Modification of Mechanical Properties of Ethylcellulose Film with Cassava Starch Nanocrystals

Anuradha Wickramanayaka* Dr.Nattawut Charoenthai** Dr.Kittiwut Kasemwong***
Dr.Satit Puttipipatkhachorn****

ABSTRACT

Ethylcellulose (EC) is a frequently used polymer in rupturable pulsatile drug delivery systembut its high sensitivity of coating level on the lag time causes the less robust coating system.Theobjective of this study was to modify mechanical properties of EC film withcassava starch nanocrystals.The results revealed that with increasing amount of cassava starch nanocrystals, the ECfilms with lower puncture strength, higherwater uptake and weight loss,and faster rate of water vapor permeation were obtained. These results were similar to the addition of magnesium stearate to ECfilm. In conclusion, cassava starch nanocrystals could improve mechanical properties of EC films, indicating a high potential to be used as a modifier for rupturablefilm for pulsatile drug delivery system.

Keywords: Ethylcellulose, Nanocrystals, Film

* *Student, Master of Science Program in Pharmaceutics, Faculty of Pharmacy, Mahidol University*

** *Lecturer, Department of Manufacturing Pharmacy, Faculty of Pharmacy, Mahidol University*

*** *Senior Researcher, National Nanotechnology of Thailand, National Science and Technology Development Agency*

**** *Associate Professor, Department of Manufacturing Pharmacy, Faculty of Pharmacy, Mahidol University*

Introduction

Pulsatile delivery systems are non-conventional dosage forms designed to release anactive ingredient after a well-defined lag-time (Maroni et al., 2010; Maroni et al., 2013; Wilson and Basit, 2005). This is time- and site-specific drug delivery, thus providing spatial and temporal delivery and increasing patient compliance. Humans exhibit endogenous circadian rhythms that are regulated by the master circadian clock of the body. Chronopharmacotherapy of diseases, e.g., bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer and hypertension that show circadian rhythms in their pathophysiology and treatment of such diseases require pulsatile drug delivery systems, by which drug is released rapidly and completely as a pulse after a lag time. Drugs that produce biological tolerance demand a system that will prevent their continuous presence and this tends to reduce their therapeutic effect (Bussemer et al., 2001). The lag time is essential for drugs that undergo degradation in gastric acidic medium (e.g., peptide drug) and irritate the gastric mucosa (Saigal et al., 2009). Targeting a drug to a distal organ of gastrointestinal tract (GIT), like the colon, requires that the release is prevented in the two-third portion of the GIT. All the above attributes can be taken into account in designing a delivery system that exhibits pulsatile release characteristics and releases the drug in a predetermined fashion at a particular site.

The earliest pulsatile delivery formulations were devised as multi-layer tablets partially enclosed in an impermeable shell, a timed controlled liberation of orally administered bioactive compounds is currently achieved mainly by the application of a functional polymeric coating to a drug-containing core (Maroni et al., 2013). The core may either be a single or a multiple unit dosage form. The performance of the coating strictly depends on the relevant physico-chemical nature and is started on exposure to the aqueous biological fluids. Accordingly, rupturable, erodible, permeable and semipermeable layers can be distinguished.

Ethylcellulose(EC) is a frequently used polymer in rupturable pulsatile delivery system, because of its water insolubility, semi-permeability, adjustable water permeability and mechanical properties (Bussemer et al., 2003). This is also a brittle material with sufficient strength to withstand mechanical stress after a certain period of time. EC is made by chemical substitution of the naturally occurring polymer, cellulose. The molecule has a structure of repeating anhydroglucose units and each anhydroglucose unit has three reactive hydroxyl sites. The hydroxyl groups of cellulose can partially or fully react with various chemicals to provide derivatives with useful properties.

Many modifications of ECfilm can be identified in pulsatile drug delivery system including composite polymer blends. The use of composite polymers with ECcan offer major advantages, including: (i) adjusting of desired drug release patterns (ii) improving film formation and storage stability (iii) developing site specific drug delivery within the gastrointestinal tract (e.g., colon targeting) (Muschert et al., 2009; Siepmann et al., 2007). Moreover, because of the high sensitivity of the pure ECcoating level on the lag time, these modifications will be advantageous to develop a less sensitive and more robust coating system (Sungthongjeen et al., 2004).

Starch is a mixture of two main components, amylose, a linear or slightly branched (1⟶4)-α-D-glucan, and amylopectin, a highly branched

macromolecule consisting of (1⟶4)-α-D-glucan short chains linked through α-(1⟶6) linkages (Wilson and Basit, 2005). All starches are biosynthesized as semicrystalline granules containing densely packed polysaccharides and a small amount of water. The conventional model for the inner structure of starch is that it is formed from two regions, crystalline and amorphous lamellae, which together form the crystalline and amorphous growth rings. In crystallites of starch, parallel stranded double helical structure is found in pairs, and all chains are packed in arrays. The pair of double helices is identical in both polymorphs and corresponds to the interaction between double helices that has the lowest energy. The crystalline regions of starch granules can be isolated by mild acid hydrolysis using hydrochloric or sulfuric acid (Zhu, 2015). It is believed that at temperatures below gelatinization temperature acid molecules preferentially attack the amorphous regions of the granule resulting in these regions being more rapidly hydrolyzed than the crystalline regions. The residue after acid hydrolysis contains the starch nanocrystals which have high crystallinity and nanoscale platelet morphology. There are two major groups of dextrins in the nanocrystals with average degrees of polymerization of 12.2 and 31.7. The distribution of branched molecules in the two dextrin populations suggests that the starch nanocrystal possesses a regular and largely homogeneous molecular structure (Zhu, 2015). Starch is abundantly available in developimg counties and it also cheap compared to other polymers which are used as secondary polymers in rupturable pulsatile drug delivery system.

In this experiment different amounts of starch nanocrystals were incorporated to EC as a modifier of EC film. The water uptake, weight loss, mechanical properties, and water vapor permeation of thin films were investigated.

Objective of the study

The aim of this study was to investigate starch nanocrystals as a modifier in the rupturableEC film for pulsatile drug delivery system.

Materials and Methods

Preparation of thin polymeric films

The free films and composites films were prepared by casting the ethanolic polymer solution on to the Teflon sheets mounted on a leveled glass plate. (area of casting 14 cm x 14 cm; amount of casting = 25g). In free film total EC 3.0 g and plasticizer 0.30 g (10% w/w based on polymer) were used. ECwas dissolved in 96 vol.% ethanol for 6 hours and 10% of dibutylsebacate(DBS) was added as a plasticizer in to the ethanolic solution of ECand further mixing was done for 30 minutes prior to casting. For composite films different ratios of ECand starch nanocrystals were constituted as 90:10, 85:15, 80:20 and 75:25 w/w(DBS 10% w/w based on polymer) were used. Both polymers were blended in 96 vol.% ethanol for 6 hours and further mixing was done with 10% DBS plasticizer for 30 minutes. The films were dried for 24 hours at 15 ^{o}C under special cover to reduce solvent evaporation in order to attain the homogeneous films. Dried films were peeled out and incubated in the oven at 50 ^{o}C for 12 hours. The films were cut into 6.5 cm x 6.7 cm test sections and were kept in a desiccator containing a saturated aqueous magnesium nitrate solution (55% RH). Then the desiccator was kept in a chamber at 25±0.5 ^{o}C for 2 days before testing.

Film characterization

The thicknesses of the films were measured (10 points for each sample, n=5) using a thickness

gauge (Minitest 600; Erichsen, Hemer, Germany). The mean thicknesses of all films were 141.2 ± 4.6 μm. The water uptake and weight loss kinetics of the films were measured gravimetrically upon exposure to simulated gastric and intestinal fluids of pH 1.2 and pH 6.8, respectively. The test was conducted as follow: pieces of films 1 cm x 2 cm were placed into disintegration apparatus (Hanson QC 21, CA, USA) filled with media, followed by horizontal shaking at 37°C (30 rpm). At pre-determined time points, samples were withdrawn, excess water was removed, the films were accurately weighed (wet mass) and dried to constant weight at 50°C (dry mass). The water uptake (%) and weight loss (%) at time t were calculated as follows:

$$\text{Water uptake (\%)(t)} = \frac{\text{wet mass (t)} - \text{dry mass (t)}}{\text{dry mass (t)}} \text{ x } 100$$

$$\text{Weight loss (\%)(t)} = \frac{\text{dry mass (t)}}{\text{dry mass (t = 0)}} \text{ x } 100$$

Mechanical properties of thin films

The mechanical properties of free films in the dry state were determined by a texture analyzer (TAXT.Plus, WinopalForschungsbedarf, Ahnsbeck, Germany). Film specimens were mounted on a film holder (n = 6). 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. Load versus displacement curves were recorded until the rupture of the film and used to determine the mechanical properties as follows:

$$\text{Puncture strength} = \frac{F}{A}$$

where F is the load required to puncture the film and A is the cross-sectional area of the edge of the film located in the path.

$$\text{\% elongation at break} = \frac{\sqrt{R^2 + D^2} - R}{R} \text{ x } 100$$

where R denotes the radius of the film exposed in the cylindrical hole of the holder and D is the displacement.

$$\text{Energy at break per unit volume} = \frac{AUC}{V}$$

where AUC is the area under the load versus displacement curve and V is the volume of the film located in the die cavity of the film holder.

Water vapor permeation of thin films

This test was carried out by gravimetrically. Disks were punched from the films, placed on open 30 mL glass vials containing 12.5 g of activated silica gel beads and the vials were held in place with lids having an 11.3 mm diameter of test area (1.003 cm^2). The vials were then placed in a desiccator containing silica gel for 12 hours and then were placed in a desiccator containing saturated aqueous sodium chloride solution (75 % RH). The desiccator was kept in a chamber at 25±0.5 °C. The weight changes were recorded periodically at 0, 2, 8, 12, 24 and 72 hours and average value of triplicate was recorded.

The water vapor permeation rate was obtained from the slope of relationship between the amount of water permeated and time. The water vapor coefficient of the film was calculated using the following equation.

$$\text{Water vapor permation coefficient} = \frac{Mh}{A\Delta P_v}$$

where M is the WVP rate, h is the mean thickness of the film, A is the area of the exposed film, and ΔP_v is the vapor pressure difference.

Results and Discussion

Water uptake and weight loss of thin films

The permeability of a polymeric film coating strongly depends on its water content. In a dry system,

the diffusion coefficients approach zero (Karrout et al., 2009a).With increasing water content, the mobility of the macromolecules increases and, thus, also the mobility of incorporated drug molecules increases. Fig. 1(a)& 1(b) shows the gravimetrically measured water uptake of thin polymeric films based on the different ratios of ECand starch nanocrystals blends upon exposure to simulated gastric fluid pH 1.2 and simulated intestinal fluid pH 6.8, respectively at 37 ^{o}C.Remarkably, the polymer blend ratio affected the resulting water penetration rate and extent. With increasing starch nanocrystals content, the amount of water taken up as well as the rate of this mass transport step was increased.

This phenomenon can be attributed to the more hydrophobic nature of EC compared to the starch nanocrystals. Thus, it can be expected that the mobility of a drug within this type of polymeric films significantly increases with increasing starch nanocrystals contents. There was no distinguishable difference in percentage of water uptake of the investigated films in simulated gastric acid pH 1.2 and simulated intestinal fluid pH 6.8.In addition to the water uptake kinetics, the weight loss behavior of polymeric films offers important insight into the latter's ability to suppress or allow drug release (Karrout et al., 2009b).

The effects of the EC: starch nanocrystals composite blend ratio on the resulting weight loss of thin films upon exposure to simulated gastric acid pH 1.2 and simulated intestinal fluid pH 6.8 are illustrated in Fig. 2(a) &2(b), respectively. Obviously, both the rate and the extent of the weight loss increased with increasing starch nanocrystals contents. This could at least partially be attributed to the leaching of this compound out into the bulk fluids. Due to the increasing water uptakes of the systems (Fig. 1), the mobility of the polymer chains increases and, thus, also cause to mobility of the starch nanocrystals into bulk media. Importantly, the dry mass loss is limited in all cases, and the presence of the water-insoluble EC in the

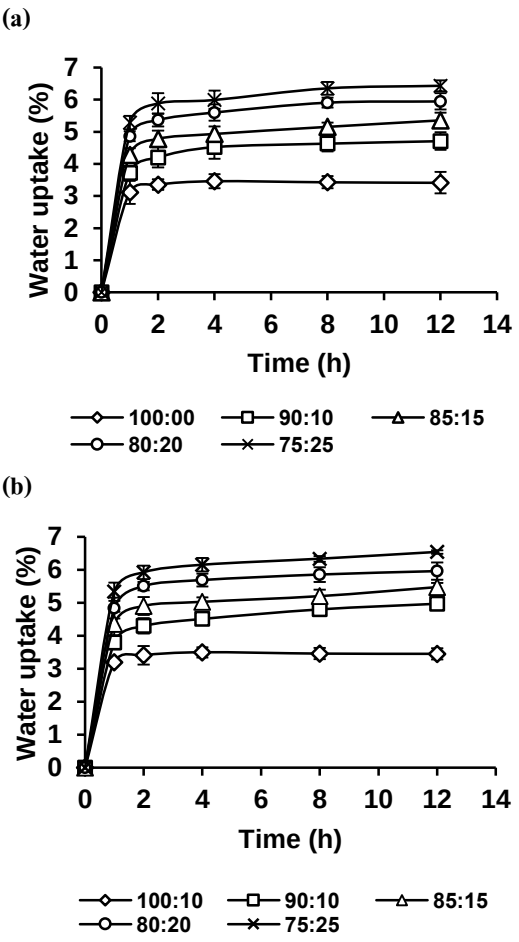

Figure 1 Water uptake of thin films consisting of EC: starch nanocrystals (the ratio is indicating in the figures) upon exposure to (a) simulated gastric fluid pH 1.2 and (b) simulated intestinal fluid pH 6.8 (DBS content, referred to polymer mass:10% w/w).

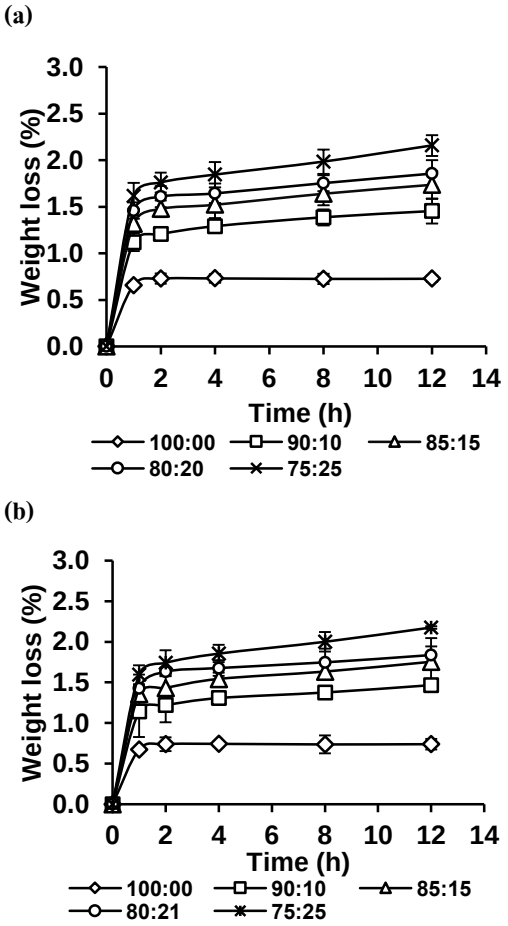

Figure 2 Weight loss of thin films consisting of EC: starch nanocrystals (the ratio is indicating in the figures) upon exposure to (a) simulated gastric fluid pH 1.2and (b) simulated intestinal fluid pH 6.8 (DBS content, referred to polymer mass:10% w/w)

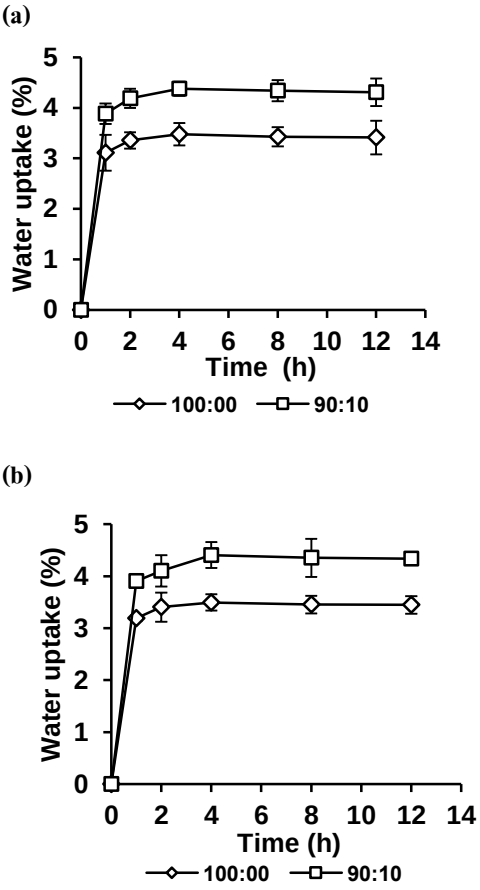

Figure 3 Water uptake of thin films consisting of EC: magnesium stearate (the ratio is indicating in the figures) upon exposure to (a) simulated gastric fluid pH 1.2and (b) simulated intestinal fluid pH 6.8 (DBS content, referred to polymer mass: 10% w/w).

films effectively hinders the leaching of the starch nanocrystals into the bulk fluids.

Fig. 3(a) &3(b) shows the gravimetrically measured water uptake of thin polymeric films based on EC: magnesium stearate (90:10) blends upon exposure to simulated gastric fluid pH 1.2 and simulated intestinal fluid pH 6.8 at 37 ^{o}C. The percentage of water uptake of the EC film containing magnesium stearate was higher than that of the EC film. A possible explanation was that the film containing magnesium stearate had more porous structure according to the phase separation of the filler(Sungthongjeen et al., 2004). Furthermore, there was no significant difference in % water uptake in these two media.

Mechanical properties of thin films

In addition to limited water uptake and weight loss in the upper GIT, a polymeric film coating

providing site-specific drug delivery must be sufficiently (mechanically) stable in order to avoid accidental crack formation due to the shear stress encountered in the stomach and small intestine *in vivo*(Karrout et al., 2009a). In addition, significant hydrostatic pressure might be built up within a coated dosage form due to the penetration of water into the system upon contact with aqueous body fluids. The presence/absence of somatically active drugs and/or excipients in the core formulation can strongly affect the importance of this phenomenon. Fragile film coatings are likely to rupture because of such shear forces from outside (caused by the motility of the GIT) and hydrostatic pressures from inside (caused by water penetration) they are exposed to. In order to be able to estimate the risk of such accidental crack formation, the energy required to break, puncture strength and percentage of elongation the investigated EC: starch nanocrystals composite films were measured in dry state using a texture analyzer. Fig. 4(a) &4(b) indicates the puncture strength and energy at break (mechanical stability) of thin EC: starch nanocrystals films (plasticized with 10% (w/w) DBS, referred to the ECcontent) in the dry state at room temperature as a function of the polymer blend ratio. Clearly, the energy at break of the films and tensile strength significantly were decreased with increasing starch nanocrystals content, indicating that made mechanically weak film under these conditions. It was observed that when adding the starch nanocrystals this may lead to break the ECpolymerinterchain interactions. This would be desirable for rupture of the coating of pulsatile drug delivery system. The film weakness can also be proved with the data of % elongation. According to Fig. 4(c) (% elongation), when increased the amount of starch nanocrystals films were ruptured at low probe

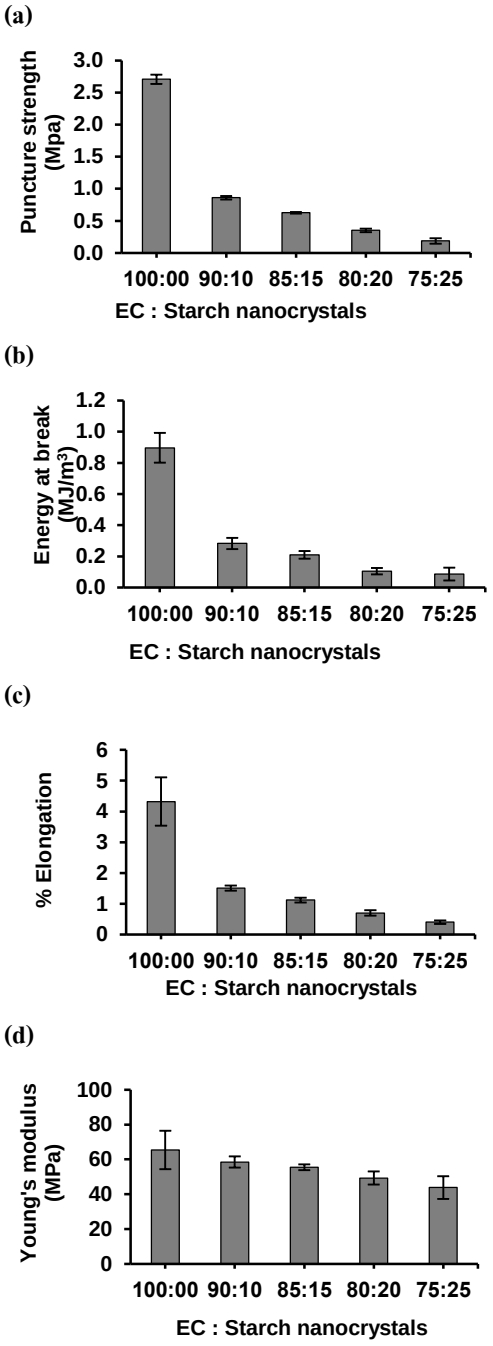

Figure 4 Effect of EC: starch nanocrystals blend ratio on (a) puncture strength, (b) energy at break, (c) % Elongation, and (d)Young's modulus (DBS content, referred to polymer mass:10% w/w).

displacement and resulted in a lower % elongation. This low % elongation can also be an advantageous to ensure a complete rupture in a rupturable pulsatile drug delivery system.

The addition of hydrophobic particulate material, magnesium stearate reduced the puncture strength and energy at break dramatically in dry state (Table 1). These results may be due to a reduced interaction between polymer chains by hydrophobic particles. The % elongation of the EC film with magnesium stearate significantly was decreased (Table 1). It was indicated that flexibility of the film was reduced.

Table1 Mechanical properties of EC and EC with magnesium stearate (90:10 w/w) films (DBS content, referred to polymer mass:10% w/w).

EC:MgStrfilms	Puncture strength (MPa)	Energy at break (mJ/m^3)	%Elongation (%)
100:00	2.71 ± 0.07	0.90 ± 0.10	4.31 ± 0.79
90:10	0.26 ± 0.03	0.10 ± 0.01	0.71 ± 0.23

Water vapor permeation of thin films:

The effects of the EC: starch nanocrystals composite blend ratios on the resulting water vapor permeation coefficient of thin films were illustrated in Fig.5. Clearly, the rate of water vapor permeation coefficient was increased with the higher amount of increasing starch nanocrystals contents. It was demonstrated that the addition of starch nanocrystals causes EC to reduce its hydrophorbicity and forms mechanically weak and soft films. Furthermore starch nanocrystals modify the polymer network more porous.

Conclusion

Cassava starch nanocrystals could improve mechanical properties of EC films, indicating a high potential to be used as a modifier for rupturable film for pulsatile drug delivery system.

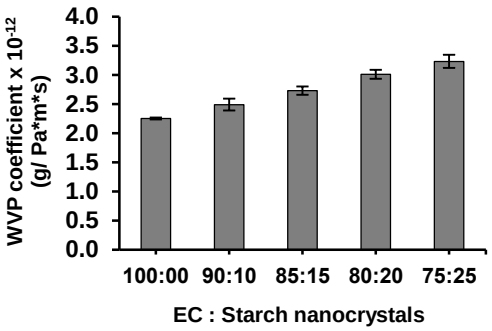

Figure 5 Water vapor permeability (WVP) of thin films consisting of EC: starch nanocrystals (DBS content, referred to polymer mass:10% w/w).

Acknowledgements

This study was granted by Thailand International Development Cooperation Agency (TICA) and Mahidol University, Thailand

References

Bussemer T, Dashevsky A, Bodmeier R. A pulsatile drug delivery system based on rupturable coated hard gelatin capsules. J Control Release. 2003;93(3):331-9.

Bussemer T, Otto I, Bodmeier R. Pulsatile drug-delivery systems. Crit Rev Ther Drug Carrier Syst. 2001;18(5):433-58.

Karrout Y, Neut C, Wils D, Siepmann F, Deremaux L, Desreumaux P, et al. Novel polymeric film coatings for colon targeting: how to adjust desired membrane properties. Int J Pharm. 2009;371(1-2):64-70.

Karrout Y, Neut C, Wils D, Siepmann F, Deremaux L, Flament MP, et al. Novel polymeric film coatings for colon targeting: Drug release from coated pellets. Eur J Pharm Sci. 2009;37(3-4):427-33.

Maroni A, Zema L, Del Curto MD, Loreti G, Gazzaniga A. Oral pulsatile delivery: rationale and chronopharmaceutical formulations. Int J Pharm. 2010;398(1-2):1-8.

Maroni A, Zema L, Loreti G, Palugan L, Gazzaniga A. Film coatings for oral pulsatile release. Int J Pharm. 2013;457(2):362-71.

Muschert S, Siepmann F, Leclercq B, Carlin B, Siepmann J. Drug release mechanisms from ethylcellulose: PVA-PEG graft copolymer-coated pellets. Eur J Pharm Biopharm. 2009;72(1):130-7.

Saigal N, Baboota S, Ahuja A, Ali J. Multiple-pulse drug delivery systems: setting a new paradigm for infectious disease therapy. Expert opin drug deliv. 2009;6(4):441-52.

Siepmann F, Hoffmann A, Leclercq B, Carlin B, Siepmann J. How to adjust desired drug release patterns from ethylcellulose-coated dosage forms. J Control Release. 2007;119(2):182-9.

Sungthongjeen S, Puttipipatkhachorn S, Paeratakul O, Dashevsky A, Bodmeier R. Development of pulsatile release tablets with swelling and rupturable layers. J Control Release. 2004;95(2):147-59.

Wilson PJ, Basit AW. Exploiting gastrointestinal bacteria to target drugs to the colon: an in vitro study using amylose coated tablets. Int J Pharm. 2005;300(1-2):89-94.

Zhu F. Composition, structure, physicochemical properties, and modifications of cassava starch. CarbohydrPolym. 2015;122:456-80.