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European Journal of Pharmaceutics and Biopharmaceutics 69 (2008) 658–666
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Asymmetric membrane in membrane capsules: A means for achieving delayed and osmotic flow of cefadroxil

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Received 20 October 2007; accepted in revised form 11 December 2007
Available online 23 December 2007

Abstract

In the present study, both disintegrating and non-disintegrating polymeric capsular system in achieving delayed as well as improved osmotic flow for the model drug cefadroxil was developed. Asymmetric membrane in membrane capsule (AMMC) was prepared on a glass mold pin via phase inversion process in two steps. Step 1 included formation of a non-disintegrating, asymmetric membrane capsule (AMC) and step 2 involved formation of a pH sensitive, disintegrating, asymmetric membrane (AM) formed over the non-disintegrating membrane. The effects of different formulation variables were studied namely, level of osmogen, membrane thickness, and level of pore former. Effects of varying osmotic pressure, agitational intensity and intentional defect in the inner membrane on drug release were also studied. Membrane characterization by scanning electron microscopy showed dense regions with less pores on the outer surface of the disintegrating membrane and porous regions on the inner surface of the non-disintegrating asymmetric membrane. In vitro release studies for all the prepared formulations were done ($n = 6$). The drug release was independent of pH, agitational intensity and intentional defect on the membrane but dependent on the osmotic pressure of the dissolution medium. The release kinetics followed the zero order and the mechanism of release was Fickian diffusion.

Keywords: Asymmetric membrane capsule; Agitational intensity; Intentional defect; Osmotic; Asymmetric membrane in membrane

1. Introduction

Osmotic devices are the most promising strategy based reliable drug delivery systems used for controlled delivery of drugs. There has been increasing interest in the development of osmotic devices in the past 2 decades, and over 240 patented osmotic pumps have been reviewed [1]. The elementary osmotic pump (EOP) was first introduced by Theeuwes in the 1970s [2]. However, this type of EOP was only suitable for the delivery of water soluble drugs. The push-pull osmotic tablet had two major disadvantages namely the tablet core was prepared by compressing two kinds of compartments together, a complex technology as compared with that of EOP. After this coating, a complicated laser-drilling technology was used to drill the orifice next to the drug compartment [3]. Osmotic tablets with an asymmetric membrane coating, which can achieve high water fluxes, have been described [4]. Asymmetric membrane capsules (AMC) formed both ex-situ and in-situ have been described [5,6]. Asymmetric membrane film core drug delivery systems are a unique embodiment of osmotic devices which uses phase inversion technology to create the semipermeable asymmetric membrane. The design performance characteristics of osmotic systems contribute to the robust clinical performance including high constant drug plasma concentrations, lack of food effect, and, frequently, an in vitro in vivo correlation [7,8]. One of the advantages of an asymmetric membrane is the higher rate of water influx, allowing the release of drugs with a lower

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doi:10.1016/j.ejpb.2007.12.011

osmotic pressure or lower solubility. Using this basic advantage of achieving higher water influx from an AMC, the present work was undertaken to prepare an enteric system of AMC by forming a disintegrating and non-disintegrating asymmetric layer for delivery of a poorly water soluble drug, having erratic gastric absorption behavior, into the intestine, a medium of greatest sink condition for the drug.

Cefadroxil 7-[D-(-)-α-amino-α-(4 hydroxyphenyl)-acetamido]-3-methyl-3-cepham-4-carboxilic acid is an important first generation semisynthetic cephalosporin broad-spectrum antibiotic effectively used against various infections caused by Gram positive and Gram negative bacteria [9,10]. Because of its poor aqueous solubility and short elimination half life of 1.5–2 h, which usually requires multiple dosing to achieve and maintain therapeutic levels, major problem associated with this drug is its erratic dissolution profile in the gastric fluid resulting in poor absorption [11] and side effects [12,13]. Drugs that cause gastrointestinal disturbances such as nausea, vomiting or to a lesser degree diarrhea maybe given as an enteric drug delivery system. However, one of the major side effects of general formulated enteric drug delivery system is the intake of alkaline natured food, which may prematurely dissolve the enteric coatings and may not allow the system to perform for what they were intended. Formulation of a system, which would not only prevent such an episode but also release the drug in a controlled manner, is highly beneficial in order to improve the drugs, bioavailability and therapeutic efficacy.

Therefore, the aim of this work was (1) to develop asymmetric membrane in membrane capsules (AMMC) of cefadroxil, and study the release of drug from these formulations as the coating variables changed from one level to another and (2) to evaluate the effect of different osmotic pressure conditions, agitational intensity and intentional defect in the non-disintegrating membrane, on drug release from the prepared AMMCs.

2. Materials and methods

2.1. Materials

Cefadroxil (381.41) was obtained as a gift samples from Elcon drugs (P) Limited, Gurgaon, India. Sodium chloride (NaCl, 58.44), sodium hydroxide (NaOH, 40.0) and acetone were procured from Qualigens Pvt. Ltd., Mumbai, India. Ethyl cellulose (EC, 50 cps), ethyl alcohol, potassium dihydrogen orthophosphate (136.09) were procured from s.d. fine chemicals, Mumbai, India. Glycerol IP (92.10) was procured from Fine Chemicals Ltd. New Delhi, India. Cellulose acetate phthalate (CAP, 75,000) and castor oil (939.5) were procured from Central Drug House (P) Ltd., New Delhi, India. Solvents of reagent grade and double distilled water were used in all the experiments.

3. Methods

3.1. Solubility studies

The kinetics of osmotic drug release is directly related to the solubility of the drug within the formulation. Therefore, to assess the solubility of the drug in various dissolution mediums, saturated solution of the drug was prepared in double distilled water (pH 6.0), 0.1 N HCl (pH 1.2), and phosphate buffer (pH 7.4) in a closed container at 37 ± 0.5 °C. Excess amounts were added to ensure saturation and the solutions were equilibrated for 72 h. The saturated solutions were filtered, ensuring the temperature was maintained at 37 ± 0.5 °C by the use of specially designed temperature regulator boxes and the concentration determined at 262 nm after suitable dilutions using a double beam UV spectrophotometer (Shimadzu-1700, Kyoto, Japan).

3.2. Preparation of asymmetric membrane in membrane capsule of cefadroxil

AMMCs were prepared using phase inversion process in two steps. Step1, included dipping of the glass mold pins of diameter 5.52 ± 0.05 and 6.1 ± 0.022 for the body and cap, respectively, into the polymeric solutions of EC (15% w/v and 18% w/v) and glycerol (10% w/v and 12% w/v) dissolved in a mixture of acetone (50% v/v) and ethanol (30% v/v and 25% v/v), respectively, followed by quenching in a 10% w/v aqueous solution of glycerol for 10 min. After quenching, the pins were withdrawn and allowed to air dry for 10 s and again dipped into a polymeric solution consisting of CAP (20% w/v and 25% w/v) and castor oil (5% w/v and 8% w/v) dissolved in a mixture of acetone (50% v/v) and ethanol (30% v/v and 25% v/v), respectively, followed by quenching in 10% w/v castor oil solution for 10 min (step 2). After quenching, the pins were withdrawn and allowed to air dry for 10 s. The capsules were then stripped off the pins, trimmed to size and kept in desicator until use. The thickness of the inner non-disintegrating EC membranes was found to be 675 ± 0.56 μm and 788 ± 0.61 μm, respectively, whereas the thickness of the disintegrating membranes of CAP was found to be 768 ± 0.64 μm and 983 ± 0.52 μm, respectively (Fig. 1A). AMMCs were filled manually with a constant loading of drug, cefadroxil (500 mg) and osmogen (100 mg NaCl) by mixing in a polyethylene bag (1 mm thick) for 10 min. The AMMCs were then capped and sealed with a sealing solution, which contained 10% w/v EC in a mixture of acetone and alcohol. The geometric characterization of the prepared AMMC was done in comparison to a conventional hard gelatin capsule (HGC) (Table 1) and the composition of AMMC is given in Table 2.

3.3. Scanning electron microscopy (SEM)

AMMCs in pure form and those with intentional defect on the releasing membrane obtained before and

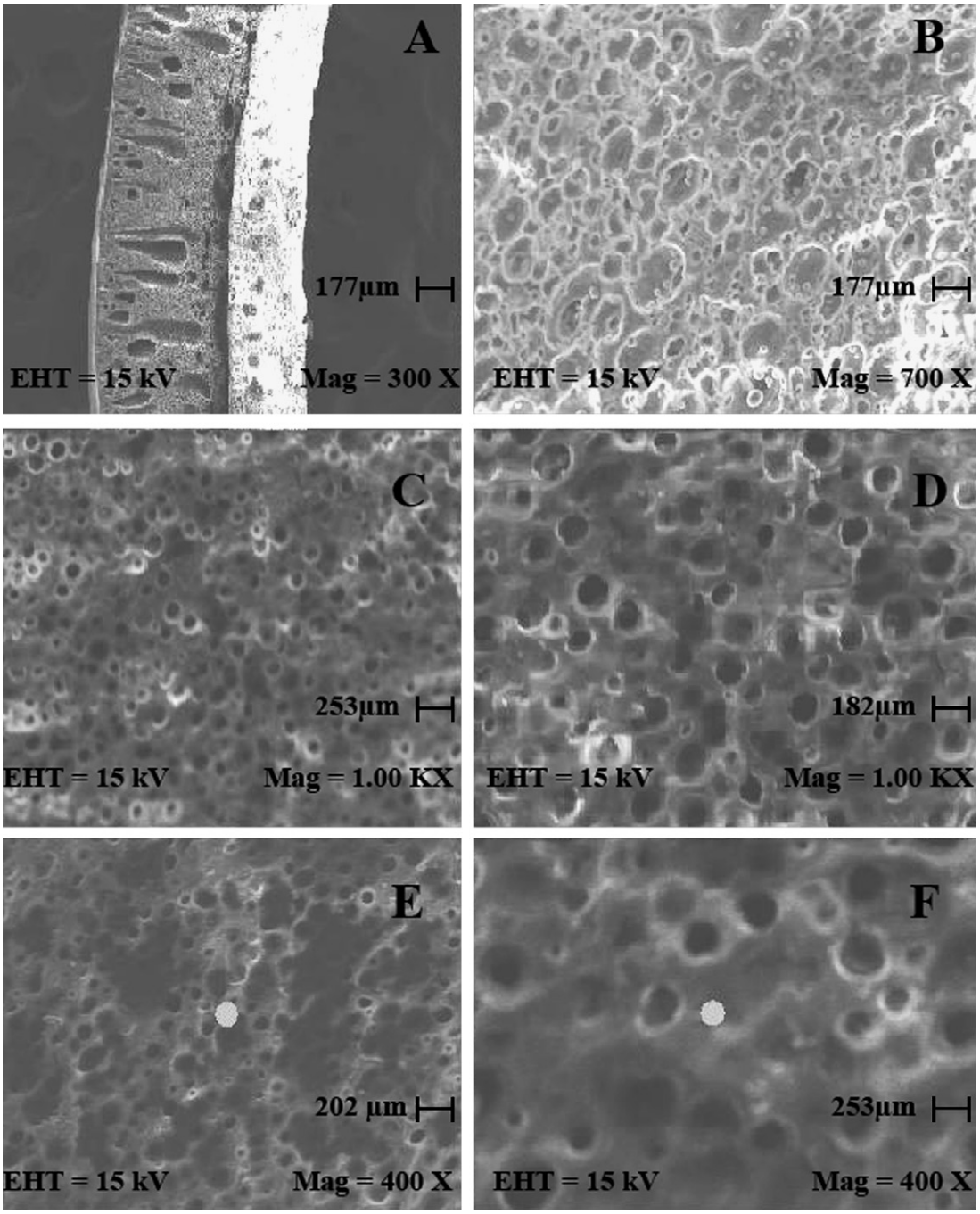

Fig. 1. SEM of coating membrane, (A) two layers of asymmetric membrane in membrane (original magnification 300×), (B) outer surface of CAP, before dissolution, 8% w/w castor oil (original magnification 700×), (C) inner surface of EC before dissolution, 12% w/w glycerol (original magnification 1000×), (D) inner surface of EC after complete dissolution, 12% w/w glycerol (original magnification 1000×), (E) inner surface of EC with intentional defect before dissolution, 12% w/w glycerol (original magnification 400×), (F) inner surface of EC with intentional defect after complete dissolution, 12% w/w glycerol (original magnification 400×).

after complete dissolution of the core contents were examined for their porous structure and thickness using F 3000 N SEM (Hitachi, Japan). After dissolution, the asymmetric membrane structures were dried at 50 °C for 8 h and stored in desicator before examination. The asymmetric membrane surfaces were then sputter coated for 5–10 min with gold by using fine coat ion sputter (Hitachi E 1010, Japan) and examined under SEM.

3.4. In vitro drug release study

In vitro cumulative drug release from the prepared formulation was studied by using USP paddle type apparatus with rotating speed and temperature set at 100 rpm and 37 ± 0.5 °C, respectively. The dissolution mediums were 0.1 N HCl, as simulated gastric fluid (SGF) (pH 1.2, 750 mL) for the first 2 h, followed by addition of 250 mL of 0.20 M tribasic sodium phosphate that had been equili-

Table 1
Characterization of AMMC with HGC

Type	Appearance	Dimensions (mm)*				
		Cap		Body		
		Length	Diameter	Length	Diameter	Sealed
HGC	Transparent	9.07 ± 0.14	6.13 ± 0.16	16.08 ± 0.17	5.14 ± 0.13	18.98 ± 0.15
AMMC	Opaque	9.87 ± 0.21	7.01 ± 0.18	17.07 ± 0.22	6.21 ± 0.09	19.56 ± 0.21

* Values are expressed as means ± SD of 3 readings ($n = 3$).

Table 2
Composition of AMMC

S. No.	Variable	Formulation code								
		*F*1	*F*2	*F*3	*F*4	*F*5	*F*6	*F*7	*F*8	*F*9
1	Cefadroxil (mg)	500	500	500	500	500	500	500	500	500
2	Sodium chloride (mg)	100	100	100	100	100	100	100	100	100
3	Ethyl cellulose (%w/v)	18	18	15	18	15	15	18	18	15
4	Glycerol (%w/v)	10	12	10	12	10	12	12	10	12
5	Cellulose acetate phthalate (%w/v)	25	20	25	25	20	20	25	20	25
6	Castor oil (%w/v)	5	8	5	8	5	8	5	5	8
7	Acetone (%v/v)	50	50	50	50	50	50	50	50	50
8	Ethanol (95%) (%v/v)	30	25	30	25	30	25	25	30	25
9	Quenching time (min)	10	10	10	10	10	10	10	10	10
10	Glycerol for quenching (%w/v)	10	10	10	10	10	10	10	10	10
11	Castor oil for quenching (%w/v)	10	10	10	10	10	10	10	10	10
12	Water (mL)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

brated to 37 ± 0.5 °C and pH adjusted to 7.4 with 2 N NaOH for creating simulated intestinal fluid (SIF) [14]. The creation of buffer stage took approximately 4 min. Five milliliters of the sample was withdrawn at specified time intervals and suitably diluted and analyzed at 262 nm.

3.5. Kinetics of drug release

In general, release of drug from an osmotic system depends upon many factors, namely osmotic pressure, pore size, coating thickness, etc. In vitro release from a conventional dosage form of 500 mg (without polymer) exhibited a limited drug release (50–60%) because of erratic dissolution profile in gastric fluid. Release from delayed formulation in form of AMMC was increased upto (80–85%). In order to describe kinetics of drug release from the drug delivery systems, various mathematical equation, have been proposed namely Zero order rate [15], First-order [16], Higuchi model [17], Hixon-Crowell cube root law [18]. In order to authenticate the release model, dissolution data were further analyzed by the Peppas and Korsmeyer equation [19]. The criteria for the best model were based on goodness of fit when incorporated in PCP Disso software (PCP Disso Version 2.08 Software, Pune, India)

3.6. Effect of osmotic pressure on drug release

The effects of osmotic pressure were determined by two methods. One was by use of an experiment, which demonstrated the release of freely water soluble dye (methylene blue) from the EC coated AMC in a medium of varying tonic solutions of NaCl. Osmotic agent inside the formulation plays an important role in deciding the release of drug from the AMC. The ability of AMMC in inhibiting the release of the drug in the gastric medium was also observed. For these studies, 50 mg methylene blue (freely water soluble dye) was taken as a color producing dye whose release from the EC coated AMC would be dependent on the molar environment created by NaCl inside the capsule. 50 mg of methylene blue with 100 mg of NaCl inside the formulation and 0 mg of NaCl in the SGF (A) represented the AMMC in gastric medium. 50 mg of methylene blue with 100 mg of NaCl inside the formulation and 50 mg of NaCl in the SIF (B) represented hypotonic conditions. 50 mg of methylene blue with 100 mg of NaCl inside the formulation and 200 mg of NaCl in SIF (C) represented hypertonic conditions. 50 mg of methylene blue with 100 mg of NaCl inside the formulation and 0 mg of NaCl in the SIF (D) represented a perfect osmotic gradient condition. The second method was by drug release studies of the optimized formulation in SIF (900 mL) (USP paddle type apparatus) (100 rpm). For this experiment (the dye was replaced by the model drug), formulation conditions were similar as mentioned above except the first formulation condition (not included in this study). An additional formulation with no osmotic agent inside and outside the formulation was also tested.

3.7. Effect of agitational intensity on drug release

In order to study the effect of agitational intensity of the release of the drug from the AMMCs, release studies of the optimized formulation were carried out in USP paddle type dissolution apparatus at 100 rpm by inducing stirred and stagnant conditions in the same run. The rotational speed was kept at 100 rpm (stirred condition), which, however was stopped intermittently to induce the stagnant conditions. The protocol used was, stirred conditions for the first 3 h (0–3 h) (which included the change from acid stage to buffer stage), stagnant condition for next 3 h (3–6 h), stirred condition for next 3 h (6–9 h), and stagnant condition for next 3 h (9–12 h). Samples were withdrawn at predetermined intervals and analyzed by UV spectrophotometer at 262 nm.

3.8. Effect of intentional defect on the asymmetric membrane

In vitro dissolution studies were conducted to assess the effect of defect in the inner, release asymmetric membrane on the release kinetics of selected best formulation. A defect (approximately 0.2 mm hole) on the face of the *F*6 was intentionally placed using a fine razor. The dissolution for this formulation (*F*′6) was carried out in the same manner as with *F*6 with no defect on the release membrane.

4. Results and discussion

4.1. Solubility studies

The solubility of cefadroxil in various dissolution mediums was 0.1 N HCl (6.205×10^{-3} g/cm^3), double distilled water (17.74×10^{-3} g/cm^3) and phosphate buffer (pH 7.4) (57.553×10^{-3} g/cm^3). Low solubility in 0.1 N HCl meant that a solubility enhancer for the drug needed to be incorporated inside the system without which, the release of the drug from the system would be uncontrolled and would result in erratic gastric absorbtion and disturbances. Whereas, a high solubility in a more alkaline medium not only meant lower side effects but also controlled osmotic delivery since the drug was now capable of being incorporated into an osmotic system (>50–300 mg/mL).

4.2. Scanning electron microscopy (SEM)

Cross-sectional view of scanning electron micrograph of asymmetric membrane in membrane obtained before dissolution (Fig. 1A) clearly indicated the presence of two layers of AMMC with an outer, dense, non-porous membranous structure of CAP, 20% w/v with oil globules (Fig. 1B) and an inner, lighter, porous layer of EC, 15% w/v (Fig. 1C). Photograph of the exhausted, integrated EC membrane obtained after dissolution showed numerous and larger pores (Fig. 1D). Photographs of intentionally defected asymmetric membrane obtained before dissolution showed approximately a 0.2 mm hole on the asymmetric membrane (Fig. 1E), which, remained almost similar with no significant change in hole diameter or position on the asymmetric membrane after dissolution (Fig. 1F).

4.3. In vitro drug release study

In vitro drug release studies were performed in three groups. In all the three groups, *F*4 and *F*5 were taken as the reference formulations to study the effect of individual variables as they changed from one level to another. All the group formulations were statistically compared with the hypothetical average release (a summarizing statistic to measure of the center of distribution) within a particular group to find the group outlier formulation at 95% confidence interval. If the values, of t (for multiple comparison test) and P, when the group formulations were compared with group hypothetical average release were greater than 2.500 and 0.5, respectively, it would have meant that the two formulations were outliers to each other, which was statistically validated by the use of simlarity factor value (f_2). *F*4 and *F*5 had all the formulation variables at lower and higher levels, respectively. Group 1, consisted of *F*4, *F*5, *F*2 and *F*3 to study the effect of both aqueous and non-aqueous plasticizers in presence of varying concentrations of the other coating variables. The order of influence in achievement of $t_{50\%}$ was *F*4 (7.52 h) > *F*2 (7.54 h) > *F*5 (7.56 h) > *F*3 (7.67 h). This order was opposite to the popular belief that higher EC concentration resulted in decreased drug release. This contradictory result might probably be due to the presence of higher concentrations of non-aqueous and the aqueous plasticizers in both the outer most and the inner layers, respectively, in *F*4 and *F*2, which enabled faster obliteration of the CAP layer and pore formation on the EC layer in the SIF. This effect could have influenced faster release in *F4 and F2* as compared to *F*5 and *F*3, which had correspondingly lower levels of both the plasticizers (Fig. 2). When compared to the average release of group 1 formulation, it was observed that both *F*4 and *F*3 were outliers of the group $t = 2.654$, $P = 0.3245$, $f_2 = 88.12$ and 79.11, zero order kinetics, $R = 0.9983$ and 0.9978, respectively, whereas *F*5 and *F*2 were significantly close to the average line ($t = 1.98$, $P = 0.0023$, $f_2 = 92.44$ and 90.55, zero order kinetics, $R = 0.9995$ and 0.9994, respectively). Group 2, consisted of *F*4, *F*5, *F*1, *F*6 and *F*7 to study the effect of varying concentrations of CAP in presence of varying concentrations of the other coating variables. The order of influence in achievement of $t_{50\%}$ was *F*6 (7.43 h) > *F*4 (7.54 h) > *F*5 (7.56 h) > *F*7 (7.63 h) > *F*1 (8 h). Both *F*6 and *F*5 had lower concentrations of CAP with lower concentrations of EC and were expected to give faster release as compared to other formulations in the group. However, on careful analysis it was observed that the shift in the release of *F*5 was probably due to the lower concentrations of both the plasticizers as compared to *F*6. *F*1 showed slow achievement of $t_{50\%}$ as it contained higher concentrations of the polymer with lower plasticizers which delayed the removal

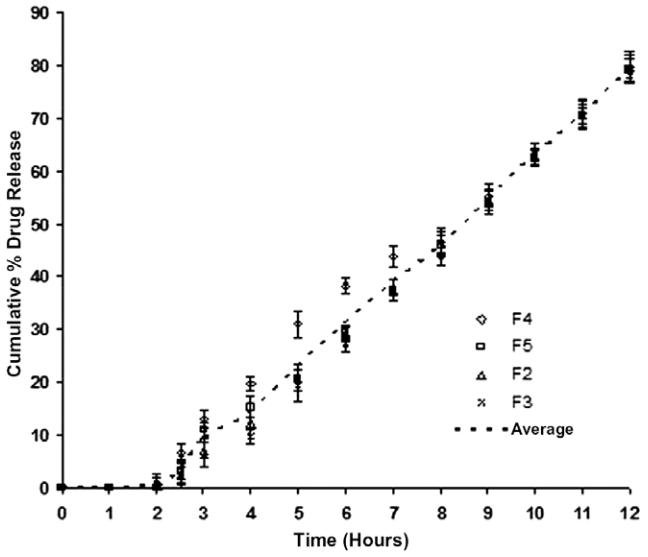

Fig. 2. Comparative dissolution profiles of group 1 formulations along with the group average.

of the CAP layer and formation of pores on the EC, AMC. Comparison with the average release for the group resulted in *F*1, *F*7 and *F*5 being the outliers in the group $t = 2.54$, 2.12 and 3.22, $P = 0.3422$, 0.3567 and 0.3987, $f_2 = 85.12$, 82.45 and 80.28, zero order kinetics, $R =$ 0.9978, 0.9973 and 0.9995, respectively, whereas *F*4 and *F*6 were significantly close to average release line ($t = 0.98$ and 1.23, $P = 0.004$ and 0.0002, $f_2 = 93.54$ and 98.45, zero order kinetics, $R = 0.9978$ and 0.9996, respectively) (Fig. 3). Group 3, consisted of *F*4, *F*5, *F*8, and *F*9 to study the effect of EC in presence of varying concentrations of the other coating variables. The order of influence in achievement of $t_{50\%}$ was *F*9 (7.49 h) > *F*4 (7.54 h) > *F*5 (7.56 h) > *F*8 (7.93 h). The order was predictable with *F*8 showing slow release due to the higher concentration of EC with lower levels of all other variables. An interesting aspect in this order was quicker achievement of $t_{50\%}$ by *F*9 as compared to *F*5. A careful investigation showed, that though *F*5 had all the variables at lower levels, *F*9 had only EC at lower level and other variables at higher levels which, meant that the outer layer would disintegrate faster in case of *F*9 due to the presence of higher levels of non-aqueous plasticizer and formation of pores on the inner EC membrane was more and large enough due to higher concentration of aqueous plasticizer in *F*9 as compared to all the lower variables in *F*5. Comparison with the hypothetical average release for the group showed *F*8 and *F*4 to be the outliers in the group ($t = 2.66$ and 2.76, $P = 0.432$ and 0.354, $f_2 = 87.65$ and 89.56, zero order kinetics, $R = 0.9923$ and 0.9983, respectively) whereas *F*5 and *F*9 were significantly close to the average line ($t = 1.13$ and 0.86, $P = 0.006$ and 0.002, $f_2 = 91.34$ and 93.22, zero order kinetics, $R = 0.9995$ and 0.9993, respectively) (Fig. 4).

4.4. Kinetics of drug release

Release models were applied on all the formulation (*F*1–*F*9) release profiles. Results showed that the best fit model in all the case except *F*1 could have followed the Zero order (describes system where drug release is independent of its concentration and is generally seen for poorly water soluble drug in matrix, transdermal, etc.), First-order (describes system in which release is dependent on its concentration and is generally seen for water soluble drug in porous matrix), Higuchi model (describes release from an insoluble matrix to be linearly related to the square root of time), Hixon Crowell model (describes release from system where the release depends on the change in surface area and diameter of particles or tablets with time. This mainly applies to system which dissolutes or erodes over time). While considering higher correlation coefficient value (*R*), the release

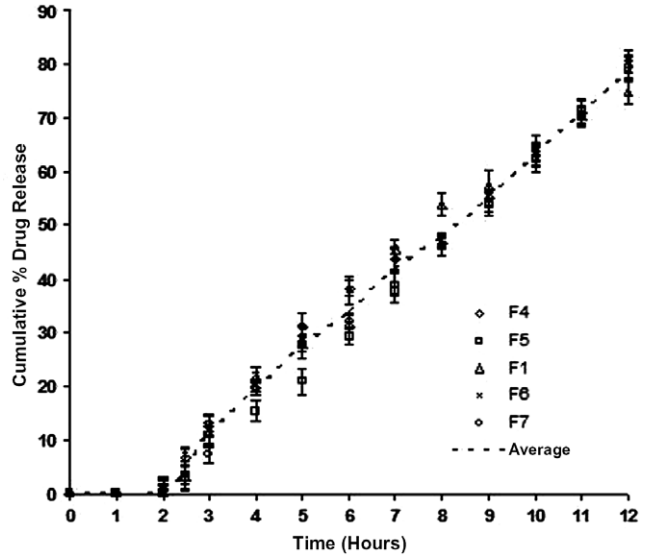

Fig. 3. Comparative dissolution profiles of group 2 formulations along with the group average.

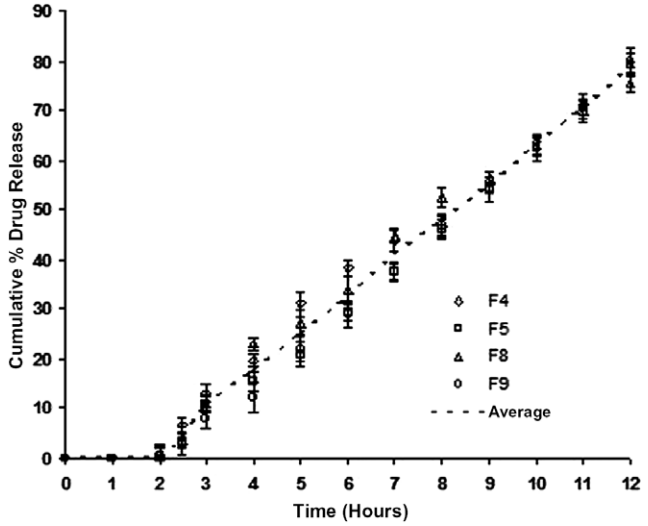

Fig. 4. Comparative dissolution profiles of group 1 formulations along with the group average.

data seems to fit zero order model better. However, considering the highest correlation coefficient value (R) for zero order release model, $F6$ seemed to be the best formulation. Drug release mechanism, using drug release data for $F6$ formulation *was* further analyzed for curve fitting based on Power law and results ($F6$: $n = 0.4359$, $k = 0.6469$, and $R = 0.9996$) confirmed that release of cefadroxil from $F6$ formulation, was Fickian diffusion.

4.5. Effect of osmotic pressure on drug release

Release of a water soluble dye (methylene blue) from AMMC and EC coated AMCs was conducted to observe the enteric release property of the capsule (Fig. 5A) and understand the underlying osmotic pumping mechanism (Fig. 5B, C, D). Observation of Fig. 5A indicated that the release of the dye was inhibited by the non-disintegration of the pH sensitive, outer CAP layer in the SGF even though a perfect osmotic gradient condition was maintained (A), whereas the dye release was observed when the formulation without the outermost layer was in SIF in a similar molar environment (D). The color tended to intensify with time (Fig. 5D). Very slight release was

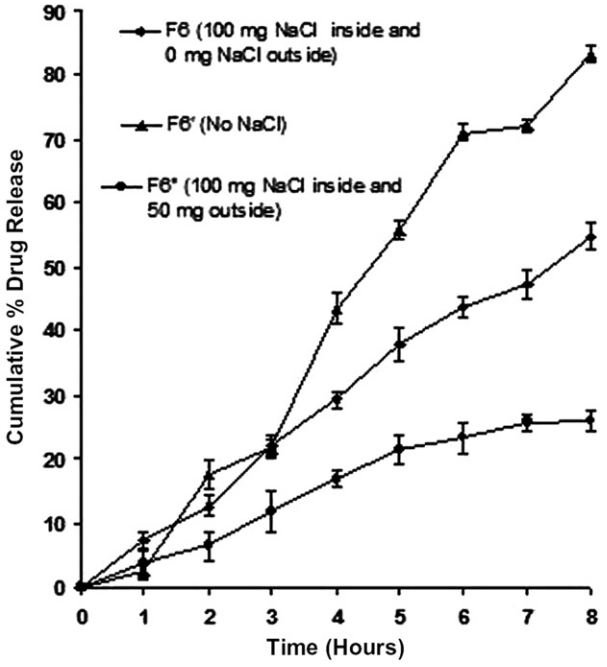

Fig. 6. Comparative dissolution profiles showing the effect of osmotic gradient.

Fig. 5. Digital photographs of water soluble dye release in (A) SGF, (B) hypotonic condition in SIF, (C) hypertonic condition in SIF and (D) perfect osmotic gradient condition in SIF.

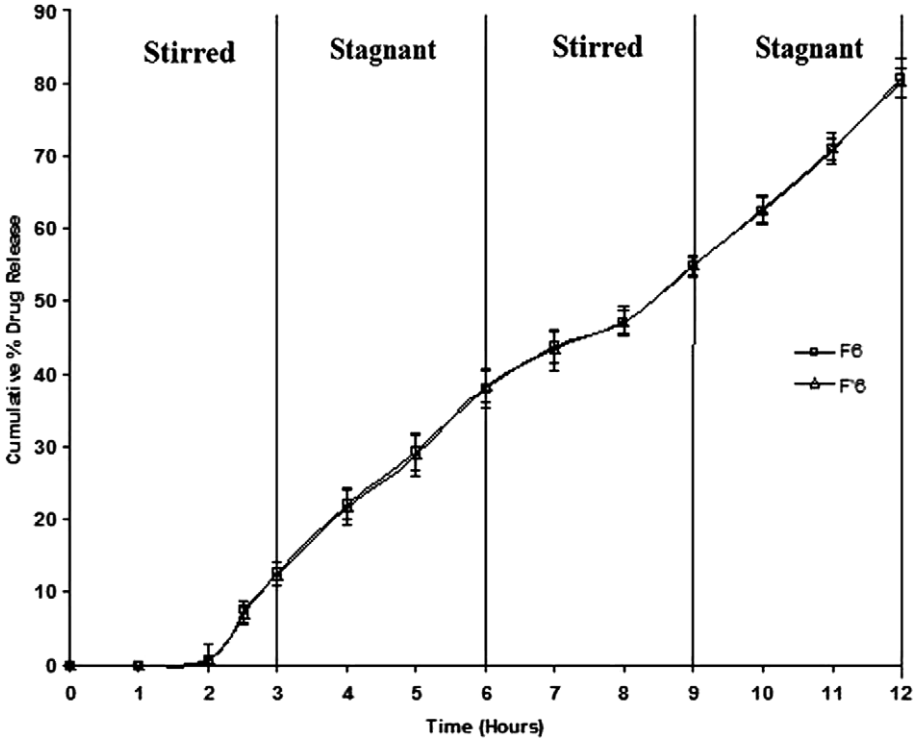

Fig. 7. Dissolution profiles of *F*6 and *F*′6 in same run stirred and stagnant conditions.

observed (B) (hypotonic condition) which became stagnant (did not intensify) with time (Fig. 5B, C, D), probably due to negligible osmotic gradient, whereas in hypertonic condition (C), since no osmotic gradient was present for release of the dye from the formulation, no dye release was found. This experiment clearly indicated that the disintegration of the outermost CAP layer was necessary for the release of the drug and that the underlying principle for drug release was osmotic pumping. The osmotic pumping mechanism was further investigated using the model drug. Results showed that the drug release was highly dependent on osmotic pressure of the release media. Cefadroxil release from *F*6′ formulation with no NaCl either inside or outside the formulation resulted in uncontrolled release of the drug, which was controlled by the molar environment created by the osmogen in formulation *F*6. The release from formulation *F*6″ with 100 mg NaCl inside and 50 mg NaCl outside the formulation was slow and low with almost a plateau reaching in the fifth hour probably due to the decreased osmotic gradient (Fig. 6). There was no release seen when hypertonic condition of the dissolution medium prevailed. Therefore, it was concluded that the primary mechanism governing the drug release from the developed formulations was osmotic pumping.

4.6. Effect of agitational intensity and intentional defect on drug release

The effects of agitational intensity and intentional defect on the drug release from the prepared formulation with (*F*′6) and without defect (*F*6) were observed by inducing stirred (100 rpm) and stagnant conditions in the same run. The results (Fig. 7) showed the release profile of cefadroxil from both the formulations to be similar at 99 % confidence interval ($t = 0.981$, $P = 0.0002$ and $f_2 = 98.43$). This meant that the release of the drug from AMMC was not only independent of agitational intensity of the medium but also the defect in the release membrane.

5. Conclusion

AMMCs were successfully prepared for delayed and controlled delivery of poorly water soluble cefadroxil. The developed system was not only able to delay the release of the drug for the first 2 h in the gastric medium and then control the release in the intestinal medium for an extended period of time (12 h) but was also independent of the agitational intensity and the defect of the release membrane. The AMMC formulation approach could be utilized for both osmotic delivery and as delayed release formulation for poorly water soluble drug.

References

[1] G. Santus, R.W. Baker, Osmotic drug delivery: a review of the patent literature, J. Control. Release 35 (1995) 1–21.
[2] F. Theeuwes, Elementary osmotic pump, J. Pharm. Sci. 64 (1975) 1987–1991.
[3] F. Theeuwes, R.J. Saunders, W.S. Mefford, Process for forming outlet passageways in pills using a laser, US patent 4,088,864 (1978).
[4] S.M. Herbig, J.R. Cardinal, R.W. Korsmeyer, K.L. Smith, Asymmetric membrane tablet coatings for osmotic drug delivery, J. Control. Release 35 (1995) 127–136.

[5] A.K. Philip, K. Pathak, Osmotic flow through asymmetric membrane: a means for controlled delivery of drugs with varying solubility, AAPS PharmSciTech. 7 (2006) 21–25. doi:10.1208/pt070356.
[6] A. Philip, K. Pathak, In-situ formed asymmetric membrane capsule for osmotic release of poorly water soluble drug, PDA-J. Pharm. Sci. Tech. 61 (2007) 24–36.
[7] S.K. Gupta, L. Atkinson, F. Theeuwes, P. Wong, J. Longstreth, Pharmacokinetics of verapamil from an osmotic system with delayed onset, Eur. J. Pharm. Biopharm. 42 (1996) 74–81.
[8] J.S. Grundy, R.T. Foster, The nifedipine gastrointestinal therapeutic system (GITS). Evaluation of pharmaceutical, pharmacokinetic and pharmacological properties, Clin. Pharmacokine 30 (1996) 28–51.
[9] F. Rosa, S. Ripa, M. Prenna, A. Ghezzi, M. Pfeffer, Pharmacokinetics of cefadroxil after oral administration in humans, Antimic. Agents Chemother. 21 (1982) 320–322.
[10] R.E. Buck, K.E. Price, Cefadroxil, a new broad spectrum cephalosporin, Antimic. Agents Chemother 11 (1977) 324–330.
[11] A.B. Schnürch, D. Guggi, Y. Pinter, Thiolated chitosans: development and in vitro evaluation of a mucoadhesive, permeation enhancing oral drug delivery system, J. Control. Release 94 (2004) 177–186.
[12] S.T. Bhagwati, S.M. Hiremath, S.A. Sreeniwas, Formulation and evaluation of cefadroxil dispersible tablets, Pharm. Rev. 4 (2006) 136–139.
[13] in S.C. Sweetman (Ed.), Martindale – The Complete Drug Reference, Pharmaceutical Press, London, 2002, pp. 161–162.
[14] The United State Pharmacopoeia, United State Pharmacopoeial Convention, Rockville 27 (2004) 2308.
[15] N. Najib, M. Suleiman, The kinetics of drug release from ethyl cellulose solid dispersions, Drug Dev. Ind. Pharm. 11 (1985) 2169–2181.
[16] S.J. Desai, P. Singh, A.P. Simonelli, W.I. Higuchi, Investigation of factors influencing release of solid drug dispersed in wax matrices. III. Quantitative studies involving polyethylene plastic matrix, J. Pharm. Sci. 55 (1966) 1230–1234.
[17] T. Higuchi, Mechanism of sustained action medication, theoretical analysis of rate of release of solid drugs dispersed in solid matrices, J. Pharm. Sci. 52 (1963) 1145–1149.
[18] A.W. Hixson, J.H. Crowell, Dependence of reaction velocity upon surface and agitation: I-theoretical consideration, Ind. Eng. Chem. 23 (1931) 923–931.
[19] R.W. Korsmeyer, R. Gurny, E.M. Doelker, P. Buri, N.A. Peppas, Mechanism of solute release from porous hydrophilic polymers, Int. J. Pharm. 15 (1983) 25–35.