert) until a weight gain of 5 to 20 % (w/w) was achieved. The aqueous poly(vinyl acetate) dispersion was plasticized with 10 % w/w TEC (based on the polymer content; plasticization time: 24 h stirring). The polymer content of the Kollicoat SR dispersion was adjusted to 10 % w/w. The process parameters were as follows: product temperature = 35 ± 2 °C, spray rate = 1-2 g/min, atomization pressure = 1.2 bar, nozzle diameter = 0.8 mm. After coating, 0.1 % of Aerosil was added and then the pellets were cured for 24 h at 60 °C in an oven.

c) Characterization of coated pellets

Propranolol HCl release from ***ensembles of pellets*** was measured in phosphate buffer pH 7.4 (USP 35) using the USP paddle apparatus (Sotax, Basel, Switzerland) (900 mL, 37 °C, 100 rpm; n = 3). Optionally, the osmotic pressure of the release medium was adjusted with sucrose, NaCl or urea (as indicated). At pre-determined time points, 3 mL samples were withdrawn (not replaced), filtered (5 µm) and analyzed UV-spectrophotometrically (λ = 289 nm, UV 1650 PC).

Drug release from ***single pellets*** was measured in 500 µL phosphate buffer pH 7.4 (USP 35) in agitated quartz micro-cuvettes (Roth, Karlsruhe, Germany), which were placed into a horizontal shaker (80 rpm, 37 °C, GFL 3033). At pre-determined time points, the micro-cuvettes were placed in an UV-spectrophotometer (λ = 289 nm, UV 1650 PC).

To monitor *pellet swelling*, the same setup as described for the single pellets release studies was used. At predetermined time points, the diameter of the pellets was measured macroscopically using an optical image analysis system (n = 6) (Nikon SMZ-U; Nikon, Tokyo, Japan), equipped with a Zeiss camera (AxioCam ICc1; Zeiss, Jena, Germany). The increase in pellet diameter (%) at time *t* was calculated as follows:

$$Increase\ in\ diameter\ (\%)\ (t) = \frac{diameter\ (t) - diameter\ (t0)}{diameter\ (t0)} . 100\ \% \qquad (9)$$

The *morphology of the surface of the pellets* before and after exposure to phosphate buffer pH 7.4 was monitored using a scanning electron microscopy (S-

400; Hitachi High-Technologies Europe, Krefeld, Germany). Withdrawn samples were frozen at -45 °C for 2 h and freeze-dried (primary drying: 0.014 mbar, -9 °C shelf temperature, 10 h; secondary drying: 0.0014 mbar, 20 °C shelf temperature, 10 h) (Epsilon 2-4 LSC; Christ, Osterode, Germany). The samples were covered with a fine carbon layer under an argon atmosphere prior to the experiments.

X-ray micro tomography: The data collection took place on a BM05 beamline at the European Synchrotron Radiation Facility in Grenoble, France. The experimental set-up was a classical SR-µCT set-up: The mean energy of the X-ray beam, delivered through a wiggler and filtered, was 68 keV and its dimensions when impinging onto the sample were 1.6 mm x 0.8 mm. The detection system consisted of a scintillator screen GGG:Eu, coupled to a x 10 visible-light microscope objective and a sCMOS 2560 x 2160 pixels camera (PCO, Kelheim, Germany). The pixel size was 0.65 µm. Pellets were placed into Eppendorf pipette tips (Eppendorf ep T.I.P.S standard volume range 2-200 µL; Sigma-Aldrich, Saint Quentin Fallavier, France), which had been sealed at the bottom by heating (1 pellet per Eppendorf tip). Two hundred µL phosphate buffer pH 7.4 were filled into each tip. The latter were closed with Parafilm and placed into a beaker filled with water kept at 37 °C (under magnetic stirring). At predetermined time points, the Eppendorf tips were removed from the beaker and placed into a BM05 beamline sample holder. Two thousand X-ray radiographs were collected on 360 ° per sample. Each series of measurements took about 15 min (during which the sample cooled down to room temperature). At each time point, a different pellet was studied. The 3D reconstructions were performed with PYHST, a paralleled software developed at ESRF, including single propagation distance phase estimation.

Solubility measurements: Excess amounts of propranolol hydrochloride were exposed to phosphate buffer pH 7.4 containing optionally sucrose, NaCl and urea in brown glass flasks agitated by horizontal shaking (37 °C, 80 rpm, n = 3; GFL 3033). The supernatant was filtered and the drug content was determined using UV-spectrophotometry as described earlier. The drug solubility was the equilibrium concentration determined in the supernatant.

II.2. Diprophylline loaded pellets and tablets coated with a polymer blend Aquacoat ECD 30 and Eudragit NM 30 D.

II.2.1. Free polymeric films

a) Preparation of free films

Thin polymeric films were prepared by spraying an aqueous polymer blend dispersion consisting of Aquacoat ECD 30 (plasticized with 20 % w/w DBS, based on the dry polymer mass) and Eudragit NM 30 D. The following Aquacoat ECD:Eudragit NM 30 D blend ratios were investigated: 10:90 and 20:80 (w/w). The mixture of Aquacoat ECD and 20 % DBS (based on the polymer content) was stirred for 24 h for the plasticization. The rest of components (demineralized water, Eudragit NM 30 D and 50 % talc) were added 30 min prior to spraying onto 20 x 20 cm teflon plates using a spraying gun (LacAir SW gravity spray gun), and subsequent controlled drying for 24 h at 60 °C in an oven. The polymer content was adjusted to 10% w/w.

b) Characterization of free films

The *thickness* of the films was measured using a thickness gauge (Minitest 600).

The *mechanical properties* (percent elongation and energy at break in the dry and wet state) of the films (Aquacoat:Eudragit NM blend ratios 10:90 and 20:80 (w/w)) were measured using a texture analyzer (TA.XT Plus) before (at room temperature) and after exposure to phosphate buffer pH 7.4 (at 37 °C). Film specimens of 8 x 8 cm were placed into 250 mL plastic flasks filled with 200 mL pre-heated medium and agitated in a horizontal shaker (80 rpm, 37 °C; GFL 3033). At predetermined time points, samples were withdrawn and mounted on a film holder. The puncture probe (spherical end: 5 mm diameter) was fixed on the load cell (5 kg) and driven downward with a cross-head speed of 0.1 mm/s to the center of the film holder's hole (diameter: 10 mm). Load versus displacement curves were recorded until rupture of the film and used to determine the mechanical properties as follows:

$$\%\ elongation\ at\ break = \frac{\sqrt{R^2+d^2}-R}{R}.100\ \% \qquad (10)$$

Here, *R* denotes the radius of the film exposed in the cylindrical hole of the holder and *d* the displacement to puncture.

$$energy\ at\ break\ = \frac{AUC}{V} \quad (11)$$

Where *AUC* is the area under the load versus displacement curve and *V* the volume of the film located in the die cavity of the film holder (the energy at break is normalized to the film's volume).

Water uptake and dry mass loss studies were investigated on films composed of Aquacoat:Eudragit NM 10:90 and 20:80 blends. These experiments were performed by placing 4 x 4 cm film pieces into plastic flaks filled with 100 mL pre-heated phosphate buffer pH 7.4 (USP 35), followed by horizontal shaking (37 °C, 80 rpm, n=3; GFL 3033). At predetermined time points, film samples were withdrawn, excess surface water carefully removed, the films accurately weighed [wet mass (*t*)], and then dried to constant mass at 60 °C [dry mass (*t*)]. The water content (%) and dry film mass (%) at time *t* were calculated as follows:

$$water\ content\ (\%)\ (t) = \frac{dry\ mass\ (t)}{dry\ mass\ (t0)}.\ 100\ \% \quad (12)$$

$$dry\ film\ mass\ (\%)(t) = \frac{dry\ mass\ (t)}{dry\ mass\ (t0)}.\ 100\ \% \quad (13)$$

Where *dry mass (t0)* denotes the dry mass of the film before exposure to the release medium.

Drug transport through initially drug-free films (Aquacoat:Eudragit NM 10:90 and 20:80 blends) was measured using *side-by-side diffusion cells:* The films (8 x 8 cm, thickness ~ 30-50 µm) were placed into horizontal side-by-side diffusion cells (2 x 100 mL; Permegear, Hellertown, PA, USA). The donor compartment was filled with a saturated solution of diprophylline in phosphate buffer pH 7.4. The acceptor compartment was filled with phosphate buffer pH 7.4 only. The system was placed in a horizontal shaker at 37 °C (80 rpm, n=3; GFL 3033). At predetermined time points, 3 mL samples were withdrawn from the acceptor compartment and replaced with fresh medium. The diprophylline quantity within the samples were determined by UV-spectrophotometry (λ = 246 nm; UV 1650 PC).

The *glass transition temperature* (Tg) of the two polymers (Eudragit NM and Aquacoat ECD with 20 % DBS) were measured using differential scanning calorimetry (DSC 1 Star System; Mettler Toledo, Greinfensee, Switzerland). The samples were prepared as follows: The polymer dispersion was directly cast in the

pan and dried 24 h in the oven at 60 °C. Concerning Aquacoat ECD, the dispersion and 20 % DBS was mixed 24 h before for plasticization. Approximately 18-20 mg samples were obtained and were heated in sealed aluminum pans from room temperature to 140 °C, cooled to -80 °C and reheated to 140 °C at a rate of 20 °C/min for the both heating and cooling. The reported Tg was determined from the second heating cycle.

II.2.2. Coated pellets

a) Preparation of starter cores with drug

Diprophylline matrixes (50 % w/w drug loading) were prepared as follows: The batch size was 300 g. Diprophylline (50 % w/w), microcrystalline cellulose (25 % w/w) and lactose fine powder (25 % w/w) were mixed in a planetary mixer (Kenwood, Hampshire, UK). The blend was wet-agglomerated using purified water (~ 200 mL). The wet mass obtained was extruded using a cylinder extruder with two counter-rotating rollers (1 mm orifice, extrusion speed = 63 rpm; Alexanderwerk GA 65; Alexanderwerk, Remscheid, Germany). The extrudates were subsequently placed in a spheronizer (Spheronizer R-250; Gabler, Malsch, Germany) to transform extrudates into spheres at a speed of 950 tr/min for 2 minutes. Then, the pellets were dried in a fluidized bed (ST15; Aeromatic, Muttenz, Switzerland) at 30 ºC for 30 min. Pellets were sieved to obtain a size range of 850 µm to 1000 µm and 1000 µm to 1250 µm. At the end, the experimental drug loading was verified by dissolving 15 mg of spheres into 200 mL volumetric flasks in phosphate buffer pH 7.4 (n = 3). The diprophylline contents were determined by UV-spectrophotometry (λ = 246 nm; UV 1650 PC).

b) Coated controlled release pellets

The diprophylline matrixes (850-1000 µm and 1000-1250 µm) were coated with a polymer blend dispersion consisting of Aquacoat ECD 30 and Eudragit NM 30 D in a fluidized bed coater (Strea 1, Wurster insert) until a weight gain of 1 to 20 % (w/w) was achieved depending on the ratio of polymer blend. The following Aquacoat ECD:Eudragit NM 30 D blend ratios were investigated: 0:100, 10:90, 20:80, 25:75, 30:70, 40:60, 50:50, 65:35, 100:0 (w/w). The aqueous ethylcellulose dispersion was plasticized with 20 % w/w DBS (based on the polymer content; 24 h stirring). The rest of the components (demineralized water, Eudragit NM 30 D and 50 % talc) were added 30 min prior to spraying. Indeed, talc (50 % w/w, based on the mass of Eudragit NM) was added to the coating formulations to avoid the pellets from sticking. The content of the polymer blend dispersion was adjusted to 10 % w/w. The process parameters were as follows: product temperature = 25 ± 2 °C, spray rate = 2-3 g/min, atomization pressure = 1.2 bar, nozzle diameter = 1.2 mm. After coating, 0.1 % of Aerosil was added and then the pellets were cured for 24 h at 60 °C in an oven.

c) Characterization of coated pellets

Diprophylline release from ***ensembles of pellets*** was measured in phosphate buffer pH 7.4 (USP 35) using the USP paddle apparatus (Sotax, Basel, Switzerland) (900 mL, 37 °C, 100 rpm; n = 3). At pre-determined time points, 3 mL samples were withdrawn and analyzed UV-spectrophotometrically (λ = 246 nm; UV 1650 PC).

Drug release from ***single pellets*** was performed with Aquacoat:Eudragit NM blend ratio 20:80. The drug released from individual pellets was measured in 6 mL phosphate buffer pH 7.4 in agitated glass flasks, which were placed into a horizontal shaker (80 rpm, 37 °C, GFL 3033; n = 6). At pre-determined time points, 500 µL of medium were withdrawn (and replaced with fresh medium) and analyzed in an UV-spectrophotometer (λ = 246 nm; UV 1650 PC).

To monitor *pellet swelling*, the same setup as described for the single pellets release studies was used. At predetermined time points, the diameter of the pellets was measured (directly within the flask) using an optical image analysis system (n=6) (Nikon SMZ-U), equipped with a Zeiss camera (AxioCam ICc1). The increase in pellet diameter (%) at time *t* was calculated as follows:

$$Increase\ in\ diameter\ (\%)\ (t) = \frac{diameter\ (t) - diameter\ (t0)}{diameter\ (t0)} . 100\ \% \qquad (14)$$

Solubility measurements: Excess of amounts of diprophylline have been exposed to phosphate buffer pH 7.4 in brown glass flaks agitated by horizontal shaking (37 °C, 80 rpm, n = 3; GFL 3033). The supernatant was filtered and the drug content was determined using UV-spectrophotometer as described earlier. The drug solubility was the equilibrium concentration in the supernatant.

II.2.3. Coated tablets

a) Preparation of tablet cores

Tablets were prepared according to the composition described in table 9.

Table 9: Composition of tablets.

Core composition	Formulation (%)
Diprophylline	50
Lactose monohydrate	17
Cellulose microcrystalline	17
Corn starch	10
Polyvinylpyrrolidone (PVP) K30	5
Magnesium stearate	1

Tablets were formulated by mixing the drug with diluents (lactose monohydrate, microcrystalline cellulose and corn starch). The powder mix was wet-agglomerated with a binder solution (PVP K 30 aqueous solution). Then, the wet mass was passed through 1 mm sieve (0.30 mm in thickness) in a oscillating granulator (Frewitt type Mg, Granges-Paccot, Switzerland) to form granules. Afterwards, granules were dried in a fluidized bed process (Aeromatic, Muttenz, Switzerland) at 40 °C for 10 min to reach a moisture content of 1–2 %. Finally, dry granules were calibrated by using the oscillating granulator sieve (1 mm in diameter, 0.65 mm in thickness) (Frewitt type Mg, Granges-Paccot, Switzerland) to obtain uniform granules. The sieved granules were mixed with magnesium stearate before compression in a turbula mixer (Bachoven, Basle, Switzerland) at 74 rpm for 4 min.

Thus, cylindrical tablets were produced with a single-punch tableting machine (EK 0; Korsch, Berlin, Germany), equipped with flat-faced punches (5 mm in diameter).

b) Film coating of tablets

The tablet cores containing 50 % of diprophylline were coated with a polymer blend dispersion of Aquacoat ECD 30 and Eudragit NM 30 D (20:80 w/w) in a coater (Lödige Hi-coater 30; Lödige, Paderborn, Germany) until a weight gain of 1.87 to 7.5 % (w/w) was achieved which is equivalent to 1 % to 20 % of coating level for pellets. The aim was to obtain the same coating thickness between pellets and tablets. The aqueous ethylcellulose dispersion was prepared as described in section

II.2.2.b. The process parameters are summarized in table 10. After coating, 0.1 % of Aerosil was added and then the tablets were cured for 24 h at 60 °C in an oven.

Table 10: Process parameters for coating tablets.

Process data	
Batch size	750 g
Nozzle diameter	0.8 mm
Distance nozzle/tablets	~ 120 mm
Inlet temperature	46-50 °C
Oulet temperature	25 °C
Tablet temperature	~ 20-23 °C
Pan speed	14 rpm
Atomizing air pressure	1.5 bar
Spray rate	2-3 g/min
Drying/curing	10 min at reduced pan speed Curing for 24 h in oven at 60 °C

c) Characterization of tablets

Some evaluations were performed before compression on the **granules** and on the **uncoated tablets** after compression. Firstly, the dry granules were analyzed for their *residual moisture* (Mettler LJ16 moisture analyzer; Mettler Toledo, Viroflay, France), *flowability test* and *tapped density* (PT-TD200; Pharmatest, Hainburg, Germany) in order to measure the powder compressibility. These tests were carried out according to the European Pharmacopoeia (8^{th} edition). Then, pharmaceutical technology controls were realized on the uncoated tablets such as: weight variation, hardness, size variation, friability, disintegration time and the drug content uniformity.

For *weight variation*, twenty tablets were accurately weighed using an analytical balance (Precisa 120 A; Precisa Gavimetrics, Dietikon, Switzerland). Then, t*he tablet dimensions* (diameter and height) were measured using a micrometer gauge (Digimatic micrometer; Mitutoyo, Tokyo, Japan). Finally, *the hardness* was checked (Tablet Tester 8 M; Dr. Schleuniger Pharma- tron, Solothurm, Switzerland). The drug content was determined on twenty uncoated tablets after dissolution in phosphate buffer pH 7.4. The solutions were filtered and diluted in order to quantify the drug content spectrophotometrically (λ = 246 nm; UV-1650 PC). Finally, the friability was carried out on 655 mg on uncoated tablets in a friability tester (Erweka Tar 10; Erweka, Heusenstamm, Germany) during 100 rotations.

Afterwards, **coated tablets** are also controlled such as: *uniformity of mass, friability* and *disintegration test.*

The *morphology* of the tablets and the *thickness* of the polymeric membrane were observed by cleaving the tablet with a scalpel. An optical image analysis system (Nikon SMZ-U; Nikon, Tokyo, Japan), equipped with a Zeiss camera (AxioCam ICc 1, Zeiss, Jena, Germany) was used for the observations before and after exposure to the release medium.

In vitro drug release from coated tablets was measured in phosphate buffer pH 7.4 (USP 35) using the USP paddle apparatus (Sotax) (900 mL, 37 °C, 100 rpm). The tablets were placed in spiral sinkers to fix the dosage forms and to avoid from sticking to the bottom of the vessel. At predetermined time points, 3 mL samples were withdrawn (not replaced), filtered (5 µm) and analyzed spectrophotometrically (λ = 246 nm; UV-1650 PC) for their drug content. All experiments were conducted in triplicate.

CHAPTER III:
RESULTS AND DISCUSSION

Part I: Systems with ruptured film coatings

In this first part, the aim was to elucidate the underlying drug release mechanisms for pellets coated with Kollicoat SR 30 D. In addition, the impact of many factors such as nature and size of starter core, the coating level and the type of API were investigated. The final goal was to develop a mathematic model to describe drug release kinetics in order to facilitate and accelerate the development of new medicines. This part was in collaboration with the pharmaceutical company Merck Sharp & Dohme (MSD).

I. Propanolol HCl layered microcrystalline cores

Propranolol HCl release from MCC cores coated with Kollicoat SR is shown in figure 24. The impact of the starter core size and the coating level were investigated at the same time. In all cases, drug release decreased with increasing coating levels (irrespective of the size of starter core) due to the increasing length of the diffusion pathways to be overcome. For all sizes, propranolol HCl was not completely released for 15 and 20 % of coating level. That means that the polymeric film was thick enough to control the drug release. Moreover, we can notice that all the kinetics of the active molecule were similar with 5 % of coating level. This can be explained by the too thin polymeric membrane to provide controlled release (Shao *et al.*, 2002).

We also observed the decrease of drug release rate when the starter core size increased. Indeed, the smaller the starter core, the thinner becomes the coating membrane because the specific surface area increases. The opposite trend is valid for the bigger starter core. Also, the volume and thus the weight of the beads increase resulting into a decrease of number of pellets. Thus, the film coating becomes thicker.

Finally, the drug release rate can be easily adapted by varying the coating level and the size of starter core.

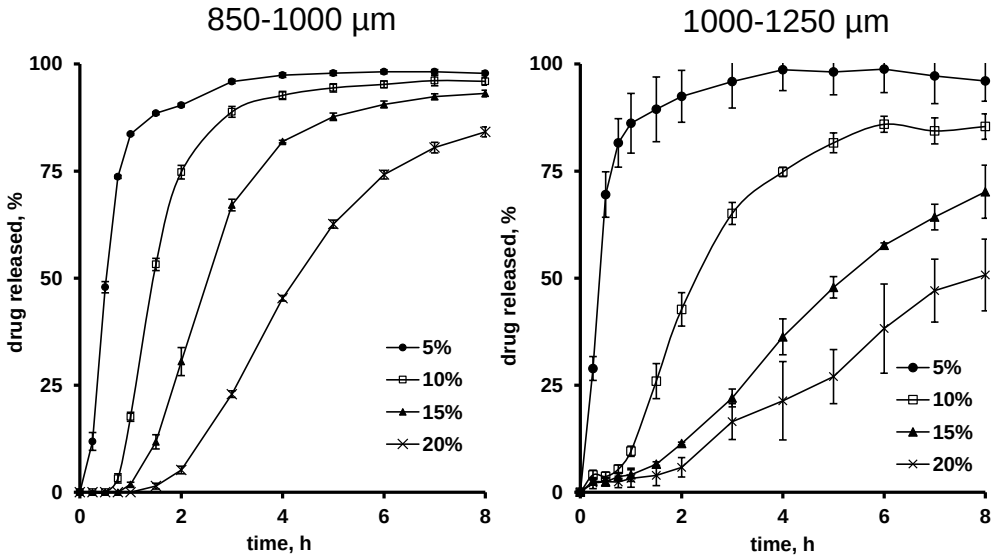


Figure 24: Effects of starter core size and coating level from Kollicoat SR 30D-coated propranolol HCl layered MCC cores in phosphate buffer pH 7.4 (10 % drug loading). The coating levels and the starter core size are indicated in the figures.

II. Propranolol-HCl layered sugar cores

The same experiment was carried out with another type of starter core, the sugar cores. The size of sugar cores and the weight gain of 5 to 20 % (w/w) were evaluated and the results are presented in figure 25. The same tendencies as obtained with MCC cores were observed, namely the drug release rate decreasing with an increase of the coating level. Besides, the increase of core size led to decrease the API release. A short lag time was observed probably due to the time necessary for the release medium to hydrate the film and to diffuse through the film coating (Dashevsky *et al.*, 2005).

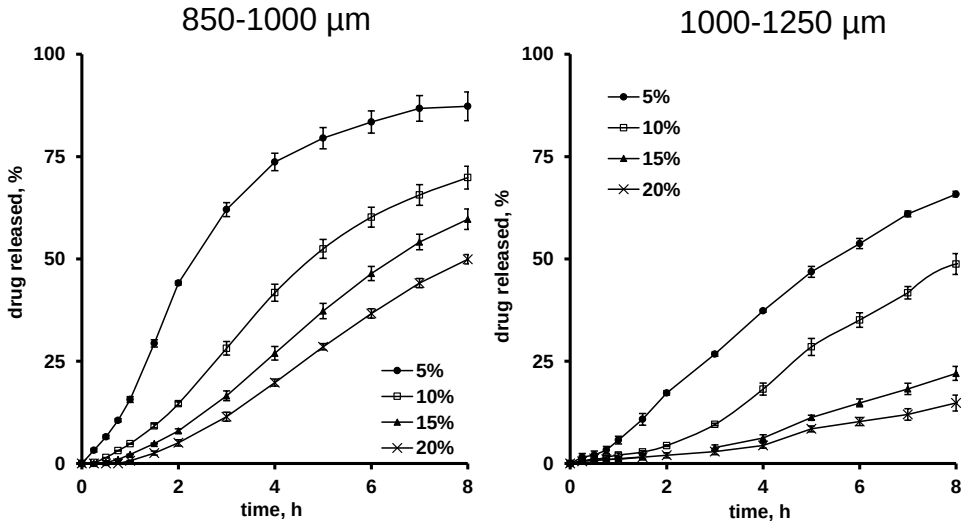


Figure 25: Influences of starter core size and coating level from Kollicoat SR coated propranolol HCl layered sugar cores in phosphate buffer pH 7.4 (10 % drug loading). The coating levels and the starter core size are indicated in the figures.

With coated layered sugar cores, the influence of the osmolality of the release medium on the drug release was investigated (figure 26). The aim was to evaluate the osmotic effect of the system and the impact of the components used. The osmolality of the release medium was adjusted with different products such as sucrose, NaCl and urea. The osmolality values of the release media are indicated in the last figures. We can notice that the osmolalities of 1.22 to 3.35 osmol/kg are not physiological (gastrointestinal tract: 0.1 - 0.4 osmol/kg) (Kállai *et al*., 2010). They are only used to get a deeper insight into the underlying drug release mechanisms.

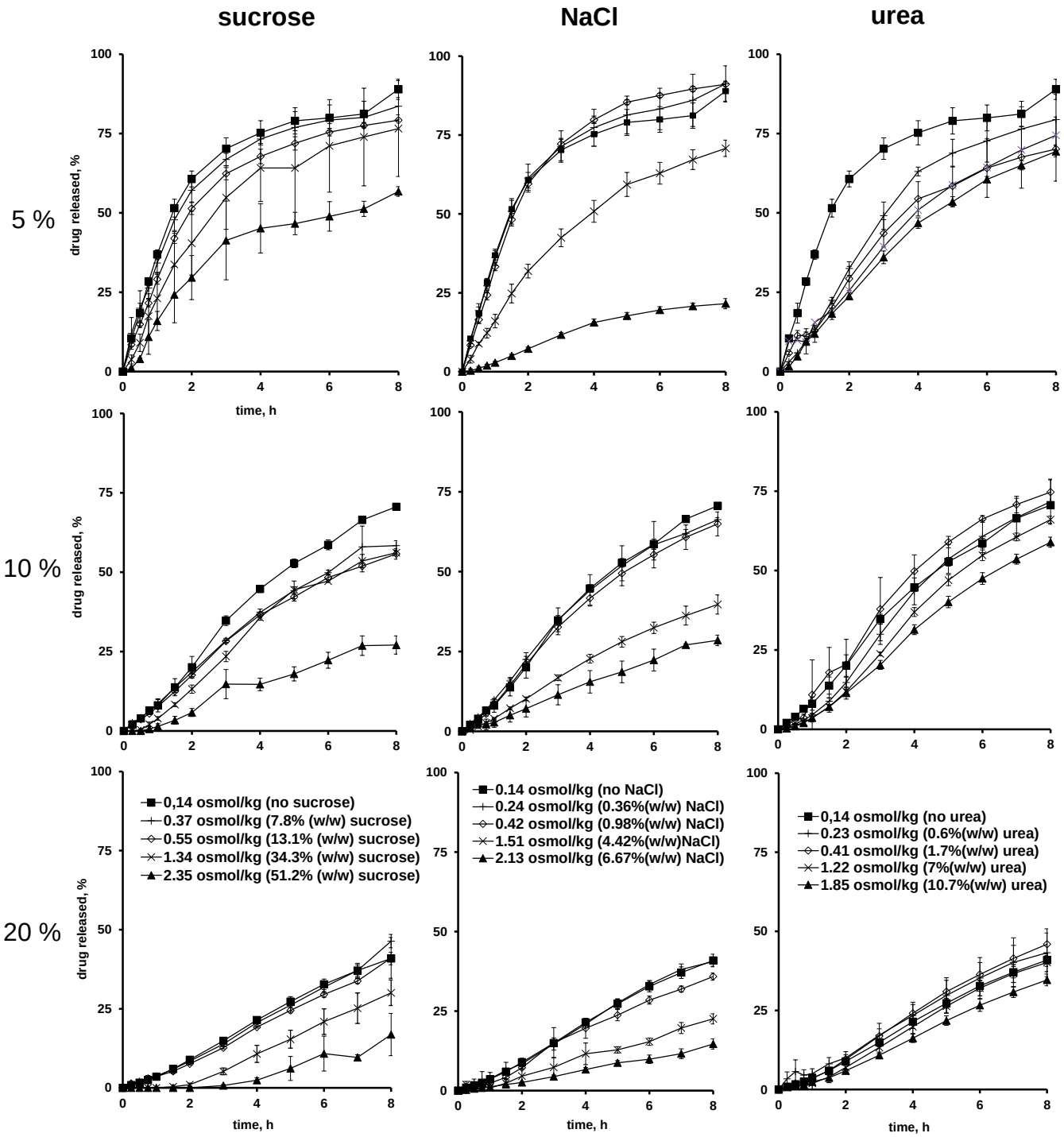


Figure 26: Effect of the osmolality of the release medium on propranolol HCl release from pellets coated with Kollicoat SR in phosphate buffer pH 7.4 and sucrose, NaCl, urea (sugar starter cores: 850-1000 µm, drug loading: 10 %). The osmolality and coating levels are indicated in the figures.

In the same way, the solubility of propranolol HCl in the different media with the same osmolality (table 11) have been analyzed in order to understand and read into the drug release kinetics. The saturation concentration of propranolol HCl in phosphate buffer without osmotic agent is around 244.9 mg/mL.

Table 11: Impact of the sucrose, NaCl and urea concentrations on the solubility of propranolol HCl in phosphate buffer pH 7.4 (in mg/mL).

	SUCROSE				
Osmolality (osmol/kg)	0.37	0.52	1.31	2.22	
Solubility (mg/mL)	216.2	194.9	94.4	37.4	↘
	NaCl				
Osmolality (osmol/kg)	0.24	0.42	1.50	2.19	
Solubility (mg/mL)	196.5	143.4	8.9	3.1	↘
	UREA				
Osmolality (osmol/kg)	0.22	0.39	1.37	1.88	
Solubility (mg/mL)	242.7	248.6	272.8	295.7	↗

Propranolol HCl has a solubility which decreases with increasing the amount of sucrose and NaCl. In the opposite, the solubility of the drug is enhanced in the presence of urea which leads to an increase in osmotic pressure within the system when exposed to the urea medium. According to Rekhi *et al.*, urea acts as a complexing agent allowing the enhancement of the solubility of propranolol HCl (Rekhi *et al*., 1995). So, regarding figure 26, we can conclude: Adding increasing amounts of sucrose to the release medium led to a substantial decrease in the drug release rate, due to osmotic effects, decreased drug solubility and plasticizing effects (see the next session). The presence of increasing amounts of NaCl in the phosphate buffer also substantially decreased the release rate, because of osmotic and solubility effects. In contrast, the addition of urea to the release media only moderately slowed down propranolol release. This effect is likely to be “the real osmotic effect”, since drug solubility is not substantially altered and urea probably doesn’t act as a plasticizer for the film coating. These results can be explained by the fact that an internal osmotic pressure is generated inside the pellets and the dissolution rate correlates with the osmotic pressure difference encountered between the inner and outer part of the pellet. Therefore, when the osmolality of the medium is higher, the osmotic gradient is lower, which slows down the penetration of water, and leads to a slower dissolution of the active substance (Kállai *et al.*, 2010).

So, when adding osmotically active compounds to the release medium to study the underlying mass transport mechanisms from coated pellets, great care should be

taken to distinguish “real osmotic effects” from potential other phenomena, such as altered drug solubility and plasticizing effects.

III. Comparison MCC cores versus sugar cores

In summary, two kinds of beads were used to prepare propranolol HCl-loaded systems (figure 27). Once with the sugar cores, water-soluble compound and the microcrystalline cores, water-insoluble beads. In the literature, some authors studied the drug release from coated pellets and found that the type of starter core has an impact on the API release pattern (Muschert *et al.*, 2009b) (Kállai *et al*., 2010).

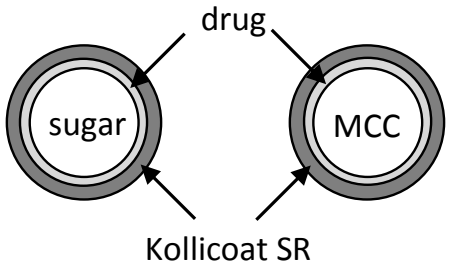


Figure 27: Schematic representation of the composition of coated pellets.

In figure 28 are summarized propranolol HCl releases from coated layered sugar cores and MCC cores in order to study the impact of the type of starter cores. The initial starter core size and coating levels are indicated in the diagrams. Interestingly, the drug release from the osmotically inert MCC starter core material was faster compared to the soluble and water attracting sucrose starter cores. The effect becomes even more pronounced with increasing initial starter core size. As already mentioned before, increasing the size of the starter cores results into thicker film coats on the individual pellets when applying sufficient amounts of polymers resulting into equal relative weight gain during fluid bed coating. Hence the impact of the starter core material on the resulting drug release velocity becomes even more pronounced the thicker the film coat and thus must at least be partially related to a sucrose polymer interaction.

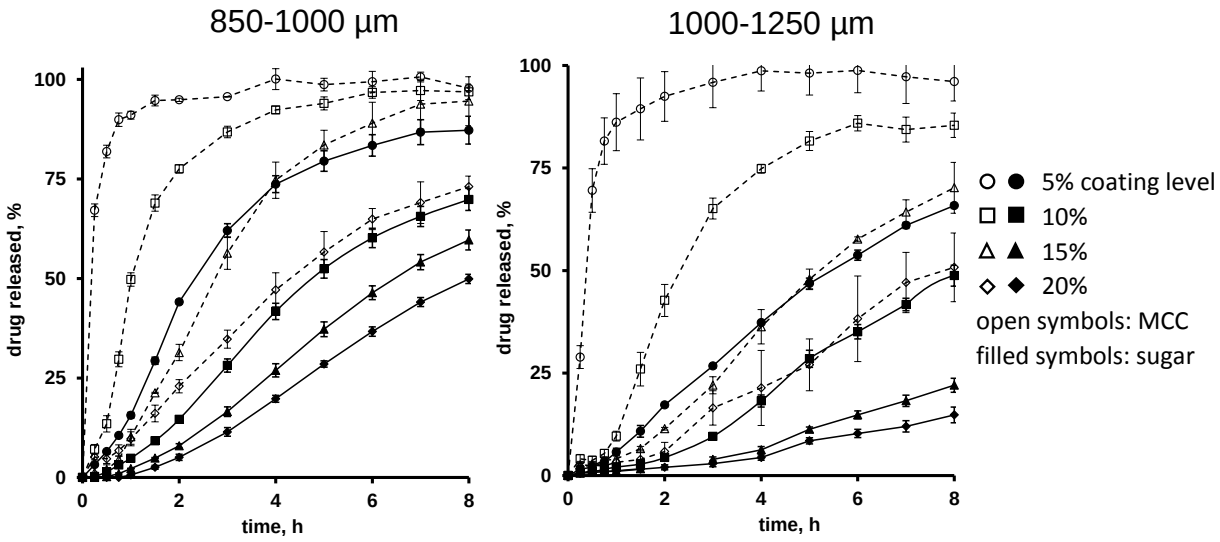


Figure 28: Importance of the type of starter core on the propranolol HCl release in phosphate buffer pH 7.4 from pellets coated with Kollicoat SR (drug loading: 10 %). The type of starter cores, the starter core size and the coating levels are indicated in the diagrams.

The objective of this study was to explain the unexpected tendencies of drug release observed with sugar and MCC starter cores. Generally, the drug release kinetic should be faster from coated layered sugar cores attributable of the accentuated attraction of water by the soluble compounds the sucrose. Indeed, sucrose attracts more water into the system, the film coating is quickly hydrated, the drug dissolved and can diffuse through the polymeric membrane. In contrast, MCC cores are osmotically inactive and don't induce a significant water influx into dosage forms upon contact with aqueous medium (Kállai *et al.*, 2010).

The different profiles between these two kinds of beads signify that fundamental changes in the underlying drug release mechanisms are involved. Maybe the sucrose inside the cores induces several modifications affecting the drug release.

III.1. Unexpected tendencies observed with propranolol HCl layered sugar cores coated with Kollicoat SR 30 D

For a better understanding of the unexpected results, further experiments were carried out to study the system in a detailed manner.

First of all, we studied the sucrose impact on the **propranolol HCl solubility,** the values are summarized in table 11. The solubility of propranolol HCl significantly decreases in the presence of co-dissolved sugar. Thus, the solubility of the drug in pellets containing sugar starter cores can be expected to be lower than in pellets containing MCC starter cores. The lower the concentration of dissolved propranolol HCl the smaller concentration differences of mobile drug between the insight and outside of the film coating and, thus decreasing the driving forces for diffusion

resulting into slower drug release. It has to be pointed out that only dissolved drug is available for diffusion.

Coated pellets with sugar cores are suspected to have a higher capacity water to take up compared to coated pellets containing inert MCC cores. As expected, it was clear in the figure 29 that coated layered sugar spheres took up more and more water during 8 h. In the opposite, coated layered MCC cores attracted less water into the system. This can be explained by the composition of the bead which is insoluble in water. This even underlines the oddness of the differences in drug release rates between the two different types of starter core material investigated, as sugar obviously attracts water in a more evident manner. The faster and the more water is soaked up by the pellets the quicker the freely soluble propranolol HCl should be dissolved but also the pellets swelling should be more rapid and thus the onset of crack formation releasing the drug molecules should occur earlier.

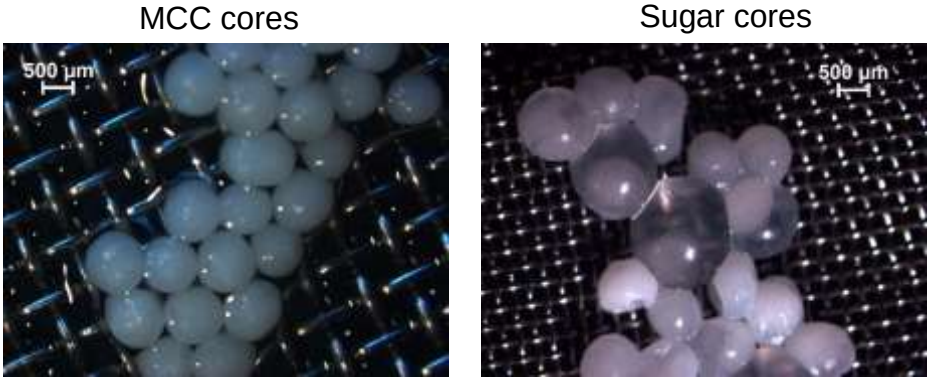


Figure 29: Macroscopic pictures of propranolol-loaded pellets after 8 h exposure to the release medium. The type of starter cores is notified above the pictures.

In figure 29 are illustrated two pictures of coated pellets MCC cores versus sugar cores after 8 h contact to the phosphate buffer medium. Clearly, at the left hand side with MCC cores, the pellet size is homogeneous and they are white. In contrast, at the right hand side with sugar cores, the size of the pellets is heterogeneous. Some of them swell a lot and uniformly after penetration of the medium becoming transparent and we can distinguish the rest of the starter core still not dissolved, consisting of starch and the rest of sucrose. This is the proof that the sucrose attracts more water into the system compared to MCC cores; after the sucrose is dissolved, as it can be not released and thus increases the volume of the pellets which can be filled by the aqueous medium. On the other hand, other pellets appear smaller and white and some of them look like a “deflated balloon”. This is probably due to a crack

formation after a swelling exceeding the elongation limit. The inter-pellet variability is reflected in these pictures.

For a short summary, we knew that the drug release from sugar starter cores was slower compared to MCC cores. Some experiments demonstrated that sugar beads attract more water into the system, dissolved the API and sucrose leading to a significant swelling and the crack formation occurred within the elongation limit was exceeded. That is why, the behavior such as **the increase in diameter** correlated to **the drug release profiles of individual pellets** during the dissolution experiments were studied. Figure 30 shows the propranolol HCl release and the swelling behavior from single pellets containing 10 % of drug loading. On the left y-axes (corresponding to the open diamonds) the percentage of drug release is plotted, on the right y-axes (corresponding to the filled squares) the increase in pellet diameter is shown (in %). Interestingly, there were three types of situations: (i) the drug layered sugar cores showed an increase in diameter (20 to 40 %) and a sudden decrease of the latter. Once the swelling of a pellet stopped and a decrease in diameter could be observed an onset of drug release coincided. (ii) The increase in size of the individual pellet came along with no drug release at all. (iii) The propranolol HCl was rapidly released as soon as the beginning with or without any swelling.

This can be explained by the fact that due to the swelling of the pellet upon contact to the dissolution medium over several hours a certain threshold value was reached at which the hydrostatic pressure built up inside the pellet forced the polymeric barrier to rupture. Upon crack formation the drug and the soluble core material were able to leave the coated pellet. Also, we can add that each pellet is unique and the behavior is very heterogeneous within one batch. So, the drug release from ensembles of pellets is the average of these single pellet release profiles leading to a slower drug release compared to MCC cores.

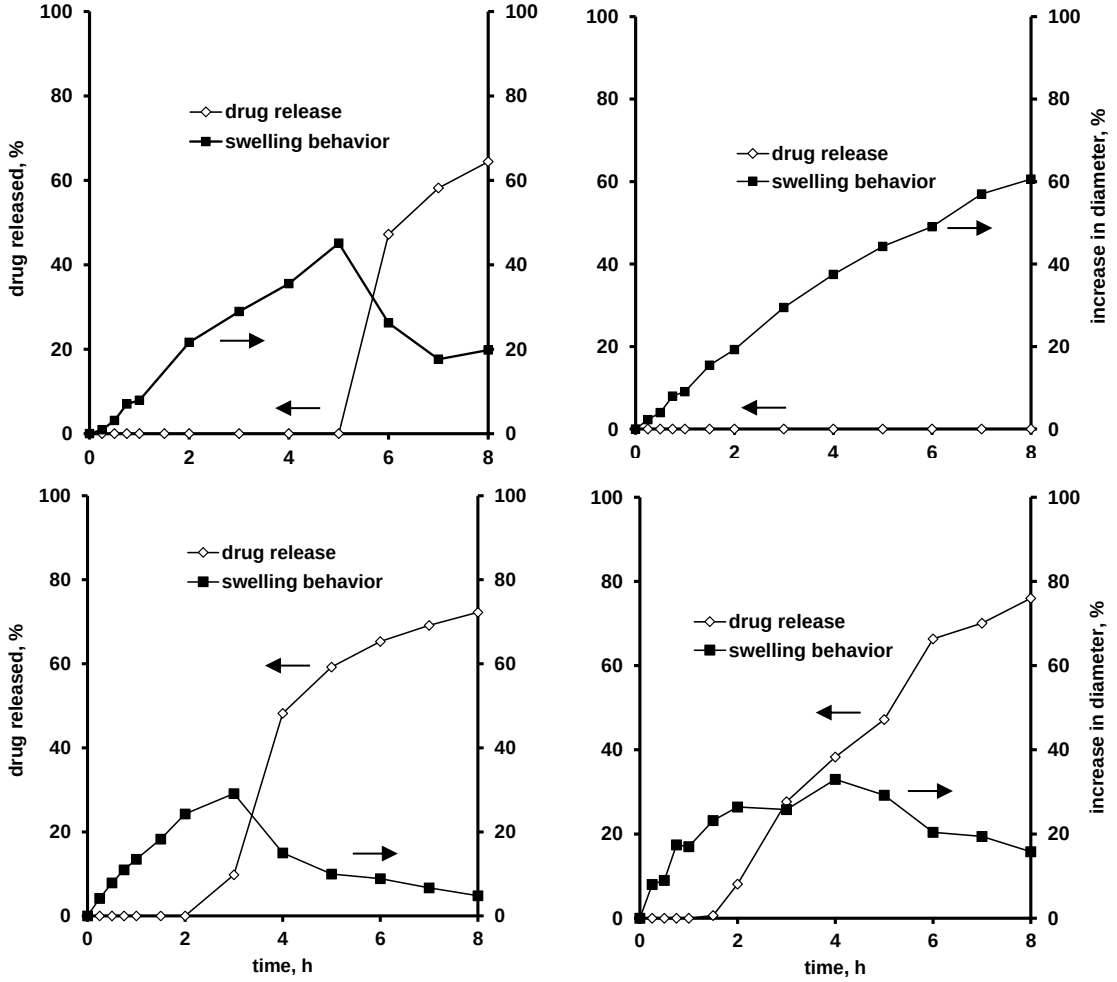


Figure 30: Drug release and swelling behavior of a single coated pellet in phosphate buffer pH 7.4 (sugar starter core size: 850-1000 µm, coating level: 10 %).

So, at this time, we understood that the drug release from the pellets coated with Kollicoat SR is more complex than expected. Indeed, not only the diffusion of the API through the intact polymeric film can be considered but also there are osmotic effects, swelling and probably crack formation.

To understand in deeper how sucrose affects drug release kinetics, the influence of this excipient on the solid dosage form was investigated. Firstly, the **mechanical properties** of free films of same composition as the film coating material of the pellets were studied in phosphate buffer pH 7.4 and in presence of 50 % sucrose (figure 31). As we can see the films became more flexible in the presence of sucrose within the medium, implicating an influence of sucrose on the elasticity of polyvinyl acetate. This enhancement of the flexibility means that the film coating can swell a lot before rupture.

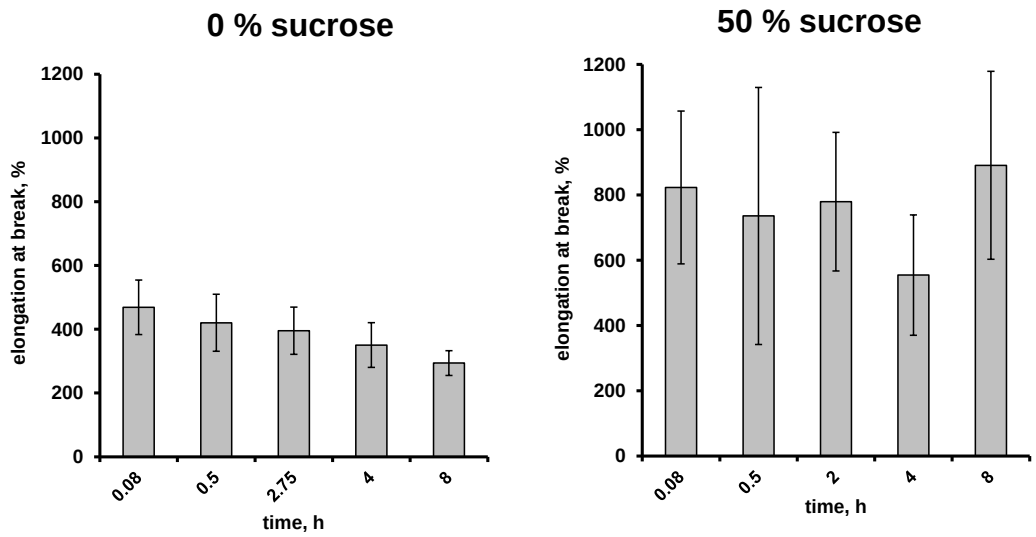


Figure 31: Effect of the sucrose concentration on the elongation at break and energy at break of free films in the wet state after exposure to phosphate buffer pH 7.4 and 50 % sucrose at 37 °C as indicated.

We can notice also that the standard deviations were higher because the medium became more viscous and interfered with the probe during measurements (background noise).

To confirm the hypothesis of the sucrose effect, the **glass transition temperature** (Tg) was measured on free films without and with various amounts of sucrose (5, 10, 30 %) (figure 32). The Tg were: 26.93 °C, 25.50 °C and 23.46 °C for 0, 10 and 30 % of sucrose respectively. So, the Tg slightly decreased with increasing quantities of sucrose meaning that sucrose acts as a plasticizer for Kollicoat SR film enhancing the elongation and the swelling. So, the sucrose-polymer interaction is partially responsible for the decrease of the drug release kinetics compared to MCC cores.

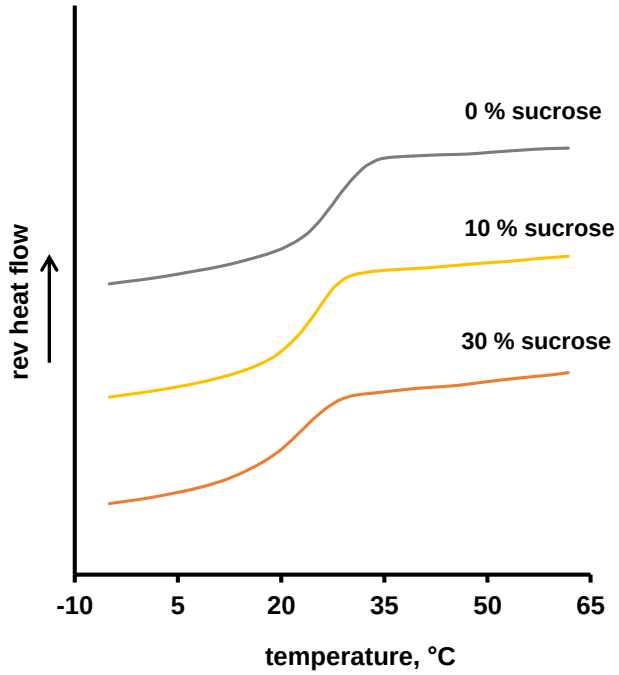


Figure 32: DSC thermograms of Kollicoat SR 30 D free films (plasticized with 10 % TEC) containing 0 %, 10 % and 30 % sucrose.

To conclude, in contrast to generally observed faster drug release from coated pellets containing sugar starter cores compared to MCC cores, in the present study the opposite trend was observed with propranolol HCl and Kollicoat SR coatings. This phenomenon might be explained by the combination of: (i) plasticizing effect of sugar for the film coating, and (ii) decrease in drug solubility in the release medium due to the presence of co-dissolved sugar.

III.2. Unexpected tendencies when increasing the drug loadings from propranolol HCl layered MCC cores coated with Kollicoat SR

Figure 33 shows that the *relative* release rate of propranolol HCl significantly increased with increasing initial drug loading from drug layered MCC cores coated with Kollicoat SR, irrespective of the coating level. Generally, the opposite trend is observed because the more the active substance the slower should be the release. The higher amounts of drug need more water to be dissolved and only dissolved drug can pass through the permeable membrane. This clearly indicates that drug release is not simply controlled by diffusion through an intact polymeric film.

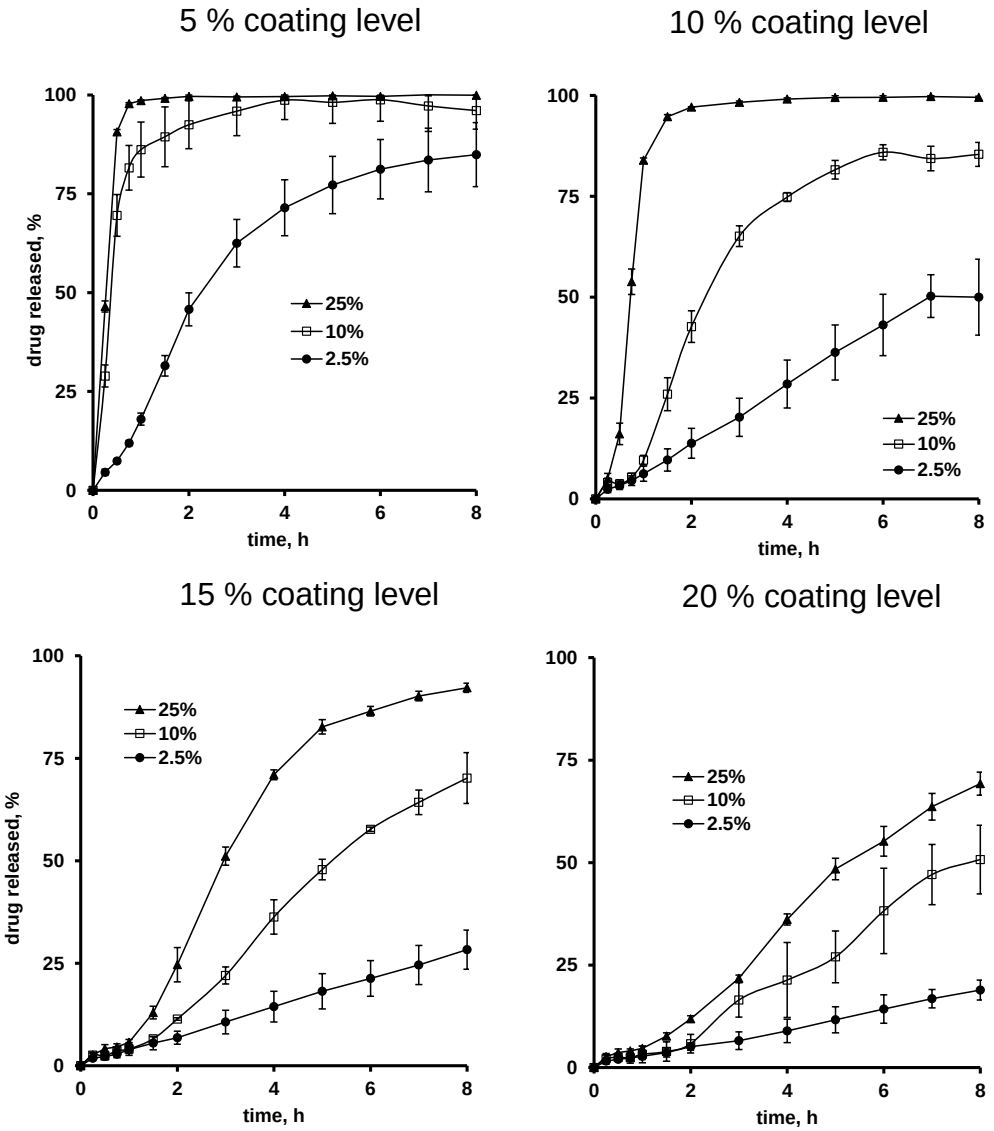


Figure 33: Effects of the initial drug loading (indicated in the diagrams) on propranolol release from coated pellets in phosphate buffer pH 7.4 (MCC cores, 1000-1250 µm). The coating level is indicated on the top of each diagram.

To better understand this unexpected trend, the swelling behavior and the single pellet release were performed and four examples are illustrated in figure 34.

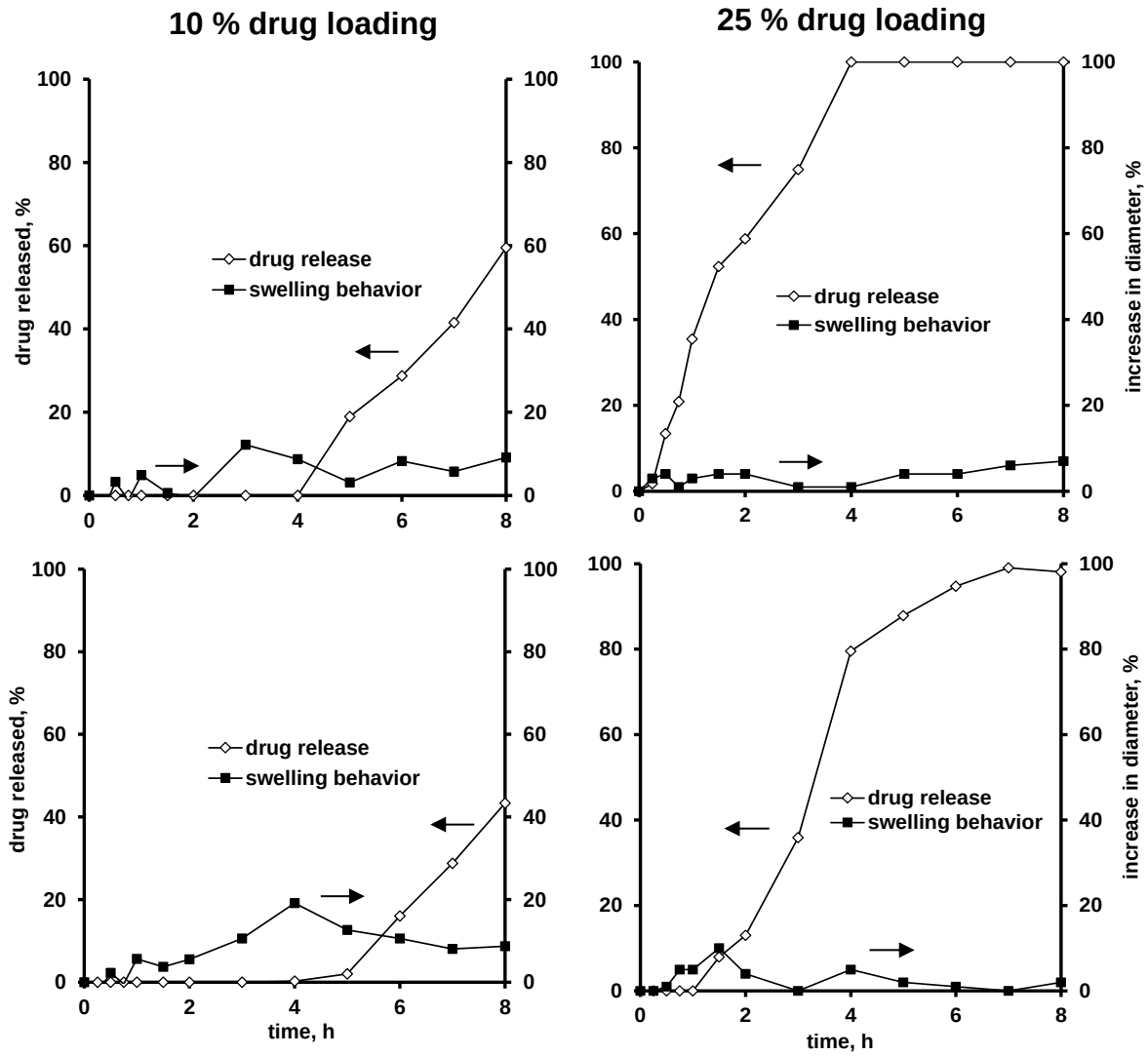


Figure 34: Drug release from and swelling of a single coated pellet in phosphate buffer pH 7.4 (MCC starter core size: 1000-1250 µm, coating level: 10 %). The drug loadings are indicated at the top.

Figure 34 shows examples for **single pellet release kinetics**, correlated with the **swelling behavior** of the same pellets. On the left side, the profiles from MCC coated pellets containing 10 % of propranolol HCl loading are represented and on the right side with 25 % of drug loading. Interestingly, the onset of drug release from a single pellet was in coincidence with an abrupt change in size behavior of the pellet. The pellet diameter initially increased (less than with sugar cores) and then at a specific time point suddenly decreased. This is an indication for the fact that crack formation is likely to occur in these film coatings, despite their high flexibility and mechanical stability. This was the case for both types of starter cores: sugar (figure 30) and MCC cores.

When both drug loadings are compared, however we can notice that the drug was released after shorter lag-times with 25 % of drug loading than 10 % of drug loading.

So, an increase in the initial loading of the freely water-soluble drug propranolol HCl leads to faster relative drug release. Especially in the case of osmotically inactive MCC cores, the presence of increasing amounts of osmotically active drug attracts more and more water into the system, favoring crack formation and drug release.

To further confirm the hypothesis of crack formation, **imaging analysis** (*e.g.* SEM and X-ray micro tomography) could be performed.

IV. Impact of the type of API on drug release from pellets coated with Kollicoat SR

After a better understanding of the propranolol HCl layered pellets coated with Kollicoat SR 30 D, we observed at first that the sucrose affects the drug release kinetics: (i) decreases the propranolol HCl solubility and (ii) plasticizes the Kollicoat SR film coating. Secondly, increasing the propranolol HCl quantity within the system leads to accelerate the drug release. To determine the major influence on the drug release profiles, another drug was used in order to compare a freely water-soluble drug **propranolol HCl** to a sparingly water-soluble drug **theophylline**.

Despite the fact that a counter current might slow down drug molecules trying to leave the reservoir system, the drug's solubility could also be altered by the highly soluble sugar. The impact of increasing sucrose concentrations present in phosphate buffer on the saturation concentration of the drug at 37 °C was investigated (table 12). As previously shown, propranolol HCl became less soluble in the presence of high amounts of sucrose. The latter came from the dissolution of core material upon contact with the medium and might be one reason for the slow propranolol HCl release rates observed from coated, layered sugar cores. Compared to propranolol HCl, the solubility of theophylline is not affected by the presence of sucrose which is important to understand which phenomena is predominantly impacting the drug release: the decrease of the solubility or the plasticizing effect of the film coating.

Table 12: Solubility of propranolol HCl and theophylline in phosphate buffer pH 7.4, optionally containing different concentrations of sucrose.

Additive	**None**	**Sucrose**		
Additive concentration (% w/w)	0	10	30	50
Solubility of propranolol HCl (mg/mL)	244.9	154.7	74.7	23.7
Solubility of theophylline (mg/mL)	9.9	9.1	9	9.1

In the two next figures are illustrated the effects of propranolol HCl (figure 35) and theophylline (figure 36) loadings from **MCC coated pellets**. In figure 35, propranolol HCl release increased with increasing drug loadings for both coating levels. We obtained the same tendency as figure 33 with different amounts of API. Then, in figure 36, the opposite trend was observed: the release of theophylline decreased with increasing of drug loadings. In conclusion, the only one difference between these two systems were the API, propranolol HCl highly water-soluble and theophylline slightly soluble in water. So, incorporating a high quantity of propranolol HCl will increase the water uptake into the system until cracks appear increasing the drug release. Contrary to propranolol HCl, theophylline attracts less water into the system and the drug release and the onset of crack formation were delayed.

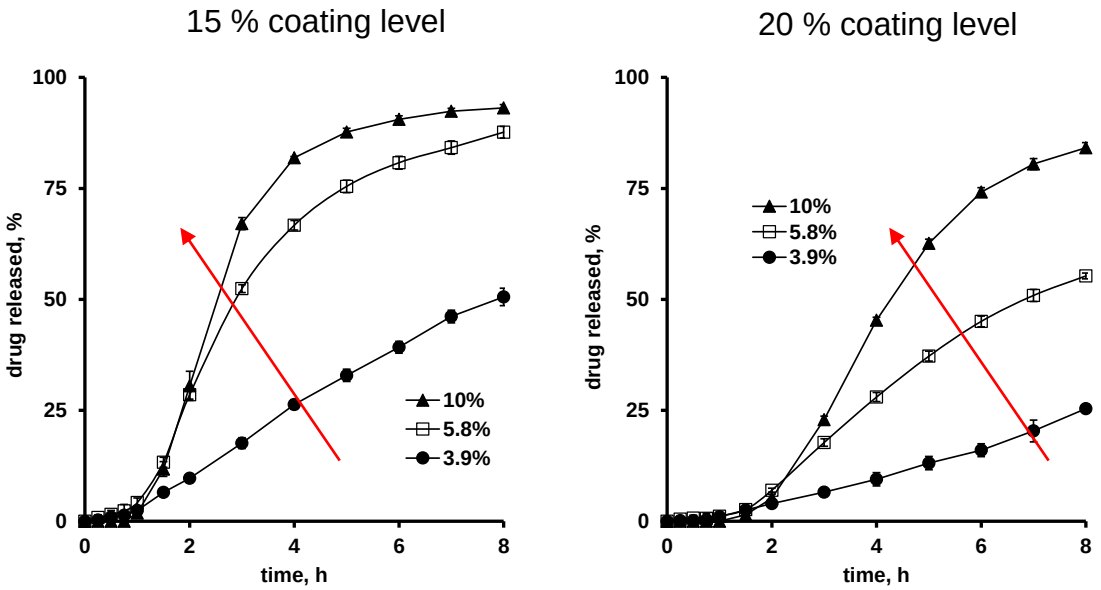


*Figure 35: Effects of the initial drug loading (indicated in the diagrams) on **propranolol** release from Kollicoat SR coated pellets in phosphate buffer pH 7.4 (MCC cores, 850-1000µm). The coating level is indicated on the top of each diagram.*

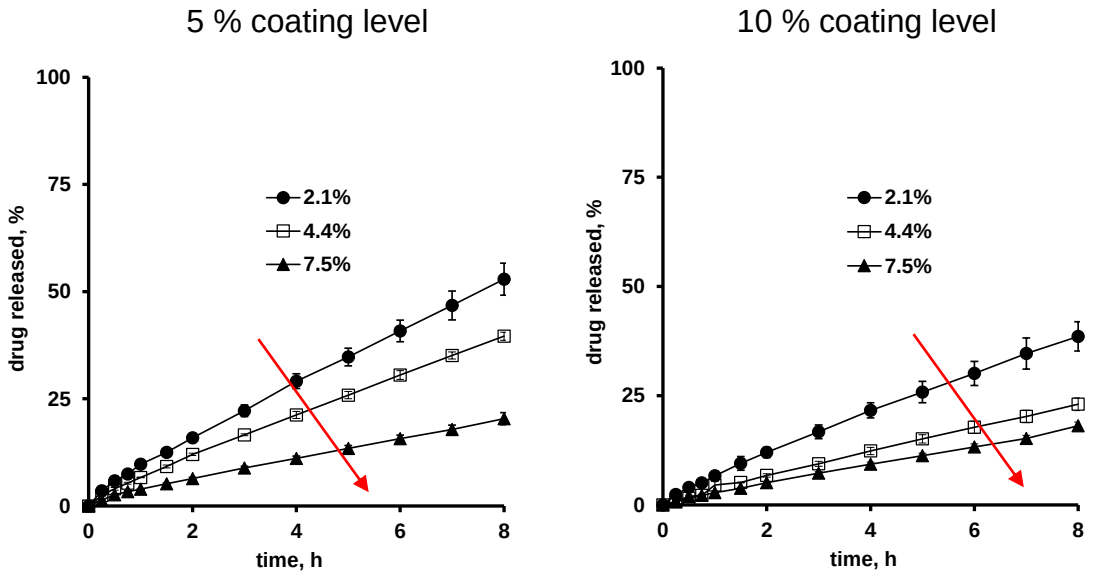


*Figure 36: Effects of the initial drug loading (indicated in the diagrams) on **theophylline** release from Kollicoat SR coated pellets in phosphate buffer pH 7.4 (MCC cores, 850-1000 µm). The coating level is indicated on the top of each diagram.*

Figure 37 shows the influence of the API and the type of starter core on the drug release. Propranolol HCl release from coated pellets containing MCC starter cores was faster compared to sugar starter cores. Interestingly, we observed the opposite effect with theophylline release from these coated systems. It can be explained by the fact that sucrose decreases the solubility of propranolol HCl and this factor have a major impact on the drug release kinetics.

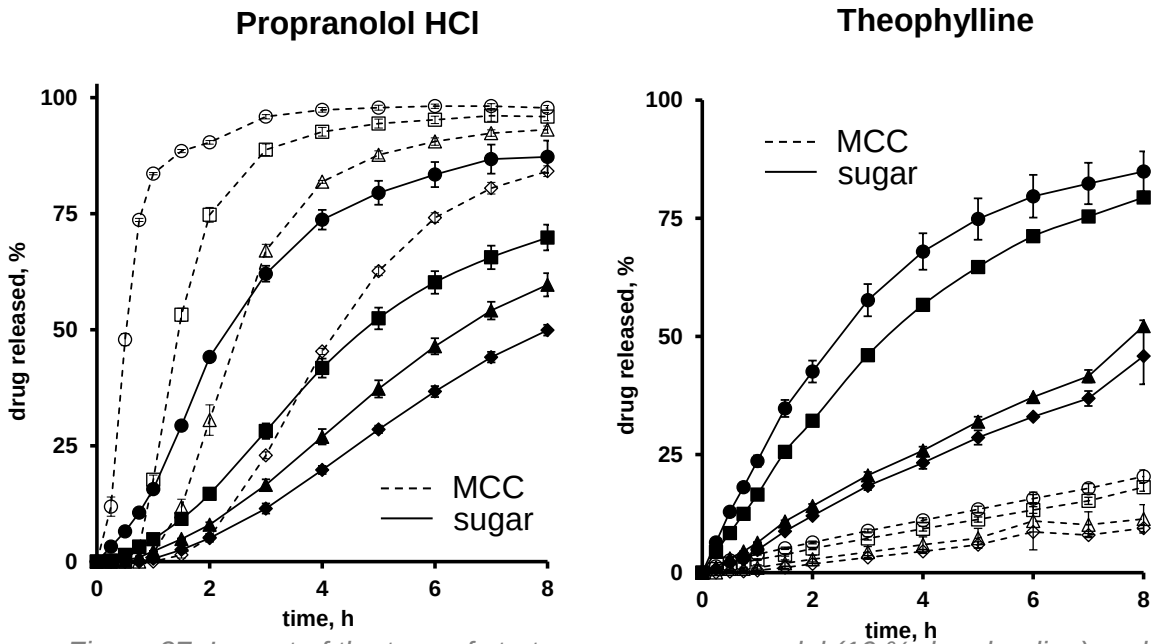


Figure 37: Impact of the type of starter core on propranolol (10 % drug loading) and theophylline (7.5 % drug loading) release from Kollicoat SR-coated pellets. The circles, squares, triangles and diamonds correspond to 5, 10, 15 and 20 % coating level, respectively.

Finally, the **macroscopic images** of theophylline-loaded pellets containing sugar and MCC cores after 8 h exposure to phosphate buffer pH 7.4 are illustrated in figure 38. Clearly, the sugar coated pellets show an important swelling compared to MCC cores, as already observed with propranolol HCl (section II.), confirming the osmotic activity of the core and the plasticizing effect of the sucrose.

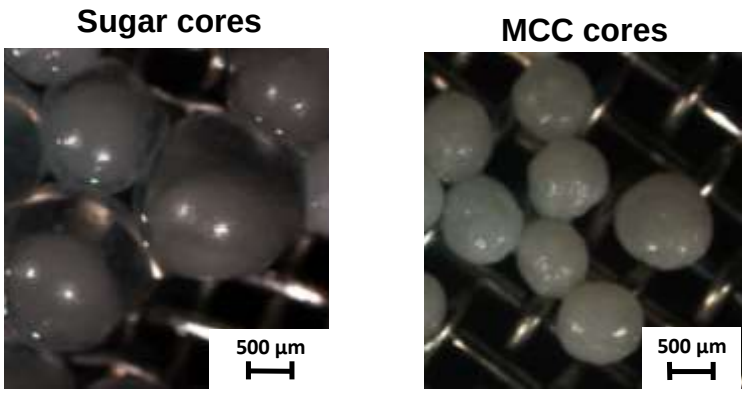


*Figure 38: Macroscopic pictures of **theophylline**-loaded pellets after 8 h exposure to the release medium. The type of starter cores is notified above the pictures.*

V. Elucidation of the underlying drug release mechanisms from pellets coated with Kollicoat SR

In the previous sections, we demonstrated that the system was complex and the underlying mass transport mechanisms controlling the drug release were not completely understood. As already mentioned, many physico-chemical phenomena can be implicated in the drug release from polymer coated pellets such as: water penetration into the system upon contact with the release medium, drug and water-soluble excipients dissolution, polymer swelling, the diffusion of dissolved substances through the polymeric membrane, the increase in pellet size, crack formation and convective mass transport.

Some complementary experiments were run to elucidate the drug release mechanisms from sugar coated pellets (Fahier *et al.*, 2016). Figure 39 shows the **water uptake kinetic** (a) and **dry mass of free films** (b) based on Kollicoat SR upon exposure to phosphate buffer pH 7.4 at 37 °C. We observed an important increase in the water content of free films occurring within the first hour, afterwards a plateau value was reached (about 70 % w/w). In parallel, the dry mass of the Kollicoat SR films only decreased by about 7 %. This dry mass loss can probably be associated to a partial leaching of the water-soluble plasticizer TEC, but also of sodium lauryl sulfate and eventually of the poly(vinyl pyrrolidone) (3 % are present in the aqueous dispersion).

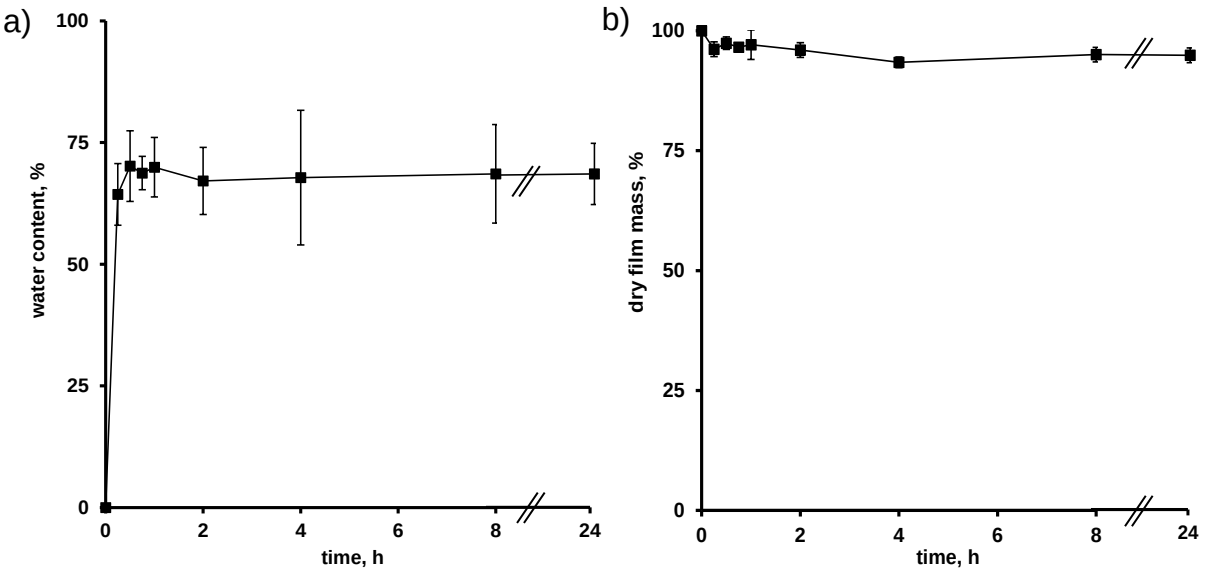


Figure 39: a) Water uptake kinetics, and b) dry mass of free films based on Kollicoat SR upon exposure to phosphate buffer pH 7.4 at 37 °C.

Nevertheless, the dry mass loss was limited during the observation period. Next to that, the investigated polymeric film coating was very flexible. In figure 40, the **percentage elongation at break** (a) and **energy at break** (b) are represented.

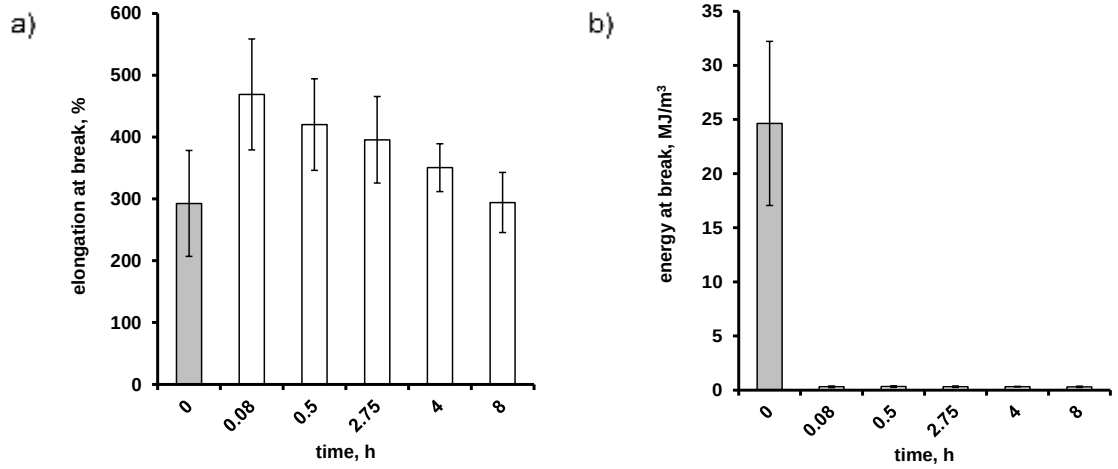


Figure 40: Mechanical properties of free Kollicoat SR films before ("Zero h" (grey bars)) and after exposure to phosphate buffer pH 7.4: a) percent elongation at break, b) energy at break.

Firstly, the elongation at break reached 293 % in the dry state at room temperature. Secondly, upon exposure to phosphate buffer at 37 °C, the films became even more flexible, which can be explained by the plasticizing effect of water as well as the increase in temperature (from room temperature to 37 °C). During the time, the film flexibility decreased probably due to the loss of the plasticizer TEC into the surrounding bulk fluid. However, the elongation of the film remained above 300 % after 8 h exposure to the release medium. On the other hand, the energy required to

break free films substantially decreased from 24.6 ± 7.4 in the dry state to 0.2 ± 0.0 MJ/m^3 in the wet state. To conclude, about the properties of investigated Kollicoat SR film coatings, they are highly flexible, take up significant amounts of water from the beginning and only limited forces are required to break them in the wet state after deformation.

Another way to resolve how the drug release is controlled, is to compare the theoretically calculated and experimentally measure drug release data. Indeed, two key properties of polymeric film coating are important, the permeability (P) for the drug and the diffusion coefficient of the drug (D), where P is equal to the D in the polymeric coating, multiplied by the partition coefficient (K) of the drug between the film and the release medium. In point of experimental view, **side-by-side diffusion cells** were used to determine both the D and the K values. It involved a drug-free film (plasticized with 10 % TEC) which was placed between a donor compartment (filled with 70 mg/mL propranolol HCl solution in phosphate buffer pH 7.4) and an acceptor compartment (consisted of phosphate buffer pH 7.4 only). In figure 41 a, the symbols show an example of experimental results through a thin Kollicoat SR film around 38 µm. We observed that the cumulative amount of drug transported through the membrane steadily increased after a lag-time. Importantly, the drug concentration gradient across the film decreased with time because the drug solution was not saturated in the donor compartment. Then, a numerical mathematical model was used to quantitatively describe the occurring mass transfer processes under these conditions (Siepmann and Siepmann, 2008) (Rongthong *et al.*, 2013). Briefly, the theory was based on the following assumptions: (i) the drug concentration in the donor compartment continuously decreases with time. (ii) Perfect sink conditions are maintained in the acceptor compartment throughout the observation period. (iii) Drug diffusion through the polymeric film is rate-limiting. (iv) The conditions for drug diffusion within the film do not significantly change during the observation period (*e.g.*, after the initial rapid water uptake, the film composition does not substantially change with time, and the obtained system specific parameters refer to the *wet* films). (v) Drug partitioning between the bulk fluids and the polymeric film is rapid compared to drug diffusion through the membrane.

In figure 41 a, the full line shows the fitting of this numerical mathematical model. The diffusion coefficient as well as the partition coefficient of the drug between the film and the bulk fluid were determined: $D = 2.3 \pm 0.7.10^{-11}$ cm^2/s and $K = 7.7 \pm 1.4$.

After have determined the drug diffusion coefficient in the polymeric membrane and the partition coefficient of the drug between the film coating and the release medium, the drug release profiles from ensemble of coated pellets can be theoretically predicted assuming that drug diffusion through the intact polymeric film coating was the release rate limiting step (Siepmann and Siepmann, 2012). In this case, the drug solubility was high and the initial drug loading was 10 % so limited. Thus, the system was considered as a non-constant activity source. All the drug is rapidly dissolved in the pellet core upon water penetration into the system and the concentration of dissolved drug in the core continuously decreases during time. The following equation was used to quantify the drug release:

$$\frac{M_t}{M_\infty} = 1 - exp\left(-\frac{3R_o DKt}{R_i^2 R_o - R_i^3}\right) \quad (15)$$

Where the perfect sink conditions were provided and the drug transport didn't change with time. M_t and M_∞ denote the cumulative amounts of drug released at time *t* and at infinite time, respectively; R_i is the radius of the drug-layered sugar core and R_o the radius of the Kollicoat SR-coated pellet; *D* represents the apparent diffusion coefficient of the drug within the polymeric film coating, and *K* the partition coefficient of the drug between the polymeric membrane and the release medium. Figure 41 b shows the curve being the theoretical prediction and the symbols represent the experimental results. The theoretical prediction was calculated considering a starter core size of 925 µm and a film coating thickness of 35 µm. Only 9 % of the drug is expected to be released after 8 h. To evaluate the validity of the model for this system, it should be compared to the experimental obtained release kinetics. As it can be seen, it is evident that the theory underestimates propranolol release from Kollicoat SR coated pellets. It is an important indication that the drug release from this system is not predominantly controlled by propranolol diffusion through the intact polymeric film coating. Some elements have already been given in the previous sections and new ones from advanced technique will be discussed in the case of coated pellets based on sugar starter cores.

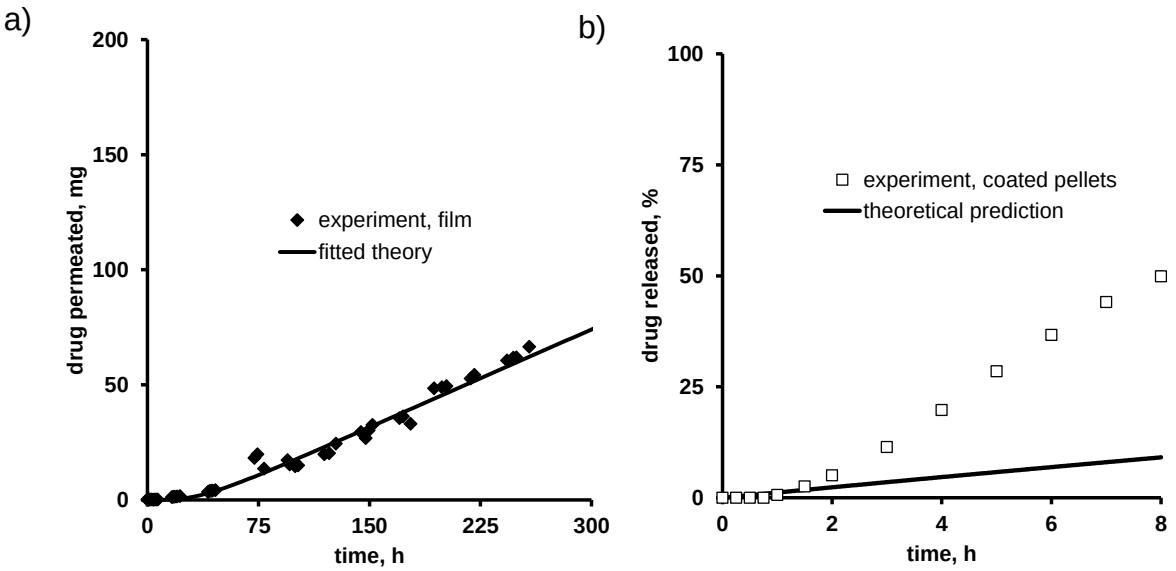


Figure 41: Theory (curves) and experiment (symbols): a) propranolol transport through an initially drug-free Kollicoat SR film in a side-by-side diffusion cell (thickness = 38 µm); the curve shows a fitting of a mathematical model; b) propranolol release from (ensembles of) pellets coated with 20 % Kollicoat SR in phosphate buffer pH 7.4, the curve shows the theoretical prediction.

Briefly, to summarize about sugar based pellets: the release and swelling kinetics of individual pellets have shown that the pellet increased in size until a certain value and then decreased. At this same time point, drug release suddenly started. It was a first indication for the fact propranolol release primarily occurs via convection through cracks in the film coating. The latter are created as soon as the hydrostatic pressure built up in the pellet core resulting from the osmotically driven water influx, sufficiently high to break the films. The system is favorable for: (i) swelling due to the considerable osmotic activity of propranolol HCl and sugar in the pellets and the high flexibility of the film coatings; (ii) crack formation due to limited energy required to break them in the wet state. In addition, we observed a variability in single pellet behavior and kinetic, expected that regions with thinner membranes can easily rupture compared to regions with thicker film coatings.

To confirm these data and evaluate the hypothesis that cracks play a major role, **SEM pictures** were taken before and after exposure to the release medium (figure 42). Before it has to be pointed out, the samples need to be dried prior to analysis by freeze-drying in this case. This process might eventually introduce artificial cracks, so the SEM pictures should be viewed with caution. Before exposure to the release medium, no cracks were visible on the pellets' surface. Nevertheless, after 30 min and 4 h, many cracks became apparent. The last picture displays a pellet accidentally damaged during the preparation. Interestingly, the pellet core became visible and revealed small particles of sugar spaced by air pores.

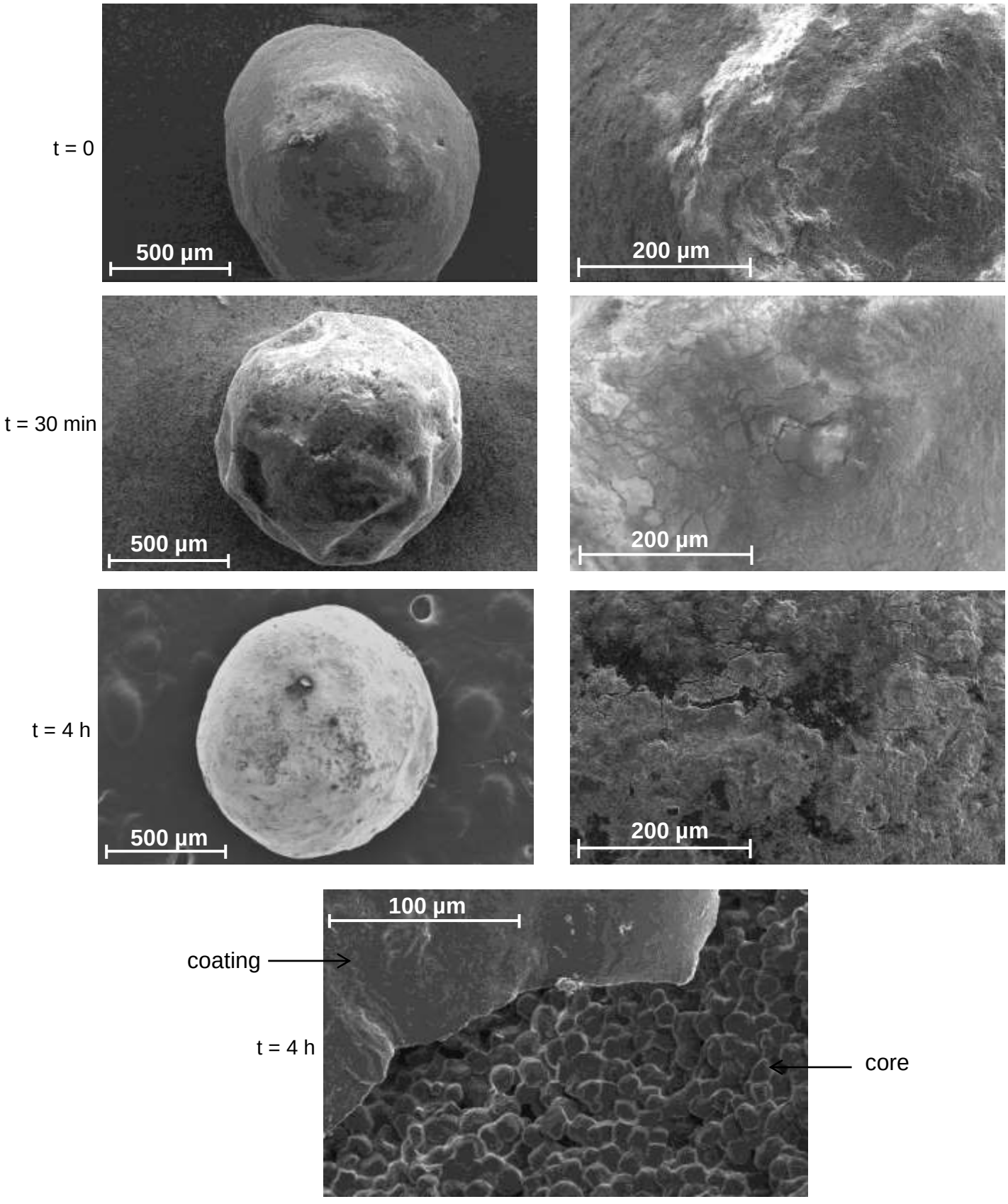


Figure 42: SEM pictures of surfaces of Kollicoat SR-coated pellets before and after 30 min or 4 h exposure to phosphate buffer pH 7.4 (as indicated) (drug loading: 10 %, coating level: 10 %). The SEM picture at the bottom shows parts of the coating and of the core of a pellet (that had been exposed for 4 h to the release medium and accidentally damaged during sample preparation).

Due to our doubts about SEM pictures, another experimental technique of characterization was applied which does not required sample preparation: **high-resolution X-ray micro tomography**.

Figure 43 illustrates the schema of experimental set-up for the synchrotron measurements: succinctly, one pellet was placed into an Eppendorf pipette tip (sealed at the bottom). This latter was filled with 200 µL phosphate buffer pH 7.4 and kept at 37 °C. At pre-determined time points, the sample (composed of Eppendorf pipette tip with release medium and pellet) was introduced into a BM 05 beamline at the European Synchrotron Radiation Facility in Grenoble. In total, two thousand X-ray radiographies were collected on 360 ° with a pixel size of 0.65 µm. Four time points (t 0, 1 h, 6 h, 8 h) were studied and for each, a different pellet was analyzed.

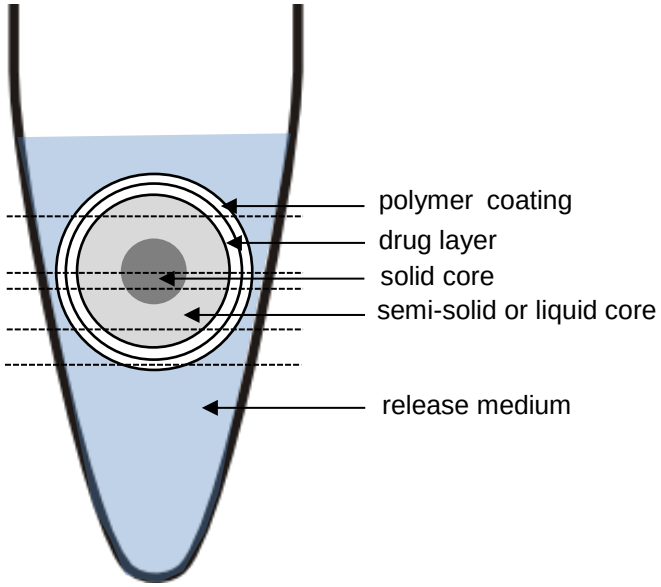


Figure 43: Schematic representation of the locations of the tomographic cross-sections (dashed lines) through a coated pellet obtained by synchrotron measurements before and during drug release.

Here, only 5 reconstructed tomographic cross-sections per sample have been selected and exhibited in the figures 44 to 47. The locations of the cross-sections within the pellets are represented by the dashed lines in the schema in figure 43 and on the left hand sides of the figures 44 to 47. The right columns present higher magnifications of the white squares marked in the middle columns.

Figure 44 summarized the cross-sections of a coated pellet before exposure to the release medium. As it can be seen at the bottom, the pictures corresponded to a cross-section through the polymeric film coating. The surrounding dark grey circle in the middle column is air. Then, in the second row from the bottom, the images show a cross-section which goes through the polymeric membrane and through the drug

layer. Next to that, in the third row, the cross-section is localized through the film coating, the drug layer and the core. Interestingly, numerous small black dots are visible in the pellet core which are probably air-filled pores. In the top, the last pictures display the same located cross-sections but further upwards in the pellet. Again, multiple small black dots are clearly visible. They are distributed throughout the core and vary in size and shape.

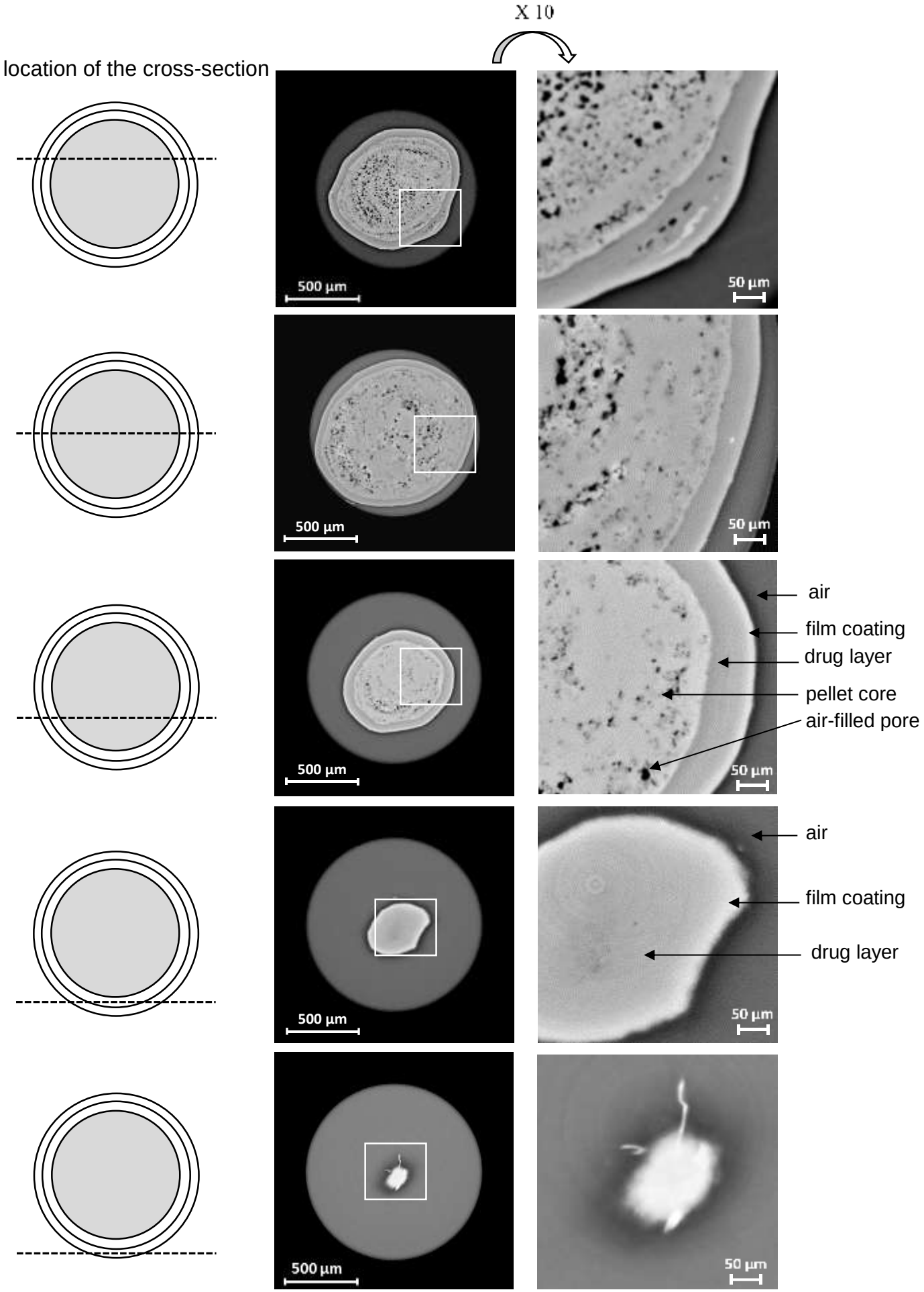


Figure 44: Reconstructed tomographic cross-sections through a coated pellet before exposure to the release medium. The right column shows a higher magnification of the white square marked in the middle column.

Then, figure 45 demonstrates the reconstructed tomographic cross-sections through a coated pellet after 1 h exposure to phosphate buffer pH 7.4. Interestingly, the air-filled pores seem to have partially fused together, forming somewhat larger air bubbles. This is likely due to the fact that water has penetrated into the pellet core and started to dissolve the drug and sugar. This renders the contents of the core semi-solid/liquid and air bubbles start moving. However, as it can be seen in the second row from the top, not the entire pellet core show big air bubbles. The region at the center of the pellet still shows the numerous small black dots (as in figure 44) and seems still in the dry state. In addition, tiny particles appearing in white are noticeable in the pellets' core (especially in the second row from the bottom on the right hand side). They correspond in size and shape to the particles observed in the pellets' core by SEM (figure 42 at the bottom). These are probably sugar particles.

Finally, a fundamental phenomenon is visible in the middle row: on the right hand side, a crack is clearly visible, through which contents of the pellet core is expulsed into the surrounding release medium. This is one of experimental evidence for the validity of the hypothesized drug release mechanism: Propranolol release from the investigated Kollicoat SR coated pellet is likely to be predominantly controlled by convection through cracks in the film coatings.

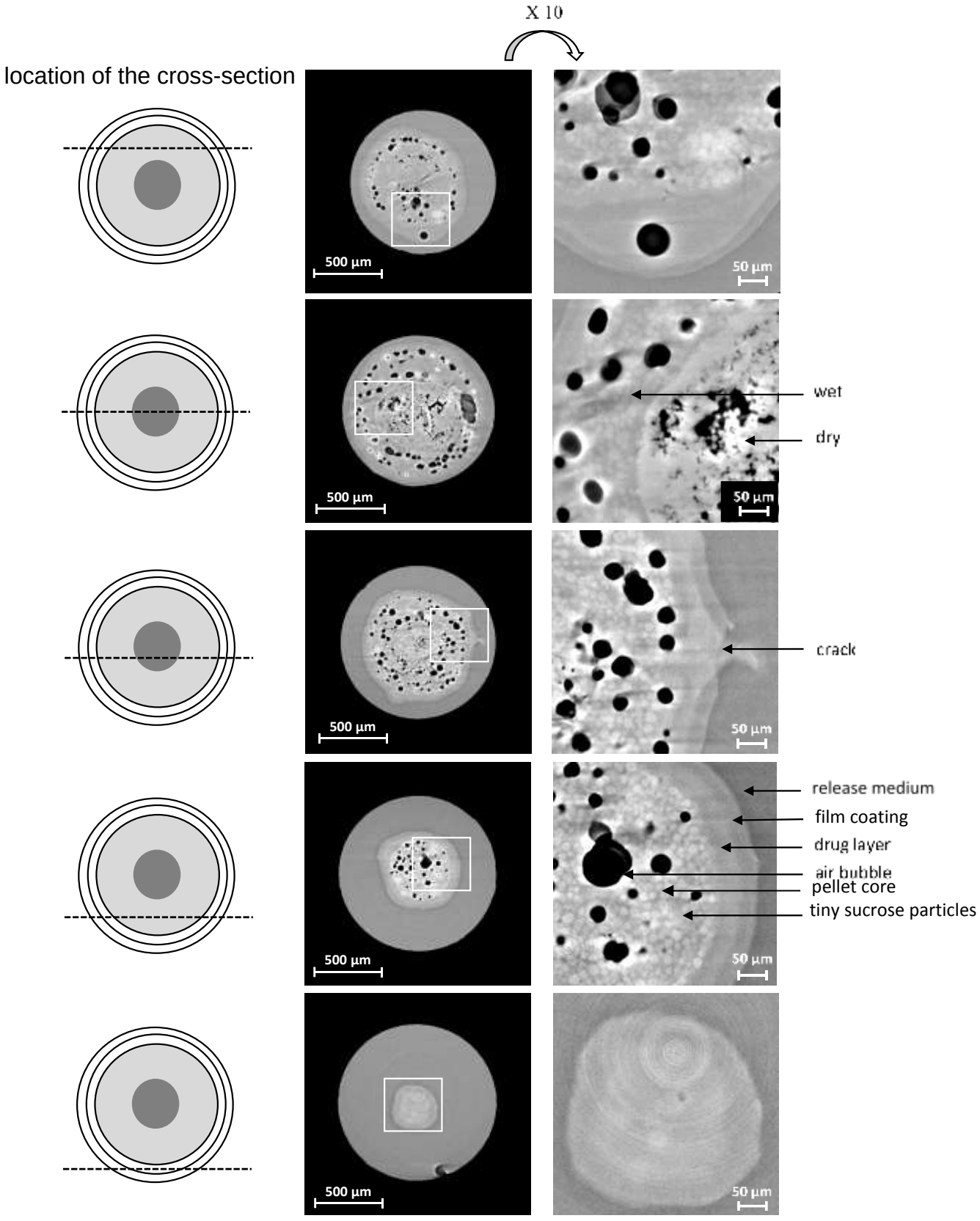


Figure 45: Reconstructed tomographic cross-sections through a coated pellets after 1 h exposure to phosphate buffer pH 7.4. The right column shows a higher magnification of the white square marked in the middle column.

Afterwards, the figures 46 and 47 concern cross-sections through pellets after 6 h and 8 h exposure to the release medium respectively. As it can be seen, the pellet core became liquid, the drug and the sugar particles dissolved and are released. All air bubbles have fused into some very few big bubbles at these time points. Note that the partially observed “spiral form” of some of them can be explained by the movement of these bubbles during the measurement, confirming their mobility.

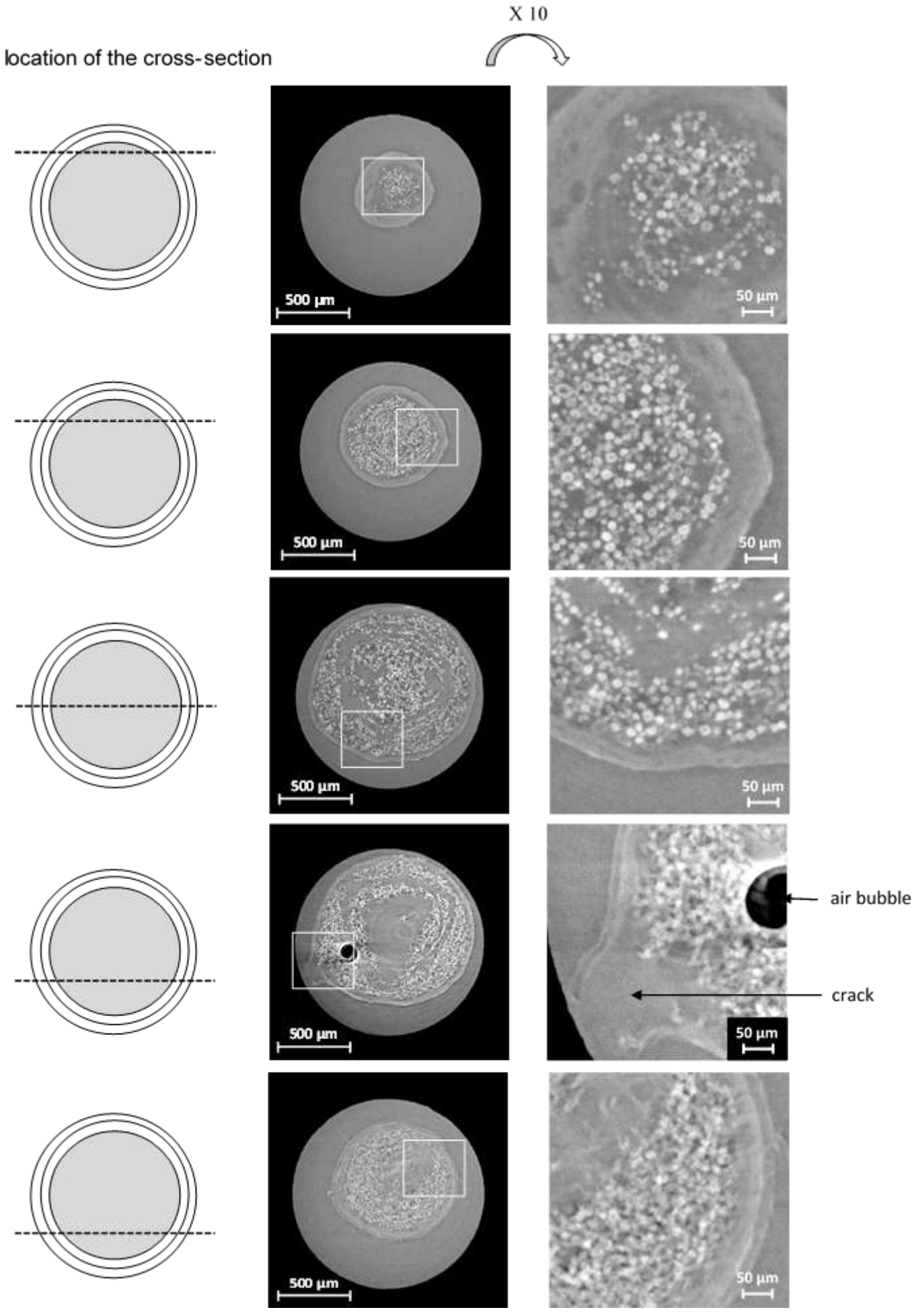


Figure 46: Reconstructed tomographic cross-sections through a coated pellets after 6 h exposure to phosphate buffer pH 7.4. The right column shows a higher magnification of the white square marked in the middle column.

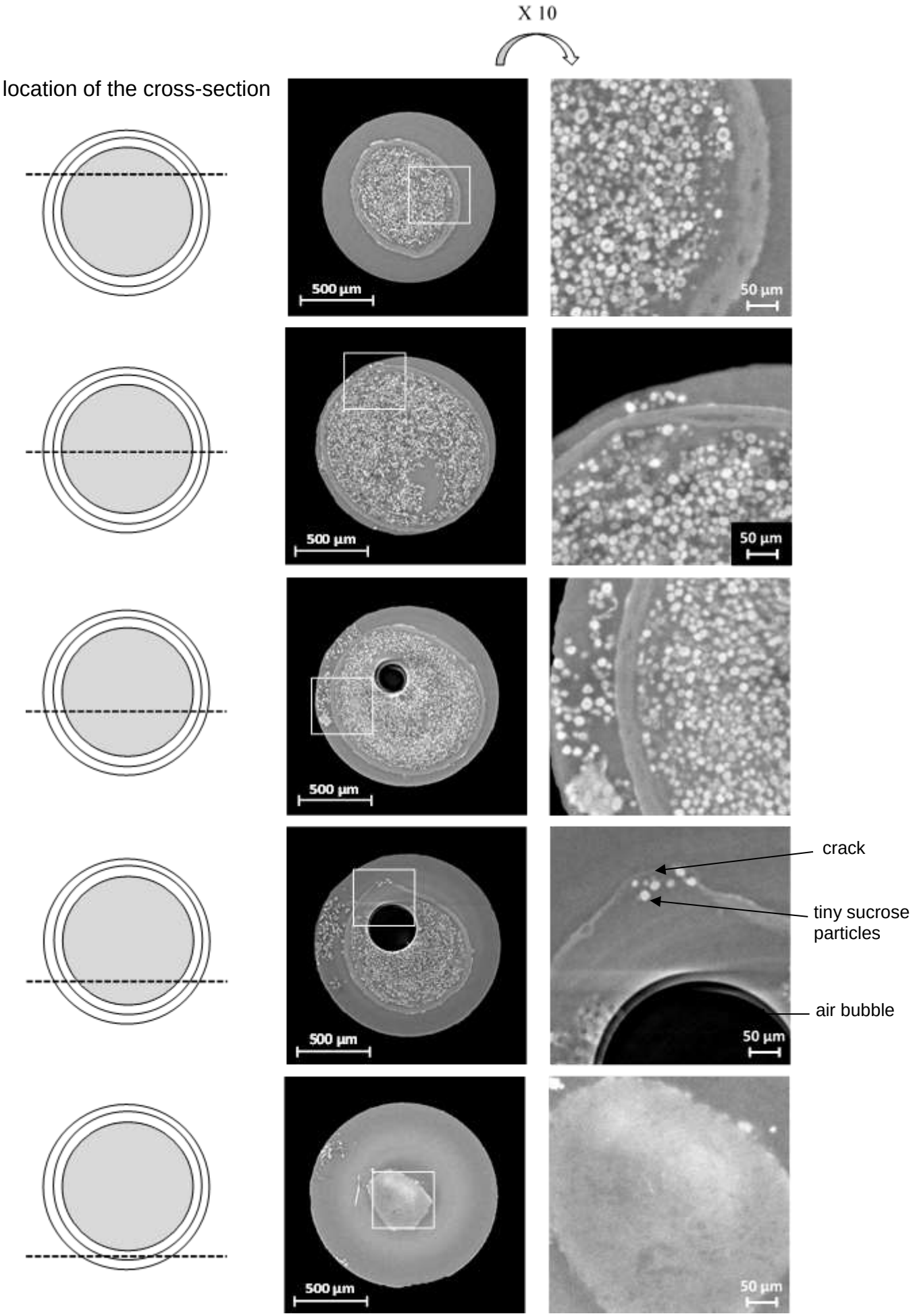


Figure 47: Reconstructed tomographic cross-sections through a coated pellets after 8 h exposure to phosphate buffer pH 7.4. The right column shows a higher magnification of the white square marked in the middle column.

Thus, the presence of numerous tiny, air-filled pores in the pellet starter cores is likely decisive for the drug release mechanism governing propranolol release from the investigated Kollicoat SR pellets. Upon water penetration into the pellet core, the latter becomes semi-solid/liquid and the initially individual and very small air pockets become mobile and fuse together (to lower their surface area and energy). This leads to the creation of bigger air bubbles, which seem to be able to sufficiently (mechanically) stress the film coatings: Crack formation is observed in the vicinity of these “big” air bubbles. It has also to be pointed out that the temperature rises from room temperature to 37 °C during drug release, which leads to an expansion of the air. Film coating regions which are particularly thin, are likely to preferentially deform in the vicinity of such “big” air bubbles and finally break. Once a hole is created in the film coating, the drug (and other compounds of the pellet core) are expulsed due to the hydrostatic pressure built up in the pellet core (the amount of water penetrating into the pellets can be significant, as shown in figure 29). Such a drug expulsion through a crack in a film coating is illustrated in figure 48 (a 3D reconstructed image of a quarter of a coated pellet, which was exposed to the release medium for 1 h, is shown).

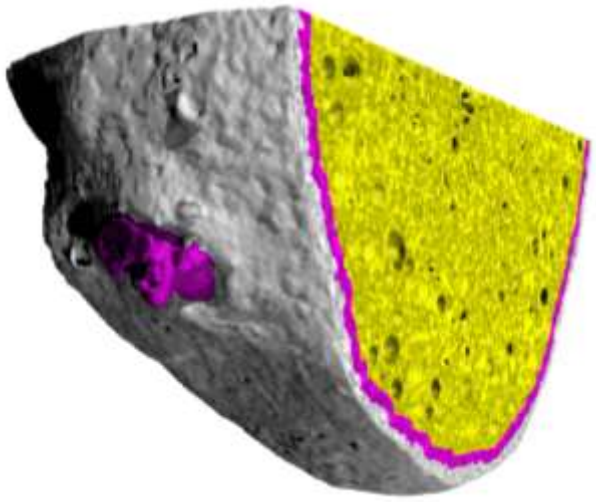


Figure 48: Reconstructed 3D image of a quarter of a coated pellet during drug release (after 1 h exposure to phosphate buffer pH 7.4), obtained by X-ray micro tomography. The following colors were used: The sugar core is marked in yellow; the drug in pink and the Kollicoat SR coating in grey.

The colors were used as follows: The sugar core is marked in yellow; the drug in pink, and the Kollicoat SR coating in grey. The crack has probably just been created, since only drug is coming out of the hole (and not yet sugar), the drug layer being located directly beneath the polymeric film coating. On reconstructed

tomographic cross-sections of pellets, which had been exposed to the release medium for 8 h, also the expulsion of tiny sugar particles through cracks is visible, *e.g.* as illustrated in the second row from the bottom in figure 47. The pictures in the middle row show that some sugar particles accumulated in the release medium at this time point.

In conclusion, the importance of air bubbles for the control of drug release from polymer coated pellets might be decisive. This is a fact, which has so far been ignored.

Part II: Diffusion controlled system

In this second part, the project, based on the conception of a controlled release solid dosage form is presented. It is related to coated pellets in which the drug is released only by diffusion through the intact polymeric film coating. The final aim is to mathematically describe the drug release kinetics. Besides, coated tablets with the same formulation have been performed in order to compare the kinetics between coated pellets and coated tablets and to analyze the impact of the dosage form.

I. Formulation and design of coated pellets

In this project, diprophylline a highly water-soluble drug was used. The experimentally observed solubility is 201.8 mg/mL in phosphate buffer pH 7.4 at 37 °C. To manufacture coated pellets, diprophylline was incorporated inside the cores, composed of 50 % diprophylline, 25 % lactose and 25 % microcrystalline cellulose, by extrusion-spheronisation. Then, the pellets were coated with a polymer blend ratio Aquacoat ECD:Eudragit NM 30 D in a fluidized bed coater. These two polymers were chosen because Aquacoat is often used for film coating (Wesseling and Bodmeier, 1999) (Harris and Ghebre-Sellassie, 2008) (J. Siepmann *et al*., 2008) but blending both has not yet been reported in the literature. Aquacoat forms rigid films in the contrary to Eudragit NM being highly flexible, so mixing both should serve to improve the mechanical properties and the coating process.

The polymer blends are often applied to facilitate the adjustment of desired drug release kinetics, to improve the film formation, to adjust drug permeability within the release barriers and to obtain appropriate mechanical film coating properties and stability. However, the use of the mixture of two different polymers is not straightforward because various phenomena can occur such as phase separation, plasticizer redistribution from one polymer into the other. So, attention must be taken with regard to this complexity (F. Siepmann *et al*., 2008).

The first challenge was to find suitable process parameters because these two polymers have different physicochemical properties (table 13) (FMC Biopolymer, 1996) (Evonik industries, n.d.).

Table 13: Properties of both polymers.

	Aquacoat ECD 30	Eudragit NM 30 D
MFT (°C)	81	5
Tg (°C)	90*	11
Requirement	Plasticizer	Antitacking agent

*The Tg of Aquacoat is lower than ethylcellulose (129-133 °C) due to the plasticizing effect of water present in the aqueous dispersion.

Regarding Aquacoat, the recommended addition of plasticizer is around 10-20 %, which lowers the MFT of 81 °C to a range of 20 to 50 °C. Dibutyl sebacate was selected in this study owing to its hydrophobic nature, which will not migrate out the film (Lecomte *et al.*, 2004). Nevertheless, lipophilic plasticizers require from 5 h to 24 h stirring time after the addition of aqueous dispersion for an optimal interaction within the polymer particles (Lippold *et al.*, 1990) (Lippold *et al*., 1999). So, 20 % of DBS was added to the aqueous dispersion of Aquacoat 24 h before spraying. Indeed, it has been demonstrated that the water-insoluble plasticizer migrated to the ethylcellulose particles after one day standing of the dispersion and 85-90 % of this one is incorporated into the polymer particles after 24 h (Lippold *et al*., 1990) (Siepmann *et al.*, 1998) (J. Siepmann *et al*., 2008). The plasticizer has to penetrate completely into the polymer particles before film formation in order to obtain optimal plasticization, the lowest MFT and high permeability of the resulting film. Thus, homogeneous films will be formed.

The MFT of Aquacoat decreases from 81 °C to about 30 °C in the presence of 20 % DBS (Lippold *et al*., 1990).

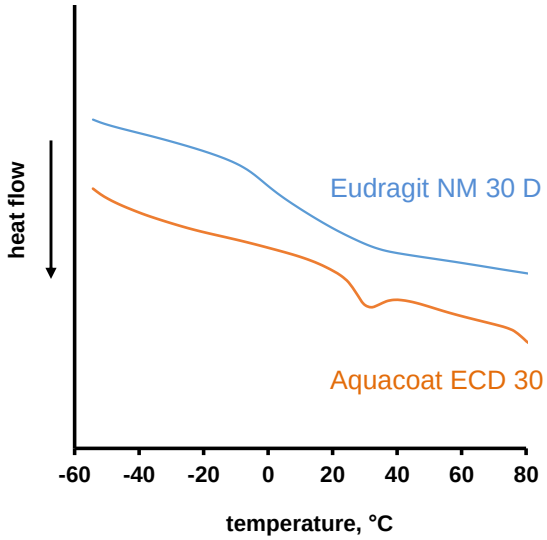


Figure 49: DSC thermograms of Eudragit NM 30 D and Aquacoat ECD 30 (plasticized with 20 % DBS). The Tg were: 8.10 °C and 20.72 °C respectively.

The **glass transition temperatures** of each polymer dispersion were analyzed in order to know the experimental Tg of Aquacoat plasticized with 20 % DBS and Eudragit NM alone (figure 49). The preparation of the samples was simplified (no talc with Eudragit) due to the difficulty for obtaining a visible signal. Indeed, the composition of both dispersions are already complex by the presence of several components. The Tg is an important parameter for the film formation and for a better adjustment of the product temperature of the fluid bed coater. As it can be seen, the Tg were determined: 8.1 °C and 20.7 °C for Eudragit NM and Aquacoat (with 20 % DBS) respectively. Regarding Aquacoat, signal was disturbed probably by a melting peak of cetyl alcohol, one of the component of the ethylcellulose dispersion. Moreover, adding a plasticizer to the dispersion leads to a reduction and a broadening of the Tg (Schmid *et al*., 2000). Unfortunately, the Tg from a polymer blend of these polymers was difficult to obtain due to the complexity of the mixture.

Next to that, the product temperature of the fluidized bed coater has to reach 10 °C above the MFT of the dispersion for a better polymer particles coalescence (Lippold *et al*., 1989). The product temperatures required for both polymers are 40 °C and 25 °C for Aquacoat and Eudragit NM 30 D respectively. So, the mixture needed several attempts to find the good compromise about process parameters and for obtaining a complete film formation and so control drug release (figure 50).

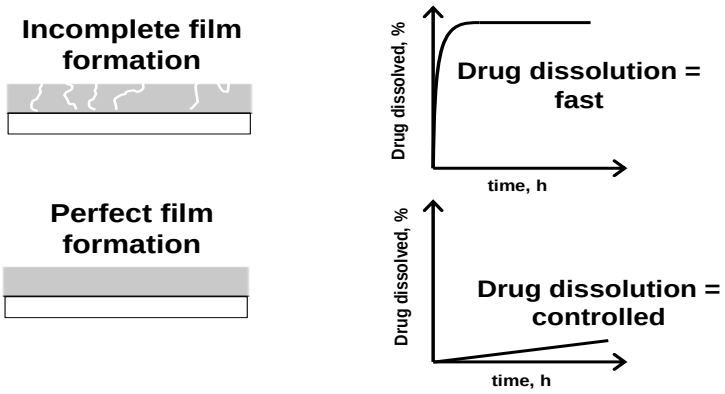


Figure 50: Schematic presentation of film formation from polymeric dispersions during film coating and curing.

Yang and Ghebre-Sellassie investigated the effect of the product temperature in a fluid bed coater on the film formation. They studied three different bed temperatures 22 °C, 35 °C and 50 °C on the Aquacoat film formation. They found that 35 °C was the suitable temperature to prevent drug migration into the film layer and to obtain a complete coalescence of the polymer particles (Yang and Ghebre-Sellassie, 1990).

In the beginning, the product temperature of 38-40 °C was tried for some polymer blend ratios but destruction of pellets was observed. Figure 51 illustrates two profiles of diprophylline release from pellets coated with Aquacoat:Eudragit NM 30:70 using two different product temperatures (38 °C versus 25 °C) during the coating process. As it can be seen on the left side, the release was very fast and complete after 1 h because of crack formation and disintegration clearly visible on the picture. On the right side, a lag-time was noticed followed by a total drug release after 8 h. The formation of the film seemed better even if the kinetics remained fast for a controlled release formulation. It is coherent because the film coating is composed of a high amount of Eudragit (70 %) and 25 °C is the suitable temperature to form a complete polymeric film. Besides, the picture didn't show any disintegration. In addition, no significant difference between the coating levels is noticeable, so the formulation parameters need to be further improved.

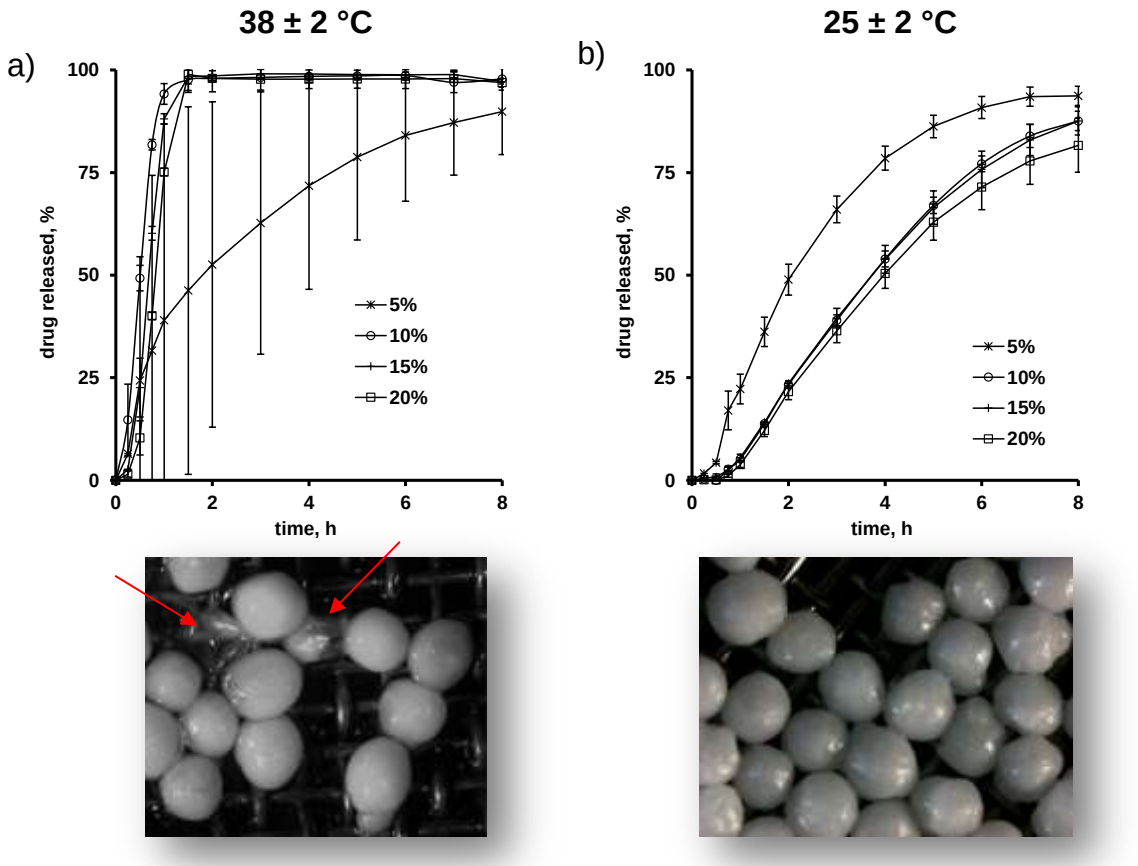


Figure 51: Comparison of the product temperature (as indicated) of the coating process on diprophylline release profiles from pellets coated with Aquacoat:Eudragit NM 30:70. Notice that the size of starter cores and the formulation are not exactly the same: a) 1000-1250 µm with talc and b) 850-1000 µm without talc.

The other attempts with 38 °C as product temperature were not convincing, so 25 °C was selected (related to the polymer blend ratio); especially since the company Evonik advises to not exceed 25 °C and also to use 50 to 100 % talc when using

Eudragit NM. Moreover, it has been shown in figure 52 that the film coatings with either 100 % Aquacoat or 100 % Eudragit NM at 25 °C as product temperature were completely formed, except for 5 % of coating level from 100 % Aquacoat. Note that only 5 % and 10 % of coating level were performed with 100 % Eudragit NM due to sticking of the pellets.

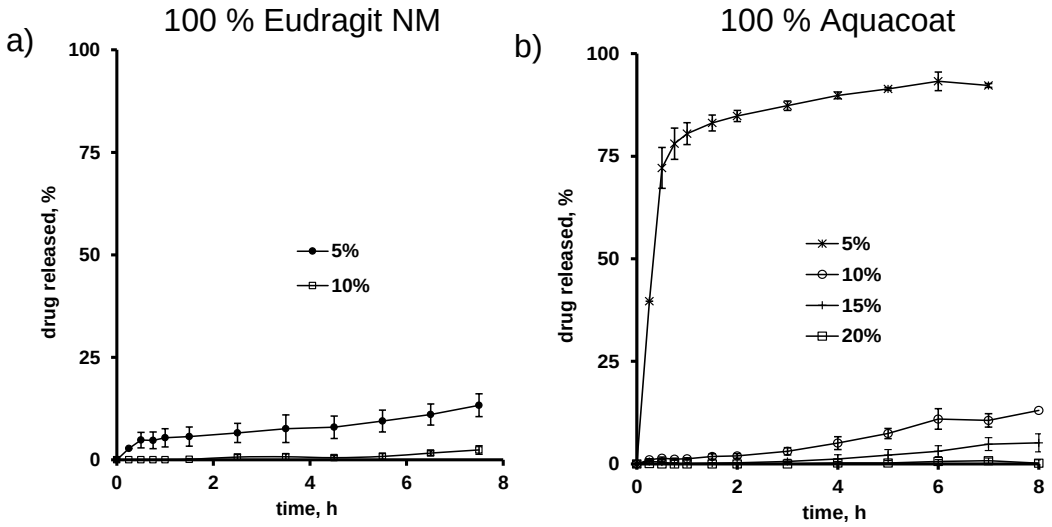


Figure 52: Diprophylline release from pellets coated a) 100 % Eudragit NM (50 % w/w talc) and b) 100 % Aquacoat ECD (20 % w/w DBS).

After the establishment of suitable process parameters and the formulation, several polymer blend ratios were tested. The variation of the latter can alter the resulting film coating properties and the drug release patterns (Lecomte *et al*., 2003). It is clearly obvious in figure 53.

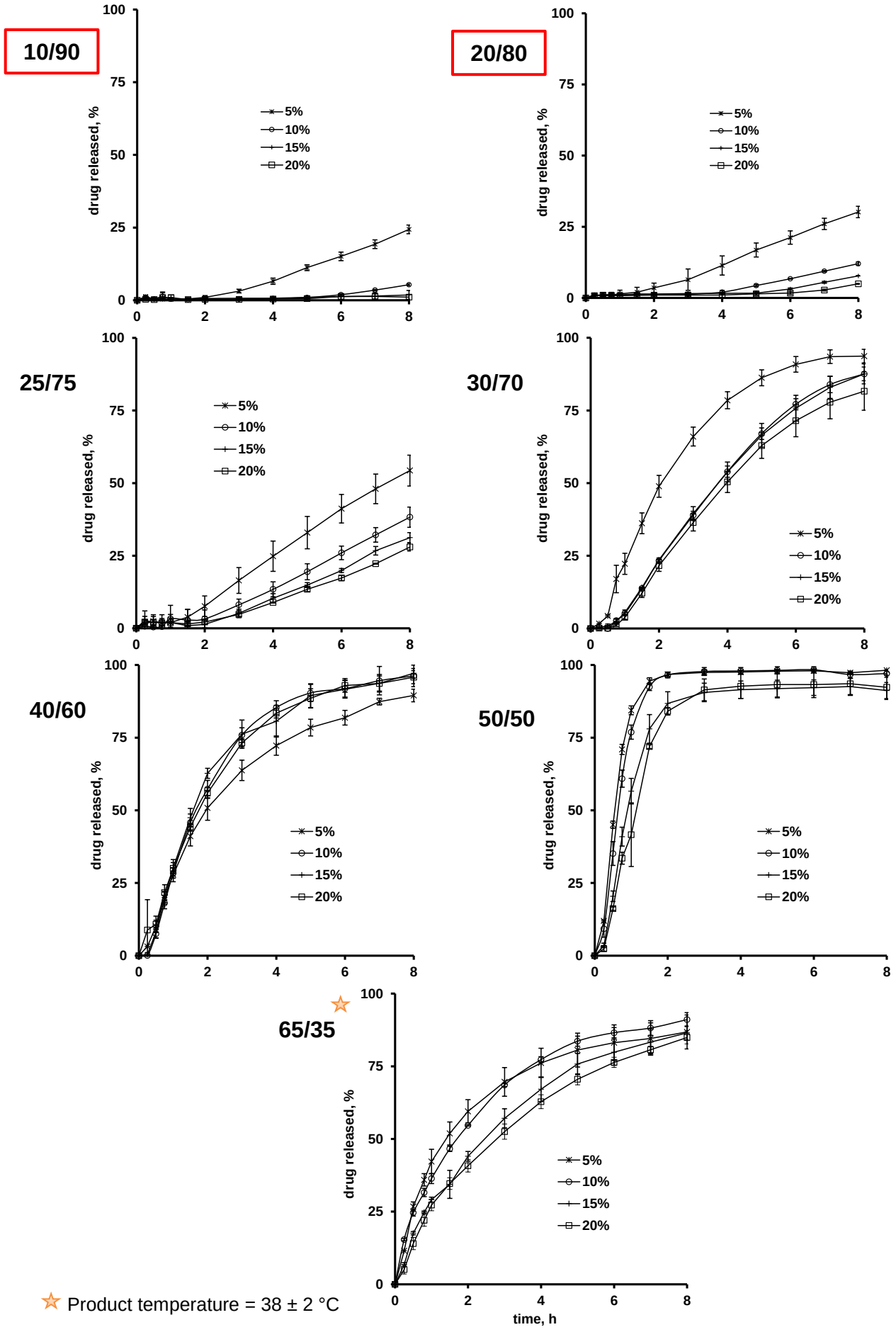


Figure 53: Diprophylline release from pellets coated with different blend ratios of Aquacoat ECD /Eudragit NM 30 D (indicated next to the figure) in phosphate buffer pH 7.4.The coating levels are mentioned in the figures.

As it can be seen, increasing the quantity of Aquacoat leads to increased drug release kinetics from Aquacoat:Eudragit NM 30:70, 40:60, 50:50 and 65:35. This can be attributed to the bed temperature (25 °C) not convenient for ethylcellulose film formation, especially if the quantity in the polymer blend become important. Therefore, notice that for 65:35, the product temperature was around 38 °C due to the presence of high amounts of Aquacoat in contrary to the rest (25 °C). It shows an enhancement of the kinetics.

So, increase the product temperature, when ethylcellulose dispersion is in majority in the coating composition, improves moderately the drug release kinetics. Now, regarding the polymer blend ratios 10:90, 20:80 and 25:75, the drug release profiles were slower, a sign for an appropriate product temperature for a complete film formation. The ratios 10:90 and 20:80 were selected for the following experiments.

The drug release was completed with different coating levels for both ratios (figure 54). They are similar due to the low difference between the two systems. At low coating level (1 to 4 %), the thickness of the film was not high enough to avoid crack formation.

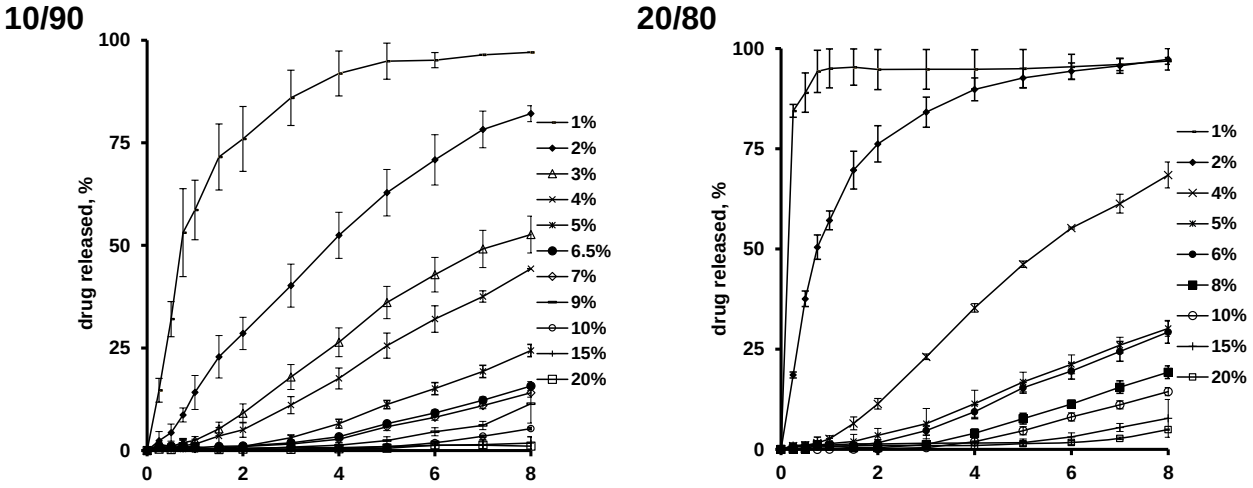


Figure 54: Diprophylline kinetics from pellets coated with Aquacoat ECD:Eudragit NM blend ratios 10:90 and 20:80. The coating levels are indicated in the figures.

To conclude, the formulation and the design of diprophylline loaded pellets coated with a polymer blend consisted of Aquacoat and Eudragit NM was a challenge especially using a polymer blend with two very different MFTs. Two ratios 10:90 and 20:80 were convincing, so the physicochemical properties of both film coatings were analyzed in deeper.

II. The study of the drug release mechanisms

The **water contents** of thin films prepared from Aquacoat and Eudragit NM blend dispersions in phosphate buffer pH 7.4 at 37 °C are illustrated in figure 55. Both films rapidly took up amounts of release medium (around 10 %) at early time points and the weight of the wet film remained subsequently constant for the rest of the observation period (figure 55 a). This can be attributed to the hydrophobicity of the components of the film coatings (ethylcellulose dispersion, DBS, talc and Eudragit NM) and their low water permeability. In consequence, the **mass loss** of the films after exposure to the dissolution medium was very limited (maximal value: 0.6 %) indicating, that the lipophilic plasticizer remained inside these films during the release process (figure 55 b).

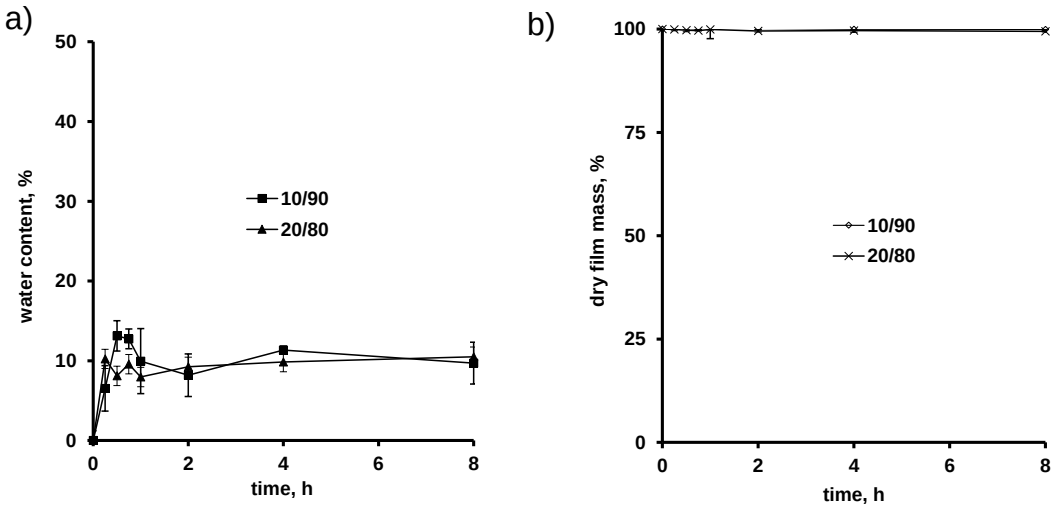


Figure 55: a) Water uptake kinetics, and b) dry mass of free films based on Aquacoat ECD:Eudragit NM upon exposure to phosphate buffer pH 7.4 at 37 °C. The blend ratios are indicated in the figures.

Also, the **mechanical properties** were studied in the dry state at room temperature and after exposure to phosphate buffer pH 7.4 at 37 °C (figure 56).

In the dry state, the elongation and the energy at break are quite similar for both polymeric films (corresponding to the dotted bars). Upon contact with the release medium, the elongation was improved owing to the plasticizing effect of water for this polymeric system as well as the increase in temperature (from room temperature to 37 °C) and the films composed of 20:80 were more flexible than 10:90 films (figure 56 a). This can be explained by the fact that the use of more Aquacoat and so plasticizer leads to improved flexibility. In addition, there is less Eudragit NM and so less talc which can decrease the elasticity of the film.

Indeed, Ammar *et al*. demonstrated that talc affects mechanical properties of the polymeric film as well as the drug release. Increasing the amount of talc delayed the drug release, increased internal stress, stiffness and brittleness by reducing the polymer chain mobility (Ammar *et al*., 2016). In any case, these films were flexible and remained constant during the observation period because the plasticizer didn't leach out of the polymeric coatings. Importantly, the "% elongation at break" was around 300 % for 20:80 and around 215 % during 8 h. In contrast, the energy required to break these films substantially decreased from 5.3 (± 0.8) to 0.8 (± 0.1) and from 4.2 (± 0.4) to 0.8 (± 0.1) MJ/m^3 for 20:80 and 10:90 respectively once the films got into contact with the bulk fluid (figure 56 b). This is probably due to the presence of water and/or the rise in temperature. In conclusion, these investigated film coatings of Aquacoat:Eudragit NM are flexible and only limited forces are necessary to break them.

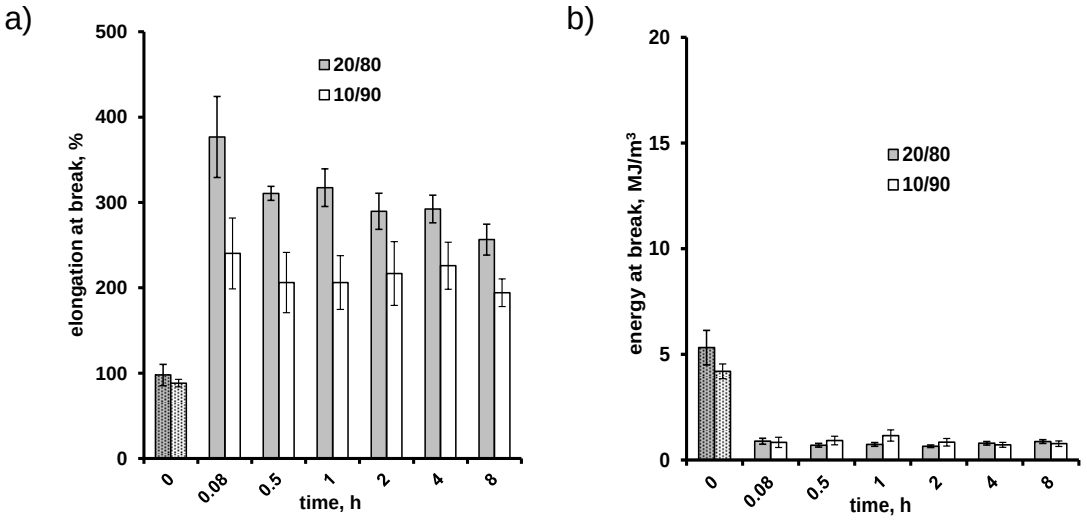


Figure 56: Mechanical properties of free Aquacoat ECD:Eudragit NM films before ("Zero h" (dotted bars)) and after exposure to phosphate buffer pH 7.4: a) percent elongation at break, b) energy at break. The blend ratios are indicated in the figures.

Between these two ratios of polymer blend, 20:80 of Aquacoat:Eudragit NM was selected for the following experiments.

In order to better understand how the drug release is controlling from this system, **the release and swelling kinetics** of individual pellets were monitored. The figures 57 and 58 show six examples of different single pellets at 4 % and 10 % of coating level respectively. On the left y-axes (corresponding to the opening diamonds) the percentage of drug release is plotted, on the right y-axes (corresponding to the filled squares) the increase in diameter is presented (in %). In figure 57, diprophylline was released after a lag-time of 2 h but in the same way as

from the ensembles of pellets (figure 53). At 10 % of coating level (figure 58), the lag-time was more important (around 6 h) and diprophylline was slowly released or not. Importantly, all the single pellets didn't change in size signifying that no swelling is occurred with this investigated system.

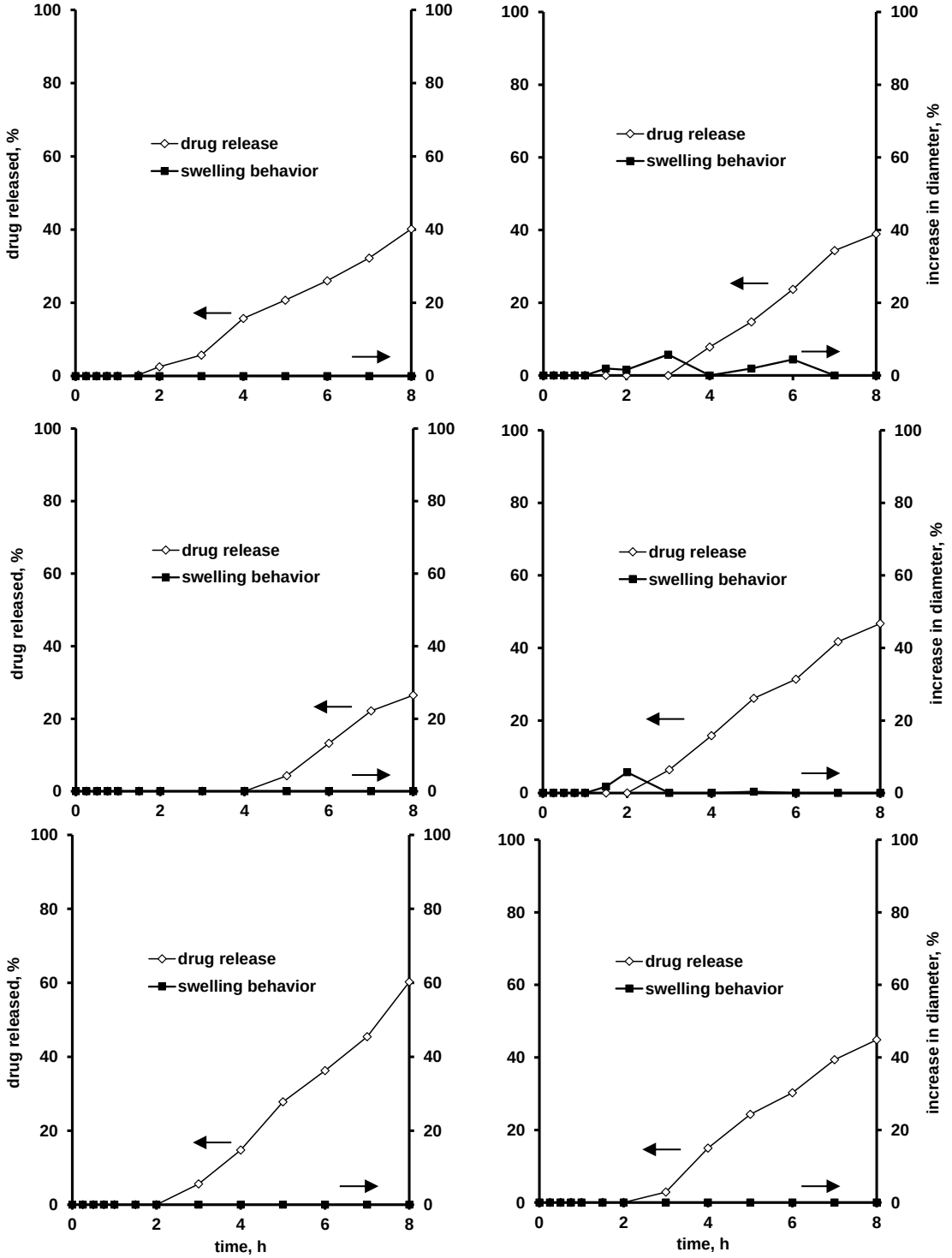


Figure 57: Drug release from and swelling of a single pellet coated with Aquacoat:Eudragit NM polymer blend ratio 20:80 in phosphate buffer pH 7.4 (starter core size: 850-1000 µm, coating level: 4 %, n = 6).

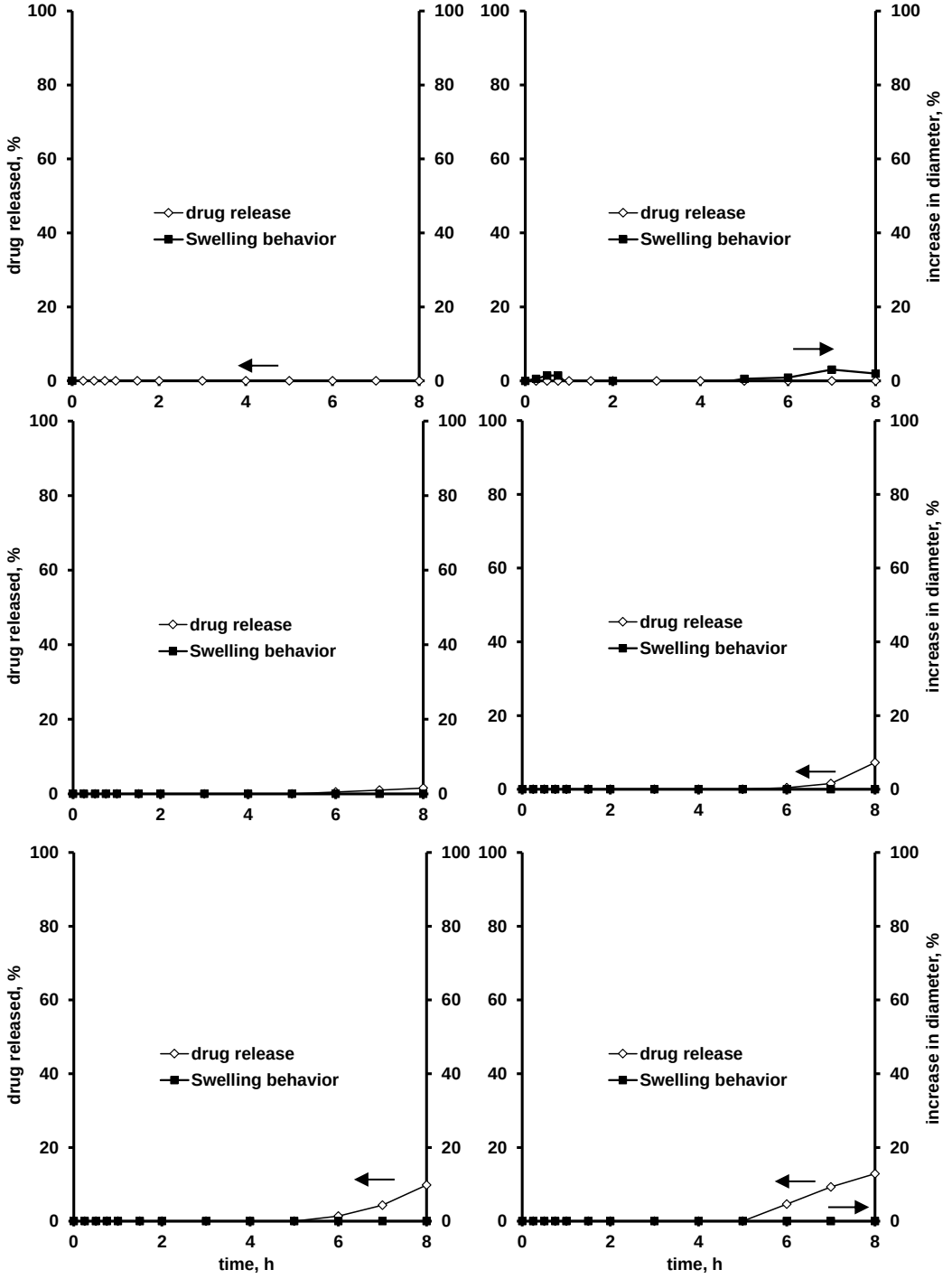


Figure 58: Drug release from and swelling of a single pellet coated with Aquacoat:Eudragit NM polymer blend ratio 20:80 in phosphate buffer pH 7.4 (starter core size: 850-1000 µm, coating level: 10 %, n = 6).

Another key property of polymeric film coating controlling the drug release from pellets is the **drug permeation**. As already explained *in the part I V.*, the permeability is equal to the diffusion coefficient D and the partition coefficient K between the barrier and the bulk fluid. The D and K are determined in the same way as previously using side-by-side diffusion cells. In this present case, the donor compartment was composed of a saturated drug solution and perfect sink conditions in the acceptor compartment. As a constant drug concentration is provide, a linear

drug amount gradient is obtained after a lag time. The slope of the linear part of the curve is equal to:

$$slope = \frac{A \cdot D \cdot K \cdot C_s}{L} \qquad (16)$$

Where A is the surface area of the film exposed in the diffusion cell, D is the apparent drug diffusion coefficient within the polymeric film, K is the partition coefficient, L is the thickness of the film and Cs the solubility of drug within the release medium.
From the observed lag time, t_{lag}, and thickness of the film, L, the apparent diffusion coefficient, can be calculated as follows:

$$D = \frac{L^2}{6 \cdot t_{lag}} \qquad (17)$$

Figure 59 shows examples of experimental (symbols) and theoretical (curves) diprophylline transport kinetics. Good agreements were obtained between theory and experiment. The apparent diffusion coefficient of the drug as well as the partition coefficient between the film and the release medium could be determined:
D = 3.0 (± 2.6).10^{-11} cm²/s and K = 7.7 (± 8.7).

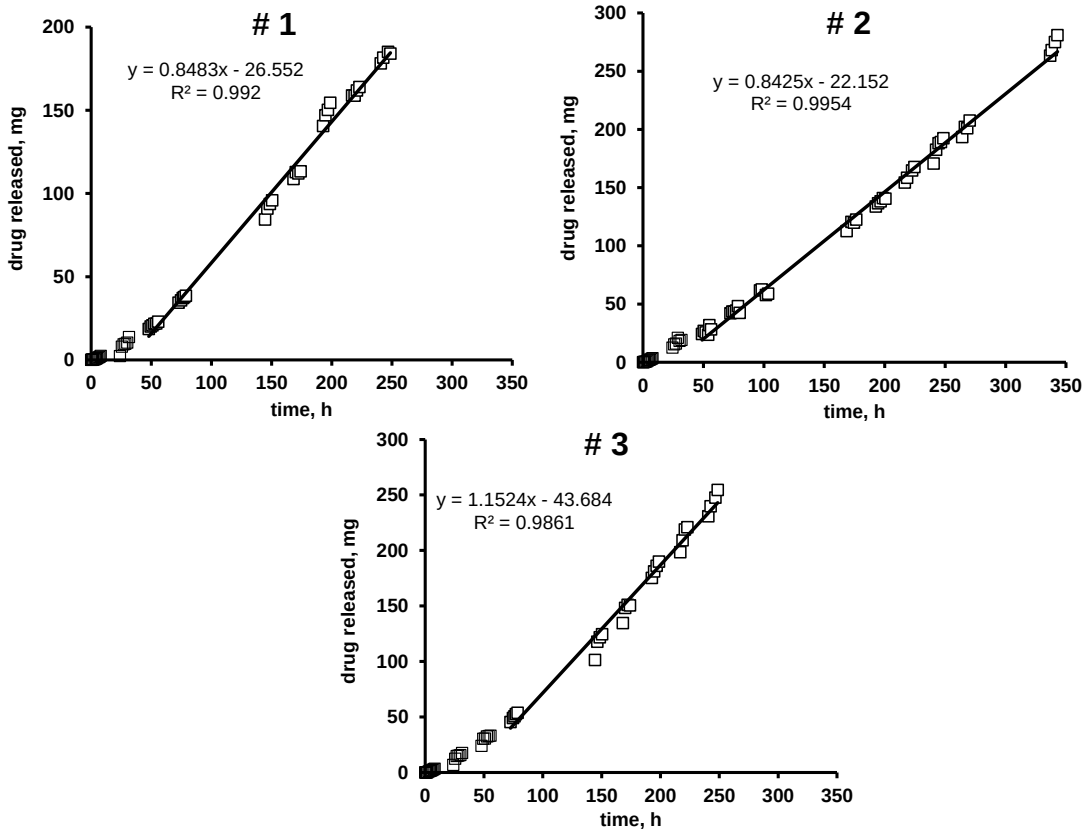


Figure 59: Theory (curves) and experiment (symbols) of diprophylline transport through an initially drug-free Aquacoat:Eudragit NM (20 :80) film in a side-by-side diffusion cell (thickness: # 1 = 48 µm, # 2 = 32 µm, # 3 = 51 µm).

Once knowing these two values D and K and assuming that diffusion through the intact polymeric membrane is the release rate controlling step from coated pellets, an appropriate solution of Fick's law can be used to theoretically predict the resulting drug release kinetics. The spherical geometry, the drug loading, the API solubility and the perfect sink conditions have been considered. So, the following solution of Fick's law can be derived allowing the quantification of the drug release:

$$M_t = 4 \cdot \pi \cdot R_o \cdot R_i \cdot (R_o - R_i) \cdot C_s \cdot K \cdot \left[\frac{D \cdot t}{(R_o - R_i)^2} - \frac{1}{6} - \frac{2}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{(-1)^n}{n^2} \cdot exp\left\{-\frac{D \cdot n^2 \cdot \pi^2 \cdot t}{(R_o - R_i)^2}\right\}\right] \quad (18)$$

Where M_t denotes the absolute cumulative amount of drug released at time t; R_i and R_o the inner and outer radii of the coated pellet; D denotes the apparent diffusion coefficient of the drug in the polymeric membrane; K represents the partition coefficient of the drug between the film coating and the release medium, n is a variable. Due to the lipophilic character of the polymeric membrane, slow water penetration in early time points was taken into consideration.

Figure 60 shows examples for such **theoretical predictions**. As it can be seen, the theory was in good correlation with the experimental results, confirming that the drug release is mainly controlled by diffusion through the intact polymeric film coating.

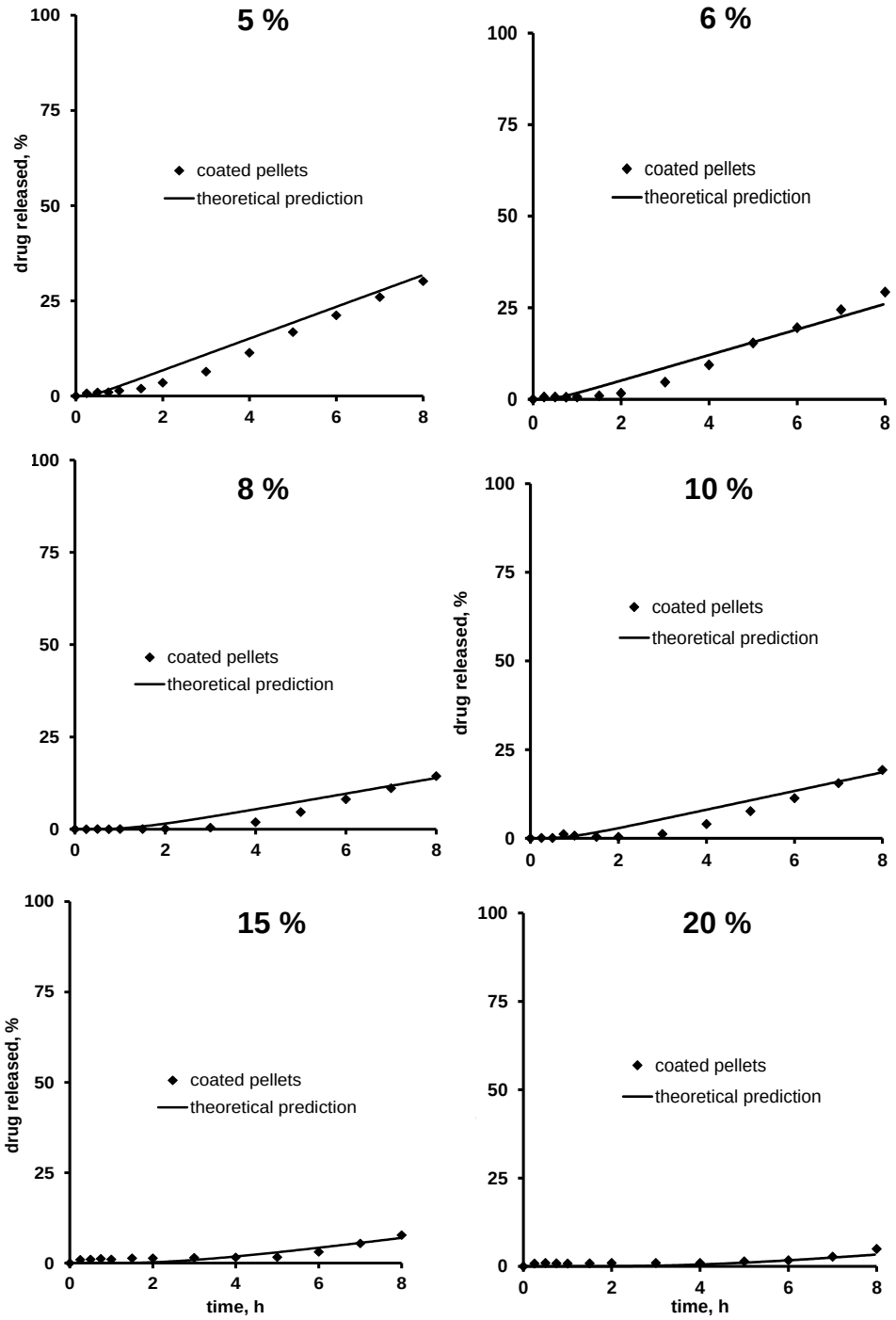


Figure 60: Theoretical predictions (curves) and independent experimental results (symbols): Diprophylline release from pellets coated with a polymer blend Aquacoat:Eudragit NM (20:80). The coating levels are indicated at the top of the figures.

III. Formulation and design of coated tablets

Once the formulation for a diffusion controlled system from coated pellets was established, the same one was used to prepare coated tablets. The aim was to study the impact of the dosage form on the drug release patterns and to predict the diprophylline release from coated tablets.

The tablet cores of almost the same composition as the pellet cores except that corn starch, PVP and magnesium stearate were added to perform the wet granulation and to obtain the good parameters (*e.g*. flowability and compressibility) for the compression step. In table 14 are summarized the results of the pharmaceutical tests. The tablet cores were conformed according to the European Pharmacopoeia (8^{th} edition).

Table 14: Pharmaceutical tests on granules and uncoated tablets according to the European Pharmacopeia 8.0.

Pharmacotechnical tests	Results	Specification*
Residual moisture	1.30 %	< 2 % *conform*
Flowability test	6 sec	< 10 sec *conform*
Tapped density	Carr index = 18.27 Hausner ratio = 1.22	*Acceptable*
Weight variation	112.55 ± 1.36	< ± 7.5 % *conform*
Hardness	59.15 ± 9.28	
Size variation	Diameter: 5.03 ± 0.02 Height: 4.66 ± 0.68	
Friability	0.61 %	< 1 % *conform*
Disintegration test	3 min	< 15 min *conform*
Drug content uniformity	55.43 mg ± 2.82	< ± 7.5 % *conform*

*Conform with the European Pharmacopoeia 8.0.

Then, the cores were coated with a polymer blend composed of 20 % Aquacoat and 80 % Eudragit NM in a coater. To obtain the same thickness of film coating as coated pellets, the mass per surface was taken into account for the calculations. The pharmaceutical tests (weight variation, friability and disintegration test) on the coated tablets were conformed to the European Pharmacopoeia.

Afterwards, the tablets were cut using a scalpel and the cross-sections were observed using an optical image analysis in order to evaluate the thickness of the final coat layer. The pictures are illustrated in figure 61.

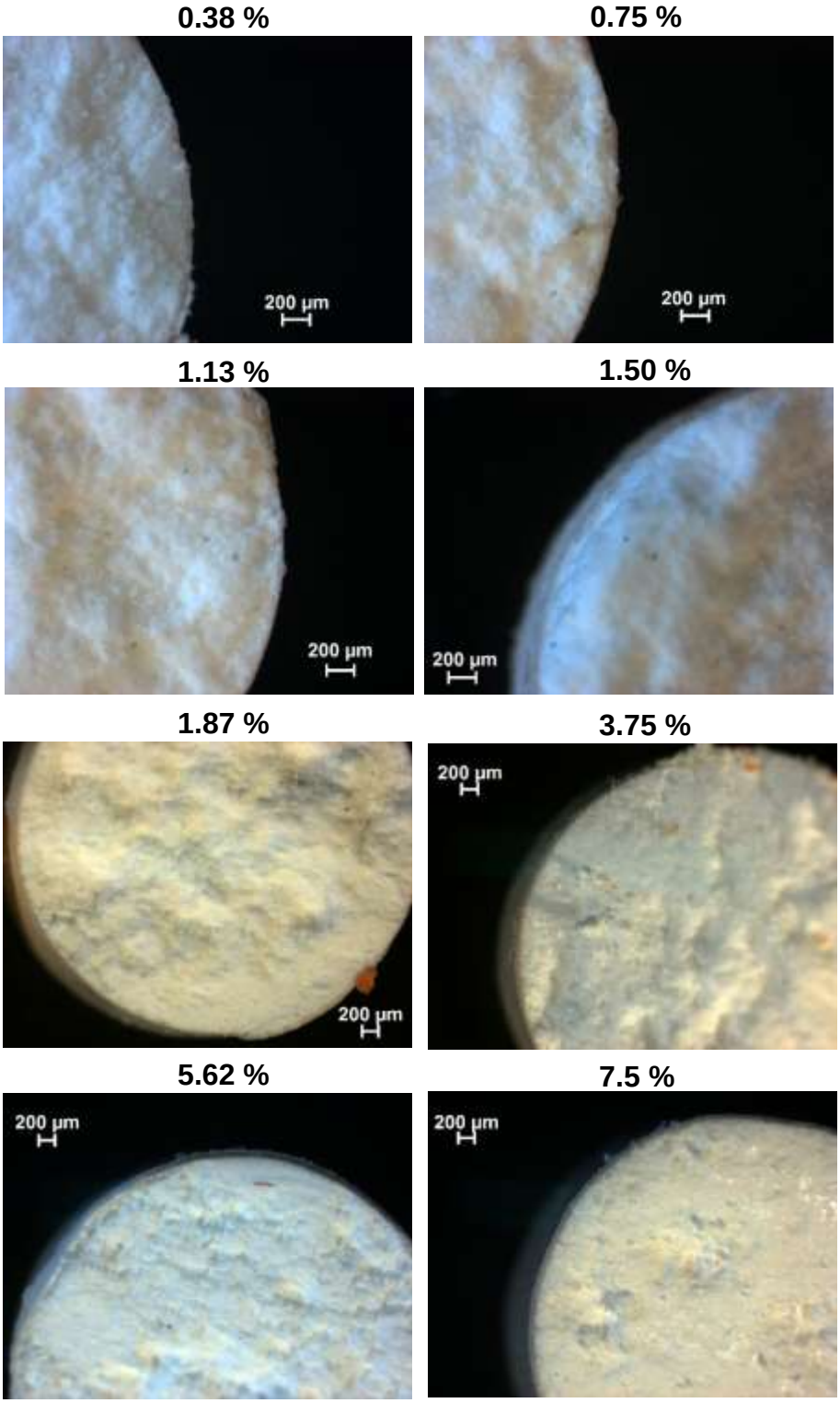


Figure 61: Macroscopic pictures of cross-sections of diprophylline-loaded tablets coated with Aquacoat ECD and Eudragit NM 20:80.The coating levels are indicated in the figures.

For the low coating levels, the thickness was not measured due to the lack of resolution. The results are presented in table 15.

Table 15: Thickness of polymeric membrane of coated tablets at different coating levels.

Coating level (%)	Thickness (µm)
1.13	10.42 ± 1.38
1.50	14.4 ± 1.08
1.84	19.89 ± 6.37
3.75	38.85 ± 3.56
5.62	55.8 ± 8.40
7.5	66.5 ± 12.74

The thickness of the tablets' coating layer was similar compared to the one of coated pellets. For example, the pellets had a coating thickness of around 50 µm for 15 % (w/w) of coating level corresponding to 56 µm for 5.62 % of coating level for the tablets.

Then, diprophylline release from coated tablets (n=6) was achieved in phosphate buffer pH 7.4. Figure 62 shows the drug release profiles.

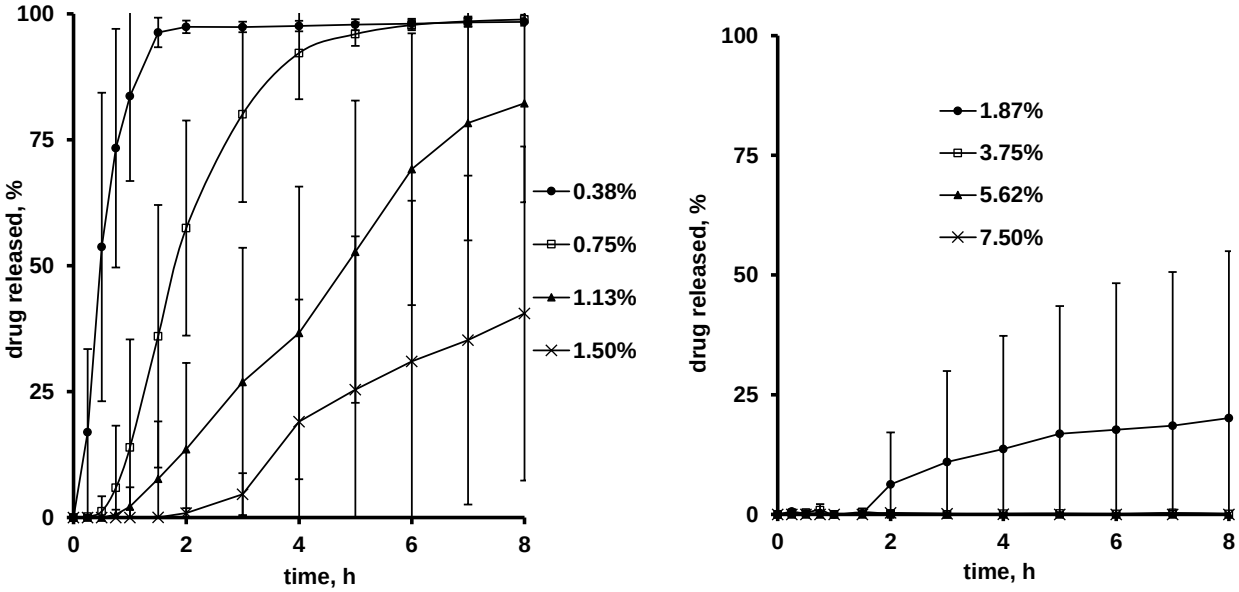


Figure 62: Diprophylline release from tablets coated with a blend ratio of Aquacoat ECD:Eudragit NM 30 D 20:80 in phosphate buffer pH 7.4.The coating levels are notify in the figures.

As it can be seen, the kinetics were very fast from 0.38 % to 1.13 % coating level. On the other hand, no drug release was observed from 3.75 % to 7.50 % coating level. In addition, the standard deviations were important signifying that each tablet was singular. Indeed, the coating of cylindrical tablets can be difficult especially on the edges and consequently the film coating was not homogeneous on the surface.
Some pictures were taken after 8 h exposure to the release medium in order to get in deeper the insight of the tablets behavior (figure 63).

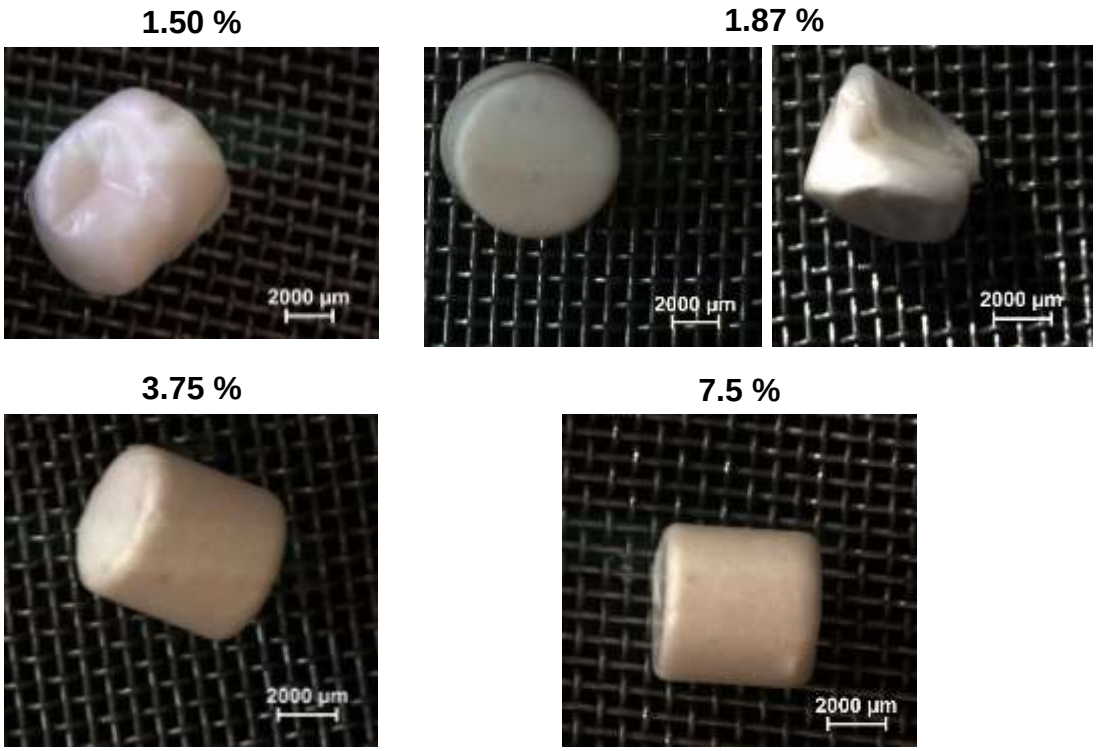


Figure 63: Macroscopic pictures of diprophylline-loaded tablets coated with Aquacoat ECD and Eudragit NM 20:80 after 8 h exposure to phosphate buffer pH 7.4. The coating levels are indicated in the figures.

For the finest thicknesses of coating level (0.38 % to 1.13 %), the cores were dissolved more or less quickly during the observation period. Concerning 1.50 % of coating level, water penetrated into the system either by diffusion through the intact polymeric film and/or by the incomplete film coating especially on the edges of the tablets resulting to the drug release more or less faster. In the case of 1.87 % of coating level, two different behaviors of coated tablets are clearly visible on the pictures (figure 63). If the film is completely formed, the release medium has difficulty in penetrating to the system and the drug was not released. On the other hand, if a defect is present in the film, water can easily enter into the tablet and dissolve the core including diprophylline and release this latter, hence the important standard deviations. For the thickest thicknesses (3.75 % to 7.50 %), the morphology of the tablets didn't change meaning that the film was completely formed and the water didn't sufficiently penetrate the system allowing the dissolution of the drug and so the release into the surrounding fluid. Indeed, after 8h exposure to phosphate buffer pH 7.4, the core was still dry. The volume of tablets is bigger than those of pellets; so water needs more time to diffuse through the tablet films and to dissolve the core compared to pellets. The drug release should be observed during a longer period of time.

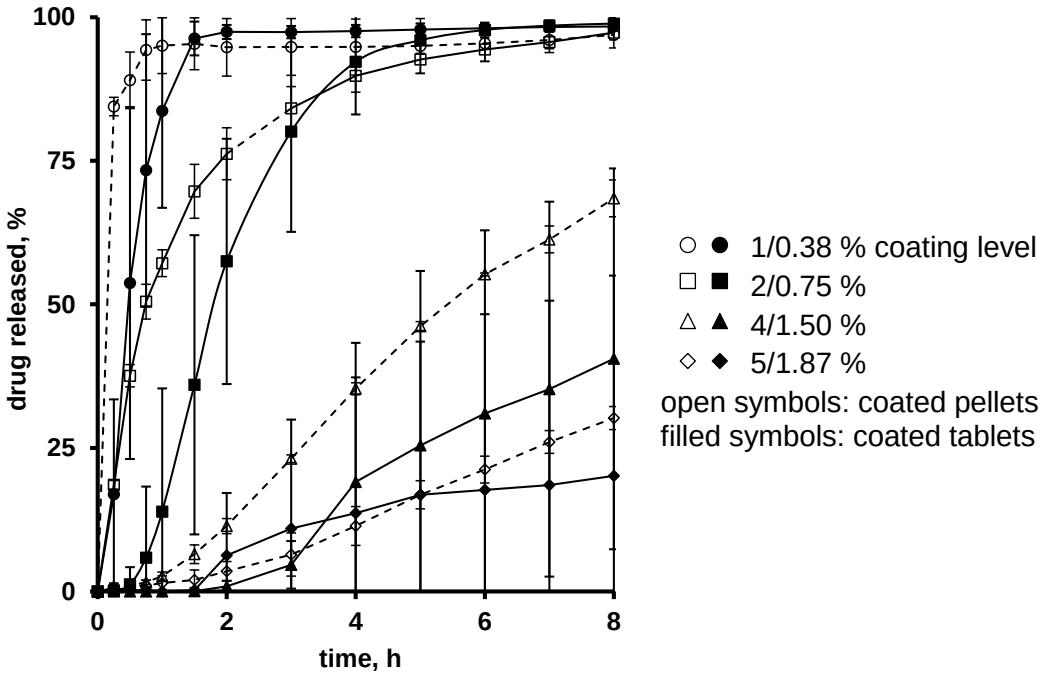


Figure 64: Comparison between coated pellets and coated tablets at different coating levels. The dosage form and the coating levels are indicated in the figure.

Figure 64 compares the drug release profiles between the pellets and the tablets only for four examples of coating levels. The tendencies were similar. However, the drug release from coated pellets should be faster than the one from coated tablets owing to their small size and so their high specific surface area leading to an increase in drug release, as observed in the figure.

In conclusion, the formulation of coated tablets need to be improved by changing the shape in order to obtain a homogeneous film coating. At the moment, no theoretical prediction was achieved. Nevertheless, the dosage form influences the drug release patterns due to the difference of the system's contact surface to the release medium allowing a more or less fast drug release.

GENERAL CONCLUSION AND PERSPECTIVES

Polymer coated pellets are commonly used for oral controlled drug delivery. Nevertheless, the underlying drug release mechanisms can be complex and are not fully understood. This can be explained by the fact that many phenomena might be involved in the drug release process: water penetration into the system, drug dissolution and diffusion, swelling and crack formation mainly. Resulting from this potential complexity, sometimes unexpected tendencies are observed when varying key formulation parameters, such as the type of API and the nature of starter core.

The main objective of this work was to elucidate the underlying drug release mechanisms from coated pellets.

First of all, numerous formulation parameters were varied with pellets coated with Kollicoat SR containing propranolol HCl. Two types of starter core were used: sugar versus MCC cores, and surprisingly, unexpected tendencies were obtained:

(i) The release of propranolol HCl from pellets coated with Kollicoat SR was slower when using sugar compared to MCC starter cores. This can be potentially explained by a combination of decreased drug solubility in the presence of co-dissolved sucrose and the plasticizing effect of sugar on this polymeric film coating.

Interestingly, it has been demonstrated that sugar cores based pellets coated with Kollicoat SR increased in size significantly due to the both osmotic activities of the sugar core and the high water-soluble drug which attract more and more water. Then, cracks occur by exceeding the elongation limit.

(ii) The relative release rate of propranolol HCl from Kollicoat SR coated pellets increased with increasing initial drug loading especially with MCC starter cores. Crack formation probably occurred, accented by the increase of propranolol HCl concentration.

Interestingly, crack formation is likely to play a major role in the control of drug release from Kollicoat SR coated dosage forms, despite the high flexibility and mechanical stability of this polymeric coating material. Furthermore, the experimental drug release kinetics were not in correlation with the theoretical predictions based on diffusion mathematical model (Fick's law).

To conclude with the first part, propranolol HCl release from Kollicoat SR coated pellets is predominantly controlled by convection through cracks in the film coatings. In addition, the starter core material used in coated pellets can be decisive for the

drug solubility in the system's core and substantially affects the resulting drug release kinetics. This phenomenon should not be neglected in practice.

Secondly, another controlled drug delivery system was formulated: diprophylline loaded pellets coated with a polymer blend Aquacoat and Eudragit NM. A drug released only by diffusion from the system can be easily predicted using a mathematical model. That is why, many polymer blend ratios were tried, and one shown conclusive drug release profiles. Afterwards, this one was characterized in order to elucidate in deeper the underlying drug release mechanisms. This investigated system composed of diprophylline loaded pellets coated with Aquacoat:Eudragit NM 20:80 didn't show any swelling and cracks. Moreover, the experimental drug release kinetics were in correlation with the theoretical predictions. So, the release of diprophylline was likely to be controlled by diffusion through the intact polymeric film coating.

In the end, coated tablets with the same composition of pellets were prepared with the aim to study the impact of the dosage form and also to predict the drug release profiles. Due to the lack of time, the formulation couldn't be improved and so no prediction was realized.

Concerning the perspectives of this work, it could be useful to understand in deeper how and why crack formation was happened in the case of coated pellets containing a non-osmotic MCC starter core. X-ray micro tomography could provide information in detail about the structure of the pellets after exposure to the release medium. The cracks will be confirmed and others data will be helpful for a better understanding. Moreover, an incompatibility between Kollicoat SR and propranolol HCl was observed but not understood and so requires further investigation to explain this phenomenon. It is probably due to a chemical interaction with the chlorhydrate and the ester function of the polymer.

In the second part, more experiments could be carried out on the pellets coated with the polymer blend Aquacoat and Eudragit NM in order to complete our conclusion and to bring more information about this system for example the behavior of this two polymers and some image analysis, *e.g.* SEM to visually determine the uniformity of the coating.

In addition, the formulation of coated tablets has to be improved to obtain a more homogeneous batch. The shape could be changed *e.g.* spherical tablets.

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SUMMARY

SUMMARY

The main objective of this work was to elucidate the underlying mechanisms controlling the drug release from coated pellets.

First of all, Kollicoat SR coated pellets were investigated: A model drug (propranolol HCl) was layered onto two types of starter cores: sugar cores and microcrystalline cellulose cores. Then, a Kollicoat SR dispersion (plasticized with 10 % TEC) was applied onto them. The impact of many factors such as the nature and the size of starter cores, the coating level and the type and loading of API were evaluated. The final goal was to predict the drug release profiles using mathematical equations in order to facilitate the development of new medicines.

Unfortunately, the system was more complex as expected; especially from sugar cores based coated pellets. The first unexpected tendency was: Propranolol HCl was released slower from sugar cores based system compared to MCC cores based pellets. For a better understanding, various experiments were carried out: the study of free film coatings, the drug release from ensemble of pellets, the osmotic effect, the release of individual pellet and their swelling behavior and image analysis (SEM and X-ray micro tomography) mainly.

Interestingly, sucrose coming from the dissolution of the sugar cores influences the drug release kinetics by a combination of two phenomena: (i) plasticizing effect of sugar for the film coating and (ii) decrease in drug solubility in the release medium due to the presence of co-dissolved sugar. Afterwards, another API was used theophylline, a sparingly water-soluble molecule with a constant solubility in presence of sugar in order to evaluate the most important factor between both. Finally, the decrease of the drug's solubility was the determinant parameter. In addition, the following of drug release from single pellets and the swelling behavior combined to image analysis (SEM and X-ray micro tomography) demonstrated a fundamental phenomenon: cracks were clearly visible, through which content of the pellet core was expulsed into the surrounding release medium. The drug release mechanism of the investigated system is: Propranolol release from the sugar cores based pellets coated with Kollicoat SR is likely to be predominantly controlled by convection through cracks in the film coatings.

Then, the second unexpected tendency was: Increasing the drug loading increased the drug release kinetics especially with MCC cores. Cracks through Kollicoat SR film probably occurred. Furthermore, adding a most important concentration of

propranolol HCl accelerated crack formation due to the osmotic activity of the drug which attracts more and more water into the system. Thus, the experimental drug release kinetics were not in correlation with the theoretical profiles established by equations based on Fick's law.

In conclusion, new insight into the underlying drug release mechanisms of coated pellets have been gained and the importance of the type of drug and the nature of starter core for the resulting drug release kinetics were elucidated.

In the second part, the objective was to formulate another drug delivery system controlling the drug release only by diffusion through the intact polymeric film coating. The system was composed of pellets coated with a polymer blend Aquacoat ECD 30 and Eudragit NM 30 D. Diprophylline was used as model and was incorporated inside the core by extrusion-spheronisation. The drug release profiles of pellets coated with different ratios of polymer blend were evaluated and one was kept for the rest of the study. The ratio Aquacoat:Eudragit NM 20:80 was chosen and the underlying drug release mechanism was studied in the same way as the first part. The results didn't show any swelling and cracks. Finally, the experimental drug release profiles were in correlation with to the theoretical prediction established on a mathematical model.

To conclude, diprophylline was released by diffusion through the intact polymeric membrane from pellets coated with Aquacoat ECD:Eudragit NM 20:80.

In parallel, diprophylline loaded tablets coated with the same polymer blend ratio was formulated in order to study the impact of the dosage form. The drug release kinetics with the same weight gain (per surface) as coated pellets were studied. Unfortunately, the standard deviations were too high meaning that each tablet in the batch was singular. Indeed, the coating of cylindrical tablets can be difficult especially on the edges and consequently the thickness of the film coating was not homogeneous. Thus, no theoretical prediction was achieved due to a lack of time to improve the formulation of the coated tablets.

Keywords: coated pellets, drug release mechanisms, film coating.

RÉSUMÉ

L'objectif principal de ce travail est d'élucider les mécanismes contrôlant la libération de la substance active (SA) à partir de mini-granules enrobés.

Tout d'abord, des mini-granules enrobés avec du Kollicoat SR 30 D ont été formulés : une SA modèle (propranolol HCl) est déposée sur deux types de noyaux : à base de sucre et composés de cellulose microcristalline. Puis, une dispersion de Kollicoat SR plastifiée avec 10 % de TEC est appliquée sur ces derniers. L'impact de plusieurs facteurs comme le type et la taille des noyaux, l'épaisseur de l'enrobage, la nature de la substance active et sa concentration ont été évalués. L'objectif final est de prédire les cinétiques de libération en utilisant des équations mathématiques afin de faciliter le développement de nouveaux médicaments. Malheureusement, le système était plus complexe que prévu, particulièrement pour les mini-granules enrobés à partir d'un noyau de sucre.

Le premier résultat inattendu est le suivant : le propranolol HCl se libère plus lentement à partir de mini-granules à base de sucre comparé aux noyaux de cellulose microcristalline. Pour une meilleure compréhension, diverses expériences ont été menées : par exemple, l'étude de films polymériques libres, les profils de libération, l'évaluation des effets osmotiques, l'étude des cinétiques de libération à partir d'un seul mini-granule et leur gonflement, et de l'imagerie (MEB et micro tomographie à rayons X) pour une visualisation plus approfondie du système.

De façon intéressante, le sucre venant de la dissolution du noyau influence la cinétique de libération du propranolol HCl par une association de deux phénomènes : (i) l'effet plastifiant dû au sucre sur le film de Kollicoat SR et (ii) la diminution de la solubilité de cette SA dans le milieu de dissolution en présence de sucre dissous.

Ensuite, une autre molécule est utilisée, la théophylline, SA peu soluble dans l'eau et non influencée par la présence de sucre, afin d'évaluer le facteur prédominant entre les deux. Finalement, la diminution de la solubilité de la SA est le paramètre le plus impactant. De plus, le suivi de la cinétique de libération et du gonflement de mini-granules individuels combiné à l'imagerie ont révélés un phénomène fondamental : des fissures ont été clairement visibles par lesquelles le contenu du mini-granule est expulsé dans le milieu environnant. En résumé, le mécanisme impliqué dans la libération de la SA du système est le suivant : la libération du propranolol HCl à partir de mini-granules composés de noyaux de sucre et enrobés avec du Kollicoat SR est

contrôlée principalement par convection à travers des fissures dans le film de polymère.

La deuxième donnée inattendue est : lorsqu'on augmente la quantité en propranolol HCl dans le système, la cinétique de libération est augmentée, particulièrement avec les mini-granules composés de noyaux de cellulose microcristalline. Des fissures apparaissent certainement dans le film de Kollicoat SR. En outre, ajouter une quantité plus importante en propranolol HCl accélère leurs formations probablement due à l'activité osmotique de cette molécule qui attire beaucoup d'eau à l'intérieur du système. Ainsi, les profils de libération expérimentaux ne sont pas en corrélation avec ceux prédits à partir des équations de la loi de Fick.

En conclusion, des nouvelles connaissances sur les mécanismes de libération à partir de mini-granules enrobés avec du Kollicoat SR ont été apportées et l'importance du type de SA et la nature du noyau composant le système ont été élucidées.

Dans une deuxième partie, un autre système à libération contrôlée est formulé dans le but d'obtenir une libération de la SA seulement par diffusion à travers le film de polymère intact. Il s'agit de mini-granules enrobés avec un mélange de deux polymères Aquacoat ECD 30 et l'Eudragit NM 30 D. La diprophylline est utilisée comme SA modèle et est incorporée par extrusion-sphéronisation dans les noyaux. Différentes proportions de ce mélange de polymère ont été évaluées et un seul a été retenu pour le reste de l'étude, 20 % d'Aquacoat ECD et 80 % d'Eudragit NM. Ensuite, les mécanismes de libération de la diprophylline à partir de ce système ont été étudiés de la même façon que précédemment.

Les résultats n'ont pas révélé de gonflement ni de fissure dans le film de polymère. De plus, les profils expérimentaux de libération sont en corrélation avec ceux prédits montrant bien que la diprophylline est libérée par diffusion à travers le film d'enrobage.

En parallèle, des comprimés enrobés de même composition que les mini-granules ont été formulés afin d'étudier l'impact de la forme galénique. Les cinétiques de libération de la diprophylline ont été évaluées. Cependant, malgré des profils concluants, les écarts-types se sont montrés trop importants signifiant que chaque comprimé est différent. En effet, l'enrobage de comprimés cylindriques peut engendrer des difficultés surtout au niveau des arêtes où des défauts sont facilement présents formant ainsi un enrobage hétérogène. Donc, aucune prédiction à partir de

ce système n’a été mise en place due au manque de temps pour améliorer la formulation.

Mots-clés: mini-granules enrobés, mécanismes de libération, film de polymère.

PUBLICATIONS & PRESENTATIONS RESULTING FROM THIS WORK

Articles:

Fahier, J., Muschert, S., Fayard, B., Velghe, C., Byrne, G., Doucet, J., Siepmann, F., Siepmann, J., 2016. Importance of air bubbles in the core of coated pellets: Synchrotron measurements allow for new insights. *J. Control. Release* 237, 125-137.

Fahier, J., Muschert, S., Velghe, C., Byrne, G., Ward, R., Djemai, A., Siepmann F., Siepmann, J.
Osmotically driven drug release from coated pellets: Why sugar cores might lead to slower release rates compared to MCC cores. ***In progress.***

Posters:

Velghe, C., Fahier, J., Muschert, S., Ward, R., Djemai, A., Siepmann F., Siepmann, J.
Mathematical modeling of drug release from Kollicoat SR coated pellets.
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Fahier, J., Velghe, C., Muschert, S., Byrne, G., Siepmann, F., Siepmann, J.
Why increasing drug loadings might lead to faster drug release from Kollicoat SR coated pellets.
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Fahier, J., Velghe, C., Muschert, S., Byrne, G., Siepmann, F., Siepmann, J.
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9th Pharmaceutical Solid State Research Cluster (PSSRC) Annual Symposium, Ghent, Belgium, 2015.

UNIVERSITÉ DE LILLE ECOLE DOCTORALE – BIOLOGIE SANTÉ

THESE DE DOCTORAT

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FAHIER Julie

FILMS D'ENROBAGE POLYMERIQUE POUR DES FORMES GALENIQUES SOLIDES A LIBERATION CONTROLEE

Résumé :

Les mini-granules enrobés offrent un grand potentiel pour la libération contrôlée de médicament par voie orale. Cependant, les mécanismes de libération impliqués ne sont pas toujours élucidés et compris. Ainsi, l'impact de certains paramètres de formulation peut être surprenant. Par exemple, il a été démontré dans ce travail :

- La libération du propranolol HCl à partir de mini-granules enrobés avec du Kollicoat SR est plus lente si les mini-granules sont composés de noyaux de sucre comparé à des noyaux de cellulose microcristalline (CMC).

Généralement, la tendance inverse est observée, car les noyaux de sucre ont une activité osmotique attirant plus rapidement l'eau à l'intérieur du système et entrainant ainsi, une dissolution et diffusion de la substance active. Ce résultat inattendu est dû à une association de 2 phénomènes : (i) l'effet plastifiant dû au sucre sur le film de Kollicoat SR et (ii) la diminution de la solubilité de cette SA dans le milieu de dissolution en présence de sucre dissous.

De plus, le Kollicoat SR 30 D [dispersion aqueuse de poly(vinyl pyrrolidone)] offre des possibilités intéressantes de formulation par sa haute flexibilité et ses propriétés mécaniques stables. En revanche, les mini-granules composés de noyaux de sucre ont tendance à gonfler de par le cumul de l'activité osmotique du noyau et de la SA jusqu'à l'apparition de « cracks », révélés par des images obtenues par micro tomographie à rayons X.

- Lorsqu'on augmente la quantité en propranolol HCl dans le système, la cinétique de libération est augmentée, particulièrement avec les mini-granules composés de noyaux de CMC.

L'opposé est souvent constaté car accroitre la quantité de SA nécessite un plus grand apport en eau afin de pouvoir tout dissoudre. Les mini-granules à base de CMC présentent probablement des « cracks » malgré un faible gonflement du système, et sont accentués par l'augmentation de la concentration en propranolol HCl.

En conclusion, des nouvelles connaissances sur les mécanismes de libération à partir de mini-granules enrobés avec du Kollicoat SR ont été apportées et l'importance du type de SA et la nature du noyau composant le système ont été élucidées.

Dans une deuxième partie, des mini-granules enrobés avec un mélange de polymère (Aquacoat ECD et Eudragit NM 30 D) ont été formulés dans le but de libérer la diprophylline, SA modèle, par diffusion à travers le film de polymère et de pouvoir modéliser sa cinétique à partir de modèles mathématiques.

Mots-clés: mini-granules enrobés, mécanismes de libération, film d'enrobage.