IN VITRO RELEASE TESTING OF MATRICES BASED ON STARCH-METHYL METHACRYLATE COPOLYMERS: EFFECT OF TABLET CRUSHING FORCE, DISSOLUTION MEDIUM pH AND STIRRING RATE

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Abstract

Direct-compressed matrix tablets were obtained from a variety of potato starch-methyl methacrylate copolymers[1] as sustained-release agents, using anhydrous theophylline as a model drug. The aim of this work was to investigate the influence of the copolymer type, the tablet crushing force and dissolution variables such as the pH of the dissolution medium and the agitation intensity on the *in vitro* drug release behaviour of such matrices. Commercial sustained-release theophylline products (Theo-Dur® 100 mg, Theolair® 175 mg) were used as standards. Test formulations were compacted into tablets at three different crushing force ranges (70-80, 90-100 and 110-120 N) to examine the effect of this factor on the porous network and drug release kinetics. *In vitro* release experiments were conducted in a pH-changing medium (1.2-7.5) with basket rotation speeds in the range 25-100 rpm to simulate the physiological conditions of the gastrointestinal tract. The release rate of theophylline was practically not affected by pH in the case of Theo-Dur® and HSMMA matrices. In contrast, Theolair® and CSMMA tablets demonstrated a biphasic drug release pattern, which appeared to be sensitive to the pH of the dissolution medium. An increase in the crushing force of the copolymer matrices was accompanied by a reduction of the matrix porosity, although the porous network depends markedly on the type of copolymer, having a strong influence on the drug release kinetics. Mathematical modelling of release data shows a Fickian diffusion or anomalous transport mechanism. Based on the similarity factor f_2, FD-HSMMA, OD-CSMMA and FD-CSMMA at 90-100N were selected for agitation studies. In general, all formulations showed an agitation speed-dependent release, with Theo-Dur® and FD-CSMMA matrices being the less susceptible to this factor.

Keywords: Potato starch-methyl methacrylate copolymers, Anhydrous theophylline, Sustained-release matrix tablet, Drug release kinetics, Tablet crushing force, pH-changing medium, Stirring rate.

[1] OD-HSMMA: oven-dried hydroxypropylstarch methyl methacrylate; FD-HSMMA: freeze-dried hydroxypropylstarch methyl methacrylate; OD-CSMMA: oven-dried carboxymethylstarch methyl methacrylate; FD-CSMMA: freeze-dried carboxymethylstarch methyl methacrylate

1. Introduction

Among the different approaches for oral sustained-release dosage forms, matrix tablets (Ceballos et al., 2005) are of major interest to the pharmaceutical industry because of their highly efficient manufacturing technology. Polymers (natural, synthetic and semi-synthetic) are the basic ingredients-carriers of these systems and their nature and characteristics may play an essential role and significantly influence the behaviour of these devices (Efentakis and Politis, 2006).

Over the past two decades, a new generation of physically and/or chemically modified starches has been introduced as matrix-forming excipients for oral sustained-release dosage forms. Different techniques such as pre-gelatinization (Odeku et al., 2008), cross-linking (Lenaerts et al., 1998), substitution (Assaad and Mateescu, 2010), complexation (Clausen and Bernkop-Schnürch, 2001), grafting (Ferrero et al., 2003) or a combination thereof (Mulhbacher et al., 2004) have been applied to alter these native biopolymers, improving both their compaction and extended-release properties.

Concerning grafting, copolymers combining potato starch derivatives (hydroxypropylstarch HS, carboxymethylstarch CS) and methyl methacrylate (MMA) have been investigated thoroughly over the last years. These materials were synthesised by free-radical polymerization (Castellano et al., 1997) and either dried in a vacuum oven or freeze-dried. The characterisation of these copolymers in terms of physico-chemical structure, particle size and morphology, thermal properties, flowability, moisture uptake, compression behaviour and porosity (Bravo-Osuna et al., 2005; Castellano et al., 1997; Ferrero et al., 1999; Ferrero and Jiménez-Castellanos, 2002) revealed promising properties as directly compressible excipients with a significant influence of the carbohydrate nature and/or the drying process. Moreover, the introduction of MMA changed the nature of starch from hydrophilic to more hydrophobic, inhibiting the characteristic swelling and gel layer formation of native starches. Consequently, the materials form, under compression, inert matrices able to control the release of the model drug

(anhydrous theophylline) by a diffusion mechanism through the matrix porous structure (Ferrero et al., 2003).

The release of drugs from an inert matrix depends on several factors such as polymer nature and content, drug loading and solubility, polymer and drug particle size, matrix additives, tablet porosity and tortuosity (Salomon and Doelker, 1980). Due to its influence on the porous network, the compression force is probably the main formulation parameter affecting the rate of release from such matrices.

In addition to formulation variables, the complex environment of the gastrointestinal tract (GI) could affect the availability of the drug from the tablet. Therefore, in the design of the *in vitro* dissolution tests for sustained release dosage forms, physiologic aspects such as pH and motility (agitation intensity) through the GI tract should be considered. Ideally, an oral sustained-release product should not be excessively sensitive to varying gastrointestinal conditions (Jorgensen and Bhagwat, 1998).

The purpose of this study is thus to investigate the influence of some dissolution tests conditions on the *in vitro* drug release behaviour of theophylline from matrix systems based on potato starch-methyl methacrylate copolymers in order to predict its *in vivo* performance. Therefore, the effect of pH of the dissolution medium and agitation rate on the drug release kinetics is evaluated. Furthermore different tablet crushing forces are tested to evaluate the influence of the porous network on the drug release behaviour of such matrices. The results obtained will be compared with two commercially available sustained release formulations of theophylline: Theo-Dur® (pH-independent release) and Theolair® (pH-dependent release).

2. Materials and methods

2.1. Materials

Copolymers (batches SS03) were synthesised by free-radical polymerization of methyl methacrylate (MMA) on two different potato starch derivatives (hydroxypropylstarch HS,

carboxymethylstarch CS) using Ce (IV) as an initiator. The preparation of the grafted copolymers (HSMMA, CSMMA) was described in detail by Castellano et al. (1997). The products were alternatively dried by two different methods: drying in a vacuum oven (6.67-13.33 hPa) at 50º C until constant weight (OD copolymers) or freeze-drying (freezing process at -20ºC for 24 h and sublimation process at 0.13 hPa and -50°C) (FD-copolymers). OD-CSMMA was crushed in a knives mill (Retsch, Haan, Germany) to obtain powdery samples.

Anhydrous theophylline (Roig Pharma, Barcelona, Spain, batch 0101072) was chosen as the model drug since its solubility is relatively little affected by pH in the normal physiological range (Shangraw, 1988). Stearic acid (Estearina® L2SM, Pulcra, Barcelona, Spain, batch 0055003) was selected as a lubricant.

Before use, materials were stored at constant relative humidity (40%) and room temperature (20ºC).

Two commercial sustained-release formulations, Theo-Dur® (100 mg theophylline tablets, Pharmacia & Upjohn S.A., Barcelona, Spain) and Theolair® (175 mg theophylline tablets, 3M España S.A., Madrid, Spain) were used as reference products.

2.2. Methods

2.2.1. Mixtures preparation

For preliminary pH studies, the composition of the mixtures agreed with that reported in our previous research (Ferrero et al., 2003). Therefore, anhydrous theophylline (24%, w/w) and copolymers (75%, w/w) were mixed for 15 min using a double-cone mixer (Retsch, Haan, Germany) at 50 r.p.m. After addition of stearic acid (1%, w/w), the mixing procedure was continued for another 5 min.

Once the pH-dependent or independent character of these formulations was established, doses of 100 or 175 mg theophylline were selected for comparative purposes with the commercial preparations. Hence, anhydrous theophylline (20%, w/w) and copolymers (79%, w/w) were

mixed for HSMMA formulations, and anhydrous theophylline (35%, w/w) and copolymers (64%, w/w) were mixed for CSMMA formulations. The proportion of stearic acid was maintained constant (1%, w/w) in all cases.

2.2.2. Preparation of tablets

The different mixtures were compacted into tablets using an instrumented (Muñoz-Ruiz et al., 1995) single punch tablet machine (Bonals AMT 300, Barcelona, Spain) running at 30 cycles/min. To investigate the compression characteristics of the mixtures, a quantity of powder (500 mg) was pre-weighed and manually fed into the die (12 mm) and flat-faced compacts were prepared at three different crushing force ranges (70-80, 90-100, 110-120 N). Compression data were collected from four tableting cycles.

In order to produce a sufficient number of tablets for physical testing, the machine was equipped with a forced feeding system and the mixtures were tableted in the same conditions outlined before (500 mg weight, 12 mm diameter, 70-80, 90-100 or 110-120 N crushing force).

2.2.3. Standard physical test of tablets

The physical testing of tablets was performed 24h after production to allow for stress relaxation.

The tablet average weight and the standard deviation (SD) were obtained from 20 individually weighed (Mettler LJ16 analytical balance, Zürich, Switzerland) tablets according to the European Pharmacopoeia (2011).

The thickness of 10 tablets was measured individually using an electronic micrometer (Mitutoyo MDC-M293, Tokyo, Japan).

The crushing force (European Pharmacopoeia, 2011) of 10 tablets was determined by diametral loading with a texture analyser TA-XT2i (Stable Micro Systems, Surrey, UK).

Tablet friability (European Pharmacopoeia, 2011) was calculated as the percentage weight loss of 20 tablets after 4 min at 25 rpm in an Erweka TA (Heusenstamm, Germany) friability tester.

2.2.4. Mercury porosimetry measurements

Mercury porosimetry runs were undertaken using a Quantachrome Autoscan 33 (Boyton Beach, FL, USA) porosimeter with a 3 cm^3 penetrometer. The volume of sample was roughly 10-30% of the penetrometer capacity. Working pressures covered the range 0.5-33000 psi and the mercury solid contact angle and surface tension were assumed to be 140º and 480 $mN \cdot m^{-1}$, respectively. Total porosity and pore size distribution were determined, in duplicate, for each tablet tested.

2.2.5. *In vitro* drug release studies

Release experiments (six tablets) were performed in an automatic dissolution apparatus 1 (Aidec, Barcelona, Spain) (European Pharmacopoeia, 2011) as a function of time (8.5 h). In order to simulate the fasting *in vivo* environment (Ashford, 2002; FDA, 1997; Jorgensen and Bhagwat, 1998), experiments were run at 37 ± 0.5 °C using the following dissolution media (500 mL) and residence times (sequential pH change method): 0.1N HCl (pH 1.2) for 1.5h; phosphate buffer (pH 2.5) for 1.5h; phosphate buffer (pH 4.5) for 1.5h; phosphate buffer (pH 7.0) for 3h and phosphate buffer (pH 7.5) for 1h. The ionic strength of the solutions was adjusted to 0.1 adding KCl.

To evaluate the effect of the hydrodynamic conditions on the drug release profiles, four basket rotation speeds were tested: 25, 50, 75 and 100 r.p.m. This range would cover the agitation intensity in the human GI tract (Katori et al., 1995).

Filtered samples (2.8 ml) were withdrawn at regular time intervals via a peristaltic pump (Hewlett-Packard 89079A, Waldbronn, Germany). Theophylline release was monitored continuously at 272 nm on a Hewlett-Packard 8452A diode-array UV-vis spectrophotometer (Waldbronn, Germany). Cumulative corrections were made for the previously removed samples when determining the total amount released.

Drug release data ($M_t/M_\infty \leq 0.6$) were analysed according to Higuchi (1963) [1], Korsmeyer et al. (1983a) [2] and Peppas and Sahlin (1989) [3] equations:

$$M_t / M_\infty = kt^{1/2} \qquad [1]$$

$$M_t / M_\infty = k't^n \qquad [2]$$

$$M_t / M_\infty = k_d t^m + k_r t^{2m} \qquad [3]$$

where M_t/M_∞ is the drug released fraction at time t (the drug loading was considered as M_∞); k and k' are kinetic constants characteristic of the drug/polymer system; t is the release time; n is the release exponent that depends on the release mechanism and the shape of the matrix tested (Ritger and Peppas, 1987); k_d and k_r are the diffusion and relaxation rate constants, respectively; m is the purely Fickian diffusion exponent for a device of any geometrical shape which exhibits controlled release.

The optimum values for the parameters present in each equation were determined by linear or non-linear least-squares fitting methods with SPSS® 18.0 software. The determination coefficient (r^2) and the F-ratio probability were used as criteria to evaluate the fit of the different models considered.

In addition, the similarity between drug release profiles from copolymer matrices and commercial products was established by means of the similarity factor, f_2, a model-independent approach (EMEA, 1999) [4]:

$$f_2 = 50 \cdot \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n}\left(R_t - T_t\right)^2\right]^{-0.5} \cdot 100\right\} \qquad [4]$$

where n is the number of experimental points in the *in vitro* dissolution assay; R_t and T_t are the mean percentages of dissolved drug from the reference and test formulations, respectively, at each time point t. Not more than one sampling time point after 85% dissolution was considered.

The Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMEA) (EMEA, 1999; FDA, 1997) recommend the use of f_2 and ensure that two dissolution profiles are declared similar if f_2 is between 50 and 100.

3. Results and discussion

3.1. Preliminary studies in pH-changing medium

This first series of experiments was used as a screening procedure to investigate the influence of the dissolution media on the *in vitro* drug release. Figure 1 illustrates the drug release profiles from HSMMA and CSMMA matrices (drug dose = 120 mg) and the commercial preparations in a pH-changing medium. Theo-Dur® (drug dose = 100 mg) and Theolair® (drug dose = 175 mg) were chosen as reference products because of their, respectively, pH-independent and pH-dependent drug release (Crombeen and De Blaey, 1983; Munday and Fassihi, 1995; Ochoa et al., 2010; Shangraw, 1988).

Two different behaviours can be distinguished. HSMMA and Theo-Dur® tablets show a uniform release pattern over the entire range of pH. Conversely, CSMMA and Theolair® release profiles are characterised by a discontinuity over pH 7.0, more noticeable for the marketed product. As theophylline (pK_a = 8.8) has an almost constant solubility between pH 2 and 7.5 (Park et al., 2008), the increase in the release rate could be attributed to the presence of ionizable groups in the polymers chains.

From Figure 1, it can be inferred that drug release rates from Theo-Dur® and Theolair® are similar until pH 4.5. Nevertheless, when Theolair® tablets are immersed in a pH 7 medium, a jump in release rate is observed and the tablets are practically dissolved at the end of the dissolution test. Theolair® is formulated in the form of theophylline tablets containing lactose and coated with cellulose acetate phthalate (CAP) (Crombeen and De Blaey, 1983; Shangraw, 1988). The carboxylic groups of CAP coating are not ionized at acid pH, maintaining the compact structure of the tablets and slowing the water uptake, which results in a prolonged drug release. When pH is above 6-7, the ionization of carboxylic groups is evident and the polymer chains relaxation leads to the dissolution of the CAP coating. As a consequence, lactose rapidly dissolves and the drug release rate increases considerably. CAP is also present in TheoDur® formulation but coating the theophylline pellets that are then compressed in a waxy matrix

containing additional drug (Munday and Fassihi, 1995; Shangraw, 1988), so the presence of the lipid materials prolongs drug release and dissolution is not markedly affected by pH.

Concerning the graft copolymers under study, HSMMA derivatives do not exhibit ionic characteristics, which explain the smooth drug release profiles over the entire pH range (Figure 1) and the integrity of the matrices after the dissolution test. By contrast, CSMMA behaves as a pH-sensitive copolymer as the ionization of the carboxylic groups of the carbohydrate backbone increases when pH becomes more basic, promoting the polymer chain relaxation (repulsion between the negatively charged carboxyl groups) and resulting in a higher theophylline release rate and an increase of matrix volume after the dissolution test. The hydrophobic character of the copolymer avoids the tablet dissolution as it happens with Theolair®. This fact, together with the lower drug dose, explain the slower drug release rates of CSMMA matrices compared with this reference product. A similar behaviour was observed with other carboxymethyl starches (Assaad and Mateescu, 2010; Mulhbacher et al., 2004).

Based on the pH-dependence described and for comparison with the commercial products, HSMMA formulations containing 100 mg theophylline and CSMMA formulations containing 175 mg theophylline were prepared for further experiments.

3.2. Influence of the tablet crushing force on the matrix structure and *in vitro* drug release kinetics

3.2.1. Compression behaviour and compact properties

In order to obtain information about the densification behaviour of the copolymers mixtures and the integrity of the matrices prepared thereof, Table 1 summarises the main compression data and results from the physical testing of these tablets at the three crushing forces evaluated (70-80, 90-100 and 110-120 N).

As expected, the applied pressure (*P*) necessary to obtain the tablets increases when increasing the crushing force required. For the same crushing force range, FD mixtures need less pressure than OD ones and the same is true when comparing CSMMA with HSMMA

formulations. This tendency was already reported in a thorough study on densification properties of the bulk copolymers compressed at 70-80 N (Ferrero and Jiménez-Castellanos, 2002).

For HSMMA formulations, lower ejection force (F_e) values are observed (Table 1) when increasing the crushing force while, for CSMMA mixtures, F_e values remain essentially unmodified with this parameter. For the same crushing force range, OD tablets show lower values than FD ones, in line with the rough particle surfaces described for FD derivatives (Ferrero and Jiménez-Castellanos, 2002). A similar trend is noticed when comparing HSMMA with CSMMA matrices, probably due to the higher drug content of the last ones. The acicular shape of theophylline crystals (Pather et al., 1998) would increase adhesion and friction, compensating the effect of the tablet thickness reduction when increasing compression pressure. Nevertheless, all formulations show F_e values lower than 750 N, the limit for direct compression excipients (Bolhuis and Lerk, 1973).

Concerning the expansion work (W_e), higher values are observed with the increase in the crushing force. For the same crushing force range, OD formulations show larger values than FD ones, in line with the higher binding capacity of FD copolymers (Ferrero and Jiménez-Castellanos, 2002). HSMMA mixtures are also characterised by higher elastic expansion during decompression than CSMMA ones. Odeku et al. (2008) reported also higher elasticity for oven-dried modified starches and for increasing compression pressures.

Finally, the increase in the crushing force reduces slightly the plasticity (Pl) percentages (Table 1), mainly in the case of HSMMA formulations. The higher compactibility of CSMMA and FD mixtures is also evident from the values of this parameter.

The physical testing of the different formulations reveals that all tablets fulfilled the requirements specified in the European Pharmacopoeia (2011) related to weight uniformity test (Table 1). As expected, the tablet thickness diminishes with the increase in the crushing force. In spite of their reduced tendency to elastic deformation, FD tablets show greater thickness values

than OD ones, which might be related to a more porous structure in FD matrices. A similar trend is detected for CSMMA tablets compared with HSMMA ones.

The crushing force test (European Pharmacopoeia, 2011) confirms the values required for all batches. Obviously, the tablet friability decreases with the increase in the crushing force, with values ≤ 1% (European Pharmacopoeia, 2011) for tablets elaborated at 90-100 N or higher crushing forces.

3.2.2. Matrix porous structure

Since knowledge of the tablet porous structure could help in the prediction of water and drug diffusivity, results from mercury intrusion-extrusion porosimetry are compiled in Table 2. The increase in the crushing force leads to a reduction of the tablet porosity, mean and median pore diameters for all formulations. For the same crushing force range, FD matrices are more porous than the corresponding OD formulations, in accordance with the higher thickness values detected (Table 1). This behaviour was also described by Ferrero and Jiménez-Castellanos (2002) for tablets from the bulk copolymers compressed at 70-80N and attributed to the effect of the drying process of the materials. Hence, evaporation of water in an oven is accompanied by a shrinking and densification process which results in smaller porosities compared with freeze-drying (Kleinebudde, 1994).

The differences in the porosity between OD and FD formulations compare also with the performance of the mixtures in relation with the applied pressure. Materials with higher surface areas, such as FD copolymers (data not shown), are more prone to interparticulate bonding (Odeku et al., 2008), requiring lower pressures to form a compact and showing higher plasticities (Table 1). The same is true for CSMMA derivatives compared with HSMMA ones.

According to IUPAC definitions, all the systems under study contain macropores (pore diameter > 500 Å) (Zdravkov et al., 2007). However, the pore size distribution profiles (Figure 2) depend basically on the type of copolymer (Ferrero and Jiménez-Castellanos, 2002; Ferrero et al., 2003): unimodal profile for HSMMA formulations and bimodal profile for CSMMA ones. For

the same crushing force range (Table 2), HSMMA tablets are characterised by similar median pore diameters but mean pore sizes are lower for matrices obtained from FD copolymers. In contrast, for CSMMA tablets, no great differences are detected in the mean pore diameters but the median pore diameters shift to smaller values in FD formulations, indicating a higher contribution of smaller pores.

3.2.3. *In vitro* drug release kinetics

Since the tablets are prepared by direct compression, this section describes the influence of tablet crushing force on the release properties. Figures 3 and 4 illustrate the theophylline release profiles from HSMMA and CSMMA matrices at the different crushing forces evaluated. The drug release patterns from the commercial products (Theo-Dur® and Theolair®) have also been included for comparison purposes. In general, HSMMA tablets show faster drug release rates than Theo-Dur® for all crushing forces evaluated (Figure 3). Concerning CSMMA matrices (Figure 4), there is a closer approximation of the drug release profiles to the reference product (Theolair®) up to pH 4.5, mainly for FD-CSMMA tablets with crushing forces of 90-100 and 110-120 N.

The effect of the tablet crushing force on the drug release profiles from HSMMA and CSMMA matrices is strongly material-dependent. So, for HSMMA formulations, the increase in the crushing force results in an acceleration of the drug release, mainly for tablets compressed at 110-120 N. To the contrary, for CSMMA formulations, the drug release rate slows down when increasing the crushing force, being the effect more prominent between tablets compressed at 80-90 N and 90-100 N. This last behaviour described for matrices containing CSMMA copolymers has been reported frequently in the literature (Crowley et al., 2004; Pather et al., 1998), as the increase in the crushing force is associated to a decrease in the tablet porosity and, hence, in a reduction of water uptake and consequent drug release. However, the performance of HSMMA matrices is the opposite of what was expected, although some authors (Korsmeyer et al., 1983b) have observed this dependence, which was attributed to the removal of the entrapped air in the

matrix structure when increasing the compaction pressure. The air trapped within the tablets acts as a transport barrier that prevents the penetration of the dissolution medium and inhibits drug release.

The effect of the entrapped air could be present in our study, since the decrease in porosity and mean pore diameter when increasing the crushing force (Table 2) could favour the air expulsion from the matrix and, therefore, the penetration of the dissolution medium inside the pores (Korsmeyer et al., 1983b), increasing the drug release rate. However, the contribution of another factor should not be dismissed, as this behaviour is not observed for CSMMA formulations.

When comparing tablets of similar crushing force, OD matrices exhibit faster release than FD tablets (Figures 3 and 4) in line with the theophylline release profiles described by Ferrero et al. (2003) when testing the copolymer matrices (70-80 N) using water as dissolution medium. Concerning the copolymer type, CSMMA matrices show less variability and more prolonged drug release profiles than HSMMA ones. Taking into account that the theophylline/copolymer ratio is higher in CSMMA tablets, it is possible to conclude that this copolymer affords a better control of the release of this drug. The strongly retarded drug release of CSMMA and FD matrices could be attributed to the better binding properties of these polymers.

To understand the mechanistic aspects of drug release from the polymeric matrices, release data ($M_t/M_\infty \leq 0.6$) were analysed according to Higuchi (1963), Korsmeyer et al. (1983a) and Peppas and Sahlin (1989) equations and the main parameters are listed in Table 3. For Peppas model, m = 0.44 was used as the matrices under study present an aspect ratio (diameter/thickness) around 3 (Ritger and Peppas, 1987).

In general, HSMMA matrices provide better fit to the different models than CSMMA tablets and a similar behaviour can be observed when comparing Theo-Dur® with Theolair® fittings. The pH-dependence of the drug release profiles (mainly from pH 4.5 to 7.0) for CSMMA and Theolair® formulations could justify their poorer correlations.

For HSMMA matrices (Table 3), the accurate fit to Higuchi equation, the *n* values (0.44-0.53) from Korsmeyer equation and the prevalence of k_d over k_r in Peppas equation reveal that Fickian diffusion is the dominant drug transport mechanism. The *n* value (0.67) obtained from the fitting of Theo-Dur® release profile to Korsmeyer model predicts an anomalous transport, in agreement with the results obtained by Ochoa et al. (2010). However, the good fit to Higuchi equation and the higher values of k_d in Peppas model suggest a predominance of diffusion over relaxation or erosion. The comparison of *k* and k_d constants corresponding to HSMMA and Theo-Dur® formulations confirm the slower theophylline release from the commercial product (Figure 3). This could be explained by the different formulation as the major part of theophylline in Theo-Dur® is contained in small cores embedded in the matrix.

For CSMMA matrices (Table 3), the n values (0.50-0.57) from Korsmeyer equation reveal a drug release mechanism controlled mainly by drug diffusion, although the adjustment to Higuchi equation is worse compared with HSMMA matrices. In the case of Peppas model, drug diffusion is also noticed as the predominant release mechanism, although the contribution of k_r is more important than in HSMMA tablets. Theolair® shows a combined mechanism of diffusion and relaxation or erosion (n = 0.63) with prevalence of the latter mechanism (poor adjustment to Higuchi equation and negative value for k_d).

The increase in the crushing force is followed by an increase of *k*, *k'* and k_d values for HSMMA formulations, especially for tablets compressed at 110-120N, which is consistent with the faster drug release profiles observed in Figure 3. In contrast, the reduction of drug release observed for CSMMA matrices when increasing the crushing force (Figure 4) is not so well appreciated in the kinetic constants from the different models. The biphasic profiles for these formulations and their poorer correlations could be responsible of this behaviour.

From Higuchi rate constants (Korsmeyer et al., 1983b), approximate values for the apparent diffusion coefficient D' in the copolymer matrices can be estimated (Table 4). *D'* is

expressed as D/τ, where τ is the tortuosity of the matrix and D is the effective diffusion coefficient of the drug in the dissolution medium.

The increase in the crushing force leads to higher *D'* values for HSMMA matrices, which mean lower tortuosity values and decreased diffusional resistance for these tablets. So, the higher porosity (more entrapped air inside the matrix) and tortuosity of tablets compressed at lower crushing forces could explain the slower theophylline diffusion rate observed for these matrices (Figure 3).

The *D'* values obtained for matrices containing CSMMA derivatives (Table 4) show an increase in the tablets tortuosity when the crushing force increases from 70-80 N to 90-100 N which could be associated to the slowest drug release of the hardest tablets (Figure 4). An additional increment of pressure to obtain tablets at 110-120 N results in a reduction of tortuosity to similar values than the ones obtained for the lowest crushing force. This would explain the similarity between drug release profiles from formulations compressed at 110-120 N and 90-100 N, in spite of the lower porosity of the former.

From the analysis of *D'* values, it can also be deduced that OD matrices are characterised by less tortuous pore networks than their homologous freeze-dried, in agreement with their less plastic behaviour (Desai et al., 1966). This could explain the faster drug release from matrices containing OD copolymers, in spite of their lower porosity. Consistent results were described by Ferrero et al. (2003) when performing water dissolution studies with these copolymer matrices.

Finally, the similarity between drug release profiles from the copolymer matrices and their respective reference products was assessed by means of f_2 (Table 5). For all CSMMA formulations, the f_2 values larger than 50 demonstrate their similarity with Theolair®. In the case of HSMMA matrices, only FD-HSMMA compressed at 70-80 N and 90-100 N show drug release profiles similar to Theo-Dur®. Based on the dissimilar release profiles, OD-HSMMA formulations will be omitted for further agitation studies. Moreover, the range of 90-100 N is selected as the more appropriate crushing force for the other three formulations (FD-HSMMA,

OD-CSMMA, FD-CSMMA), as f_2 values higher than 50 (Table 5) and friability values ≤ 1 are obtained (Table 1).

3.3. Effect of the stirring rate on the *in vitro* drug release kinetics

The susceptibility of the matrices to changes in agitation can be considered as an indication of the robustness of the delivery system, since mechanical stresses could result in dose dumping or the crushing of the dosage form at an unexpected site in the GI tract. So, as stated in the introduction, it would be desirable that an oral sustained-release system does not show excessive sensitivity to this factor (Jorgensen and Bhagwat, 1998).

Several authors have examined the effect of varying agitation intensities on the drug release profiles (Morihara et al., 2002; Wu et al., 2004). Rotational speeds of 25, 50, 75 and 100 r.p.m. were selected for our study and the influence of this factor on the drug release profiles is collected in Figures 5-9 for the different theophylline formulations.

The drug release from FD-HSMMA matrices as well as the variability between replicates (Figure 5) increase as the agitation rate increases from 25 to 75 r.p.m. Further increase is not observed at 100 r.p.m. In contrast, Theo-Dur® formulation (Figure 6) seems to be less susceptible to the agitation intensity, probably because of the more complicated formulation and method of manufacture (coated beads embedded in a slowly disintegrating waxy matrix).

In the case of OD-CSMMA matrices (Figure 7), the increase in the agitation rate results in an acceleration of the drug release while, for FD-CSMMA tablets (Figure 8), the drug release fastens as the stirring rate increases from 25 to 50 r.p.m., and then remains nearly constant. Moreover, it is worthwhile to mention the pH independence of the drug release profiles at 25 r.p.m. for both formulations. Regarding Theolair®, biphasic profiles are evident for the different agitation rates (Figure 9). This factor shows no effect at acid pH_s whereas, at basic pH_s, the drug release accelerates with agitation rates higher than 50 r.p.m. These results are in good agreement with those reported by Crombeen and De Blaey (1983) and could be explained by the erosion of CAP coating under the influence of motility. In the presence of buffer medium (pH = 6-7), the

more intense agitation increases the influx of buffer species in the diffusion region at the releasing surface which leads to dissolution of CAP. Then, the matrix erodes at such a velocity that the dissolution rate of theophylline is considerably increased.

Results from the kinetic analysis of the drug release data are illustrated in Table 6. FD-HSMMA matrices show a diffusion-controlled mechanism with an increase in the drug release rate constant as the rotational speed raises (up to 75 r.p.m.). Theodur® is characterised by an anomalous transport with predominance of the diffusion mechanism. The low susceptibility of this formulation to the agitation rate (Figure 6) is reflected also in the similar *k* values of Higuchi equation and the relative contributions of k_d and k_r in Peppas model.

For CSMMA formulations, the best fitting to the different equations is obtained for the profile at 25 r.p.m., confirming the pH-independent release observed for these matrices at this agitation rate (Figures 7-8). Although diffusion seems to be the predominant mechanism for all CSMMA matrices, the effect of the agitation rate on the drug release kinetics depends on the copolymer type. Hence, for OD-CSMMA tablets, the increase in drug release with the rotation speed is mainly due to an increase in drug diffusion (k_d values). In the case of FD-CSMMA tablets, the reduction in k_d values at increased agitation rates is compensated by the increase in k_r values, leading to similar drug release rates.

Finally, Theolair® shows a combined diffusion-erosion mechanism, although the poor fitting to the kinetic models makes it difficult to elucidate the agitation effect on the drug release constants.

4. Conclusions

The present study demonstrates that the tested copolymers were suitable as matrix-forming excipients and allowed preparation of direct-compressed, sustained-release theophylline tablets, comparing well with the marketed products Theo-Dur® and Theolair®. The *in vitro* drug release

behaviour was markedly influenced by the copolymer nature and the tablet crushing force, parameters affecting the porosity and tortuosity of the matrices.

The formulations were tested over the physiological pH range (1.2-7.5) to examine the pH-dependency of drug-release patterns. Release profiles of HSMMA and Theo-Dur® were not affected by the pH of the dissolution medium while CSMMA and Theolair® showed a pH-dependent release. For all copolymer tablets, the diffusion mechanism appeared to play a dominant role in drug release, providing CSMMA and FD derivatives a better control of theophylline release.

The intensity of agitation was also an important factor in determining the release rate but the extent of its influence depended on the product tested and the pH of the dissolution medium. In general, the greater the agitation the faster the drug release from the matrices, being FD-CSMMA tablets the less affected by this parameter.

The analysis of these properties gives a better understanding and application of these materials as polymeric systems for sustained drug release. Based on the results obtained *in vitro*, FD-HSMMA, OD-CSMMA and FD-CSMMA compressed at 90-100 N were selected for further *in vivo* drug absorption evaluation.

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Table(s)

Table 1.- Main compression parameters and tablet test results from the copolymers formulations at different crushing forces (CF): maximum applied upper punch pressure (P), maximum ejection force (F_e), expansion work (W_e), plasticity (Pl), weight (W), thickness (T), friability (*F*).

Formulations	CF (N)	P (MPa)	F_e (N)	W_e (J)	Pl (%)	W (mg)	T (mm)	F (%)
OD-HSMMA	70-80	149.1 (2.7)	222.5 (13.7)	1.1 (0.2)	92.8 (0.4)	498.0 (5.3)	4.3 (0.0)	1.3
	90-100	211.3 (0.5)	206.4 (8.1)	2.0 (0.0)	90.4 (0.2)	498.0 (3.9)	4.1 (0.0)	0.7
	110-120	273.8 (0.4)	181.8 (6.9)	3.2 (0.2)	87.1 (0.4)	497.9 (3.3)	4.0 (0.0)	0.5
FD-HSMMA	70-80	106.1 (2.3)	244.1 (7.4)	0.6 (0.1)	95.5 (0.3)	491.1 (3.2)	4.5 (0.0)	1.0
	90-100	127.5 (4.2)	240.6 (9.9)	0.9 (0.1)	94.0 (0.1)	494.3 (5.5)	4.3 (0.0)	0.9
	110-120	162.8 (0.2)	173.3 (7.0)	1.3 (0.1)	92.7 (0.1)	494.6 (3.4)	4.1 (0.0)	0.5
OD-CSMMA	70-80	108.2 (0.9)	330.5 (5.2)	0.5 (0.1)	94.0 (0.1)	501.8 (3.7)	4.3 (0.0)	1.7
	90-100	129.8 (4.5)	344.7 (6.2)	0.7 (0.1)	93.1 (0.1)	504.4 (5.5)	4.2 (0.0)	1.0
	110-120	144.5 (0.8)	307.5 (1.3)	0.7 (0.1)	93.2 (0.6)	496.3 (5.0)	4.0 (0.0)	0.9
FD-CSMMA	70-80	62.9 (0.3)	341.7 (11.9)	0.2 (0.0)	96.7 (0.1)	499.7 (5.9)	4.7 (0.0)	1.4
	90-100	72.2 (0.5)	357.4 (13.9)	0.3 (0.1)	96.3 (0.1)	497.1 (5.2)	4.5 (0.0)	1.0
	110-120	84.3 (1.2)	342.1 (5.7)	0.3 (0.0)	96.7 (0.3)	498.2 (6.3)	4.4 (0.0)	0.9

Table 2.- Parameters characterising the porous structure of the copolymers matrices at different crushing forces (CF).

Formulations	CF (N)	Porosity (%)	Mean pore diameter (Å)	Median pore diameter (Å)
OD-HSMMA	70-80	23.9 (0.6)	957.9 (93.6)	15575 (163)
	90-100	20.3 (0.2)	815.3 (15.7)	12930 (113)
	110-120	17.7 (0.1)	688.6 (61.7)	10995 (163)
FD-HSMMA	70-80	26.4 (0.4)	697.6 (33.3)	15025 (149)
	90-100	23.8 (0.1)	621.0 (11.2)	12890 (170)
	110-120	19.9 (0.6)	542.9 (22.6)	10185 (106)
OD-CSMMA	70-80	22.6 (0.2)	676.9 (1.8)	5087 (111)
	90-100	21.3 (0.1)	601.5 (6.4)	3487 (88)
	110-120	18.6 (0.1)	489.3 (13.4)	2285 (175)
FD-CSMMA	70-80	29.0 (0.4)	699.5 (2.5)	1981 (54)
	90-100	28.1 (0.2)	656.6 (6.2)	1756 (47)
	110-120	25.3 (0.1)	570.2 (7.0)	1428 (1)

Table 3.- Mathematical modelling and drug release kinetics from the formulations under study.

Formulations	CF (N)	Higuchi equation		Korsmeyer equation			Peppas equation		
		k ($min^{-1/2}$)	r^2	n	k' (min^{-n})	r^2	k_d ($min^{-0.44}$)	k_r ($min^{-0.88}$)	r^2
OD-HSMMA	70-80	0.029	0.9998 (*F*=181751)	0.46	0.039	0.9997 (*F*=114390)	0.039	$2.68\ 10^{-4}$	0.9999 (*F*=130338)
	90-100	0.030	0.9993 (*F*=45210)	0.47	0.039	0.9998 (*F*=118291)	0.045	$0.45\ 10^{-4}$	0.9998 (*F*=77627)
	110-120	0.037	0.9977 (*F*=8538)	0.46	0.048	0.9990 (*F*=20660)	0.063	$-5.27\ 10^{-4}$	0.9997 (*F*=31206)
FD-HSMMA	70-80	0.026	0.9995 (*F*=70591)	0.53	0.021	0.9989 (*F*=34432)	0.037	$1.16\ 10^{-4}$	0.9997 (*F*=60693)
	90-100	0.026	0.9966 (*F*=11106)	0.52	0.023	0.9968 (*F*=12004)	0.045	$-2.71\ 10^{-4}$	0.9992 (*F*=22307)
	110-120	0.029	0.9943 (*F*=5454)	0.44	0.047	0.9981 (*F*=16225)	0.057	$-7.11\ 10^{-4}$	0.9996 (*F*=36055)
OD-CSMMA	70-80	0.028	0.9907 (*F*=3395)	0.50	0.028	0.9951 (*F*=6468)	0.023	$11.5\ 10^{-4}$	0.9941 (*F*=2610)
	90-100	0.027	0.9954 (*F*=8190)	0.53	0.022	0.9974 (*F*=14740)	0.024	$9.14\ 10^{-4}$	0.9983 (*F*=10621)
	110-120	0.028	0.9853 (*F*=2554)	0.57	0.016	0.9909 (*F*=4140)	0.010	$16.6\ 10^{-4}$	0.9980 (*F*=9104)
FD-CSMMA	70-80	0.026	0.9873 (*F*=2944)	0.53	0.020	0.9951 (*F*=7741)	0.014	$13.3\ 10^{-4}$	0.9962 (*F*=4850)
	90-100	0.023	0.9891 (*F*=3438)	0.52	0.019	0.9957 (*F*=8825)	0.014	$11.1\ 10^{-4}$	0.9963 (*F*=4980)
	110-120	0.024	0.9929 (*F*=5342)	0.54	0.017	0.9944 (*F*=6721)	0.017	$10.3\ 10^{-4}$	0.9983 (*F*=11034)
Theo-Dur®		0.024	0.9985 (*F*=24707)	0.67	0.008	0.9984 (*F*=24091)	0.025	$6.12\ 10^{-4}$	0.9993 (*F*=26675)
Theolair®		0.028	0.9481 (*F*=584)	0.63	0.011	0.9877 (*F*=2566)	-0.005	$27.2\ 10^{-4}$	0.9754 (*F*=615)

k, Higuchi kinetic constant; *n*, release exponent; *k*', Korsmeyer kinetic constant; k_d, Peppas diffusion kinetic constant; k_r, Peppas relaxation kinetic constant; r^2, determination coefficient; *F*, F distribution for residual variance analysis (p = 0.000)

Table 4.- Apparent diffusion coefficients D' (obtained from Higuchi rate constant) for drug release studies.

Formulations	D' (cm^2/min)		
	70-80 N	**90-100 N**	**110-120 N**
OD-HSMMA	$5.26\ 10^{-4}$	$6.69\ 10^{-4}$	$11.4\ 10^{-4}$
FD-HSMMA	$3.72\ 10^{-4}$	$4.09\ 10^{-4}$	$6.09\ 10^{-4}$
OD-CSMMA	$10.2\ 10^{-4}$	$8.72\ 10^{-4}$	$10.4\ 10^{-4}$
FD-CSMMA	$5.90\ 10^{-4}$	$5.01\ 10^{-4}$	$5.87\ 10^{-4}$

Table 5.- Values of f_2 for HSMMA and CSMMA matrices, considering Theo-Dur® and Theolair®, respectively, as reference products.

Formulations	f_2		
	70-80 N	**90-100 N**	**110-120 N**
OD-HSMMA	39.9	37.6	37.4
FD-HSMMA	55.8	52.8	36.7
OD-CSMMA	57.8	63.2	67.0
FD-CSMMA	63.5	56.8	57.0

Table 6.- Mathematical modelling and drug release kinetics from the formulations under study at different basket rotation speeds.

Formulations	r.p.m.	Higuchi equation		Korsmeyer equation			Peppas equation		
		k ($min^{-1/2}$)	r^2	n	k' (min^{-n})	r^2	k_d ($min^{-0.44}$)	k_r ($min^{-0.88}$)	r^2
FD-HSMMA	25	0.023	0.9980 (*F*=18614)	0.47	0.029	0.9983 (*F*=22337)	0.039	$-1.64\ 10^{-4}$	0.9999 (*F*=209589)
	50	0.025	0.9973 (*F*=13437)	0.44	0.041	0.9993 (*F*=50568)	0.044	$-2.58\ 10^{-4}$	0.9998 (*F*=107883)
	75	0.032	0.9998 (*F*=117854)	0.44	0.047	0.9996 (*F*=61324)	0.044	$2.86\ 10^{-4}$	0.9999 (*F*=101066)
	100	0.030	0.9997 (*F*=93249)	0.44	0.047	0.9996 (*F*=78208)	0.041	$2.49\ 10^{-4}$	0.9999 (*F*=69805)
OD-CSMMA	25	0.025	0.9934 (*F*=5726)	0.60	0.012	0.9986 (*F*=27926)	0.017	$11.5\ 10^{-4}$	0.9995 (*F*=40134)
	50	0.033	0.9892 (*F*=3482)	0.61	0.015	0.9983 (*F*=18699)	0.022	$14.3\ 10^{-4}$	0.9965 (*F*=4390)
	75	0.029	0.9949 (*F*=5615)	0.45	0.041	0.9955 (*F*=6445)	0.036	$4.51\ 10^{-4}$	0.9952 (*F*=2904)
	100	0.035	0.9962 (*F*=5508)	0.46	0.047	0.9951 (*F*=4265)	0.064	$-7.35\ 10^{-4}$	0.9995 (*F*=20584)
FD-CSMMA	25	0.022	0.9983 (*F*=21924)	0.55	0.016	0.9992 (*F*=47778)	0.022	$5.63\ 10^{-4}$	0.9995 (*F*=37643)
	50	0.028	0.9901 (*F*=3497)	0.56	0.018	0.9974 (*F*=13639)	0.017	$14.1\ 10^{-4}$	0.9973 (*F*=6188)
	75	0.026	0.9833 (*F*=2232)	0.51	0.022	0.9913 (*F*=4322)	0.010	$15.9\ 10^{-4}$	0.9963 (*F*=4968)
	100	0.027	0.9855 (*F*=2249)	0.50	0.025	0.9934 (*F*=4944)	0.013	$15.5\ 10^{-4}$	0.9943 (*F*=2807)
Theo-Dur®	25	0.023	0.9950 (*F*=7526)	0.70	0.006	0.9991 (*F*=42013)	0.018	$9.14\ 10^{-4}$	0.9989 (*F*=16992)
	50	0.024	0.9985 (*F*=24707)	0.67	0.008	0.9984 (*F*=24091)	0.025	$6.12\ 10^{-4}$	0.9993 (*F*=26675)
	75	0.024	0.9992 (*F*=46218)	0.59	0.013	0.9995 (*F*=69900)	0.027	$5.25\ 10^{-4}$	0.9997 (*F*=60363)
	100	0.025	0.9983 (*F*=21789)	0.57	0.015	0.9988 (*F*=32034)	0.027	$5.99\ 10^{-4}$	0.9992 (*F*=23262)
Theolair®	25	0.025	0.9419 (*F*=519)	0.54	0.019	0.9745 (*F*=1225)	0.006	$18.4\ 10^{-4}$	0.9561 (*F*=338)
	50	0.028	0.9481 (*F*=584)	0.63	0.011	0.9877 (*F*=2566)	-0.005	$27.2\ 10^{-4}$	0.9754 (*F*=615)
	75	0.027	0.9173 (*F*=311)	0.53	0.022	0.9712 (*F*=945)	0.004	$22.5\ 10^{-4}$	0.9329 (*F*=188)
	100	0.027	0.9064 (*F*=252)	0.52	0.022	0.9691 (*F*=814)	0.006	$21.1\ 10^{-4}$	0.9195 (*F*=143)

k, Higuchi kinetic constant; n, release exponent; k', Korsmeyer kinetic constant; k_d, Peppas diffusion kinetic constant; k_r, Peppas relaxation kinetic constant; r^2, determination coefficient; F, F distribution for residual variance analysis ($p = 0.000$)

FIGURE LEGENDS

Figure 1.- Anhydrous theophylline release profiles from copolymer matrices (HSMMA and CSMMA 120 mg) and commercial products (Theo-Dur® 100 mg, Theolair® 175 mg) in a pH-changing medium (mean ± SD).

Figure 2.- Pore size distribution profiles for FD-HSMMA (a) and FD-CSMMA (b) matrices. Lines A, B and C correspond to crushing forces of 70-80, 90-100 and 110-120 N, respectively.

Figure 3.- Anhydrous theophylline release profiles from Theo-Dur® and OD-HSMMA and FD-HSMMA matrices (drug dose 100 mg) at different crushing forces (mean ± SD).

Figure 4.- Anhydrous theophylline release profiles from Theolair ® and OD-CSMMA and FD-CSMMA matrices (drug dose 175 mg) at different crushing forces (mean ± SD).

Figure 5.- Anhydrous theophylline release profiles from FD-HSMMA matrices (drug dose 100 mg) at different basket rotation speeds (mean ± SD).

Figure 6.- Anhydrous theophylline release profiles from Theo-Dur® 100 mg at different basket rotation speeds (mean ± SD).

Figure 7.- Anhydrous theophylline release profiles from OD-CSMMA matrices (drug dose 175 mg) at different basket rotation speeds (mean ± SD).

Figure 8.- Anhydrous theophylline release profiles from FD-CSMMA matrices (drug dose 175 mg) at different basket rotation speeds (mean ± SD).

Figure 9.- Anhydrous theophylline release profiles from Theolair® 175 mg at different basket rotation speeds (mean ± SD).

Figure(s) B/W

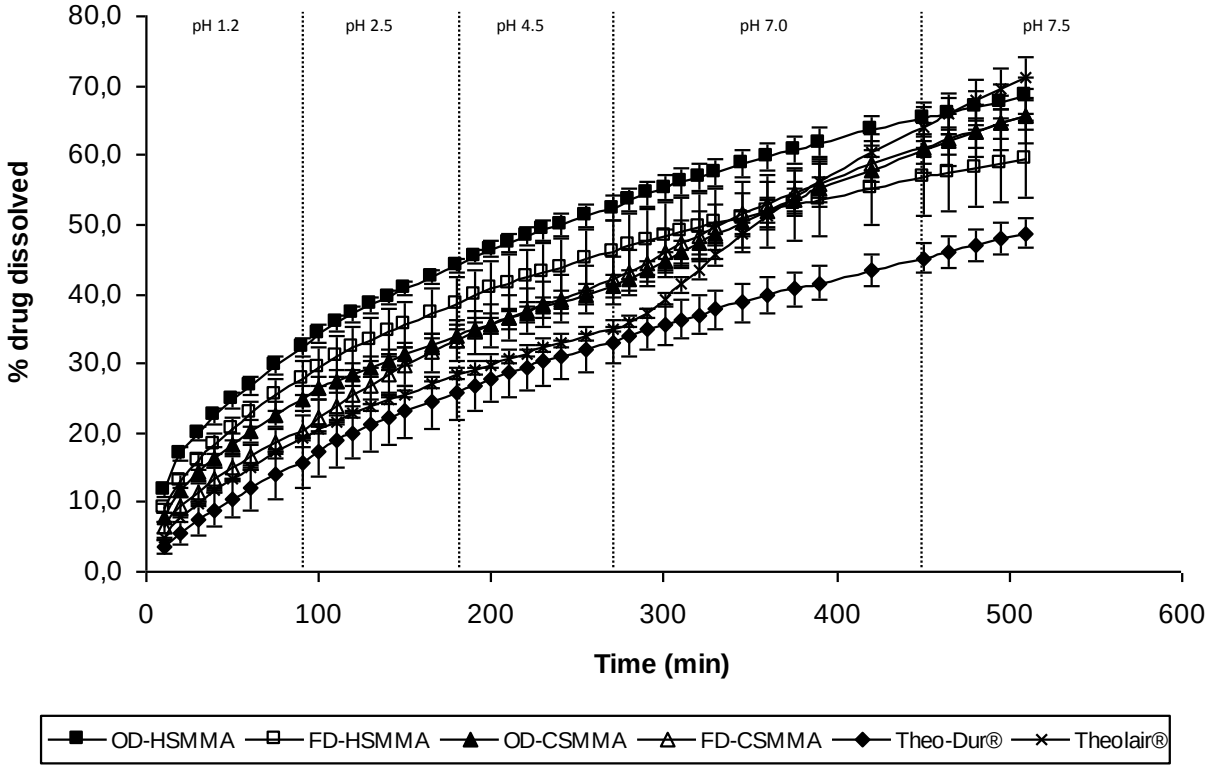
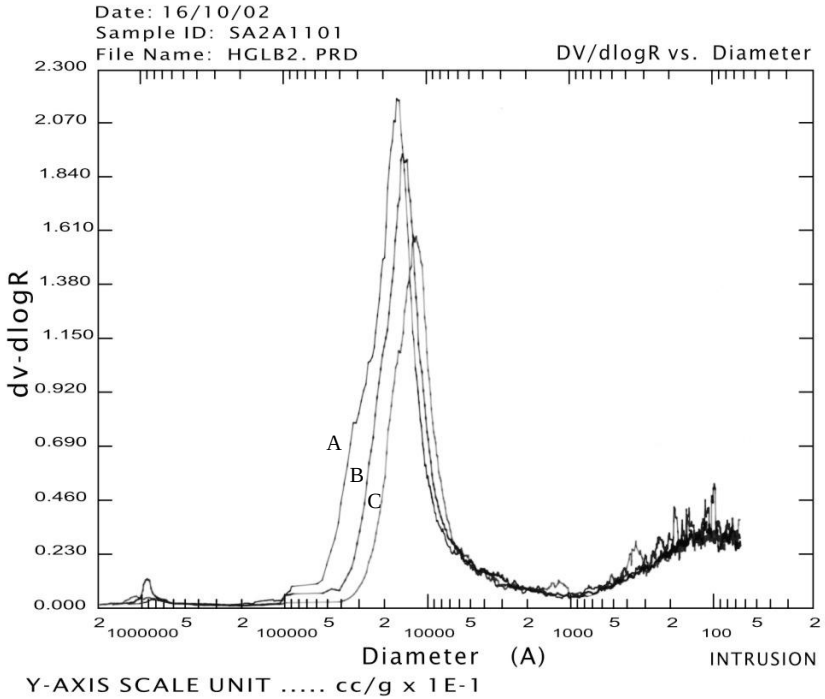


Figure 1.-

a)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Sample ID: SA2A1101
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DV/dlogR vs. Diameter
dv-dlogR
2.300
2.070
1.840
1.610
1.380
1.150
0.920
0.690
0.460
0.230
0.000
A
B
C
2 1000000 5 2 100000 5 2 10000 5 2 1000 5 2 100 5 2
Diameter (A)
INTRUSION
Y-AXIS SCALE UNIT ..... cc/g x 1E-1

b)

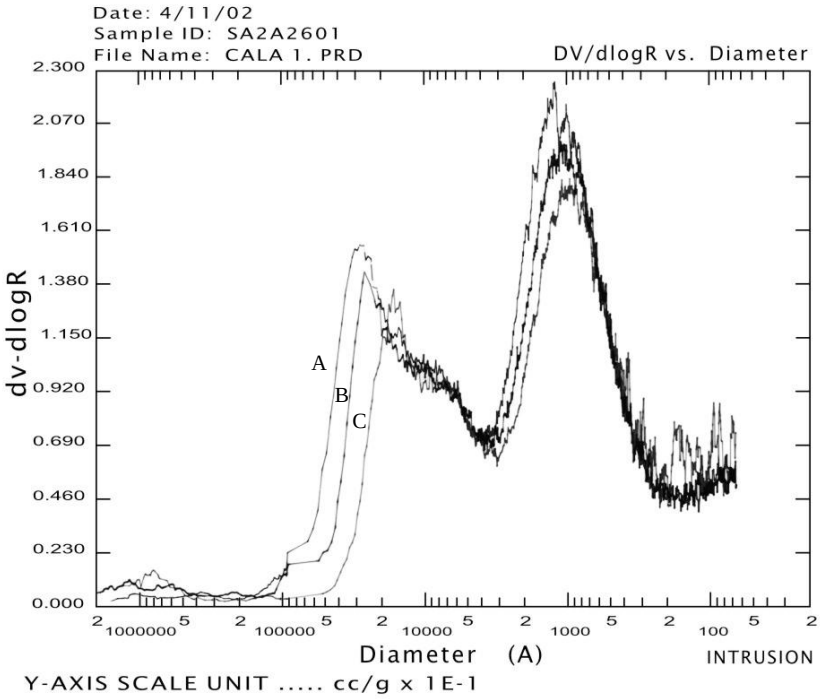

Date: 4/11/02
Sample ID: SA2A2601
File Name: CALA 1. PRD
DV/dlogR vs. Diameter
dv-dlogR
2.300
2.070
1.840
1.610
1.380
1.150
0.920
0.690
0.460
0.230
0.000
A
B
C
2 1000000 5 2 100000 5 2 10000 5 2 1000 5 2 100 5 2
Diameter (A)
INTRUSION
Y-AXIS SCALE UNIT ..... cc/g x 1E-1

Figure 2.-

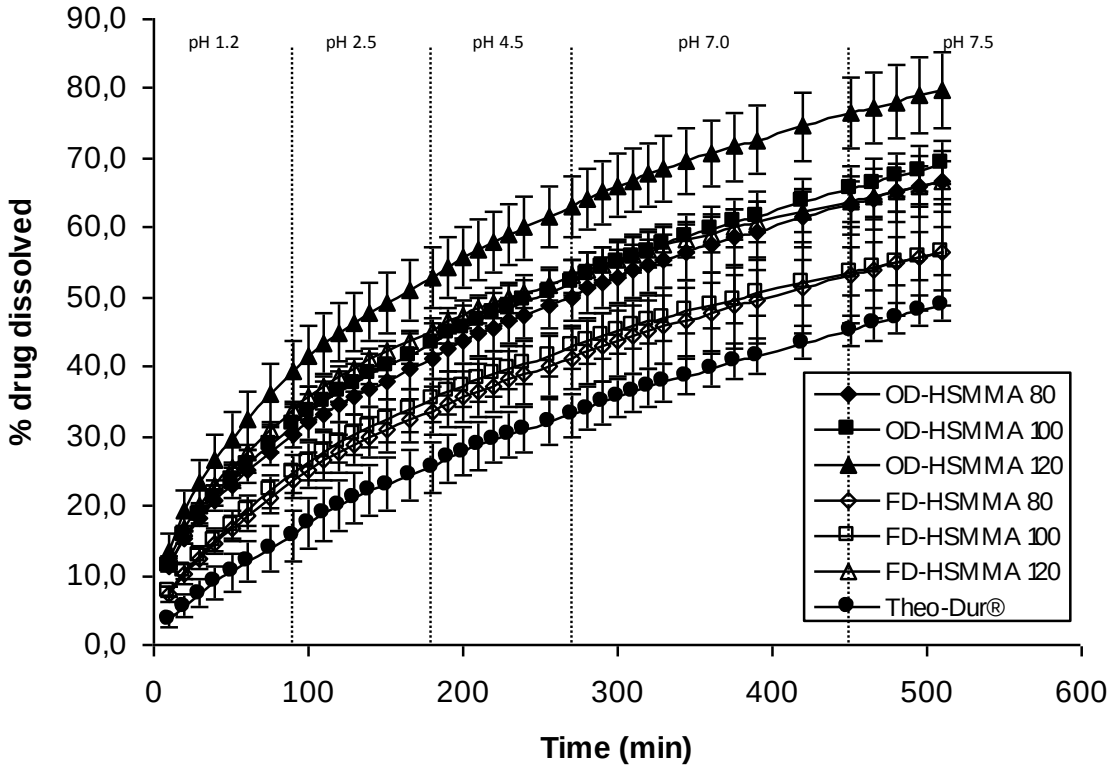

90,0
80,0
70,0
60,0
50,0
40,0
30,0
20,0
10,0
0,0
% drug dissolved
pH 1.2
pH 2.5
pH 4.5
pH 7.0
pH 7.5
0
100
200
300
400
500
600
Time (min)
OD-HSMMA 80
OD-HSMMA 100
OD-HSMMA 120
FD-HSMMA 80
FD-HSMMA 100
FD-HSMMA 120
Theo-Dur®

Figure 3.-

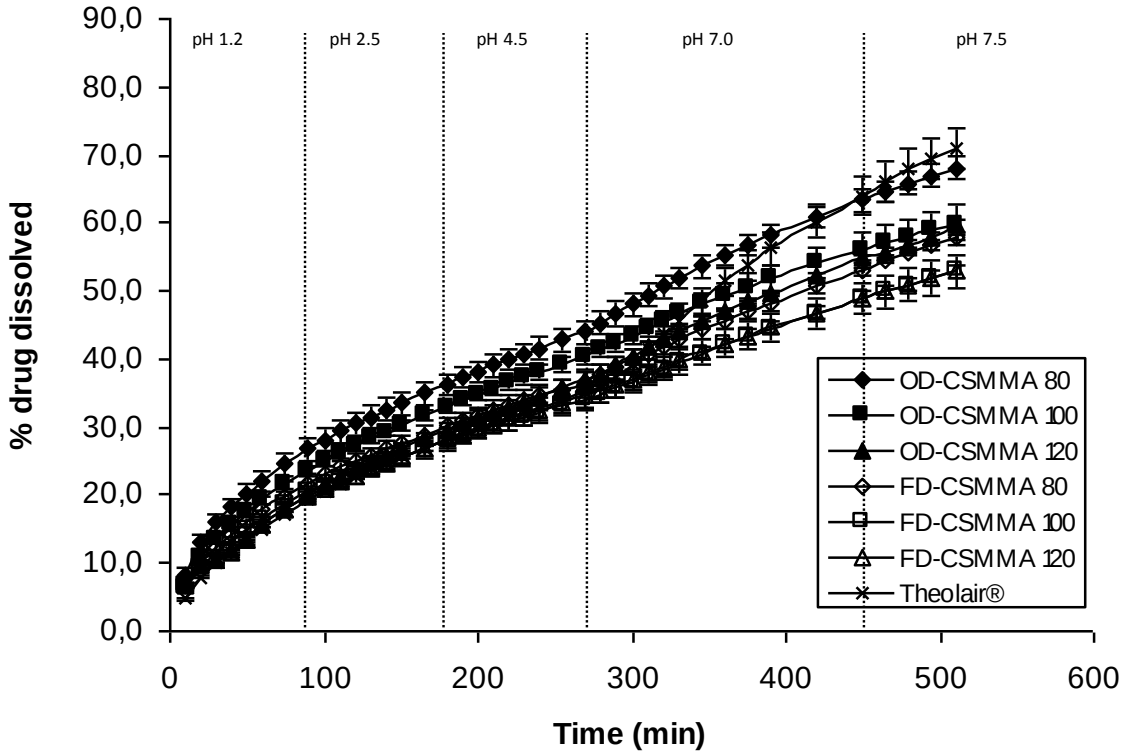

90,0
80,0
70,0
60,0
50,0
40,0
30,0
20,0
10,0
0,0
% drug dissolved
pH 1.2
pH 2.5
pH 4.5
pH 7.0
pH 7.5
0
100
200
300
400
500
600
Time (min)
OD-CSMMA 80
OD-CSMMA 100
OD-CSMMA 120
FD-CSMMA 80
FD-CSMMA 100
FD-CSMMA 120
Theolair®

Figure 4.-

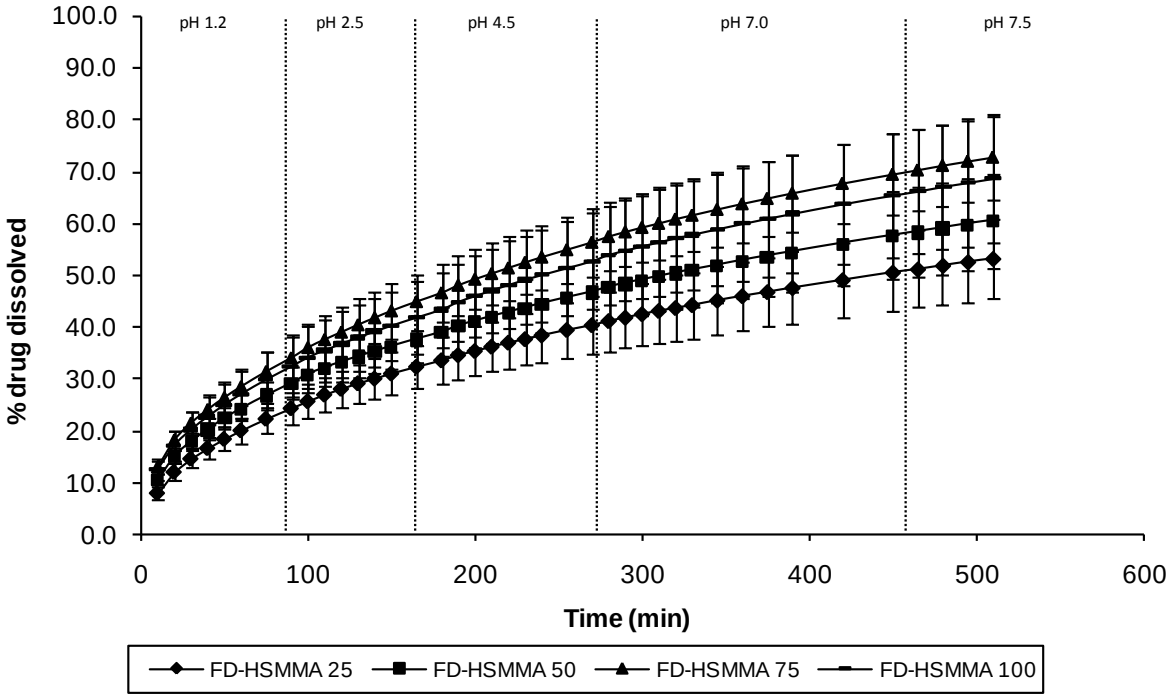

100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
% drug dissolved
pH 1.2
pH 2.5
pH 4.5
pH 7.0
pH 7.5
0
100
200
300
400
500
600
Time (min)
FD-HSMMA 25
FD-HSMMA 50
FD-HSMMA 75
FD-HSMMA 100

Figure 5.-

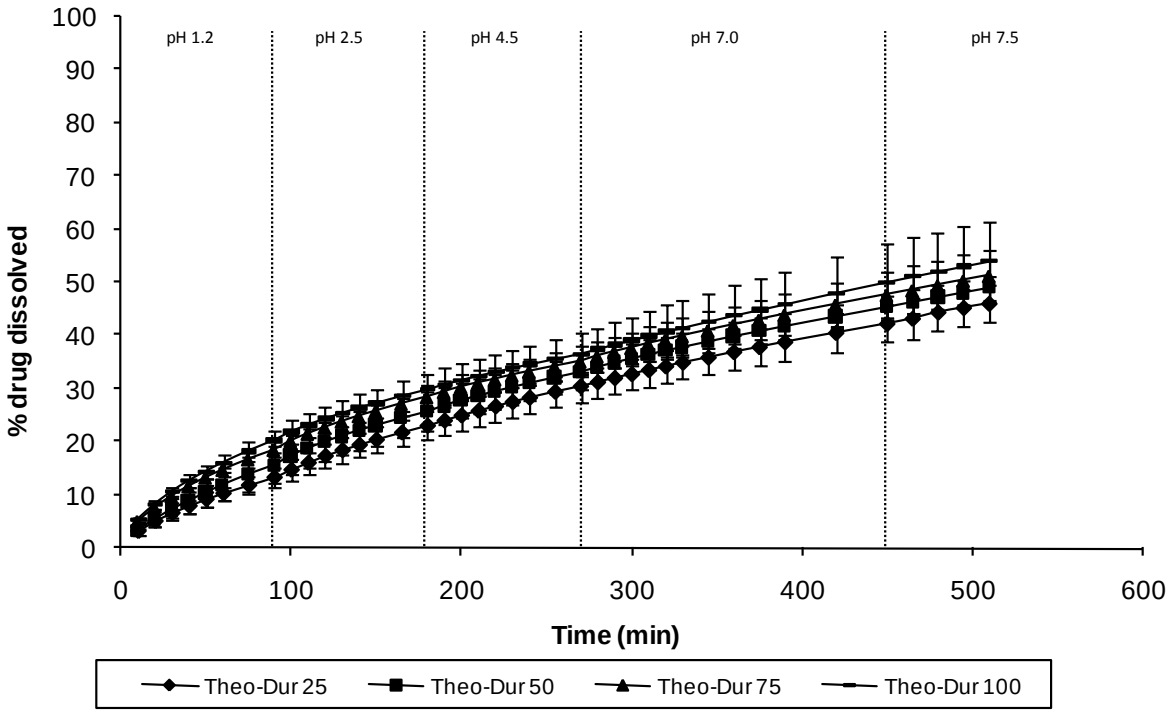

pH 1.2
pH 2.5
pH 4.5
pH 7.0
pH 7.5
% drug dissolved
Time (min)
Theo-Dur 25
Theo-Dur 50
Theo-Dur 75
Theo-Dur 100

Figure 6.-

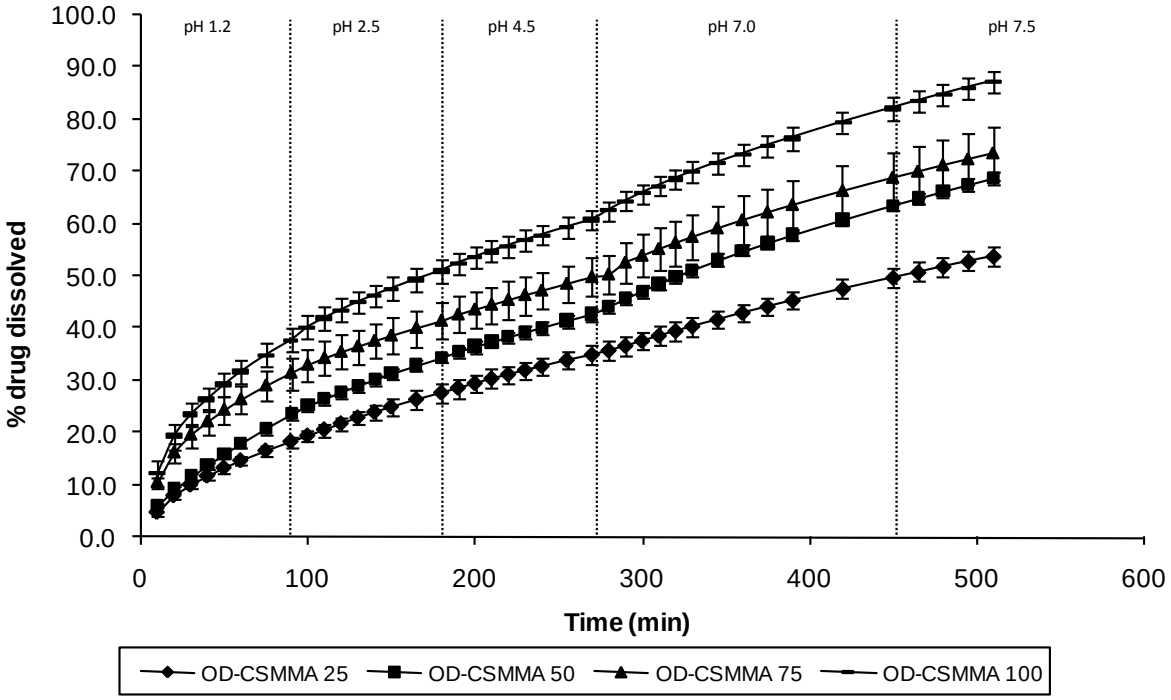

100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
% drug dissolved
pH 1.2
pH 2.5
pH 4.5
pH 7.0
pH 7.5
0
100
200
300
400
500
600
Time (min)
OD-CSMMA 25
OD-CSMMA 50
OD-CSMMA 75
OD-CSMMA 100

Figure 7.-

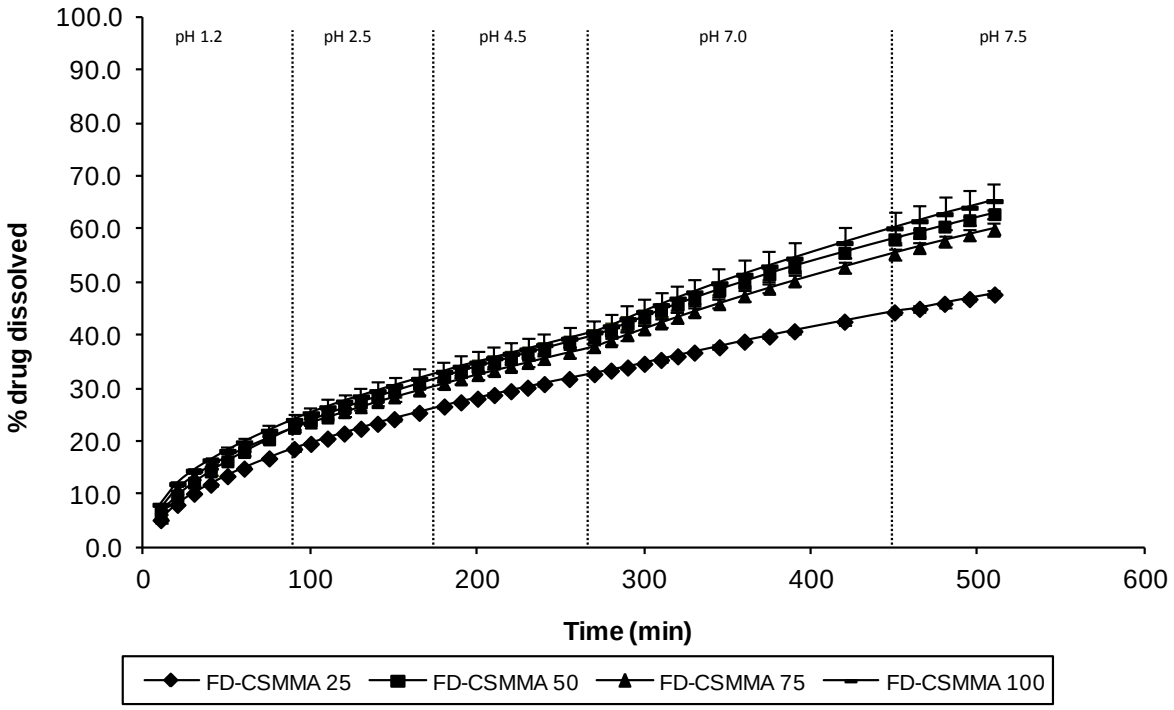

100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
% drug dissolved
pH 1.2
pH 2.5
pH 4.5
pH 7.0
pH 7.5
0
100
200
300
400
500
600
Time (min)
FD-CSMMA 25
FD-CSMMA 50
FD-CSMMA 75
FD-CSMMA 100

Figure 8.-

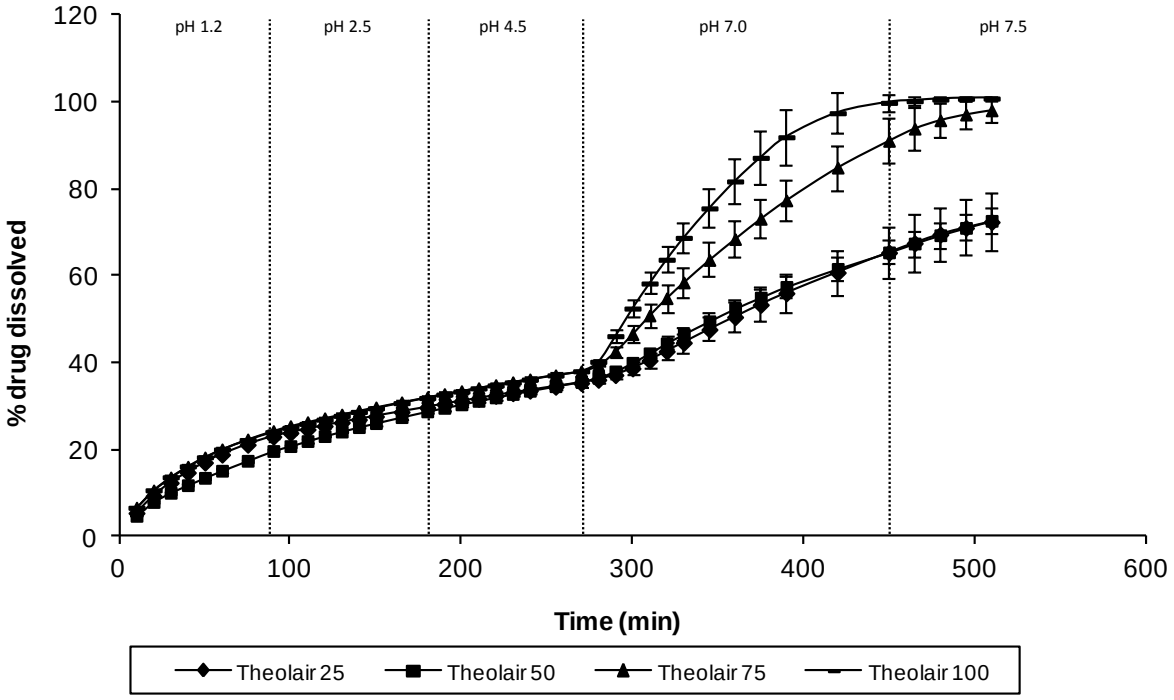

120
100
80
60
40
20
0
% drug dissolved
pH 1.2
pH 2.5
pH 4.5
pH 7.0
pH 7.5
0
100
200
300
400
500
600
Time (min)
Theolair 25
Theolair 50
Theolair 75
Theolair 100

Figure 9.-

Appendix A. Figures with essential colour discrimination for the on-line version

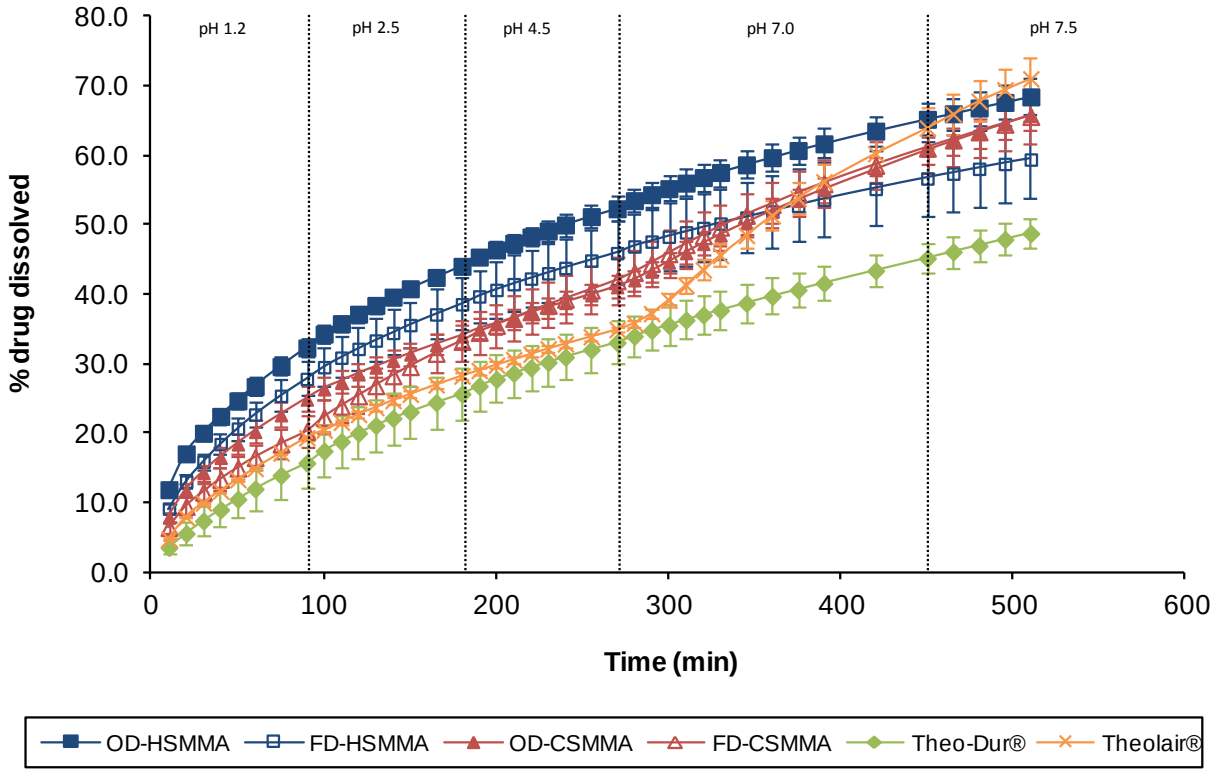
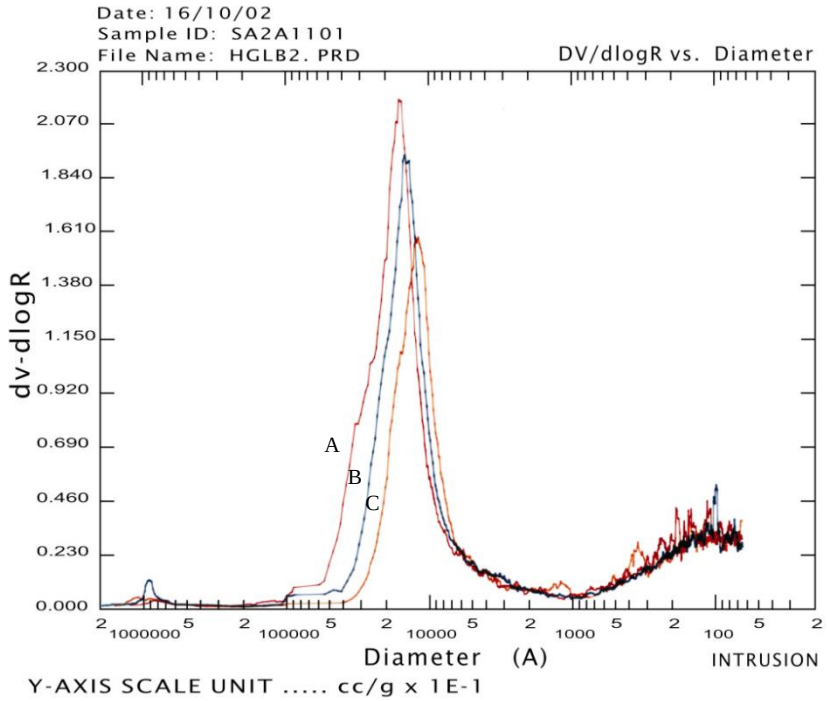


Figure 1.-

a)


Date: 16/10/02
Sample ID: SA2A1101
File Name: HGLB2. PRD
DV/dlogR vs. Diameter
dv-dlogR
2.300
2.070
1.840
1.610
1.380
1.150
0.920
0.690
0.460
0.230
0.000
A
B
C
2 1000000 5 2 100000 5 2 10000 5 2 1000 5 2 100 5 2
Diameter (A)
INTRUSION
Y-AXIS SCALE UNIT ..... cc/g x 1E-1

b)

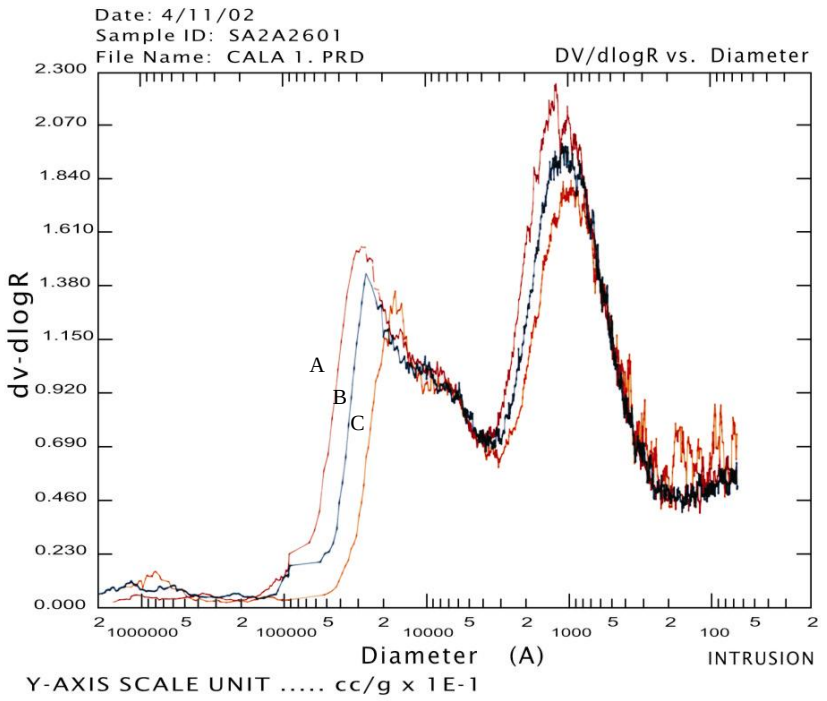

Date: 4/11/02
Sample ID: SA2A2601
File Name: CALA 1. PRD
DV/dlogR vs. Diameter
dv-dlogR
2.300
2.070
1.840
1.610
1.380
1.150
0.920
0.690
0.460
0.230
0.000
A
B
C
2 1000000 5 2 100000 5 2 10000 5 2 1000 5 2 100 5 2
Diameter (A)
INTRUSION
Y-AXIS SCALE UNIT ..... cc/g x 1E-1

Figure 2.-

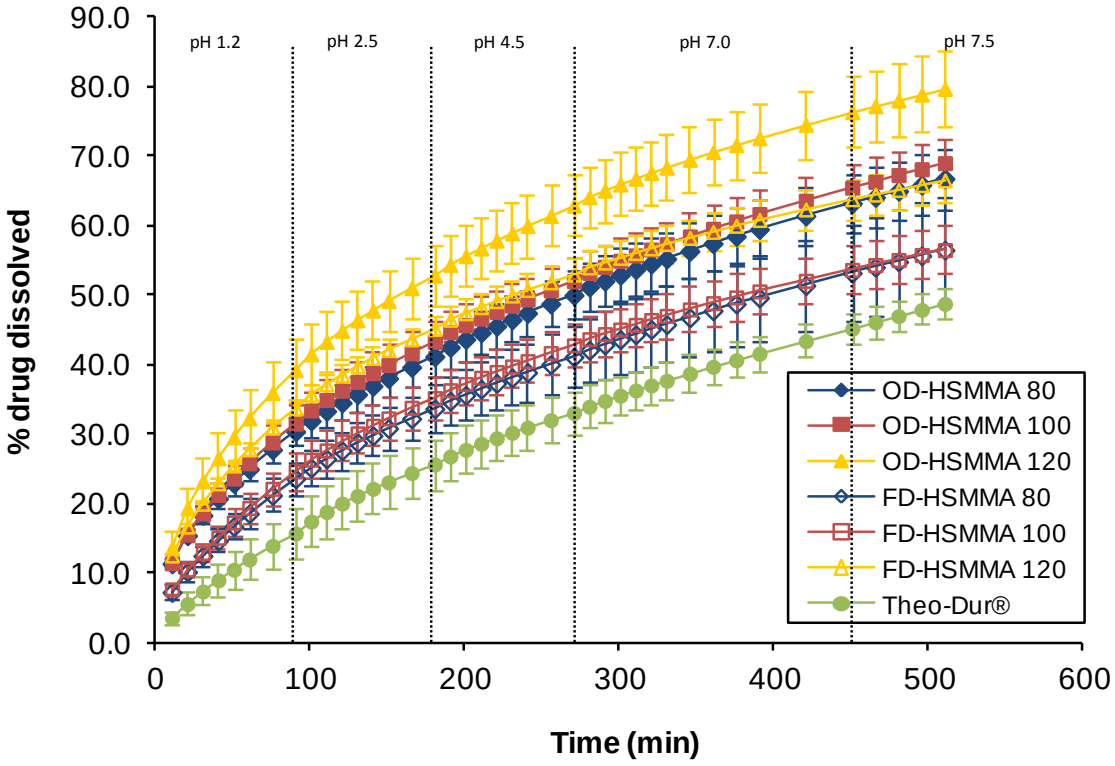

90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
% drug dissolved
pH 1.2
pH 2.5
pH 4.5
pH 7.0
pH 7.5
0
100
200
300
400
500
600
Time (min)
OD-HSMMA 80
OD-HSMMA 100
OD-HSMMA 120
FD-HSMMA 80
FD-HSMMA 100
FD-HSMMA 120
Theo-Dur®

Figure 3.-

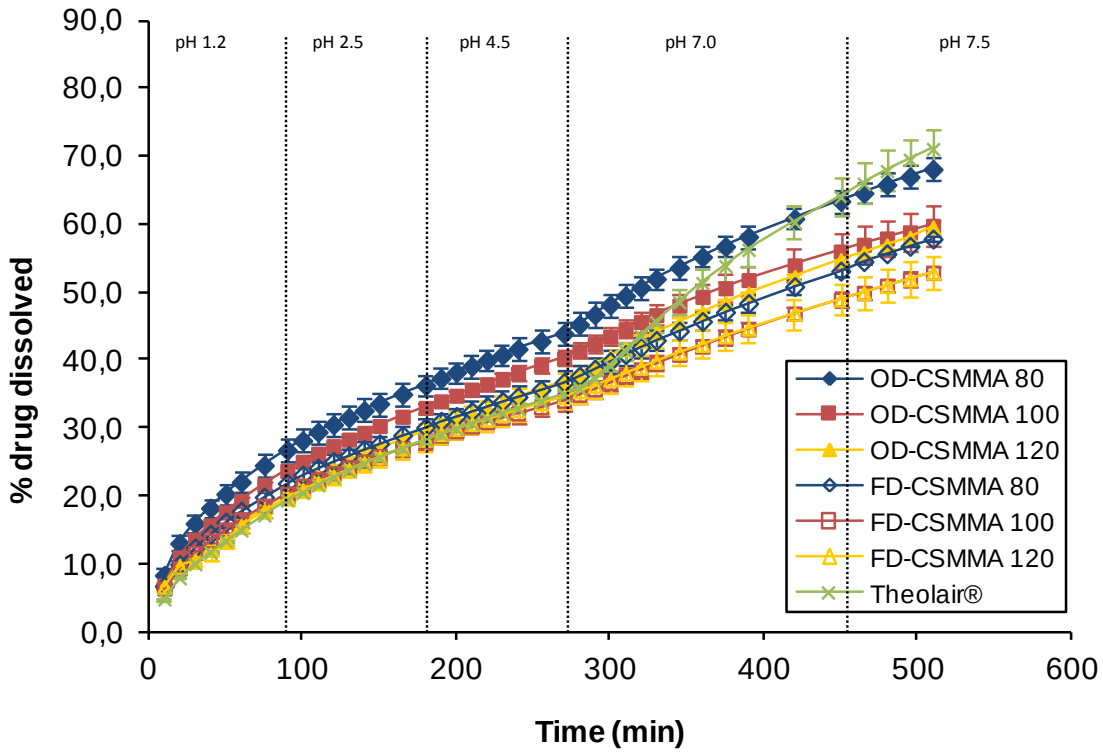

90,0
80,0
70,0
60,0
50,0
40,0
30,0
20,0
10,0
0,0
% drug dissolved
pH 1.2
pH 2.5
pH 4.5
pH 7.0
pH 7.5
0
100
200
300
400
500
600
Time (min)
OD-CSMMA 80
OD-CSMMA 100
OD-CSMMA 120
FD-CSMMA 80
FD-CSMMA 100
FD-CSMMA 120
Theolair®

Figure 4.-

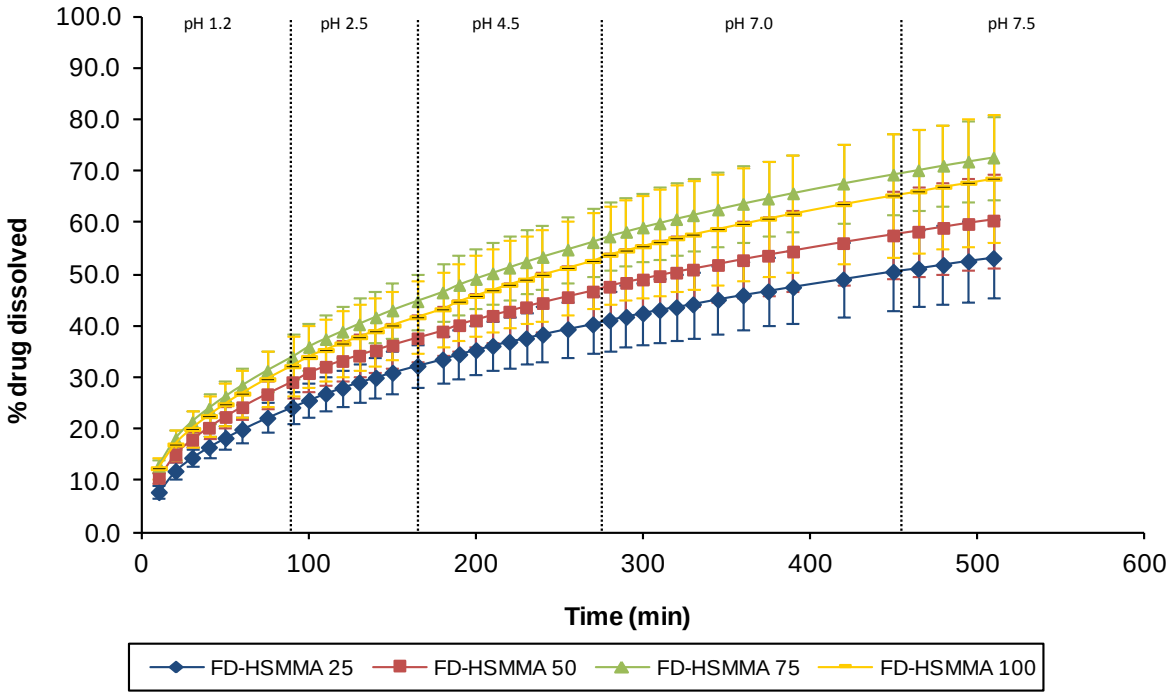

100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
% drug dissolved
pH 1.2
pH 2.5
pH 4.5
pH 7.0
pH 7.5
0
100
200
300
400
500
600
Time (min)
FD-HSMMA 25
FD-HSMMA 50
FD-HSMMA 75
FD-HSMMA 100

Figure 5.-

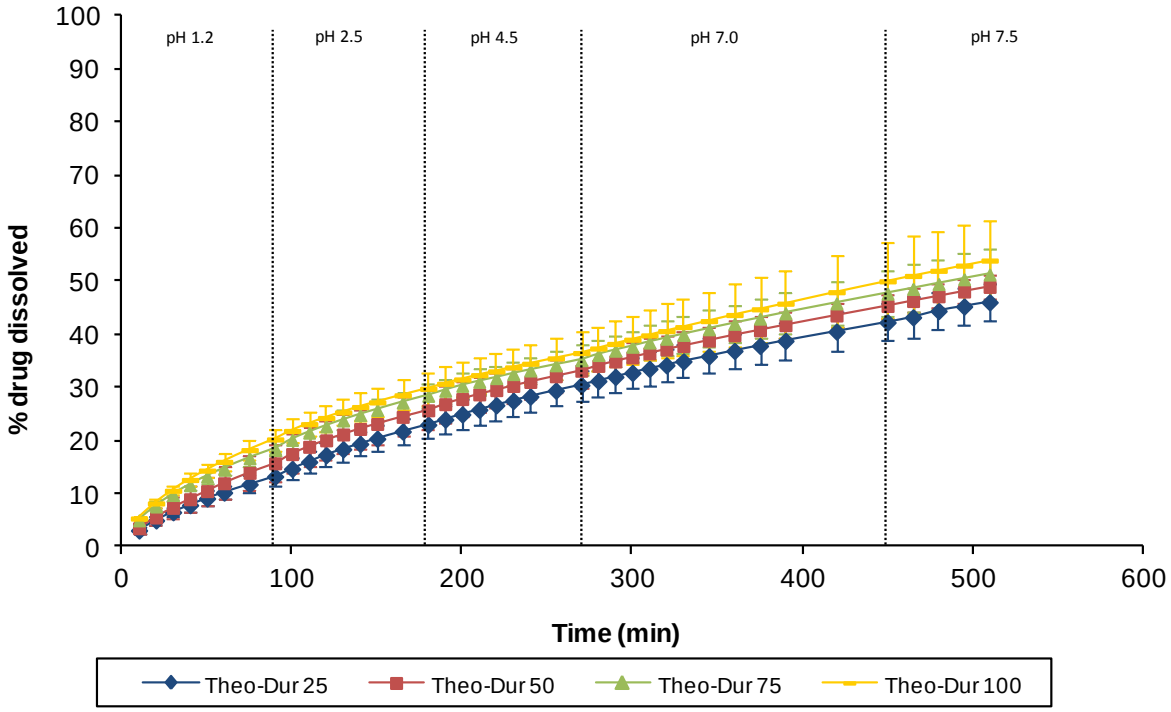

100
90
80
70
60
50
40
30
20
10
0
% drug dissolved
pH 1.2
pH 2.5
pH 4.5
pH 7.0
pH 7.5
0
100
200
300
400
500
600
Time (min)
Theo-Dur 25
Theo-Dur 50
Theo-Dur 75
Theo-Dur 100

Figure 6.-

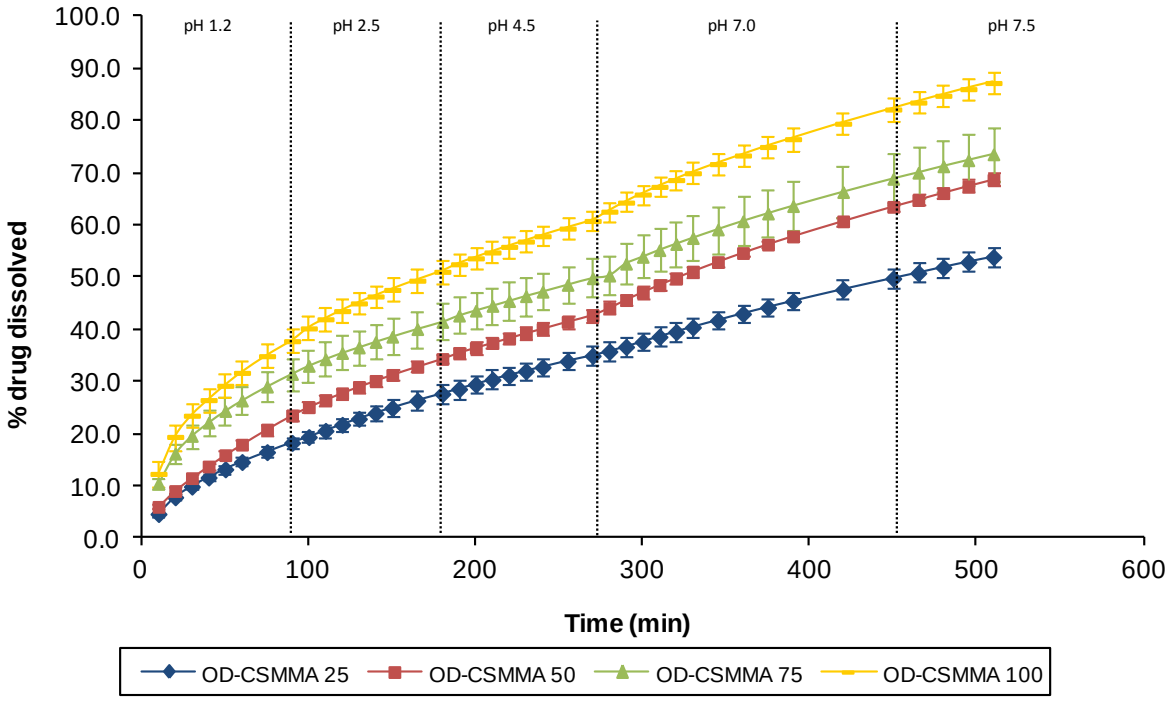

100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
% drug dissolved
pH 1.2
pH 2.5
pH 4.5
pH 7.0
pH 7.5
0
100
200
300
400
500
600
Time (min)
OD-CSMMA 25
OD-CSMMA 50
OD-CSMMA 75
OD-CSMMA 100

Figure 7.-

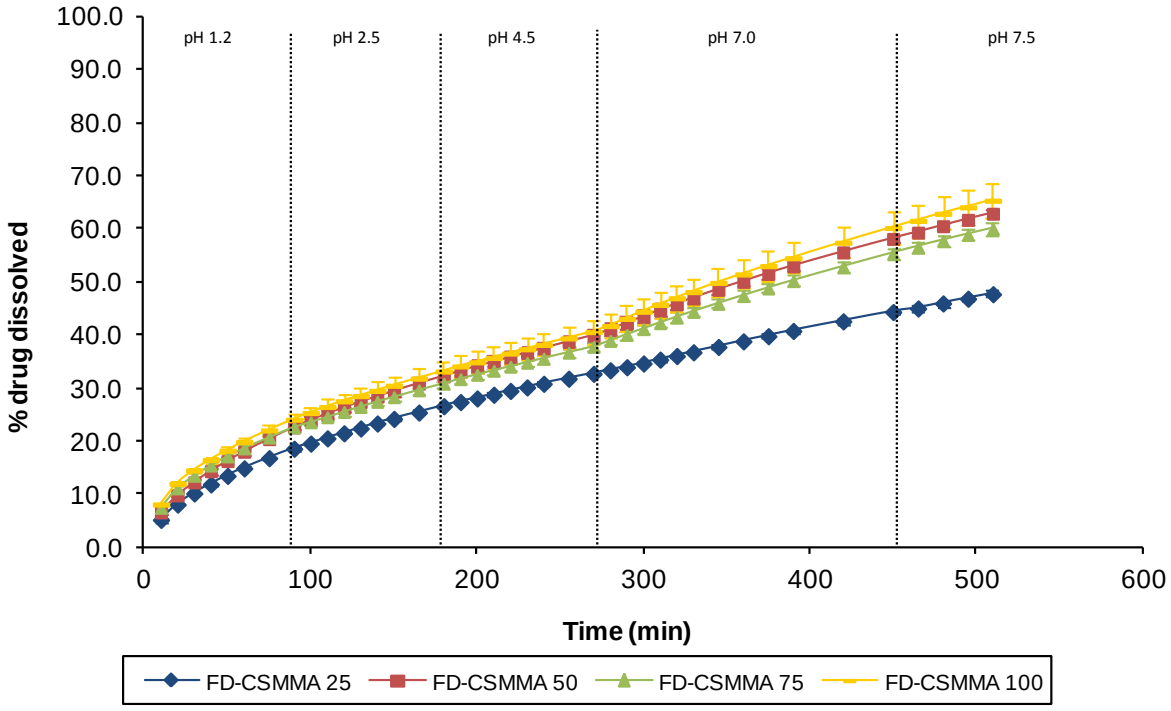

100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
% drug dissolved
pH 1.2
pH 2.5
pH 4.5
pH 7.0
pH 7.5
0
100
200
300
400
500
600
Time (min)
FD-CSMMA 25
FD-CSMMA 50
FD-CSMMA 75
FD-CSMMA 100

Figure 8.-

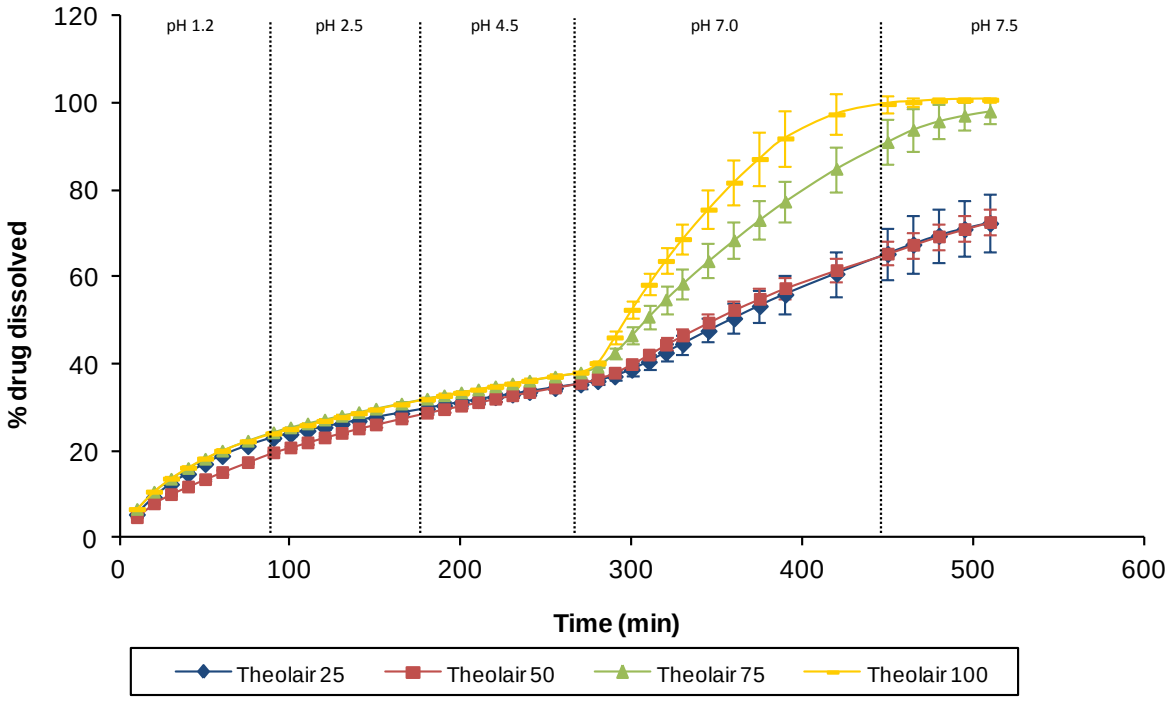

120
100
80
60
40
20
0
% drug dissolved
pH 1.2
pH 2.5
pH 4.5
pH 7.0
pH 7.5
0
100
200
300
400
500
600
Time (min)
Theolair 25
Theolair 50
Theolair 75
Theolair 100

Figure 9.-