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## Formulation and Evaluation of Osmotically Controlled Release System of Diclofenac

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### ABSTRACT

Controlled porosity osmotic pump contains water soluble additive in the coating membrane which in contact with aqueous environment dissolves and outcome in creation of micro porous membrane. The resulting membrane is substantially permeable to both water and dissolved drug. The goal of this investigation is, to gain the benefit of pH and confrontation independent release performance leading to similar in vitro/in vivo delivery. Osmotically driven system embrace a prominent place because of their trustworthiness and knack to deliver the contents at predetermined zero-order rates for extended periods. In the present investigation, efforts have been made to study the release mechanism of drug having low water solubility by means of controlled porosity osmotic pump. The capsule membrane was prepared by phase inversion technique. The drug selected for this study, diclofenac, has low water solubility and hence is unable to create osmotic pressure to cause drug release. To augment the solubility and its osmotic pressure, this study was conducted with a solubility enhancers like Polyethylene glycol (PEG-6000) and osmogens KCl and Mannitol. Diclofenac has a short plasma half life of 1.2-2 hours. Hence, diclofenac was chosen as a model drug with an aspire to develop a controlled porosity system for periods of 10 hours. This system was found to deliver diclofenac at a zero order rate for 10 hours.

**Keywords:** Cellulose acetate, Controlled porosity, Glycerol and Asymmetric membrane.

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## INTRODUCTION

The asymmetric membrane is composed of a thin, dense skin layer supported by a thicker porous substrate layer. These found their use in separation process like demineralization of saline water. Osmotic system consists of a core surrounded by a semi permeable membrane; the core may or may not contain osmotically active agent depending upon the solubility and osmotic pressure of the drug [1]. To ensure the delivery of drug from the osmotic system, osmotically active agents called osmogens are used for drugs with low osmotic pressure and solubilizing agents for the drugs having low solubility [2-4]. The rate of release of drug can be made independent of variables like pH and rate of agitation by the use of semi permeable membrane and osmotic excipient. The capsule membrane of controlled porosity osmotic pump is an asymmetric membrane [5]. Asymmetric membrane capsule is prepared by phase inversion technique. The capsule body and cap are formed by precipitation and cap is formed by precipitation of membrane onto stainless steel mould pin. These moulds are dipped into polymer solution and then immersed into a non solvent quench bath where by the polymer undergoes phase inversion; the shells so formed are removed from moulds. The capsule consists of a drug core surrounded by an asymmetric membrane. The solubility of drugs can be manipulated in simulated gastric and intestinal medium by such controlled porosity osmotic pump [6-8]. Similarly the solubility of water soluble drug can be increased by using solubilizing agents, effervescent mixtures, cyclodextrin derivatives, lyotropic crystals and wicking agents in the core or decreased by using resin modulated approach or using alternate salt form. The porosity of asymmetric membrane can be easily controlled by the choice and variation in concentration of pore forming agent [9-12]. While in controlled porosity osmotic pump, using asymmetric membrane, the water soluble additives like glycerol, in contact with aqueous medium results in-situ formation of micro porous membrane [13, 14].

## MATERIAL AND MEHTODS

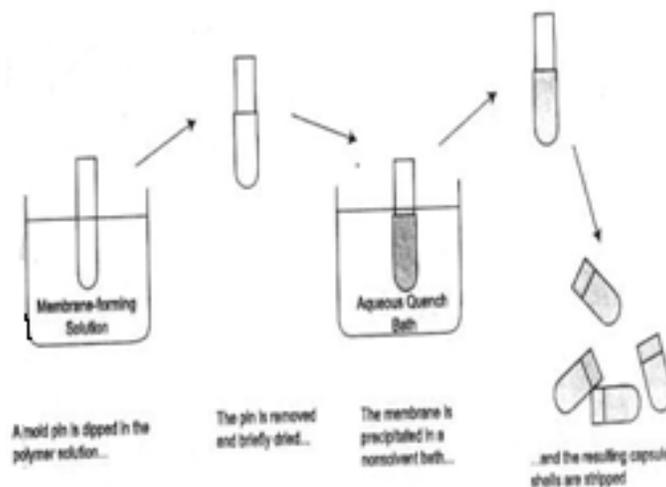
Cellulose acetate, PEG- 6000 was procured from S. D. Fine Chem. Ltd. Mumbai and Glycerol was procured from Mark Limited, Worli, Mumbai. Drug (Diclofenac) was procured from Cadila Pharmaceuticals as gift sample.

### **Process for manufacturing asymmetric membrane capsules [3, 4, 6, 15]**

The asymmetric membrane capsule was made by a phase inversion process in which the membrane structure was precipitated on a stainless steel mold pin by dipping the mold pin in a coating solution followed by quenching in an aqueous solution (**Figure 1**). Solutions of cellulose acetate (16 % w/v) were prepared in acetone/water (90/10) solvent system. Weighed quantity of cellulose acetate was added to the acetone/water solvent system and the resulting mixture was stirred in a well closed beaker until a homogenous solution was formed. While stirring the required quantity of pore forming agent glycerol and mixture of glycerol & PEG-400 was added (70 % w/w of cellulose acetate). The stainless steel mould pins were fabricated with the dimensions so as to form a capsule body and cap. The mould pins were dipped in the coating

solution of cellulose acetate and glycerol for 2 min. and 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 sec, followed by quenching in aqueous solution (10 % w/v glycerol). This resulted in phase inversion and formation of asymmetric membrane. The resulting membrane was stripped off and trimmed to desired size and stored for future study.

**Figure 1: Dip coating process manufacturing of asymmetric membrane Capsule Preparation of asymmetric membrane capsule**



**Formulation code of asymmetric membrane capsules**

Asymmetric membrane capsules were fabricated and filled with the desired amount of drug and excipients mixture manually. Different ratios of Mannitol, PEG-6000 & KCl with drug were filled. After filling operation the capsules were capped and sealed with sealing solution

**Table 1: Asymmetric Membrane Capsules with Different Pore Forming Agent**

S. No.	Capsule code	Pore forming agent	Concentration (% w/w of CA)
1.	A	PEG-400	70
2.	B	Glycerol	70

\*CA- Cellulose acetate.

**Table 2: Formulation code of asymmetric membrane capsules (A, B) filled with different osmogens at different ratios**

**For Asymmetric membrane capsule A**

Code	Drug: PEG-6000	Code	Drug: Mannitol	Code	Drug: KCl
AP <sub>1</sub>	1:1	AM <sub>1</sub>	1:1	AK <sub>1</sub>	1:1
AP <sub>2</sub>	1:2	AM <sub>2</sub>	1:2	AK <sub>2</sub>	1:2
AP <sub>3</sub>	1:3	AM <sub>3</sub>	1:3	AK <sub>3</sub>	1:3
AP <sub>4</sub>	1:5	AM <sub>4</sub>	1:5	AK <sub>4</sub>	1:5

## For Asymmetric membrane capsule B

Code	Drug: PEG-6000	Code	Drug: Mannitol	Code	Drug: KCl
BP <sub>1</sub>	1:1	BM <sub>1</sub>	1:1	BK <sub>1</sub>	1:1
BP <sub>2</sub>	1:2	BM <sub>2</sub>	1:2	BK <sub>2</sub>	1:2
BP <sub>3</sub>	1:3	BM <sub>3</sub>	1:3	BK <sub>3</sub>	1:3
BP <sub>4</sub>	1:5	BM <sub>4</sub>	1:5	BK <sub>4</sub>	1:5

**Filling of asymmetric membrane capsule:** The fabricated asymmetric membrane capsules were filled with the mixture of drug and solubilizing agent osmogents respectively. The physical mixture of drug and HPMC, PEG-6000 & KCl was prepared separately by mixing them thoroughly in laboratory blender for 10 min. and subsequently passing them through sieve No. 80. Each of the asymmetric membrane capsule containing different pore forming agent i.e. Glycerol & Glycerol+PEG-400 (70% w/w of cellulose acetate) were filled with mixture of drug and solubilizing agent and osmogens in the ratios of 1:1,1:2, 1:3,1:5 keeping the quantity of drug constant. Each of the mixture of drug and PEG-6000, Mannitol & KCl was filled in the body of each of these capsules and the cap was snugly fitted to the body of capsule. Body and cap of the filled capsule were finally sealed with a sealing solution of 16 % cellulose acetate only to ensure that no release takes place from these seals during the dissolution run.

**Physical evaluation of asymmetric membrane capsules**

Physical Evaluation of Asymmetric membrane capsules was done with the following parameters; Weight variation, Surface characterization, checking of in- situ formation of pores and Void volume determination, Surface area determination.

**In vitro drug release:** The in vitro dissolution was carried out using USP dissolution methodology (Apparatus II, 50 rpm,  $37 \pm 0.5^{\circ}$  C, and 900 ml phosphate buffer pH 7.4). A temperature of  $37 \pm 0.50$  C was maintained throughout the study. The release profile was studied in phosphate buffer pH 7.4 periodically; 5 ml of aliquots of dissolution medium were withdrawn and replaced with 5 ml of fresh dissolution media kept at  $37 \pm 0.5^{\circ}$ C. The collected samples were filtered and analyzed at the respective -max of the drug using UV visible spectrophotometer against the dissolution media taken as blank. The release profile data was analyzed for percent cumulative release at different time interval.

**RESULT AND DISCUSSION**

**Differential Scanning Calorimetry of Diclofenac:** The DSC thermogram of Diclofenac showed sharp peak at 161.82°C. The identity of a compound was also confirmed by comparison with that of an authentic sample and verification of the presence of functional groups in an unknown molecule was done by IR spectra (**Figure 2**).

Figure 2: DSC thermograms of Diclofenac exhibiting a sharp endothermic peak at 161.82°C

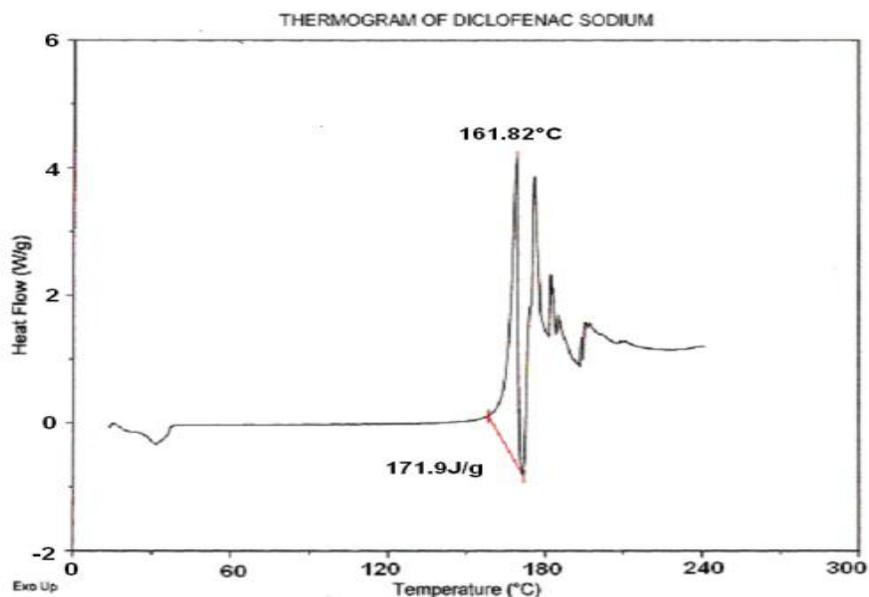
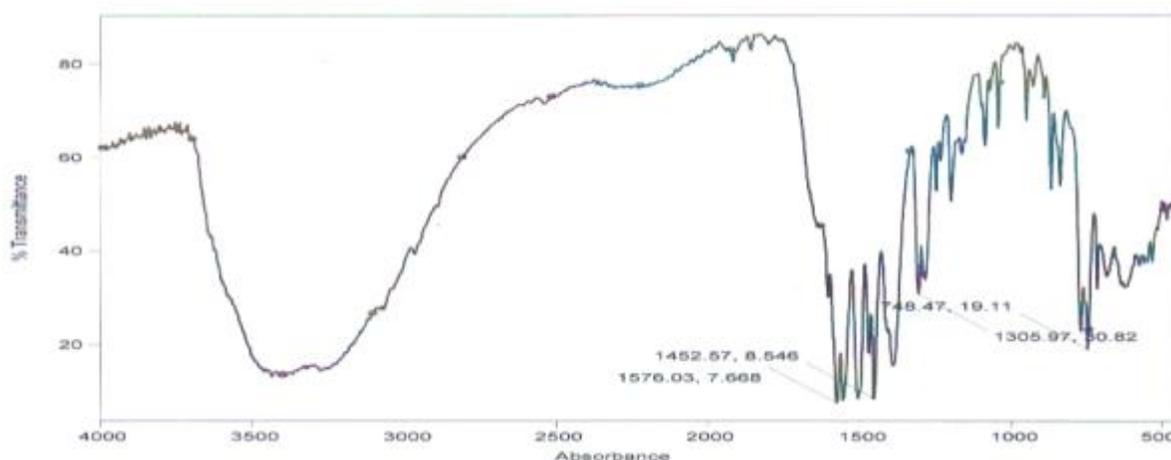


Figure 3: Infrared spectra of Diclofenac



**Infrared Spectroscopy:** An I.R. spectrum was recorded on Shimadzu-470 spectrophotometer using KBr pellets. The I.R. obtained was elucidated for important chromophore groups (**Figure 3**).

Table 3 Evaluation of Asymmetric membrane capsules A, B

S.No.	Membrane Thickness ( $\mu\text{m}$ )	Surface area in ( $\text{mm}^2$ )	Weight variation
Capsule A	816	$909.66 \pm 4.92$	$148.9 \pm 0.85$
Capsule B	778	$811.75 \pm 4.95$	$149.3 \pm 0.74$

**Evaluation of Asymmetric membrane capsules A & B:** Membrane thickness was determined by the micrometer. For different asymmetric capsules A and B it is found to be 816, 778  $\mu\text{m}$

respectively. The observed weight variation, surface area and void volume data seen in (Table 3). The order of membrane thickness was – Capsule A > Capsule B By the scanning electron microscopy, also determined the pore diameter of different asymmetric membrane capsules A, B. The order of pore diameter was – Capsule A > Capsule B So according to the data of pore diameter, maximum drug should release through the capsule A in comparison to B. Void volume was also determined for asymmetric membrane capsules A& B Maximum void volume was determined in the capsule A, followed by B. So the porosity of the capsule A is maximum, so maximum drug released by the asymmetric membrane capsule A.

The order of porosity was – Capsule A > Capsule B

**In vitro release kinetics of Diclofenac from CPOP capsules – A and B in the presence of PEG-400, Mannitol & KCl:** In vitro kinetic treatment to release of diclofenac from asymmetric membrane capsule – A & B in the presence of PEG-6000, Mannitol & KCl determined by the  $r^2$  &  $k$  values. The correlation coefficient of linear relationship between the percent cumulative drug released and the in vitro release time suggest that the system follows zero-order release irrespective of the concentration of pore forming agent and the ratio of osmotic excipient drug.

**Influence of drug: osmogens ratio on drug release:** The release of valsartan from the capsule was determined and results shows that amount of osmogen KCl in the core formulation had a marked influence on diclofenac release. The release of poorly water soluble drug diclofenac increases with the increase in the amount of osmogen KCl, when added to the core of the formulation due to the increased osmotic pressure (Table 4).

Table 4 (a) For Capsule A, (b) for capsule B

A]Osmogens	Code	1:1	Code	1:2	Code	1:3	Code	1:5
KCl	AK <sub>1</sub>	49.98	AK <sub>2</sub>	60.9	AK <sub>3</sub>	75.67	AK <sub>4</sub>	87.24
Mannitol	AM <sub>1</sub>	39.67	AM <sub>2</sub>	55.58	AM <sub>3</sub>	75.04	AM <sub>4</sub>	92.82
B]Osmogens	Code	1:1	Code	1:2	Code	1:3	Code	1:5
KCl	AK <sub>1</sub>	52.81	AK <sub>2</sub>	61.15	AK <sub>3</sub>	75.8	AK <sub>4</sub>	88.39
Mannitol	AM <sub>1</sub>	49.42	AM <sub>2</sub>	65.33	AM <sub>3</sub>	80.1	AM <sub>4</sub>	90.98

**Influence of drug: solubilizing agent ratio on drug release:** The release of diclofenac from the capsule was determined shows that amount of solubilizing agent PEG-400 and in the core formulation had a marked influence on diclofenac release (Table 5).

Table 5: (a) For Capsule A

Solubilizing agent	Code	1:1	Code	1:2	Code	1:3	Code	1:5
PEG-6000	AP <sub>1</sub>	35.35	AP <sub>2</sub>	46.66	AP <sub>3</sub>	65.34	AP <sub>4</sub>	77.75

Table 5 (b) For Capsule B

Solubilizing agent	Code	1:1	Code	1:2	Code	1:3	Code	1:5
PEG-6000	AP <sub>1</sub>	38.61	AP <sub>2</sub>	49.92	AP <sub>3</sub>	68.6	AP <sub>4</sub>	81.01

**Correlation between zero order rate constant ( $K_0$ ) and ratio of osmotic excipient:** Correlation coefficient of linear relationship between the zero order rate constant ( $K_0$ ) and the ratios of drug and different osmotic excipients encapsulated in capsule A is shown in (Figure 4), in capsule B is shown in (Figure 5). A high degree of correlation was observed when KCl was encapsulated along drug suggesting that KCl acts as a good osmogen.

Figure 4: Correlation of the zero-order rate constant ( $K_0$ ) and Drug: Osmotic excipients ratio encapsulated in capsule A.

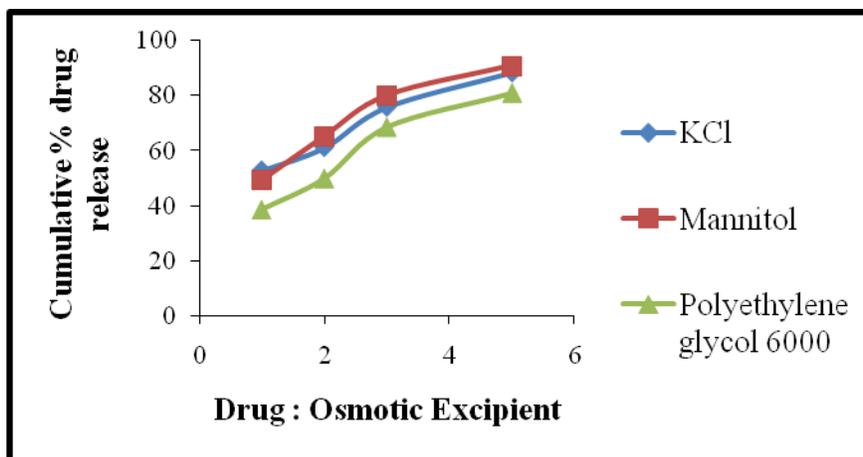
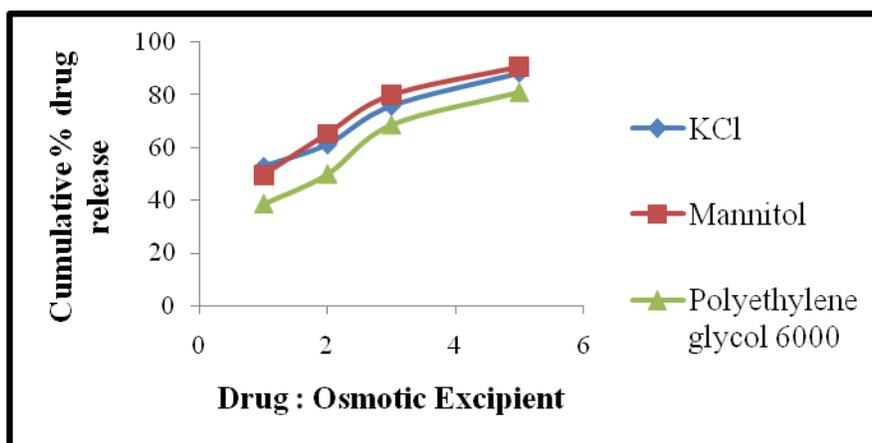


Figure 5: Correlation between the zero-order rate constant ( $K_0$ ) and Drug: Osmotic excipient ratio encapsulated in capsule B.





## CONCLUSION

A porous osmotic pump based drug delivery system successfully designed for controlled release of drug diclofenac. It is evident from the results that showed, the rate of drug release can be controlled through osmotic pressure of the core, level of pore forming agent and weight of membrane with release to be fairly independent of pH and hydrodynamic conditions of the body. The release of poorly water soluble drug diclofenac increases with the increase in the amount of PEG-6000, Mannitol & KCl added to the core of the formulation. The in vitro drug release was fitted into different kinetic models. The line of equation and regression value shown that the system formulated followed zero order release kinetic because the regression values in zero-order graph were closer to one.

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