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Osmotically controlled oral delivery of ciprofloxacin through asymmetric membrane capsules

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Asymmetric membrane capsules (AMCs) are based on the concept of osmotic pressure but are much simpler to manufacture. Further, they can be suitably optimized by varying the parameters like concentration of pore former, polymer, osmotic agents and solubility enhancers to cater the specific needs of a particular formulation. The main objective of the present work was to exploit the concept of AMCs for the controlled delivery of poorly soluble anti-infective drugs. Ciprofloxacin was chosen as the model drug. Nine AMCs (F1-F9) with varying concentrations of cellulose acetate [CA] (polymer-12% w/v, 16% w/v and 20% w/v) and glycerol (pore former- 50% w/w, 60% w/w and 70% w/w of polymer) were prepared. AMCs F1-F3 were discarded because of poor rigidity. 18 formulations (F4A-F9C) were prepared with the remaining 6 AMCs by varying concentrations of mannitol in the core (osmogen-15% w/w, 25% w/w and 50 % w/w of drug). F6C prepared with 16% CA, 70% glycerol and 50% mannitol gave highest release (57.93 ± 0.93 %) after 12 h. Scanning electron microscopy revealed asymmetric structure of the membrane and osmotic release (zero order) through pores formed *in situ* was confirmed. Three concentrations of tartaric acid were used in F6C (T1-5%, T2-15%, T3-20%) for further optimization. T3 gave maximum release after 12 h (82.21 ± 0.71 %) and was selected as final optimized formulation. The study concluded that AMCs containing a suitable osmogen and a solublizer, can successfully deliver poorly soluble anti-infective drugs in a controlled manner.

1. Introduction

Osmotically controlled oral drug delivery systems are innovative and highly versatile systems (Eckenhoff et al. 1981), utilizing principles of osmosis for controlled delivery of drugs. These systems release the drugs independent of GI physiological factors to a large extent (Theeuwes et al. 1985). Oral controlled release (CR) systems like matrix or reservoir pose problems of bioavailability fluctuations due to variations in gastric pH and hydrodynamic conditions of the body (Sastry et al. 1997).

Alza® Corporation of USA was the first to develop an oral osmotic pump (Verma et al. 2002). The simplest design consists of an osmotically active core surrounded by a semi permeable membrane, with one or more delivery ports through which the drug is delivered in a controlled fashion. Various modifications of this basic design have been reported (Santus et al. 1995), and reviewed (Verma et al. 2000).

One modification is the utilization of asymmetric membrane coating for osmotic drug delivery (Cardinal et al. 1997a). Their use as tablet coatings for osmotic drug delivery (Herbig et al. 1995) and as a capsule dosage form (Thombre et al. 1997), has been recently described. Asymmetric membrane capsules (AMCs) are the simplest and a unique embodiment of osmotic devices with *in situ* pore formation, avoiding laser drilling and can also be used for the controlled delivery of poorly soluble drugs (Swarbrick et al. 1991). It consists of a drug containing core surrounded by a membrane which has an asymmetric structure (Fig. 1) i.e., it has a relatively thin, dense region supported on a thicker, porous region (Thombre et al. 1999a). Most of the resistance to mass transfer is exerted by the dense portion of the membrane while the porous substrate provides mechanical strength and durability. The system maintains control over the drug release by controlling the porosity of the asymmetric

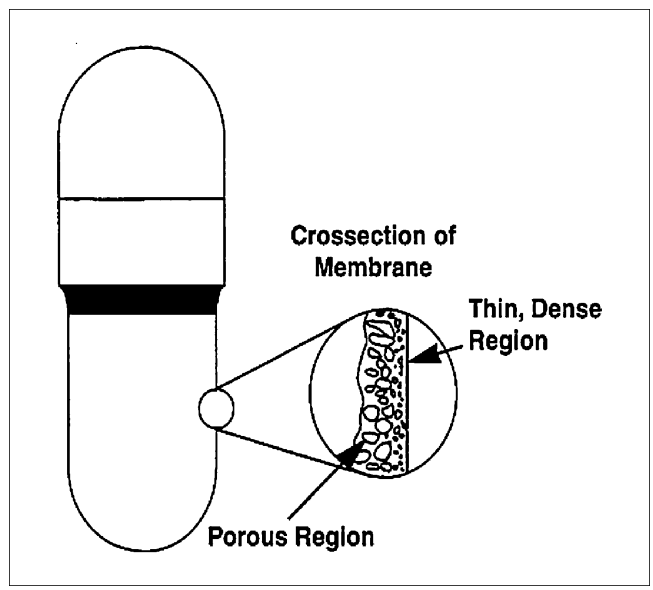

Fig. 1: Schematic view of asymmetric membrane capsule (Thombre et al. 1999b)

Table 1: Length and diameter of different asymmetric membrane capsules

AMCs	Length (mm)			Diameter(mm)	
	Cap	Body	Joined	Cap	Body
F1	9.21 ± 0.02	14.22 ± 0.02	18.40 ± 0.23	6.52 ± 0.09	6.12 ± 0.56
F2	9.20 ± 0.25	14.20 ± 0.03	18.40 ± 0.31	6.50 ± 0.52	6.12 ± 0.56
F3	9.15 ± 0.06	14.21 ± 0.62	18.39 ± 0.09	6.50 ± 0.69	6.10 ± 1.22
F4	9.50 ± 0.77	14.51 ± 0.16	18.95 ± 0.27	6.75 ± 0.78	6.25 ± 0.56
F5	9.45 ± 0.54	14.50 ± 0.25	18.89 ± 0.81	6.69 ± 1.02	6.26 ± 0.36
F6	9.51 ± 0.06	14.47 ± 0.08	18.98 ± 0.74	6.80 ± 0.98	6.25 ± 0.35
F7	9.80 ± 0.29	14.79 ± 0.67	18.45 ± 0.58	6.95 ± 0.75	6.32 ± 0.05
F8	9.78 ± 0.12	14.78 ± 0.59	18.56 ± 0.26	6.92 ± 0.85	6.30 ± 0.62
F9	9.82 ± 0.38	14.80 ± 0.26	18.55 ± 0.04	6.92 ± 0.12	6.30 ± 0.41

Values are indicated in mean ± S.D. (n = 20)

membrane, hence the name controlled porosity osmotic pump (Zentner et al. 1985b).

The capsule shell does not dissolve instantly to release the drug; instead it is released over a prolonged duration *via* osmotic pumping through pores formed in situ and by diffusion to a minor extent through the walls of the membrane (Zentner et al. 1990). The total amount of drug delivered from AM dosage form per unit time, $(dm/dt)_t$ is (Swarbrick et al. 1991):

$$(dm/dt)_t = (dm/dt) + (dm/dt)_d$$

$$(dm/dt)_t = (A/h)k\Delta\pi\, S + (P_d\, AS)/h$$

where, (dm/dt) is the amount released by osmotic pumping, $(dm/dt)_d$ is the amount released due to diffusion, A is the cross sectional area for transport, h is the membrane thickness, k is permeability of the membrane, $\Delta\pi$ is the osmotic pressure difference across the membrane ($\Delta\pi_{in}$ - $\Delta\pi_{out}$), S is the solubility of the drug and P_d is the dissolved drug permeability in the membrane.

The present study aims at evaluating the AMCs as a controlled delivery system for poorly soluble anti-infective drugs. Anti-infective drugs with short half life require more than once daily administration which reduces patient compliance and increases incidence of resistance development. Frequent administration of these drugs produce fluctuations in plasma levels that either exceed safe therapeutic concentration or quickly fall below the MEC. All these factors greatly contribute to the failure of anti-infective therapy. Ciprofloxacin was chosen as the model drug, which is a poorly soluble, broad spectrum, class II flouroquinolone antibiotic with short half life and is widely used extensively in human health applications (Clarke's Analysis 2004).

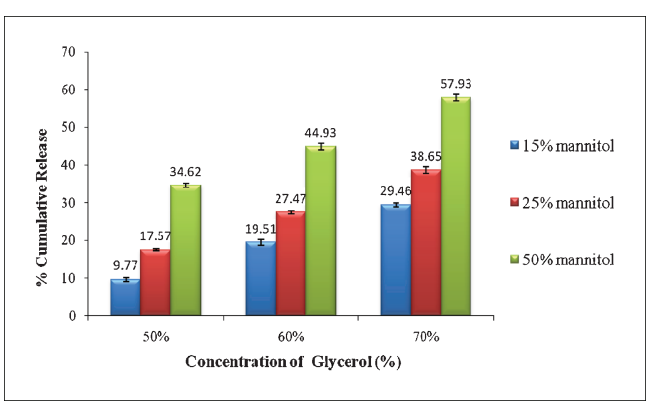

Fig. 2: Effect of concentration of glycerol (pore former) on the release profile of Asymmetric Membrane Capsules (F4A-F6C)

Thus it was envisaged to develop and access AMCs as a means to deliver poorly water soluble anti-infective drugs such as ciprofloxacin, in a controlled manner. Further the study was carried out to evaluate the effect of membrane thickness (polymer concentration) and membrane porosity (pore former concentration) on the drug release from AMCs. Effects of osmogen and solublizer were also studied. Drug release mechanisms and membrane structure are discussed.

2. Investigations, results and discussion

2.1. Physical parameters of empty capsules

All the capsules (F1-F9) appeared to be white, opaque and glossy with no visible imperfections. This shows that the concentration of polymer (CA) and pore former (glycerol) has no effect on the physical appearance of AMCs. This further confirms that the process of producing these AMCs was reproducible (Lin et al. 2003).

The rigidity was found to be variable among AMCs fabricated with different concentrations of CA and glycerol. The AMCs (F1-F3) were very soft with slight difference between F1, F2, F3. The shells of capsules (F4-F6) were softer than those of capsules (F7-F9) but were more rigid than shells of AMCs (F1-F3). No significant difference was found within F4, F5 and F6. The same pattern of difference was observed within F7, F8 and F9. The result showed that the concentration of CA rather than glycerol concentration has a more pronounced effect on the rigidity. Rigidity increases with increase in CA concentration due to proportionate increase in thickness. The slight increase in rigidity with increase in glycerol concentration is because glycerol acts as a plasticizer (Thombre et al. 1999b).

Separate and joined lengths and separate diameter of caps and bodies (Table 1) were found to be consistent within the 20 AMCs from each batch (F1-F9). This confirms that the process of producing these AMCs was reproducible and robust (Lin et al. 2003). Length as well as diameter was found to be very slightly increasing with increase in CA concentration. Glycerol did not show any effect on the length and diameter.

Twenty AMCs from each batch gave no variation in weight and membrane thickness within themselves. This confirms the uniformity of weight as well as robustness of the process employed in their fabrication (Lin et al. 2003). The membrane thickness was found to increase significantly ($p < 0.05$) with increase in CA concentration, however a non significant difference was observed with increase in glycerol concentration (Table 2). This is because glycerol acts as a pore former (Cardinal et al. 1995), and thus do not contribute to membrane thickness. Weight of the capsules was found to increase with increase in concentration of CA and glycerol in the membrane. The increase in weight with

Table 2: Thickness and weight variation of different asymmetric membrane capsules

AMCs	Thickness (mm)	Weight variation (mg)
F1	0.22 ± 0.59	40.51 ± 0.97
F2	0.20 ± 0.87	47.75 ± 0.11
F3	0.23 ± 0.74	52.59 ± 2.11
F4	0.56 ± 1.02	77.41 ± 0.55
F5	0.55 ± 0.23	84.40 ± 0.71
F6	0.54 ± 0.19	90.10 ± 0.64
F7	0.84 ± 0.77	105.01 ± 1.11
F8	0.79 ± 0.89	114.07 ± 0.32
F9	0.85 ± 0.63	125.11 ± 0.74

Values are indicated in mean ± S.D. (n = 20)

concentration of CA was much greater than that with glycerol. This corresponds with the fact that concentration of polymer has more pronounced effect on the weight of the AMCs, as compared to that of pore former (Philip et al. 2007a, 2008).
It was observed from the physical evaluation that AMCs formed with 12 % CA (F1, F2, F3) were very soft and easily broken. So they were discarded. Further studies were carried out only with rest of the AMCs after filling and sealing them (F4-F9).

2.2. *In vitro release studies*

A statistically significant increase in total release ($p < 0.05$) was observed with increase in glycerol concentration (in capsule shell), in both the groups i.e (F4A-F6C) (Fig. 2) and (F7A-F9C) (Fig. 3) from 50 % to 70 %. This is probably due to the pore forming activity of the glycerol (Cardinal et al. 1997a). Increased concentration of glycerol led to increased pore formation on the capsule shell thus enhancing porosity and permeability of the membrane, hence leading to increased release.
The total percentage drug release was found to increase significantly ($p < 0.05$) with increase in the concentration of mannitol (in the core) in both the groups i.e (F4A-F6C) (Fig. 4) and (F7A-F9C) (Fig. 5), from 15 % to 50 %. Mannitol acts as an osmogen. Increasing concentration of mannitol leads to pumping of more and more dissolution media into the core thus enhanced internal osmotic pressure and osmotic driving force, $\Delta\pi$ ($\Delta\pi = \pi_{in} - \pi_{out}$) hence, enhancing the release of the drug from the capsules (Kanig et al. 1964).
AMC (F6C) and (F9C) prepared with 70 % glycerol and containing 50 % mannitol was found to be significantly greater ($p < 0.05$) than the cumulative release of remaining eight AMCs. This is due to the synergistic release enhancement effect of increased glycerol and mannitol.

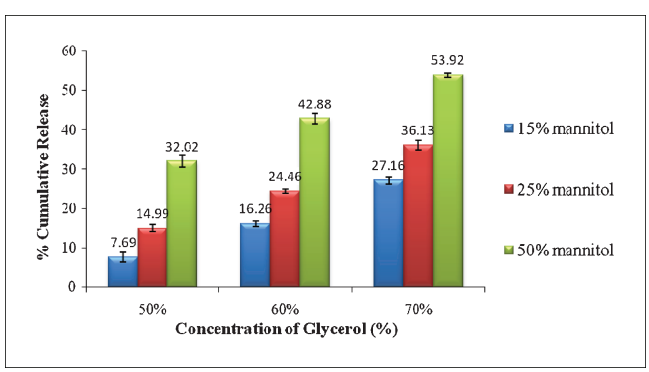

Fig. 3: Effect of concentration of glycerol (pore former) on the release profile of Asymmetric Membrane Capsules (F7A-F9C)

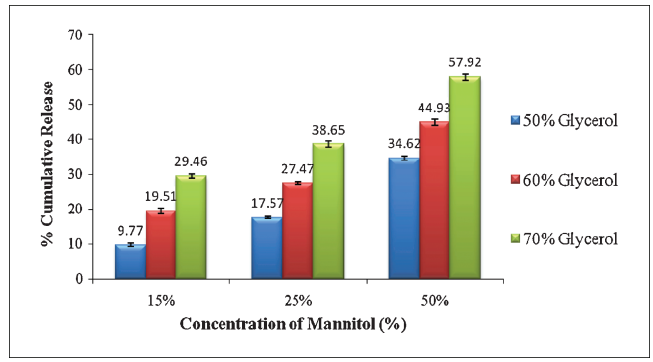

Fig. 4: Effect of concentration of mannitol (osmogen) on the release profile of Asymmetric Membrane Capsules (F4A-F6C)

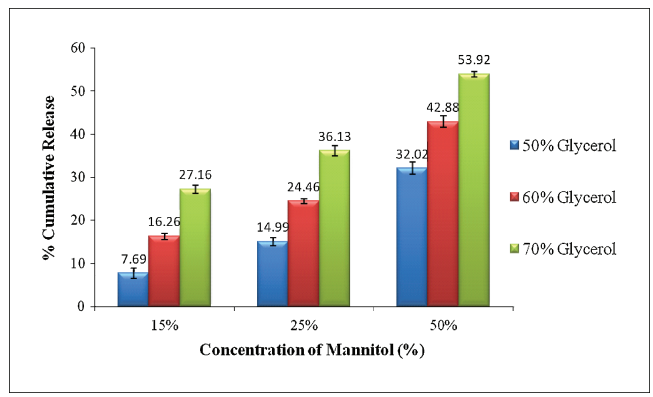

Fig. 5: Effect of concentration of mannitol (osmogen) on the release profile of Asymmetric Membrane Capsules (F7A-F9C)

No statistical significant difference was observed between the formulations F6C and F9C (Table 3). This was probably attributed to the presence of glycerol which might have reduced the drug holding capacity of the polymer due to pore formation. The observed slight difference in the drug release might be due to the increased diffusional path for the drug to traverse before being released from the capsules with 20 % CA as compared to those with 16 % CA. Thus, the CA concentrations used in the present study and hence thickness of the membrane did not play a major role in controlling the release.
AMC, F6C with 16 % CA gave maximum release in 12 h (57.93 ± 0.93 %), thus was selected as the most suitable candidate among all the formulations to be taken to the next level of formulation development.

2.3. *Drug release kinetics*

All the formulations F4A-F9C were subjected to zero order, first order, Higuchi and Hixson-Crowell kinetic models. Mostly all of them showed poor linearity with Higuchian kinetics indicating that diffusion through the walls played a minor role in drug release. A poor linearity with Hixson-Crowell indicated that the surface area of the capsule did not change with time. This confirmed that the capsule wall did not erode or disintegrate with

Table 3: Comparative total percentage release (12 h) of asymmetric membrane capsules prepared with different cellulose acetate (CA) concentrations

Formulation Code	% CA (w/v)	% Cumulative release ± S.D. (in 12 h)
F6C	16	57.93 ± 0.93
F9C	20	53.92 ± 0.64

Table 4: Release rate constants (k) and correlation coefficients (R^2) of different formulations

Formulation	Zero order		First order		Higuchi		Hixson-Crowell	
	k	R^2	k	R^2	k	R^2	k	R^2
F4A	0.873	0.992	–0.004	0.988	3.078	0.924	–0.039	0.984
F4B	1.536	0.992	–0.007	0.989	5.449	0.934	–0.026	0.989
F4C	2.941	0.995	–0.015	0.982	10.335	0.908	–0.051	0.991
F5A	1.720	0.991	–0.008	0.984	6.016	0.909	–0.028	0.919
F5B	2.332	0.990	–0.011	0.985	8.179	0.912	–0.039	0.980
F5C	3.884	0.989	–0.012	0.977	13.580	0.910	–0.071	0.971
F6A	2.483	0.994	–0.012	0.981	8.578	0.885	–0.042	0.984
F6B	3.464	0.987	–0.018	0.983	12.124	0.908	–0.061	0.981
F6C	5.078	0.996	–0.030	0.979	18.022	0.939	–0.096	0.986
F7A	0.672	0.984	–0.003	0.981	2.378	0.923	–0.011	0.979
F7B	1.189	0.973	–0.005	0.945	4.094	0.815	–0.019	0.948
F7C	2.795	0.974	–0.014	0.970	9.801	0.916	–0.048	0.961
F8A	1.437	0.993	–0.006	0.989	5.020	0.908	–0.023	0.992
F8B	2.128	0.991	–0.010	0.987	7.467	0.916	–0.035	0.989
F8C	3.619	0.985	–0.019	0.981	12.843	0.929	–0.065	0.978
F9A	2.365	0.988	–0.011	0.982	8.214	0.893	–0.040	0.984
F9B	3.040	0.984	–0.015	0.970	10.450	0.871	–0.053	0.976
F9C	4.669	0.993	–0.027	0.986	16.361	0.913	–0.088	0.991

time to release the drug. On comparing correlation coefficients (R^2), all of them were found to release the drug in accordance to zero order kinetics (Table 4) which shows that the release mechanism of AMCs consists of dissolution of drug inside the capsule followed by slow release which is independent of drug concentration inside the capsule (Costa et al. 2000). The mechanism is also consistent with osmotic release of the drug (Theeuwes et al. 1985). Thus it can be considered that osmosis might play a major role in drug release from AMCs.

2.4. Surface characterization of optimized capsule shell using SEM

A relatively thin dense region supported on a porous substrate with longer micropores (Fig. 6a) was clearly visible in the SEM micrograph of the capsule wall (F6C) obtained before dissolution, confirming that the capsule membrane was asymmetric. The formation of asymmetry was a result of phase inversion which occurred during membrane preparation (quenching). Numerous pores were visible in the porous region (Fig. 6b). No pore structures were shown in the dense region (Fig. 6c). After complete dissolution, the exhausted membrane showed large number of pores similar to a net like structure (Fig. 6d).

2.5. Confirmation of in situ pore formation

A deep red colored stream was observed after a lag time, when AMC (F6) encapsulated with amaranth dye, was suspended in water (Fig. 7). This continued upto 0.5 h. The red color was released from one or multiple holes formed *in situ*, in the thin structure of asymmetric membrane (Thombre et al. 1999b). No particular position on the capsule wall was favored for pore formation.

2.6. Two excipient system

Formulation F6C with 70 % glycerol (pore former), 16 % CA (polymer) and containing 50 % mannitol (osmogen) was found to give maximum release after 12 h (section) but only 57.93 ± 0.93 %, due to very poor solubility of Ciprofloxacin and inability of the mannitol to increase its solubility (Cardinal et al. 1997b). Hence, the rationale to study the effect of solublizer on the drug release from F6C was chosen.

The total percentage drug release after 12 h (Table 5) from all the three formulations (T1, T2, T3) was found to be significantly greater ($p < 0.05$) than that without tartaric acid (F6C). This was due to the solublization effect of tartaric acid on the drug. The release was found to increase significantly from T1-T3 ($P < 0.05$) consistent with the increase in the concentration of tartaric acid in the three AMCs (Fig. 8). T3 containing the highest concentration of tartaric acid (20 %) gave the maximum release (82.21 ± 0.71 %) after 12 h.

2.7. Demonstration of osmotic release mechanism

It was observed during *in vitro* release studies of AMCs that for a constant capsule shell composition, the release rate was a function of the contents within the capsule. A direct correlation was observed between the release profile (rate and amount) and the concentration of osmogen i.e. mannitol (section 2.2) and with that of solublizer i.e. tartaric acid (section 2.6). These observations are consistent with drug release by osmotic mechanism.

The total percentage drug release after 12 h was found to decrease significantly (Fig. 8) with increase in concentration of NaCl in the external medium ($p < 0.05$) from 0.5 % to 2 %, due to increase in external osmotic pressure with increase in NaCl concentration in the external environment. Increased external osmotic pressure leads to decreased osmotic pressure differential ($\Delta\pi$) between the capsule core and the medium ($\Delta\pi = \pi_{in} - \pi_{out}$), thus reducing driving force for osmotic pumping ($\Delta\pi$) of

Table 5: Comparative total percentage release (12 h) of different asymmetric membrane capsules containing different concentrations of tartaric acid (n = 3)

Formulation Code	Taratric acid (% w/w)	% Release ± S.D (in 12 h)
F6C	0	57.94 ± 0.94
T1	5	65.93 ± 0.98
T2	15	76.27 ± 1.51
T3	20	82.21 ± 0.71

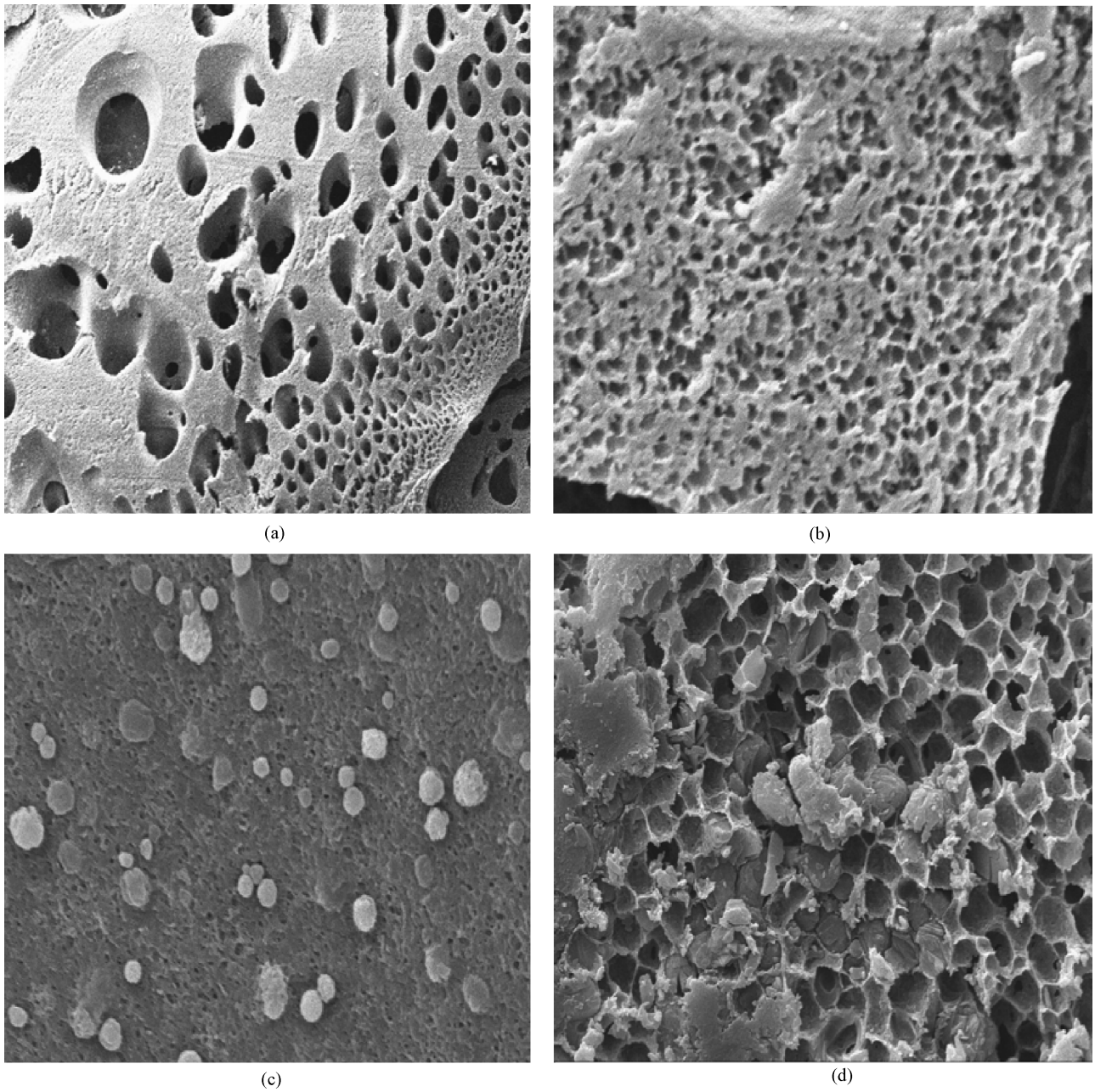

Fig. 6: SEM photographs of Asymmetric Membrane Capsule (F6C) shell at 2.38 KX magnification. (a) Cross section showing dense region supported over porous substrate, before dissoution. (b) Before dissolution showing inner porous region. (c) Before dissolution showing outer dense region (d) After complete dissolution showing net like structure

the drug from the capsule. From this, it can be concluded that the osmosis is the primary mechanism governing the drug release from the developed formulations.

2.8. Evaluation of two-excipient system

On comparing the correlation coefficients (R^2) it was observed that all the three formulations containing tartaric acid showed similar pattern and release mechanism (Table 6). They were also found to exhibit zero order kinetics like formulations which did not contain tartaric acid (Section 2.3). Thus, it can be concluded that kinetics and release mechanism of AMCs was not affected by the addition of tartaric acid.

Individual weights of all the 20 capsules from the optimized formulation batch (T3), were found to vary between 566.5 mg and 463.5 mg (average 515 mg), which complied with USP. Drug distribution was found to be uniform, with average uniformity of content $98.58 \pm 0.82\%$.

2.9. Stability studies

A 3 month accelerated stability study did not show a change in physical appearance of AMCs. A non-significant decrease occurred in drug content from 98.95 ± 0.55 % to 97.58 ± 0.37 % in 3 months (Table 7). Total percentage drug release after 12 h also showed a non-significant decrease from 82.21 ± 0.71 % to 80.10 ± 0.23 % in 3 months (Table 8). Thus it could be concluded that the analyzed formulation was chemically stable during the storage time and bioavailability of the formulation is not affected by storage conditions.

3. Experimental

3.1. Materials

Ciprofloxacin was obtained as a gift sample from Lupin Pharmaceuticals Pvt. Ltd. Cellulose acetate (Eastman-CA-398-10) was a kind gift from Ranbaxy India Ltd. Acetone, Ethyl alcohol and D(-) Mannitol were purchased from Merck Pvt. Ltd. Glycerol was purchased from Loba Chemie Pvt. Ltd. L (+)-

Table 6: Release rate constants (k) and correlation coefficients (R^2) of formulations containing different concentrations of tartaric acid

Formulation codes	Zero order		First order		Higuchi		Hixson-Crowell	
	k	R^2	k	R^2	k	R^2	k	R^2
T1	5.958	0.993	–0.040	0.989	21.09	0.932	–0.001	0.989
T2	6.589	0.997	–0.049	0.970	23.32	0.937	–0.011	0.987
T3	7.171	0.997	–0.059	0.967	85.41	0.933	–0.014	0.987

Fig. 7: *In situ* pore formation

Tartaric acid, Sodium chloride and Sodium lauryl sulphate were obtained from CDH Pvt. Ltd. Stainless steel capsule mold were a product of M.K. Scientific, New Delhi.

3.2. Preparation of asymmetric membrane capsules of ciprofloxacin

The asymmetric membrane capsule shells were prepared by a phase inversion method (Thombre et al. 1999a). Wet process was used for carrying out phase inversion where the membrane structure was precipitated on stainless steel mold pins having a diameter of 6.1 ± 0.05 mm and 6.5 ± 0.02 mm and a length of 16 ± 0.14 mm and 9 ± 0.11 mm for the body and cap respectively (Wang et al. 2005). The dip-coating (Thombre et al. 1999a, 1997), process was carried out in following steps. Composition of capsule shells is given in Table 9.

Dipping: Accurately weighed quantities of CA were dissolved in acetone-ethanol solvent system to form membrane forming solutions (dipping solutions) of CA (12 % w/v, 16 % w/v, and 20 % w/v) at 250 rpm until homogenous solution was obtained. Glycerol (50 % w/w, 60 % w/w, and 70 % w/w) was added to the resulting solutions separately under stirring. Mold pins dimensioned so as to form the capsule body and cap were dipped for 1 min in different dipping solutions.

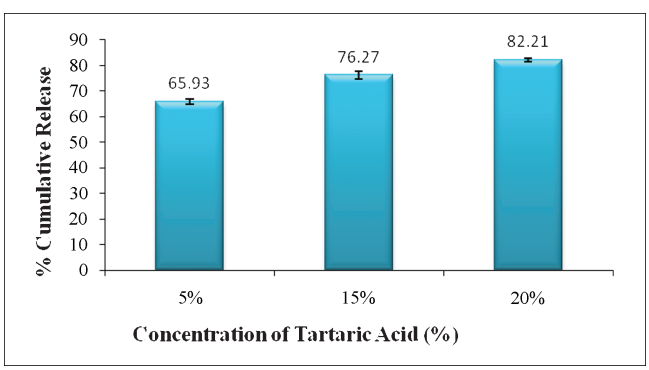

Fig. 8: Effect of concentration of tartaric acid (solublizer) on the release profile

Table 7: Effect of storage conditions on the drug content

Time (months)	% Content ± S.D. (40 °C ± 2 °C/75%RH ± 5%)
0	98.95 ± 0.55
1	98.55 ± 0.56
2	97.99 ± 0.29
3	97.58 ± 0.37

Values are indicated in mean ± S.D. (n = 3).

Spinning: Dipped mold pins were slowly withdrawn and rotated twice to distribute the polymer evenly around the pins. As the phase separation takes place the polymer become progressively more viscous to form a capsular shape over the mold pins.

Quenching: The fixtures so obtained were lowered for 15 min into the aqueous quench bath containing 10 % w/v glycerol in water.

Stripping, drying and trimming: After quenching, the pins were withdrawn and asymmetric membranes in the shape of body and cap were stripped off the pins. They were dried at ambient room temperature for 6–8 h and trimmed to size.

The bodies of the fabricated AMCs (F4-F9) were filled manually with prepared physical mixtures of drug (250 mg) and osmogen (mannitol; 15 % w/w, 25 % w/w, 50 % w/w of drug); caps were snugly fitted over them and cleaned. Finally the cap and body were sealed with a sealing solution (16 % w/v CA in 90:10, acetone:ethanol) to ensure that no release takes place through the seal (Thombre et al. 1999a).

3.3. Evaluation of asymmetric membrane capsules

Fabricated AMCs were visually inspected for colour, appearance, presence of imperfections, rigidity and gloss (Lin et al. 2003). Length, diameter and thickness (Wang et al. 2005) were measured for each batch (F1-F9). To determine uniformity of weight, weight variation (Chauhan et al. 2007) was calculated for each (F1-F9).

In vitro drug release studies (USP XXVII/NF 22, 2004f), of all the 18 formulations (F4-F9) were performed in triplicate using USP dissolution methodology (USP Type I dissolution test apparatus, basket type). A rotating speed of 100 rpm at 37 ± 1 °C was maintained throughout the study. The dissolution medium (900 ml) was 0.1 N HCl (pH 1.2) for first 2 h followed by phosphate buffer (pH 6.8) containing SLS (2 %) for subsequent hour of study. The sink condition was maintained throughout the study.

Asymmetric membranes of AMC (F6C) obtained, before and after complete dissolution of core contents were examined for their porous structure using Leo Scanning electron microscopy, USA. Membranes were dried at 45 °C for 12 h and stored between sheets of wax paper in a dessicator before examination. The membranes were cut into a patch, sputter coated for 5–10 min

Table 8: Effect of storage conditions on the total percentage release

Time (months)	% Cumulative release (in 12 h) ± S.D.
0	82.21 ± 0.71
1	82.10 ± 0.51
2	81.30 ± 0.33
3	80.10 ± 0.23

Values are in indicated in mean ± S.D. (n = 3).

Table 9: Composition of various asymmetric membrane capsule shells

Ingredients	Membrane forming solutions									Quenching Solution	Sealing Solution
	F1	F2	F3	F4	F5	F6	F7	F8	F9		
Cellulose acetate (% w/v)	12	12	12	16	16	16	20	20	20	–	16
Acetone (ml)	90	90	90	90	90	90	90	90	90	–	90
Ethanol (ml)	10	10	10	10	10	10	10	10	10	–	10
Glycerol (% w/w of CA)	50	60	70	50	60	70	50	60	70	10 % (w/v in water)	–
Water (ml)	–	–	–	–	–	–	–	–	–	100	–

F1-F9 – Asymmetric membrane capsules, CA - Cellulose acetate.

with gold by using a fine coat ion sputter and examined under SEM (Chauhan et al. 2007).

A capsule (from F6C) filled with highly water soluble amaranth dye (50 mg) was visually observed for the release of dye in 100 ml distilled water (Lin et al. 2003).

In vitro drug release studies of T1, T2 and T3 (F6C filled with varying concentrations of tartaric acid i.e 5 % w/w, 15 % w/w, 20 % w/w of drug, respectively) were carried for 12 h, using USP dissolution methodology (USP Type I dissolution test apparatus, basket type, 100 rpm, $37 \pm 1\,^{\circ}C$). The dissolution medium (900 ml) was 0.1 N HCl (pH 1.2) for first 2 h followed by phosphate buffer (pH 6.8) containing SLS (2 %) for subsequent hours.

In order to demonstrate the osmotic release mechanism, release studies of optimized formulation (T3) were conducted (Thombre et al. 1999b), using USP dissolution methodology (USP Type I dissolution test apparatus, basket type, 100 rpm, $37 \pm 1\,^{\circ}C$) in media (900 ml) of varying osmotic pressure (0.1 N HCl, pH 1.2 for first 2 h followed by phosphate buffer, pH 6.8, SLS 2 %; both containing 0.5 % w/v, 1 % w/v and 2 % w/v NaCl).

Weight variation test for optimized formulation (T3) was carried out as defined by USPXX to ensure that AMCs contain proper amount of the drug (USP XX/NF15, 1980).

The test for optimized formulation (T3) was carried out as defined by USPXX for conforming uniformity of drug loading in AMCs (USP XX/NF15, 1980).

Release kinetics of ciprofloxacin from the all the 18 AMCs (F4A-F9C) as well as from the 3 formulations containing tartaric acid (T1-T3) was determined using various kinetic equations: zero order release kinetics (Varelas et al. 1995), first order release kinetics (Gibaldi and Feldman, (1967), and Higuchi model (Higuchi, 1961, 1963) and Hixson-Crowell (Hixson and Crowell 1931) kinetics.

The optimized AMC (T3) was subjected to accelerated stability studies for 3 months at $40\,^{\circ}C \pm 2\,^{\circ}C/75\%RH \pm 5\%RH$ as per ICHQ1AR2. The AMCs were analyzed at the end of 0, 1, 2, and 3 months for physical appearance, drug content and *in vitro* release.

Analysis of variance (Kruskal-Wallis One-way ANOVA, Two-way ANOVA) along with multiple comparison test (Student-Newman-Keuls Method) and t-test (for two samples) were employed by SigmaStat® 3.5 software at $P < 0.05$.

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