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ORIGINAL RESEARCH ARTICLE

Formulation And Evaluation Of Controlled Porosity Osmotic Pump Of Valsartan

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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 delivery orifices so formed were inveterate by release of an encapsulated dye from the capsule and scanning electron microscope (SEM).The drug selected for this study, valsartan, 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 enhancer HPMC (Hydroxy propyl methyl cellulose), PEG-6000 and osmogents KCl. Valsartan has a short plasma half life of 3-5 h. Hence, valsartan was chosen as a model drug with an aspire to develop a controlled porosity system for periods of 9 hours. This system was found to deliver valsartan at a zero order rate for 9 hours.

Key words: Cellulose acetate, Controlled porosity, Glycerol and Asymmetric membrane.

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 semipermeable 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 osmogents are used for drugs with low osmotic pressure and solubilizing agents for the drugs having low solubility [2, 3,4]. The rate of release of drug can be made independent of varaibles like pH and rate of agitation by the use of semipermeable membrane and osmotic excipient .The capsule membrane of controlled porosity osmotic pump is an asymmetric membrane5. 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 [6,7,8]. 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 varation in concentration of pore forming agent [9,10,11,12]. While in controlled porosity osmotic pump, using

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asymmetric membrane, the water soluble additives like glycerol, in contact with aqeous medium results in-situ fromation of microporous membrane [13,14].

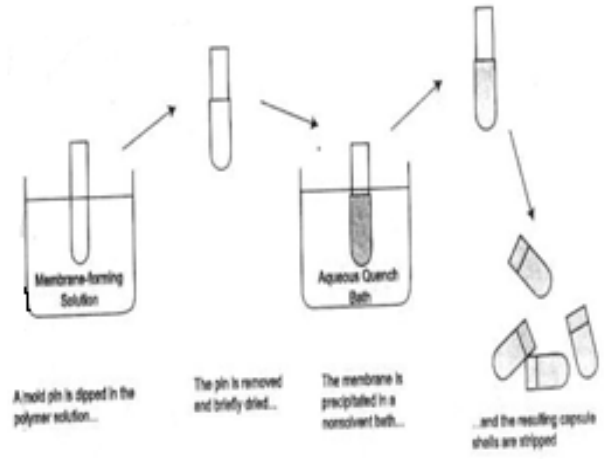
MATERIAL AND MEHTODS:

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

Process for manufacturing asymmetric membrane capsules [3,4,6,13]:

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 (**Fig. 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.

Fig. 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 HPMC, PEG-6000 & KCl with drug were filled. After filling operation the capsules were capped and sealed with sealing solution (**Table 1& 2**).

Table 1. Asymmetric Membrane Capsules with Different Pore Forming Agent

S.N	Capsule code	Pore forming agent	Concentration (% w/w of CA)
1.	A	Glycerol + PEG-400	70
2.	B	Glycerol	35 + 35

* CA – Cellulose Acetate

Table 2. Formulation code of asymmetric membrane capsules (A, B) filled with different osmogent at different ratios –

For Asymmetric membrane capsule A

Code	Drug: hpmc	Code	Drug: peg-6000	Code	Drug: kcl
AH_1	1:1	AP_1	1:1	AK_1	1:1
AH_2	1:2	AP_2	1:2	AK_2	1:2
AH_3	1:3	AP_3	1:3	AK_3	1:3
AH_5	1:5	AP_5	1:5	AK_5	1:5

For Asymmetric membrane capsule B

Code	Drug: hpmc	Code	Drug: peg-6000	Code	Drug: kcl
BH_1	1:1	BP_1	1:1	BK_1	1:1
BH_2	1:2	BP_2	1:2	BK_2	1:2
BH_3	1:3	BP_3	1:3	BK_3	1:3
BH_5	1:5	BP_5	1:5	BK_5	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 osmogent 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 HPMC, PEG-6000 & 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, Void volume determination, Surface area determination and Scanning Electron Microscopy.

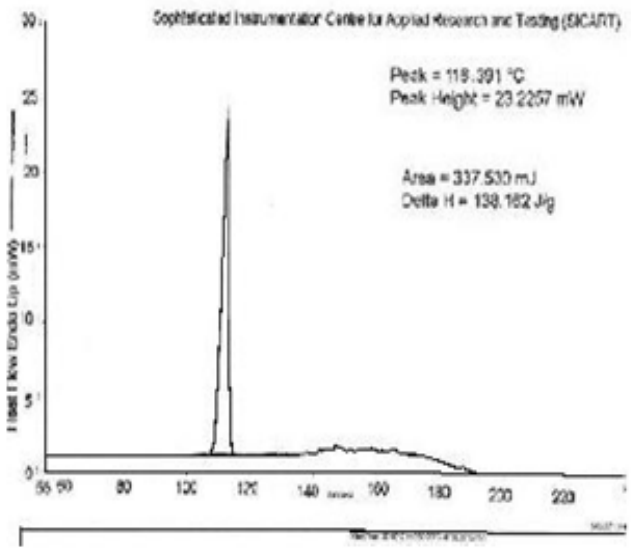
***In vitro* drug release:** The *in vitro* dissolution was carried out using USP dissolution methodology (Apparatus II, 50 rpm, 37 ± 0.50 C, and 900 ml phosphate buffer pH 7.4). A temperature of 37 ± 0.50 C was maintained throughout the study. The release profile was studied in phosphate buffer pH 7.4 periodically; 5 ml of aliquots of dissolution medium were withdrawn and replaced with 5 ml of fresh dissolution media kept at 37 ± 0.50C. 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

DSC of Valsartan:

The DSC thermogram of Valsartan showed sharp peak at 116.30C. 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**.** (**Fig. 2**)

Fig. 2 DSC Thermogram of Valsartan



IR Spectroscopy: An I.R. spectrum was recorded on schimadzu-470 spectrophotometer using KBR pellets. The I.R. obtained was elucidated for important chromophore groups.

Evaluation of Asymmetric membrane capsules A & B:

Membrane thickness was determined by the scanning electron microscopy (SEM). For different asymmetric capsules A and B it is found to be 360, 218 µm 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

Table 3 Evaluation of Asymmetric membrane capsules A, B

S.NO	Membrane Thickness (µm)	Surface area in (mm^2)	Weight variation
Capsule A	360	409.66 ± 4.92	41.63 ± 0.76
Capsule B	218	411.75 ± 4.95	45.49 ± 0.79

Physical evaluation of asymmetric membrane capsules:

The asymmetric membrane capsules appeared to be white, opaque and glossy with no visible imperfection. This confirms that the process of producing these capsules is reproducible. Scanning electron micrographs of the capsule wall show that the membrane was asymmetric with a relatively thin dense region on a porous substrate with longer micro porous structures. In the cross section of Asymmetric membrane wall of capsule A at 115 x magnification (**Fig 3a**) showing pores with the membrane thickness 360 µm. The porous region in the asymmetric membrane wall of capsule A showing at 1500 x magnification (**Fig 3b**) reveals numerous pore structures and also find out the pore diameter through these pores.In the cross section of Asymmetric membrane wall of capsule B, showing the pores at 200 x magnifications (**Fig 3c**)with the membrane thickness 218 µm.

Fig 3(a) SEM of the Asymmetric membrane wall of capsule-A (cross section): 115 x magnification

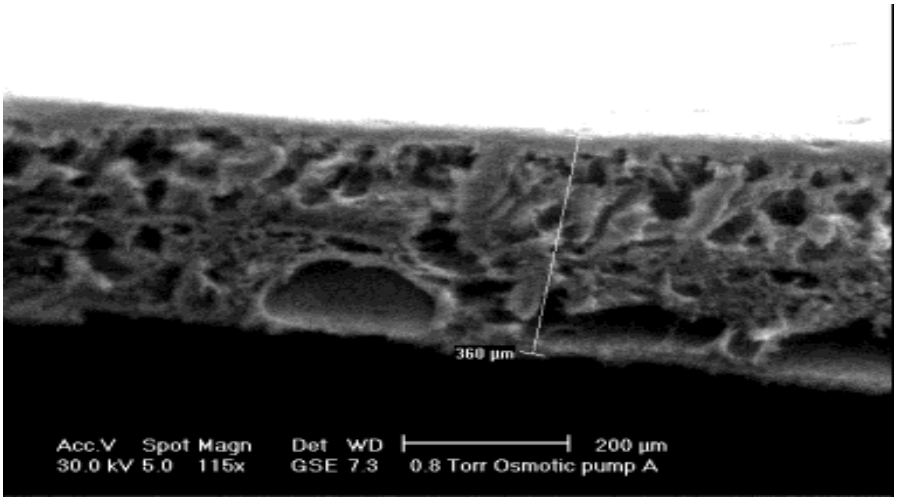


Fig 3(b) SEM of the asymmetric membrane wall of capsule – A (showing pores): 150 x magnification

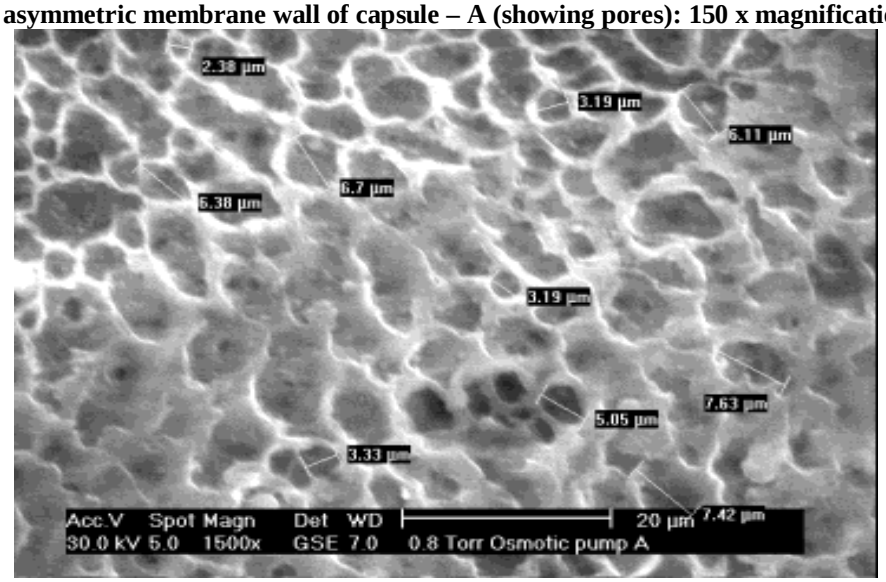
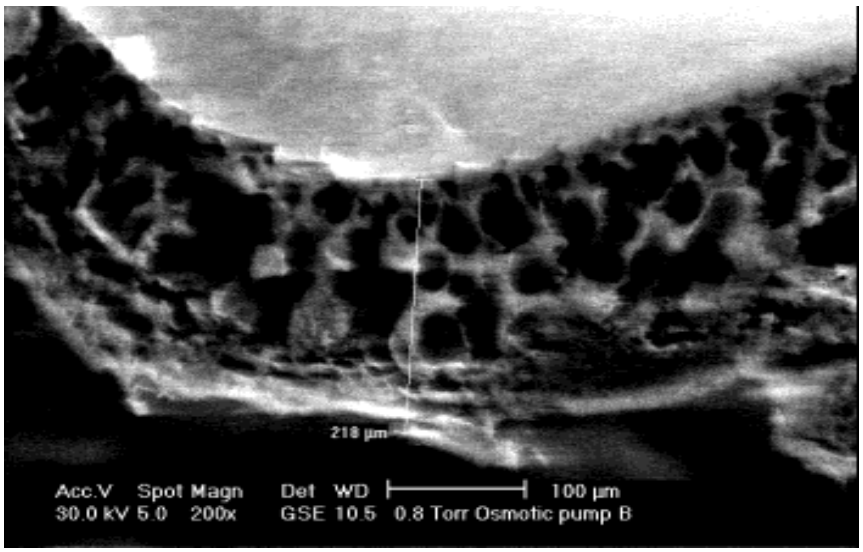


Fig 3(c) SEM of the Asymmetric membrane wall of capsule-B (cross section): 200 x magnification



***In vitro* release kinetics of Valsartan from CPOP capsules – A and B in the presence of HPMC, PEG-6000 & KCl:**

In vitro kinetic treatment to release of valsartan from asymmetric membrane capsule – A & B in the presence of PEG-6000, HPMC & KCl determined by the *r2* & *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: osmogent ratio on drug release:

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

Table 4. Comparison of cumulative percent drug release after 9 hours

Table 4 (a) For Capsule A

Osmogents	Code	Ratio 1:1	Code	Ratio 1:2	Code	Ratio 1:3	Code	Ratio 1:5
KCl	AK_1	8.59	AK_2	19.76	AK_3	34.41	AK_5	45.85

Table 4 (b) For Capsule B

Osmogents	Code	Ratio 1:1	Code	Ratio 1:2	Code	Ratio 1:3	Code	Ratio 1:5
KCl	BK_1	8.02	BK_2	16.92	BK_3	31.69	BK_5	44.41

Influence of drug: solubilizing agent ratio on drug release:

The release of valsartan from the capsule was determined shows that amount of solubilizing agent PEG-6000 & HPMC and in the core formulation had a marked influence on valsartan release (**Table 5**).

Table 5 (a) For Capsule A

Solubilizing agent	Code	Ratio 1:1	Code	Ratio 1:2	Code	Ratio 1:3	Code	Ratio1:5
HPMC	AH_1	12.58	AH_2	28.49	AH_3	47.95	AH_5	63.89
PEG-6000	AP_1	9.98	AP_2	21.29	AP_3	39.97	AP_5	52.38

Table 5 (b) For Capsule B

Solubilizing agent	Code	Ratio 1:1	Code	Ratio 1:2	Code	Ratio 1:3	Code	Ratio1:5
HPMC	AH_1	12.58	AH_2	28.49	AH_3	47.95	AH_5	63.89
PEG-6000	AP_1	9.98	AP_2	21.29	AP_3	39.97	AP_5	52.38

Correlation between zero order rate constant (Ko) and ratio of osmotic excipient:

Correlation coefficient of linear relationship between the zero order rate constant (K0) and the ratios of drug and different osmotic excipients encapsulated in capsule A is shown in (**Fig. 4**), in capsule B is shown in (**Fig 5**). A high degree of correlation was observed when HPMC was encapsulated along drug suggesting that HPMC besides acting as a solubilizing agent also acts as an osmogent.

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

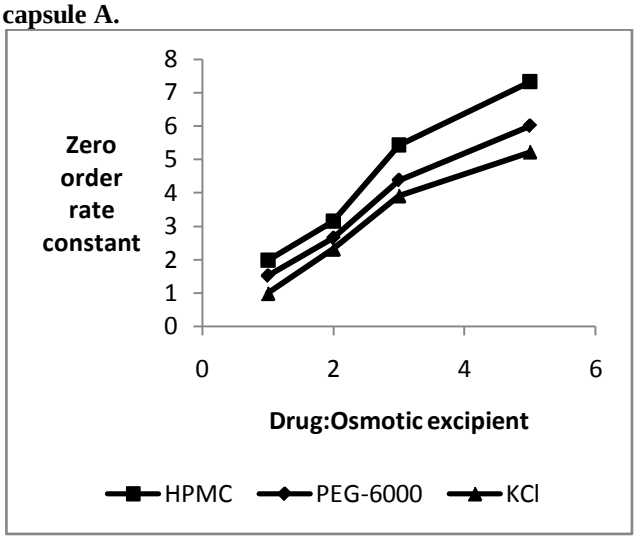
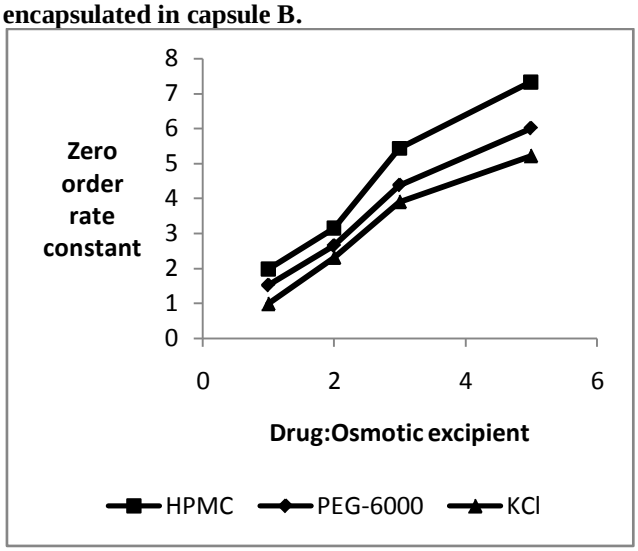


Figure 5 Correlation between the zero-order rate constant (K_0) and Drug: Osmotic excipient ratio encapsulated in capsule B.



CONCLUSION

A porous osmotic pump based drug delivery system successfully designed for controlled release of drug valsartan. 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 valsartan increases with the increase in the amount of HPMC, PEG-6000 & KCl added to the core of the formulation. Results of SEM studies inveterate the formation of pores in the asymmetric membranes after coming into contact with the aqueous environment. 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.

REFERENCES

1. Thombre AG, Cardinal JR, Denoto AR, Herbig SM, Smith KL (1999): Asymmetric membrane capsules for osmotic drug delivery- I Development of a manufacturing process, J Control Release57, 55-64.
2. Theeuwes F, Swanson D, Wong P, Bonsen P, Place V, Heimlich K, Kwan KC(1983): Elementary osmotic pump for indomethacin, J Pharm Sci, 72, 253-258.
3. Philip AK, Pathak K (2006): Osmotic flow through asymmetric membrane, a means for controlled delivery of drugs with varying solubility, AAPS Pharm. Sci. Tech, 721-725.
4. Makhija SN, Vavia PR (2003): Controlled porosity osmotic pump-based controlled release systems of pseudoephedrine-I Cellulose acetate as a semipermeable membrane, J Control Release 89, 5-18.
5. Lui LX (1999): Preparation and characterization of cellulose acetate membrane for monolithic osmotic tablets, Kor. Polym. J 7(5), 289–296.
6. Zentner GM, Rork GS, Himmelstein KJ (1990): Controlled porosity osmotic pump. U.S. Patent 4,968,507.
7. Thombre AG, DeNoto AR, Gibbes DC (1999): Delivery of glipizide from asymmetric membrane capsules using encapsulated excipients, J Control Release 60, 333-341.
8. Swarbrick J, Boyian CJ (1991): Encyclopedia of Pharmaceutical Technology, 1V, Marcel Decker, New York, 310.
9. Liu H, Yang XG, Nie SF, Wei LL, Zhoub LL, Liu H, Tang R, Pan WS (2007): Chitosan- based controlled porosity osmotic pump for colon-specific delivery system, Screening of formulation variables and in vitro investigation, International Journal of Pharmaceutics 332, 115–124.
10. Verma RK, Krishna DM, Garg S (2002): Formulation aspects in the development of osmotically controlled oral drug delivery systems, J Control Release 79, 7–27.
11. Gondaliya D, Pundarikakshudu K (2003): The Fabrication and evaluation of the formulation variables of a controlled-porosity osmotic drug delivery System with Diltiazem Hydrochloride, Pharmaceutical technology, 58-68.
12. Jian-Hwa G (1993): Effect of Plasticizers on water permeation and mechanical properties of cellulose Acetate: Antiplasticization in slightly plasticized polymer film, Drug Dev Ind Pharm 19(13), 1541–1555.
13. Ende MT, Herbig SM, Krsmeyer RW, Childlaw MB (2001): In Handbook of pharmaceutical controlled release technology, Marcel Dekker, New York, 751-85
14. Lin Y, Ho H (2003): Investigation on the drug releasing mechanism from an asymmetric membrane coated capsule with an *in situ* formed delivery orifice, J Control Release 89, 57-69.
15. Kumar P, Singh S, Mishra B (2009): Development and Evaluation of elementary osmotic water soluble drug Tramadol Hydrochloride, Current drug delivery 6, 130-139.