Research Article

Development and Evaluation of Asymmetric Membrane Capsules of Indomethacin: New Prospect in Osmotic Drug Delivery

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ABSTRACT

Asymmetric membrane capsules (AMC) are an osmotic system with in-situ pore formation that can be used for the controlled delivery of poorly water soluble drugs, consist of a drug containing core surrounded by a membrane which has an asymmetric structure that is it has a relatively thin dense region supported on a thicker, porous region. In present investigation asymmetric membrane capsules, having in-situ pores for achieving the osmotic controlled release of Indomethacin, were successfully designed by using cellulose acetate (CA 398-10) as semipermeable membrane forming polymer and glycerol and PEG-400 as pore forming agent. The in vitro release study showed that that the percent of drug released with glycerol was found to be highest, followed by PEG-400. As the proportion of pore forming agent and osmogent was increased the release rate also increased.

Keywords: Asymmetric membrane capsules, Controlled drug delivery, Osmosis, Osmotic drug delivery system.

INTRODUCTION

A Significant change milestone in the oral NDDS is the development of the osmotic drug delivery system (ODDS), an innovative and highly versatile drug delivery system. ODDS are most promising strategy based systems for the controlled drug delivery. They are among the most reliable controlled drug delivery systems and could be employed as oral drug delivery systems or implantable devices.[1,2] An osmotic system releases a therapeutic agent at a predetermined, zero order delivery rate based on the principle of Osmosis, which is movement of a solvent from lower concentration of solute towards higher of solute across a semi-permeable membrane.[3] The present day osmotic devices are modified versions of Rose Nelson pump, which was introduced by two Australian physiologists Rose and Nelson in 1955. Next quantum leap in osmotic dosage form came in 1972 when Theuwes invented elementary osmotic pump. Alza corporation of the USA was first to develop an oral osmotic pump named OROS (1989).[4,5] 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 drug is delivered in a controlled manner.[6] Osmotic systems for moderate to low water soluble drugs are limited because of the more thick coatings impede the permeability. To overcome this problem, asymmetric membrane osmotic drug delivery systems have been developed.[1] Asymmetric membrane capsules (AMCs) were first introduced in 1999 for osmotic delivery of drugs.[7] These systems offer significant advantages over the membrane coatings used in conventional osmotic systems.[1]

Asymmetric membrane capsules are an osmotic system with in-situ pore formation that can be used for the controlled delivery of poorly water soluble drugs, consist of a drug containing core surrounded by a membrane which has an asymmetric structure that is it has a relatively thin dense region supported on a thicker, porous region.[8]

Indomethacin [1-(4-chlorobenzoyl)-5-methoxy-2- methyl indol-3-acetic acid], is a non steroidal anti inflammatory drug (NSAID) and COX inhibitor, used for relief of symptoms of rheumatoid arthritis, osteoarthritis, primary dysmenorrhea, spondylosis deformans, acute gout and periarthritis humeroscapularis.[9,10] Because of its short elimination half-life (4.5 hours), multiple dosing is required to achieve and maintain therapeutic concentration, and adverse gastrointestinal (GI) reactions can occur. Therefore, development of oral controlled-release formulations of this drug is highly desirable in order to achieve improved therapeutic efficacy and patient compliance.[11] The aim of the work is to develop an asymmetric membrane capsules to deliver poorly water soluble drug indomethacin based on osmotic technology and to evaluate the influence of core formulation variables on the release characteristics.

MATERIALS AND METHODS

Materials

Indomethacin was obtained as gift sample from Cipla Pvt.Ltd. Cellulose acetate (398-10) was purchased from All Well Pharmaceutical Company, Chandigarh. Sodium hydroxide, Fructose Mannitol and Glycerol were purchased from Loba chemie, Mumbai. Sodium chloride, PEG-400 was purchased from Nice chemicals pvt Ltd, Cochin.

Methods

The AMCs were prepared by using phase inversion process in which the membrane structure was precipitated on a stainless steel mould pin of diameter

0.70 cm ± 0.018 and 0.62 cm ± 0.004 for the cap and body respectively, by dipping the mould pin in a coating solution followed by quenching solution in an aqueous solution as shown in Figure 1. The coating solution of cellulose acetate (15%) was prepared in acetone: ethanol (9:1) solvent system. Weighed quantity of cellulose acetate was added to the acetone: ethanol solvent system and the resulting mixture were stirred in a well-closed beaker until a homogeneous solution was formed. To this homogeneous solution of cellulose acetate different pore forming agents (glycerol, PEG-400) at different levels (60% and 70% w/w of cellulose acetate) were added respectively, while stirring to ensure proper distribution of pore forming agent in cellulose acetate solution.

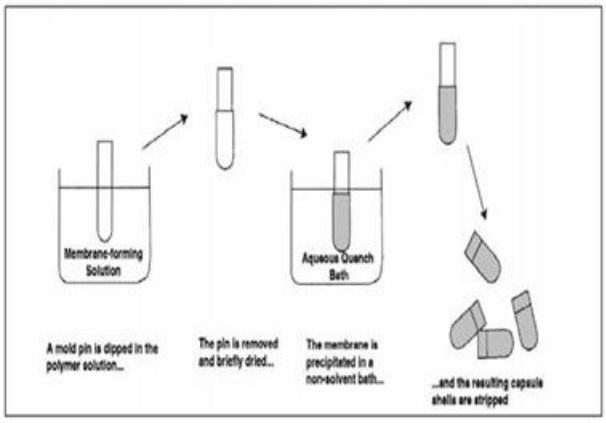


Figure 1: Process for preparation of asymmetric membrane capsules

Table 1: Composition of polymeric solution

Formulation Code	Polymers (15% w/v)	Casting solvent (9:1)	Plasticizer (%w/w)*	
			Glycerol	PEG-400
G6	Cellulose Acetate	Acetone: Et.OH	60	_
G7	Cellulose Acetate	Acetone: Et.OH	70	_
P6	Cellulose Acetate	Acetone: Et.OH	_	60
P7	Cellulose Acetate	Acetone: Et.OH	_	70

*based on total weight; Et.OH- Ethanol

The moulds were dipped in the coating solution of cellulose acetate containing different pore forming agent for 1 min, and then recovered carefully so as to form a thin layer of solution on the mould. The pins were taken out of the coating solution and briefly dried for 30 s followed by quenching in aqueous solution of glycerol (10% w/v) for 3 min. This resulted in phase inversion and formation of asymmetric membrane. The resulting membrane was stripped off and trimmed to desired size. Formula for dip coating solutions, and solution used for quenching and sealing the capsules are listed in Table 1 and 2.

Table 2: Formula of quenching and sealing solution

Component	Quenching Solution (%)	Sealing Solution (%)
Cellulose acetate	--	15.0
Acetone	--	80.0
Water	90.0	5.0
Glycerine	10.0	--

Filling of asymmetric membrane capsules

Asymmetric membrane capsules were filled manually with a constant loading of drug, Indomethacin (75 mg) and osmogents (in varying proportions) as shown in Table 3 and 4. The AMCs were then capped and sealed with a sealing solution.

Physical evaluation of asymmetric membrane capsules

Weight variation

Twenty capsules were weighed individually. The average weight was calculated and was compared with the weight of each capsule.

Thickness

Twenty capsules were randomly selected from each batch and individually measured the thickness of the wall and the effective surface area of the asymmetric membrane capsules using the digital micrometer. The average weight and standard deviation of 20 capsules was calculated.

Void volume determination

The void volume of each of the asymmetric membrane as the function of the pore forming agents present at different levels was determined. The weight of the empty capsule (W_o) was obtained. The weighed capsule was put into a vial filled with distilled water and left overnight to effect complete quenching of the pore forming agent present in the wall of the capsule shell. It was made sure that the capsule was completely immersed in the water. The capsule was taken out of the vial, wiped with tissue paper and immediately weighed (W_w). The capsule was then placed into an oven at 50º C; it was periodically weighed until a constant weight was obtained (W_d). The volume of the pore forming agent (V_p) present in the capsule wall was measured by $(W_o-W_d)/\rho$ where, ρ = density of pore forming agent used. The total volume of water (V_w) present in the dry film was measured by $(W_w-W_d)/1$ (density of water =1 g/cm^3). The void volume of the

polymer per unit weight of polymer was determined by $(V_w-V_p)/W_d$.

Tensile strength

A small strip of the membrane of the capsule was cut on a glass plate with a sharp blade so it had a smooth margin. One end of the membrane was fixed between adhesive tapes to give support to the membrane when placed in the film holder. Another end of the membrane was fixed between the adhesive tape with a small pin sandwiched between them to keep the strip straight while stretching. A small hole was made in the adhesive tape near the pin where hook was inserted. A thread was tied to this hook, passed over the pulley and a small pin attached at the other end to hold this weight. A small pointer was attached to thread, which travelled over the graph paper affixed on the wooden plate. To determine the tensile strength weights were gradually added to the pan increase the pulley force till the membrane was broken. The weight required to break the membrane was noted as the break force. Tensile strength was calculated by using formula:

$$\% \text{ Tensile strength} = \left[\frac{\text{Break force}}{a \times b} \right] \left[1 + \frac{\Delta L}{L} \right]$$

Table 3: Core component of asymmetric membrane capsules (glycerol as pore forming agent)

Formulation Code	Sodium chloride	Fructose	Mannitol	Drug: Osmogent
G6M1	--	--	+	1: 2.5
G7M1	--	--	+	
G6F1	--	+	--	
G7F1	--	+	--	
G6S1	+	--	--	
G7S1	+	--	--	
G6M2	--	--	+	**1:5**
G7M2	--	--	+	
G6F2	--	+	--	
G7F2	--	+	--	
G6S2	+	--	--	
G7S2	+	--	--	

Table 4: Core compnonent of asymmetric membtane capsules (PEG 400 as pore forming agent)

Formulation Code	Sodium chloride	Fructose	Mannitol	Drug: Osmogent
P6M1	--	--	+	1: 2.5
P7M1	--	--	+	
P6F1	--	+	--	
P7F1	--	+	--	
P6S1	+	--	--	
P7S1	+	--	--	
P6M2	--	--	+	1:5
P7M2	--	--	+	
P6F2	--	+	--	
P7F2	--	+	--	
P6S2	+	--	--	
P7S2	+	--	--	

Table 5: Average physical characteristics of the asymmetric membrane capsules

Capsule shell code	G6	G7	P6	P7
Capsule shell weight (mg)	73.9 ± 0.002	80.6 ± 0.001	63.2 ± 0.001	73.0 ± 0.001
Membrane thickness (cm)	0.224 ± 0.24	0.226 ± 0.21	0.243 ± 0.19	0.254 ± 0.24
Void volume (cm3/g)	3.370 ± 0.001	4.013 ± 0.001	2.568 ± 0.002	3.125 ± 0.002
Tensile strength (Kg/cm2)	0.439 ± 0.32	0.486 ± 0.31	0.456 ± 0.28	0.521 ± 0.28

Surface characterization

Scanning electron micrograph of each capsule formulation was taken.

Conformation of in situ pore formation

The in-situ pore formation in asymmetric membrane capsules should take place due to the virtue of leaching of the pore forming agent present in the asymmetric membrane into the release medium. To confirm this phenomenon in the prepared system dye-test was conducted. The asymmetric membrane capsule with different concentrations of pore forming agent were filled with a highly water soluble amaranth dye (20 mg).

The dye was filled in each of the capsule body manually and the cap was snugly fitted to the capsule body and finally sealed with a sealing solution of cellulose acetate only (14% w/v), to ensure that no release takes place from the seal. The capsules filled with dye were placed in 50 mL distilled water and observed for release of dye through the membrane. To demonstrate that the prepared system follows the osmotic principle to release its encapsulated contents, the capsules filled with amaranth dye were placed in a release medium of higher osmotic pressure (50 mL 10% w/v sodium chloride solution) and the capsules were visually observed for the release of dye.

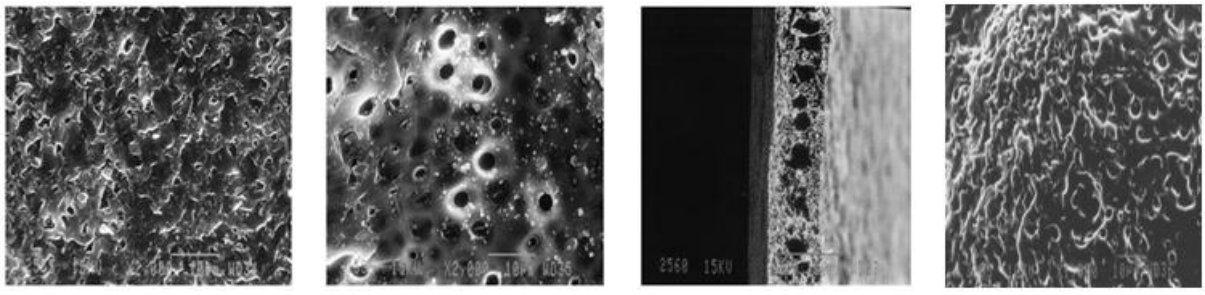
***In vitro* drug release study**

The dissolution studies of AMC containing indomethacin and different type and portion of osmogents and pore forming agents were carried out using eight station USP type II dissolution test apparatus. The capsules were placed in dissolution vessel containing 900 ml phosphate buffer (pH 7.2) with 0.5% w/v SLS maintained at 37 ± 0.5°C and stirred at 50 rpm. Samples (10ml) were collected periodically (0.5, 1, 1.5, 2, 4, 6, 8, 12, 18, 24 h) and replaced with fresh dissolution medium. The percent drug release from different formulation was determined spectrophotometrically at 238.5 nm.

RESULTS AND DISCUSSION

Membrane thickness and surface area (Table 5) was found to be almost same for all the asymmetric membrane capsules with slight variation. However the weight of the capsule increased as the concentration of pore forming agent was increased. The capsule with glycerol as pore forming agent weighed heavier as compared to capsules with PEG-400.

Cross-sectional view of SEM of AMC before dissolution (Figure 2C) clearly indicated the presence of two layers outer, dense, non-porous membranous (Figure 2A) and inner, lighter, porous layers (Figure 2B). Photograph of exhausted membrane obtained after dissolution showed a larger number of pores similar to a net-like structure (Figure 2D).



(A) (B) (C) (D)

Figure 2: Scanning electron microphotographs of asymmetric membrane osmotic capsule: (A) Outer region of capsule shell, before dissolution (original magnification×2000); (B) inner region of capsule shell, before dissolution (original magnification×2000); (C) cross section (original magnification×100); (D) capsule shell, after dissolution (original magnification×1000).

Table 6: Composition of final formulations

Formulation code	Drug (mg)	Osmotic agents (mg)		
		NaCl	Fructose	Mannitol
F1	75	100	100	--
F2	75	200	200	--
F3	75	100	--	100
F4	75	200	--	200

In situ pore formation in AM wall for releasing drug was proven by filling the capsule with water soluble dye, amaranth. A stream of coloured dye was observed to be diffusing from capsule wall when suspended in water after a lag time. This indicates *in-situ* pore formation of delivery orifice due to leaching of pore forming agent present in the AM. However, no release was observed when such capsule was suspended in 10% w/v solution of sodium chloride. In such case the osmotic effect gets nullified, suggesting that the prepared system follows osmotic principle for releasing its encapsulated contents.

The *in vitro* results revels that as the concentration of pore forming agent is increased the percent of drug released also increases and pore forming agent used also has a prominent effect on the percent of drug released. The percent of drug released with glycerol was found to be highest, followed by PEG-400. The release profile of G6 and G7 formulation with different type and proportion of osmogents viz. sodium chloride, fructose and mannitol were used to study the influence of amount of osmogents which showed that the amount of osmogents had marked influence on indomethacin release. Drug release was found to be in following order: Sodium chloride> Fructose> Mannitol.

In vitro release of final formulations

Out of 24 formulations six were selected (G7S1, G7F1, G7M1, G7S2, G7F2 and G7M2) on the basis of the maximum percentage of drug release as compared to others. Later, these formulations were modified as shown in Table 6 and subjected to in-vitro release studies in phosphate buffer (pH 7.2) with 0.5% w/v SLS.

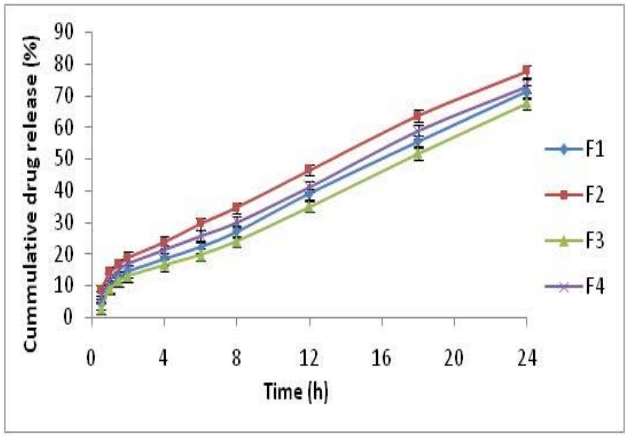


Figure 3: Dissolution profile of Indomethacin from asymmetric membrane capsules containing glycerin and combination of osmogents.

Kinetics of drug release

In order to understand the mechanism of drug release from the optimized system, the data were treated according to first-order (log cumulative percentage of drug remaining versus time) along with zero-order (cumulative amount of drug released versus time). When the data were plotted according to the first-order equation, the formulations showed a comparatively poor linearity, with regression value of 0.755, whereas the regression value for zero-order equation was 0.994 (Table 7), which indicated that drug release from the optimized formulation was independent of drug concentration.

Table 7: Kinetics of *in vitro* release of indomethacin from the asymmetric membrane capsules

Formulation code	Zero order (R^2)	First order (R^2)
F1	0.9932	0.9739
F2	0.9939	0.9796
F3	0.9905	0.7553
F4	0.993	0.977

CONCLUSION

The higher percent released from the AMC containing glycerol is due to its high porosity causing higher influx of dissolution medium resulting in quick build-up of osmotic pressure inside the system. Osmogents had comparable and profoundly positive effect on drug release. It was found that drug release rate increases with the amount of osmogent due to increase in water uptake hence increased driving force for drug release. *In-vitro* release study showed that the F2 formulation showed higher drug release, this may be attributed by the additive effect of both of osmogents used. So, we can conclude that the AMC formulation approach could be used for both osmotic delivery and as controlled release formulation for poorly soluble drugs.

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