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Original Article

DEVELOPMENT AND EVALUATION OF ASYMMETRIC MEMBRANE CAPSULE OF KETOROLAC TROMETHAMINE

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ABSTRACT

Object: Osmotic systems for moderate to low water soluble drugs are limited because of the thicker coatings impede the permeability. To overcome this problem, asymmetric membrane osmotic drug delivery systems have been developed.

Methods: In present investigation asymmetric membrane capsules (AMC), having in-situ pores for achieving the osmotic controlled release of ketorolac tromethamine, were successfully designed by using cellulose acetate 398-10 (CA 398-10) as semi-permeable membrane forming polymer and glycerol, polyethylene glycol 400 (PEG-400) as pore forming agent and osmotic agents *viz.* Sodium chloride, fructose and mannitol. The prepared AMC were physically evaluated for various parameters such as length, weight variation, thickness, elongation at break, tensile strength, void volume determination and surface characterization. The dissolution studies of AMC containing ketorolac tromethamine and different type and proportion of osmogents and pore forming agents were carried out using eight station USP type II dissolution test apparatus (Labindia 2000). The optimized formulation was subjected to stability testing as per ICH Q1 A

Results: Capsules prepared did not show visible physical defects. Role and effect of polymers were identified on different physical parameters. *In vitro* release profiles of ketorolac tromethamine were investigated. It is evident from the results that the percent of drug released with glycerol was funded to be highest, followed by PEG-400. No significant change was observed in stability study of AMC.

Conclusion: It was concluded that the drug release rate increase with the amount of osmogent due to increase in water uptake hence increased the driving force for drug release. The percent drug released at the end of dissolution time from the control capsule (containing drug only) was lower as compared to capsules filled with various proportions of drug/osmogents.

Keywords: Ketorolac tromethamine, Asymmetric membrane capsules, Cellulose acetate, Osmotically controlled gastro retentive delivery

INTRODUCTION

Utilization of osmotic pressure as a driving force for the 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 major advantages that have been contributed to osmotic drug delivery were that the delivery rate of zero order is achievable with this system and has been established by both *in vivo* and *in vitro* experiments. The drug release is independent of gastric pH and hydrodynamic conditions and is minimally affected by the presence of food in GIT. AMC is a controlled drug delivery device which consists of a drug-containing core surrounded by a membrane which has an asymmetric structure, i.e., it has a relatively thin, dense region supported on a thicker, porous region [2]. AMCs are the unique embodiment of osmotic devices which uses inversion phase technology to create the semi-permeable Asymmetric membrane [3]. Similar to a conventional hard gelatin capsule, the AMC consists of a cap and a body that snugly fit into each other. In contrast to gelatin capsules, however, the walls of AMC are made from a water-insoluble polymer such as cellulose acetate (CA) ethyl cellulose (EC), cellulose acetate butyrate (CAB), and their mixtures [4]. Thus, the capsule shell does not dissolve to release instantly the drug filled in it. Instead, the drug is released over a prolonged duration by diffusion through the capsule walls and/or via osmotic pumping, i.e., by convection through pores in the capsule walls.

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug (NSAID) chemically related to indomethacin and tolmetin. Its anti-inflammatory effects are believed to be due to inhibition of both cylooxygenase-1 (COX-1) and cylooxygenase-2 (COX-2) which leads to the inhibition of prostaglandin synthesis leading to decreased the formation of precursors of prostaglandins and thromboxanes from arachidonic acid [5]. It is a highly potent inhibitor of prostaglandin synthesiSDose related adverse effects of ketorolac tromethamine have been reported, as it has a short half-life of 5 h, thereby requiring two to three times daily dosing in a large number of patients, which often leads to non-compliance [6].

Thus, the aim of the project was to formulate cellulose acetate AMCs for osmotically controlled gastro retentive delivery of ketorolac tromethamine. Ketorolac tromethamine was selected as an active agent as it met the desired criteria for being the potential candidate for asymmetric membrane technology controlled drug delivery system. For this study CA 398-10 was chosen as membrane forming a polymer.

MATERIALS AND METHODS

Materials

Ketorolac tromethamine was obtained as a gift sample from Cipla Pharmaceutical Pvt. Ltd, (Mumbai, India). CA 398-10 was purchased from Signet Chemical Corporation Pvt. Ltd, Mumbai. Sodium Chloride was purchased from Loba Chemical Pvt. Ltd, Mumbai. Fructose was purchased from Central Drug House, Mumbai. Potassium Chloride, Methanol and Potassium dihydrogen phosphate were purchased from Merck Chemicals Corporation Mumbai, India. All other chemicals and solvents are of reagent grade. Double distilled water (DDW) was prepared using the in-house distillation unit.

Osmotic pump capsule preparation [7, 8]

AMC was prepared by phase inversion process in which the membrane structure was precipitated on a stainless steel mould pin by dipping the mold pin in a coating solution. The coating solution of cellulose acetate (20% w/v) 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 homogenous solution was

formed. To this homogeneous solution of cellulose acetate, different pore forming agents (glycerol, PEG-400) at different levels (50% and 60% w/w of cellulose acetate) were added respectively. Followed by coating, the capsules were dipped in an aqueous solution for quenching. Then, the capsules were stripped off, trimmed to size and physically characterized. The compositions of quenching Solution were water and glycerine while sealing solution contains cellulose acetate, acetone, and water. Asymmetric membrane capsules were filled with the desired amount of drug-excipients mixture by hand. After filling the capsules were capped and sealed with a sealing solution.

Evaluation of asymmetric membrane capsule shell [9]

Length

Twenty empty capsules were randomly selected from each batch and the length of body cap, and the complete capsule was individually examined using the digital micrometer (Mututoyo, Japan).

Weight variation

The weight variation of each of the prepared capsule, after snugly fitting the cap and body of each of the capsule was determined using an electronic balance (Mututoyo, Japan).

Thickness

Twenty empty 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 (Mututoyo, Japan). The average weight and standard deviation of 20 capsules were calculated.

Elongation at break

Percent elongation of each prepared asymmetric membrane was determined. Percent elongation was determined by using Equation

$$\% \text{ Elongation} = \left[\frac{L_t - L_o}{L_o}\right] \times 100$$

Where,

Lt = length of strip before applying force

Lo = length of strip after applying force

Tensile strength

Procedure used for tensile strength is same as used in elongation determination and tensile strength was calculated by using Equation mention below

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

Where,

a = width,

b = thickness,

L = length of the test membrane and

ΔL = elongation

Void volume determination

The void volume of each of the asymmetric membrane as the function of pore forming agents present at different level was determined. The volume of the pore forming agent (V_P) present in the capsule wall was measured by $(W_o\text{-}W_d)/\rho$ Where ρ = density of pore forming agent used. The total volume of water (V_w) present in the dry film was measured by $(W_w\text{-}W_d)/1$ (density of water = 1 g/cm^3).

The void volume of the polymer per unit weight of polymer was determined by $(V_w\text{-}V_p)/W_d$

Surface characterization

Asymmetric membranes obtained before and after complete dissolution of core contents were examined for their porous structure and thickness using Jeol 6100 SEM (Tokyo, Japan). After dissolution, asymmetric membrane structures were dried at 50 °C for 8 h and stored in desiccators before examination [10, 11].

Osmotic release studies from asymmetric membrane capsules

The prepared asymmetric membrane capsules of different polymers will be characterized for osmotic release behavior by conducting a dye test [12]. The capsules containing the dye were placed in the distilled water and solution of sodium chloride (10%w/v) respectively. The capsules were then observed for the release of the colored dye in each of the media [13]. The time taken for the initial release of the dye from the capsule was recorded and correlated to the concentration and type of pore-forming agent present in the shell of each of the capsule.

Filling of asymmetric membrane capsules [14]

Asymmetric membrane capsules were fabricated and filled manually with a constant loading of drug, ketorolac tromethamine (80 mg) and osmogens (in varying proportions) by mixing in a polythene bag for 10 min. The AMCs were then capped and sealed with a sealing solution. Osmogens selected for the present investigation included sodium chloride, fructose, and mannitol. The ratio of the drug and osmogen was 1:2 and 1:4 in all the formulations.

***In vitro* drug release study**

The dissolution studies of AMC containing ketorolac tromethamine and different type and proportion of osmogents and pore forming agents were carried out using eight station USP type II dissolution test apparatus (Labindia 2000) [15, 16]. The capsules were placed in dissolution vessel containing 900 ml phosphate buffer (pH 7.2) maintained at 37±0.5 °C and stirred at 50 RPM. Samples (10 ml) 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 233 nm [17, 18]

Selection of formulations for further studies

The screening of osmotic capsules was based on the cumulative percent drug release. The formulation selected for further studies was containing glycerol as a pore forming agent along with different osmogents. But the overall release percentage of the drug was not satisfactory. Therefore, modifications were made in above formulations by adding a combination of osmogents i.e. NaCl, fructose and mannitol. The compositions of the final formulations were shown in table 1. *In vitro* dissolution studies of the final formulations were done according to the method explained above and data obtained after performing studies on each formulation is listed in table 2 and fig. 1.

Table 1: 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

Kinetics of drug release [19, 20]

In general, the release of drug from an osmotic system depends on upon many factors, namely osmotic pressure, pore size, capsule thickness, etc. In order to describe the kinetics of drug release from the drug delivery system various mathematical equations, have been proposed viz. Zero order rate, First order, and Higuchi model. The data from the *in vitro* study of final formulations was fitted to the above mentioned kinetic models to determine the kinetics of drug release. Various statistical parameters were also calculated and reported in table 3. To authenticate the release model, dissolution data were further analyzed by the peppas and korsmeyer equation given below. The criteria for the best model were based on the goodness of fit.

$$M_t/M_\infty = at^n$$

Where, M_t and M_∞ = cumulative absolute amount of drug released at time t and at ∞ time a = constant

n = drug release exponent, indicative of mechanism of drug release.

Stability studies

In order to assess the long-term stability of the various formulations prepared, selected formulation (F2) were stored at 40±2 °C/75±5 %RH for 28 d. During the study period, the formulations were observed at predetermined time intervals of 0, 7, 14, 21 and 28 d for change in physical appearance, drug content and *in vitro* drug release characteristics. The initial (zero time) results were compared with post stability testing period results for statistical difference [21].

The similarity factor (f2) and dissimilarity factor (f1) [22](as per US FDA) [23] were also calculated using Equation stratified for determination for f_2 and f_1 value respectively. *In vitro* drug release data of both formulations and compared for sameness in the dissolution profile.

$$f_2 = 50 \log \{[1+1/n \Sigma_{n=1} (R_t-T_t)^2]^{-0.5}\} \times 100$$

$$f_1 = \{ \Sigma_{n=1} |R_t-T_t|/\Sigma_{n=1} R_t\} \times 100$$

RESULTS AND DISCUSSION

The prepared AMC were physically evaluated for various parameters such as length, weight variation, thickness, elongation at break, tensile strength, void volume determination and surface characterization and data is summarized in table 2. The results showed uniformity in length, but capsule with glycerine (as pore forming agent) weighed heavier followed by PEG-400 of all the prepared batches. The increase in concentration of pore forming agent leads to increase in the percentage elongation at break. The capsules containing PEG-400 as pore forming agent showed better tensile strength than glycerine. The void volume per unit weight of the polymer was found to be highest in a formulation containing glycerol followed by PEG-400. Cellulose acetate membrane of AMC containing glycerine as a pore forming agent was subjected to SEM studies and cross-sectional view of SEM of AMC clearly indicated the presence of two layers outer, dense and non-porous membranous.

Table 2: Data showing various physical parameters of AMC

Formulation Code	Length* (mm) (mean±SD)**	Weight variation (mean±SD)**	Thickness (mm) (mean±SD) **	Tensile strength (g/mm^2) (mean±SD) **	Elongation at break (%) (mean±SD) **	Void volume (g/cm^3) (mean±SD)*
G5	24.2±70.02	73.9±0.002	0.224±0.24	0.439±0.32	8.26±0.33	3.370±0.001
G6	24.1±0.04	80.6±0.001	0.226±0.21	0.486±0.31	8.45±0.21	4.013±0.001
P5	24.3±0.03	63.2±0.001	0.243±0.19	0.456±0.28	8.33±0.23	2.568±0.002
P6	24.1±0.02	73.0±0.001	0.254±0.24	0.521±0.03	8.79±0.28	3.125±0.002

* Joined (Cap+Body), ** Each value is an average of twenty independent determinations.

***In vitro* drug release study**

The *in vitro* release study of ketorolac tromethamine from AMC having different pore forming agent reveals that as the concentration of the pore-forming agent was increased, the percent of drug released also increases and pore forming agent used 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 difference in the percent of drug released from each of the systems attributed to the porosity of the asymmetric membrane. The higher percent released from the AMC containing glycerol was due to its high porosity causing a higher influx of dissolution medium resulting in quick build-up of osmotic pressure inside the system. The percent drug release increased as the amount of osmogents and pore forming agents increased. Thus, leading to the rapid pore formation and hence, more water could be imbibed and the more core formulation liquefied, as a consequence, ketorolac tromethamine release was increased. The maximum release was shown by NaCl followed by Fructose and Mannitol. The release rate was attributed to osmotic pressure created by individual osmogen. The percent drug released at the end of dissolution time from the control capsule (containing drug only) was lower as compared to capsules filled with various proportions of drug/osmogents. Therefore, we can conclude that osmogents at comparable and profoundly positive effect on drug release

***In vitro* release of final formulations**

The data on the relationship between percent cumulative drug release at 24 h and capsule formulations were determined, which portrays that percent release at 24 h was increased by using a combination of osmogents. The F2 formulation showed higher drug release; this may be attributed by the additive effect of both polymers used.

Table 3: Ketorolac tromethamine release from different formulations containing glycerol as pore forming agent and combination of osmogents

Time (h)	Cumulative % drug release (mean±SD)*			
	F1	F2	F3	F4
0.5	4.11±1.87	8.59±1.52	2.733±2.00	6.45±1.74
1	9.65±1.98	14.21±1.64	8.94±2.11	11.65±1.81
1.5	12.79±2.05	16.46±1.44	11.62±1.92	14.86±1.71
2	14.53±2.41	18.66±1.78	13.06±2.03	17.13±2.00
4	18.38±1.96	23.53±1.61	16.6±1.94	21.09±1.86
6	22.23±1.84	29.66±1.71	19.66±2.05	25.79±1.94
8	27.09±2.04	34.69±1.67	24±1.91	30.13±1.77
12	39.07±2.00	46.47±1.55	35.01±1.84	41.28±1.69
18	55.66±1.99	63.58±1.80	51.83±2.18	58.72±2.01
24	71.23±2.02	77.87±1.77	67.66±2.22	73.09±1.98

*each value is average of six independent determinations with standard deviation

All the final formulations were subjected to kinetic analysis to access the order of release. It was found that release from AMC followed zero order kinetics irrespective of the proportion of drug/ osmogents, as depicted by their higher correlation coefficient value (R^2), as shown in table 4. However, considering the highest correlation coefficient value (R^2) for zero order release model, (F2) seems to be the best formulation.

Stability studies

No difference was observed in the release profile of each F2 Formulation indicating that the fabrication process employed was reliable and reproducible. Further, there was no change in the physical appearance of different formulations at the end of 28 d storage period at accelerated conditions.

The F2 formulation was subjected to estimation of drug content and *in vitro* release and there was no change in drug content as reported in table 4. *In vitro* release studies carried out on F2 formulation at accelerated test conditions for 28 d indicated no significant change in drug release profile when compared to formulation analyzed at zero time. Thus, the results imply good stability of different products for short term storage.

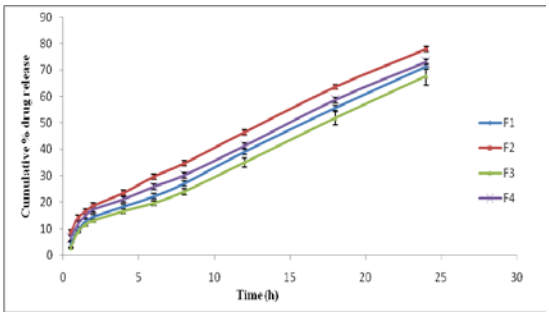

Fig. 1: Dissolution profile of ketorolac tromethamine from asymmetric membrane capsules containing glycerol and combination of osmogens

Table 4: Statistical parameter of various formulations obtained after fitting the drug release data out of various kinetic models

Formulation code	Zero order		First order		Higuchi		Peppas		Hixon	
	R^2	Slope	R^2	Slope	R^2	Slope	R^2	n	R^2	Slope
F1	0.989	2.69	0.963	-0.02	0.948	14.83	0.968	0.65	0.976	-0.06
F2	0.993	2.84	0.969	-0.02	0.964	15.76	0.963	0.53	0.982	-0.07
F3	0.988	2.56	0.745	-0.04	0.936	14.05	0.923	0.70	0.972	-0.02
F4	0.985	2.69	0.967	-0.02	0.955	14.87	.0958	0.57	0.975	-0.06

Table 4: Effects of storage condition on drug content of the osmotic capsule at 40±2 °C/75±5%RH

Formulation code	Time period (Days)	Physical appearance	% Drug content (mean±SD)*	% Drug release (mean±SD)*	Similarity factor (f2)	Dissimilarity factor (f1)
F2	0	White color	74.987±0.56	77.87±1.56	96.96	0.064
	7	White color	74.987±0.51	77.86±1.65		
	14	White color	74.986±0.46	77.85±1.38		
	21	White color	74.985±0.61	77.85±1.47		
	28	White color	74.984±0.57	77.82±1.78		

*Each value is average of three independent determinations.

The dissolution profile comparison showed that the calculated f1 and f2 values for formulation F2 (0.064 and 96.96) fall in the range specified in the literature [23]. This indicated that the *in vitro* drug release profiles of both the formulations were not affected after storage.

CONCLUSION

Osmotically controlled drug delivery system provides a mean of eliminating the effect of pH and agitation on drug release. The desired zero order release profile can be obtained by proper selection of drug: osmogents ratio, polymer concentration and channeling agents (type and concentration). The developed AMC can be used once-a-day controlled release formulation, thus increase patient compliance. This system is cost effective and simple to prepare as no drilling is required and can be used for controlled delivery of water insoluble drug. On the other hand, the release % of poorly water soluble drugs from the capsule with asymmetric membrane could be enhanced by using solubilizing agents, the formation of inclusion complex, etc. so, we can conclude that AMC formulation approach could be used for both osmotic delivery and as controlled release formulation for poorly soluble drugs.

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CONFLICT OF INTERESTS

Declared none

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