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Original research paper

Asymmetric membrane capsule for osmotic delivery of flurbiprofen

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An asymmetric membrane capsule of cellulose acetate for osmotic delivery of flurbiprofen has been developed and influence of osmogents and solubilizing agent on *in vitro* drug release were evaluated. The capsule membrane was prepared by the phase inversion technique. To ensure the osmotic delivery of drug, two approaches were adopted: (*i*) the drug was encapsulated with osmogents like sodium chloride and mannitol to increase the osmotic pressure of the core, and (*ii*) the drug was encapsulated with sodium lauryl sulfate in the core of the formulation to increase the solubility and thus its osmotic pressure. Scanning electron microscopy of the membrane confirmed its porous, dense asymmetric nature. Dye test revealed *in situ* pore formation. The *in vitro* release study showed that as the proportion of osmogent and solubilizing agent was increased the release rate also increased. A good correlation was observed between the zero-order rate constant and the amount of the osmogent and solubilizing agent used.

Keywords: osmotic delivery, asymmetric membrane, cellulose acetate, flurbiprofen, osmogent

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Utilization of osmotic pressure as a driving force for delivery of pharmaceutical agents in a controlled pattern for a prolonged period of time is a well-established fact. The concept of osmotic drug delivery was first introduced by Theeuwes (1). The simplest design of an osmotic drug delivery system consists of an osmotically active core surrounded by a semipermeable membrane, with one or more delivery orifices through which the drug is delivered in a controlled fashion. Various modifications of the basic design of osmotic pump have been reported (2) and reviewed (3, 4).

One such modification is the utilization of asymmetric membrane coating for osmotic drug delivery. The walls of an asymmetric membrane capsule are prepared by the phase inversion technique. As the name suggests, the membrane is asymmetric in nature, *i.e.*, it has a relatively thin dense region supported on a thicker porous region (5).

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Asymmetric membrane capsule consists of a cap and a body, which fit snugly. The wall of the asymmetric membrane capsule is made from a water-insoluble polymer like cellulose acetate, ethyl cellulose, cellulose acetate butyrate or their mixture, thus the capsule shell of the asymmetric membrane, unlike the gelatin capsule, does not dissolve instantaneously and osmotically delivers the drug for a prolonged period of time, depending upon the core composition (6).

The critical difference between the asymmetric membrane osmotic dosage form and other osmotic devices is a higher rate of water influx due to the micro porous nature of the asymmetric membrane. It aids in delivery of a drug with lower osmotic pressure and solubility (7). For drugs of poor solubility, high water influx is desirable, which can be easily achieved with the asymmetric membrane by proper choice and concentration of the pore forming agent. Further, the solubility of the poorly water-soluble drug inside the core can be increased by encapsulating the drug with osmogents or solubilizing agent to ensure its osmotic delivery (8).

Unlike other osmotic systems where a delivery orifice is required in the semipermeable membrane for delivery of the drug, the asymmetric membrane coating provides a distinct advantage of *in situ* pore formation. The *in situ* pore formation takes place due to leaching of the water-soluble additives incorporated in the asymmetric membrane. The leaching of water-soluble additives takes place when such a system comes in contact with the aqueous medium, resulting in formation of a micro porous membrane, through which the drug is osmotically delivered (9). This membrane is permeable to both water and dissolved solute, economically viable, less time consuming compared to a mechanical drill or laser drilling. Drug release from this system is to a large extent independent of pH and other physiological factors (10).

In our previous study (11), influence of the asymmetric membrane porosity on the release of poorly water-soluble drugs was investigated. The release rates were found to significantly increase with an increase in concentration of the pore forming agent in the asymmetric membrane. In the present study, the effect of osmogents (sodium chloride, mannitol) and solubilizing agent (sodium lauryl sulfate, SLS) on the osmotic release of the poorly water-soluble drug flurbiprofen (FL) from the asymmetric membrane capsule of cellulose acetate has been investigated.

EXPERIMENTAL

Cellulose acetate was obtained from Glaxo Lab. Ltd. (India), sodium lauryl sulfate, sodium chloride and mannitol were obtained from S.D. Fine Chemicals Ltd. (India); the drug flurbiprofen was a gift sample from FDC Pharmaceutical Ltd. (India).

Asymmetric membrane capsule preparation

Cellulose acetate (CA) solution (15% *m/V*) was prepared in an acetone/water (90/10, *V/V*) solvent system. Accurately weighed quantity of CA was added to acetone/water and the resulting mixture was stirred in a well-closed beaker to obtain a solution. The required quantity of the pore forming agent glycerol (10 g) was added to the solution un-

der stirring. The stainless steel moulds dimensioned so as to form the capsule body and cap were dipped in the coating solution for 2 minutes and then removed carefully so as to form a thin layer of solution on the mould. The pins were taken out of the coating solution and briefly air dried for 30 seconds, followed by quenching in aqueous solution (10%, *m/V*, glycerol) to effect phase inversion and formation of the asymmetric membrane. The resulting membrane was stripped off and trimmed to desired size and stored for future use. The porosity and structure of the asymmetric membrane were characterized by scanning electron microscopy (SEM) (LEO-340, Lyca Electron Optics, UK).

Filling and sealing of the asymmetric membrane capsule

The asymmetric membrane capsule was filled with a mixture of drug/osmogent (sodium chloride, mannitol) and drug/solubilizing agent (SLS) each in the ratio of 1:1, 1:5 and 1:10 (*m/m*), keeping the drug quantity constant (100 mg). One such capsule was filled with pure drug, 100 mg, without any osmogent or solubilizing agent; this capsule served as control. Each of the mixtures was filled in the body of the capsule and the cap was snuggly fitted to the body and finally sealed with a 16% (*m/V*) solution of CA, only so as to ensure that no release took place through the seal of the capsule. The physical mixtures of drug/osmogent and drug/solubilizing agent were prepared by mixing them thoroughly in a laboratory blender for 10 minutes and subsequently passing the mixture through sieve No. 80 (aperture size 180 μm, US Standard).

Osmotic release study

The prepared asymmetric membrane capsules of cellulose acetate were characterized for osmotic release behaviour by conducting a dye-test. For this purpose, capsules were filled with the water-soluble dye amaranth (12), mixture of dye with osmogent (sodium chloride) and solubilizing agent SLS. The capsules were then suspended separately in 50 mL water and 50 mL sodium chloride solution (10%, *m/V*). The capsules were observed visually for release of any coloured dye.

Release rate study

The *in vitro* study of drug release from each capsule was studied as the function of the increasing amount of added osmogent and solubilizing agent in each system. The filled capsules were subjected to a release rate study using a USP 24 (13) dissolution apparatus II (50 rpm, 37± 0.5 °C) and phosphate buffer pH 7.2 as dissolution medium. The samples were withdrawn hourly for nine hours and analyzed using a UV spectrophotometer (UV/VIS-1 Spectrophotometer, Thermo Spectronic, UK) at 247 nm. The experiments were performed in triplicate.

Statistical analysis

Experimental results were expressed as mean ± SD values. Student's *t* test was performed to determine the level of significance between the control capsule and the capsule filled with various proportions of osmogents and solubilizing agent. Two-way analysis

of variance was used to assess the difference in release rate from the capsules filled with different types of osmogent and proportions of osmogents and solubilizing agent. Differences were considered to be statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

A stream of dye was observed diffusing from the capsule suspended in distilled water after a lag time of 36 minutes, suggesting *in situ* pore formation that acts as a delivery port for release of the colored dye. However, no stream of dye was observed when another such capsule was placed in 10% (*m/V*) solution of sodium chloride. This was due to high osmotic pressure of the release medium, which nullifies the osmotic release of the encapsulated dye, suggesting that the prepared system follows the osmotic principle for releasing encapsulated materials. But when the capsules were filled with a mixture of dye/osmogent (sodium chloride) and dye/solubilizing agent (SLS), a reduction in lag time was observed due to the increase in the osmotic pressure inside the system. The decrease in lag time may be due to the increase in the osmotic pressure inside the system causing early release of the dye. This concept was utilized in the present study to ensure the osmotic delivery of (FL) by increasing the osmotic pressure of the core. The SEM of the asymmetric membrane (Fig. 1) indicates the presence of a porous region at 60 magnification confirming the porous and asymmetric nature of the membrane.

The *in vitro* drug release study from the asymmetric membrane capsule filled with various ratios of osmogents (sodium chloride and mannitol) and solubilizing agent SLS is shown in Fig. 2. and indicates that as the proportion of osmogent and solubilizing agent is increased, the amount of drug released also increases (Table I). However, the amount of drug released at the end of the dissolution run from the control capsule was significantly lower as compared to capsules filled with various proportions of drug/osmogent (sodium chloride, mannitol) and drug/SLS (Table I). The findings of two-way ANOVA at 5% level of significance reveal that those is a significant difference in drug re-

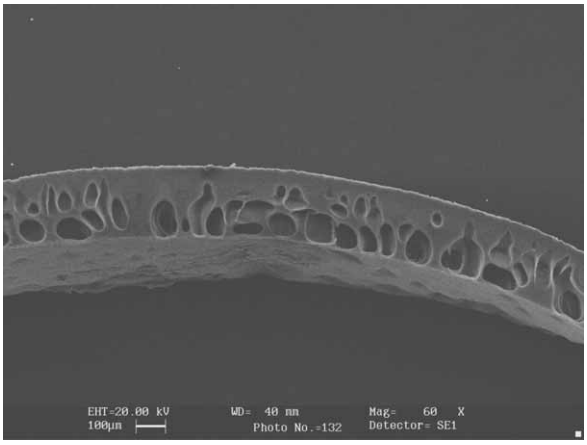

Fig. 1. Cross-section of the asymmetric membrane at 60x magnification.

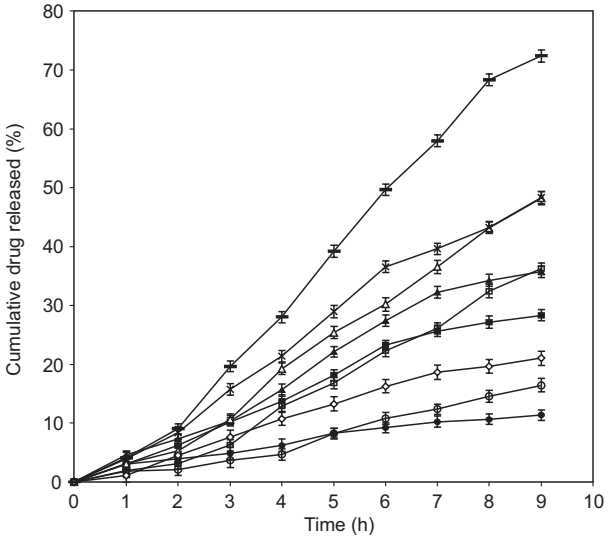

Fig. 2. Release profile of flurbiprofen from the asymmetric membrane capsule filled with various ratios of: FL/NaCl: 1:1 (•), 1:5 (■), 1:10 (▲); FL/mannitol: 1:1 (○), 1:5 (□), 1:10 (△); FL/SLS: 1:1 (◇), 1:5 (×), 1:10 (—). Each point represents mean ± SD value (n = 3).

lease between different types of osmogents and osmogent and solubilizing agent as well as their proportions (between ratios F = 19.85, between NaCl, manitol and SLS F = 7.55; see Table I).

Influence of osmogents and solubilizing agent

Though osmotic pressure of sodium chloride is higher compared to mannitol (14), higher release rates were observed with drug/mannitol combination. The lower release rate from the system with sodium chloride can be attributed to its ionic nature and high osmolarity. Both these factors would lead to rapid ionization of sodium chloride com-

Table I. Maximum flurbiprofen released from the asymmetric membrane capsule

Ratio (m/m)[a]	Maximum FL released (%)[b]			
	Control	NaCl	Mannitol	SLS
FL only (100 g)	5.6 ± 0.5	–	–	–
1:1	–	11.3 ± 1.0[c]	16.4 ± 1.1[c]	21.0 ± 1.3[c]
1:5	–	28.3 ± 1.1[c]	36.4 ± 1.0[c]	48.3 ± 1.1[c]
1:10	–	35.8 ± 0.9[c]	48.2 ± 1.1[c]	72.4 ± 1.1[c]

[a] FL: Osmogent/solubilizing agent ratio (m/m).
[b] Mean ± SD (n = 3).
[c] Significant difference compared to the control: $p < 0.05$.

pared to (FL) and suppress its ionization due to the common ion effect, and also compete with the drug to get released from the system. This would reduce residence time of sodium chloride in the system necessary to impart the osmotic pressure required to effect substantial release of the drug from the system.

The higher release rates from the system with mannitol can be attributed to its non-ionic nature and low osmolarity. The phenomenon of competing with the drug to get released from the system and suppression of drug ionization due to the common ion effect will not occur in the case of mannitol. Hence mannitol would have extended residence time in the system, required to impart the necessary osmotic pressure to cause prolonged drug release from the system.

Higher release rates were observed from the systems with the solubilizing agent, SLS, compared to systems filled with osmogent (sodium chloride, mannitol). This may be due to the solubilization effect of SLS causing increased solubility of the drug, increasing the osmotic pressure of the drug itself, resulting in an increased amount of drug being released from the system. It appears that SLS, besides imparting, solubilization effect, also acts as an osmogent in dissolved form.

The correlation coefficient of the linear relationship between the percent cumulative drug released and the *in vitro* release time suggests that the system follows zero-order release irrespective of the proportion of the drug/osmogent and drug/solubilizing agent encapsulated in the system (Table II).

The amount of the drug released from each system does depend upon the amount of osmogent and solubilizing agent encapsulated along with the drug, as evident from the zero-order release rate constants (Table II). The correlation coefficient between the zero-order release rate constant and the amount of osmogent and solubilizing agent was found to be 0.918 for sodium chloride, 0.967 for mannitol and 0.994 for SLS. The good linear relationship in the case of mannitol and SLS suggests that the amount of mannitol and SLS required to achieve 100% release of drug can be predicted from the regression equation.

Table II. Kinetics of in vitro *release of flurbiprofen from the asymmetric membrane capsule*

Ratio (*m*/*m*)[a]	Zero-order	
	R^2	k_0 (*mg* h^{-1})
FL/NaCl (1:1)	0.966	1.223
FL/NaCl (1:5)	0.987	3.423
FL/NaCl (1:10)	0.983	4.372
FL/mannitol (1:1)	0.975	1.891
FL/mannitol (1:5)	0.976	4.283
FL/mannitol (1:10)	0.988	5.674
FL/SLS (1:1)	0.984	2.532
FL/SLS (1:5)	0.995	5.678
FL/SLS (1:10)	0.992	8.720

[a] Flurbiprofen/osmogent or flurbiprofen/solubilizing agent ratio.
k_0 – Zero-order rate constant.

CONCLUSIONS

This study suggests that drug delivery from the asymmetric membrane capsule is principally controlled by the osmotic pressure of the core formulation. The *in situ* formed delivery orifice in the asymmetric membrane is mainly responsible for drug delivery. Solubilization of a poorly water-soluble drug in the core increases its release rate and the amount of drug released.

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S A Ž E T A K

Kapsule s asimetričnom membranom za osmotsku isporuku flurbiprofena

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U radu je opisan razvoj kapsula s asimetričnom membranom od celuloznog acetata za osmotsku isporuku flurbiprofena. Proučavan je utjecaj osmotski-aktivnih tvari i tvari za povećanje topljivosti na oslobađanje ljekovite tvari *in vitro*. Membrane kapsula su priređene metodom inverzne faze. Osmotska isporuka je osigurana na dva načina. Ljekovita tvar je kapsulirana s: *i)* osmotski-aktivnim tvarima poput natrijeva klorida i manitola koji su povećali osmotski tlak jezgre, *ii)* natrijevim lauril-sulfatom koji je povećao topljivost te ujedno i osmotski tlak. Pretražna elektronska mikroskopija ukazuje na poroznu membranu asimetrične gustoće, a test boje na stvaranje pora *in situ*. *In vitro* pokusi su pokazali da oslobađanje ljekovite tvari iz kapsula raste s povećanjem količine osmotski-aktivnih tvari i tvari za povećanje topljivosti te da postoji dobra korelacija između upotrebljene količine tih tvari i konstante oslobađanja nultog reda.

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