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SWELLABLE OSMOTIC DRUG DELIVERY SYSTEM OF AMITRIPTYLINE HYDROCHLORIDE – DESIGN AND EVALUATION

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ABSTRACT

The objective of the present study is to develop swellable osmotic drug delivery system of Amitriptyline hydrochloride. Amitriptyline hydrochloride is a tricyclic anti depressant widely used for the treatment of depression and neurogenic pain. It is freely soluble in water. In order to achieve controlled release and to improve the bioavailability swellable systems were prepared using hydrophilic polymers hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), methyl cellulose (MC) and coated using cellulose acetate. *In vitro* release studies of different formulations with different orifice diameters were compared. The formulations showed controlled release and good stability during short term accelerated stability studies.

Key words: Amitriptyline hydrochloride, Swellable osmotic drug delivery, Orifice, SCMC, HPMC, MC.

INTRODUCTION

Controlled release delivery systems of drugs have recently become an important field of research because of their extended and safe use. Among various controlled release devices, osmotically driven system hold a prominent place because of their reliability and ability to deliver the contents at a predetermined rate for prolonged periods. Of the several osmotic devices, Elementary osmotic pumps (EOPs) are the most commercially important osmotic devices because they are easy to formulate, simple in operation, production scale up is easy and most importantly releases the drug at an approximate zero order rate. Drugs of extreme solubility can be formulated as osmotically controlled systems. Amitriptyline hydrochloride, the model drug is a widely used tricyclic anti-depressant. It is rapidly absorbed from GI after oral administration because of its high solubility.

The objective of this study is to design and evaluate a new EOP called swellable elementary osmotic pump (SEOP) of the freely water soluble drug, amitriptyline hydrochloride (1 g /mL) by adding water-swellable polymers in the core. The hydrophilic polymers included in the core retard the highly water soluble drug by producing hydrogel within the core, which may restrict and delay the solvent contact with drug molecules and may increase the diffusional length of the solvent to achieve a constant release rate. Thus, this technology can be exploited to achieve constant drug release at predetermined rate especially for highly water soluble drugs.

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EXPERIMENTAL

Materials and methods

Materials

Amitriptyline was obtained as a gift sample from Paris Dakner, Chennai. Cellulose acetate, sodium carboxy methyl cellulose (Loba Chemie, Mumbai, India), hydroxy propyl methyl cellulose and polyethylene glycol (S. D. fine Chemicals, Boisar, India) were procured from local market. Methyl cellulose was obtained from Ottokemi, Mumbai, India. All other solvents and reagents used were of analytical grade.

Preparation of Amitriptyline hydrochloride core tablets[1-4]

Different formulations of amitriptyline hydrochloride were prepared as shown in the Table 1. The granules were prepared by wet granulation technique. Amitriptyline hydrochloride and all other ingredients were passed through sieve No. 60, granulated with PVP K_{30} dissolved in isopropyl alcohol. The coherent mass was then passed through standard sieve No. 10. The granules were dried at 50°C for 2 hours and the dried granules after passing through sieve No. 22 were lubricated with talc and magnesium stearate. The granules were then compressed into tablets using cadmach single punch tablet machine fitted with 10 mm standard concave punches.

Swellable osmotic drug delivery system of Amitriptyline hydrochloride – design and evaluation

Table 1: Composition of core tablets

Ingredients (mg/tablet)	Formulation code									
	CMC 15%	CMC 25%	CMC 50%	HPMC 15%	HPMC 25%	HPMC 50%	MC 15%	MC 25%	MC 50%	C
	SA	SB	SC	HA	HB	HC	MA	MB	MC	C
Amitriptyline HCl	75	75	75	75	75	75	75	75	75	75
Sodium carboxy methyl cellulose	11.25	18.75	37.5	-	-	-	-	-	-	-
Hydroxy propyl methyl cellulose	-	-	-	11.25	18.75	37.5	-	-	-	-
Methyl cellulose	-	-	-	-	-	-	11.25	18.75	37.5	-
PVP K_{30}	15	15	15	15	15	15	15	15	15	15
Lactose	168.75	161.25	142.5	168.75	161.25	142.5	168.75	161.25	142.5	180
Magnesium stearate	15	15	15	15	15	15	15	15	15	15
Talc	15	15	15	15	15	15	15	15	15	15

Coating of core tablets[10]

Cellulose acetate (5% w/w) dissolved in dichloromethane and methanol mixture (4 : 1) containing PEG 400 as plasticizer in the concentration of 15% w/w (w.r.t. cellulose acetate) was used as coating solution. The coating operation was performed using spray pan coating machine. Pan was made up of stainless steel, having diameter of 22 cm and rotating speed of 32 rpm. The spray rate and atomization pressure were fixed at 4 mL/min and 1.5 Kg/cm^2 respectively. The inlet air temperature of 40-45°C was

maintained. The manual coating procedure was used based on intermittent spraying and drying techniques. After coating, the coated tablets were dried at 50°C for 12 hours to remove the residual solvent.

Drilling of coated tablet

The drug delivery orifice was made on the surface of one side of the tablets by using Microdrill. High speed stainless steel drill bits of various diameters (0.4, 0.6, 0.8, 1 mm) were used for drilling.

Evaluation

Preformulative studies[5-8]

Differential scanning calorimetry[13]

The possibility of drug-polymer interaction was investigated by Differential scanning calorimetry (DSC 60 SHIMADZU, Japan). The DSC thermograms of pure drug and the polymers were recorded to study the interactions between drug and polymers. The samples were separately sealed in aluminium cells and set in a thermal analyzer. The thermal analysis was performed at a scanning rate of 10°C per minute over a temperature range of 50-300°C. Alumina was employed as the reference standard.

Post formulative studies[5-8]

Physical properties

The granules of all the formulations were evaluated for angle of repose, loose and tapped bulk density, Carr's index and drug content. Similarly the prepared tablets were evaluated for hardness, thickness, diameter, friability, drug content, and weight variation.

Percentage weight increase

Twenty tablets (before and after coating) from each formulation were selected randomly, weighed individually and average weight was calculated. The average weight increase due to coating was determined from the difference in weight of coated and uncoated tablets.

Measurement of orifice diameter

The orifice diameter of the drilled tablets was measured by using reflecting optical microscope. The image was transduced to the computer screen using Cannon zoom browser and their size was measured. Only those tablets having orifice diameter of tabulated value ± 0.01% (Average ± SEM) were selected for further studies.

***In vitro* release studies**[9,11]

In vitro release studies of all the formulations and control (without polymer) were performed in a USP Dissolution Apparatus Type II using the paddle method. The dissolution media used was hydrochloric acid buffer pH 1.2 (900 mL) for first 2 hrs and phosphate buffer pH 6.8 (900 mL) for subsequent 6 hrs. The temperature and the stirring rate were maintained at 37 ± 1°C and 50 ± 1 rpm respectively. Aliquot samples (5 mL) of dissolution medium were withdrawn at regular intervals to maintain the sink conditions and analyzed at 239 nm using UV spectrophotometer to find out the percentage drug release.

Similarity factor (f_2) was employed to evaluate the release profiles of all the formulations compared with the theoretical release profile. The f_2 was a logarithmic transformation of the sum squared error of differences between the testing drug release and the ideal release over all time points. The f_2 value greater than 50 indicates that the testing profile is similar to the ideal profile[19].

Extension of dissolution studies

The formulations having the similarity factor of more than 50 were selected and dissolution studies were extended for 12 hours. (pH 1.2 for first 2 hours and pH 6.8 for remaining 10 hours)

Kinetic analysis[1,18]

The *in vitro* release profiles obtained from the osmotic tablets were fit to zero order, first order, Higuchi, Hixson Crowell, to find out the mechanism of drug release.

Zero order - $C = k_0 t$

First order - $\text{Log } C = \text{Log } C_0 - kt / 2.303$

Hixson-crowell - $Q_0^{1/3} - Q_t^{1/3} = KH_C t$

Higuchi - $Q = K t^{1/2}$

Scanning electron microscopy[12]

The porous morphology and orifice diameter of coating membranes (before and after dissolution studies) were examined using Scanning Electron Microscope (JEOL JSM – 6360). The samples were placed on spherical brass stubs with a double backed adhesive tape. The mounted samples were sputter coated for 5-10 min with gold using fine coat ion sputter and examined under SEM.

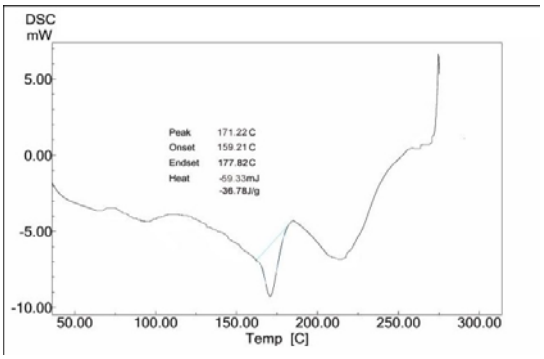
Stability Studies[14-16]

Stability studies were conducted on the formulated elementary osmotic tablets containing varying concentrations of SCMC, HPMC and MC. The stability was assessed with respect to their physical appearance and drug content by storing at ambient room temperature and 40 ± 2° maintained at RH 75% for 3 months. The drug content of the different formulations was evaluated biweekly in at 239 nm UV-Visible Spectrophotometer.

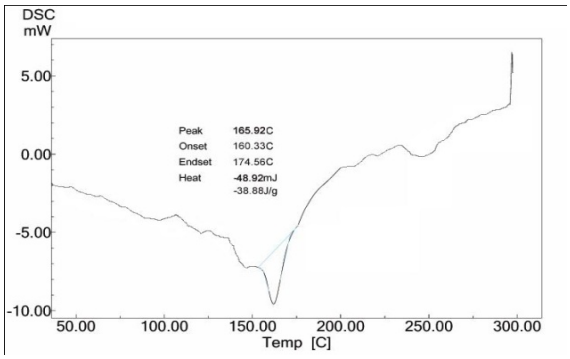
RESULTS AND DISCUSSION

Differential scanning calorimetry

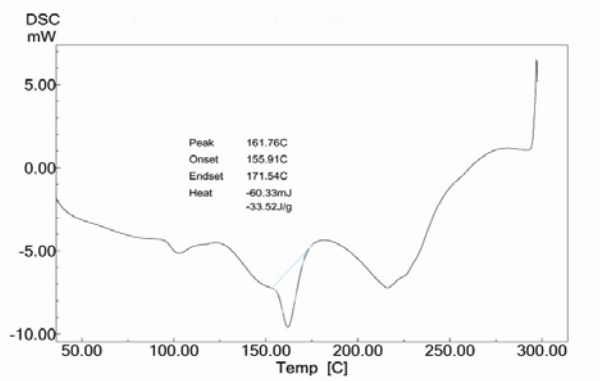
The DSC thermo grams of pure drug and the different polymers showed that an endothermic peak corresponding to the melting point of pure drug was prominent in all the drug polymer mixture, which suggested clearly that there was no interaction between the drug and the polymers and the drug was existed in its unchanged form as shown in the Fig. 1.



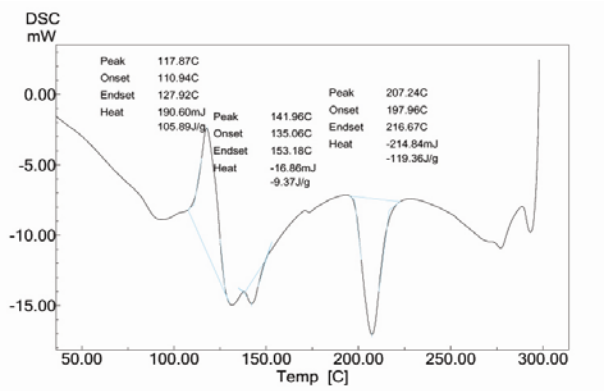
(A) Pure drug



(B) MC



(C) CMC



(D) HPMC

Fig. 1: DSC thermograms

Physico-chemical evaluation of uncoated and coated tablets[1,8]

The granules of all the formulations were found to possess good flow property which was indicated by angle of repose 24-29^o, bulk density 0.38-0.42 g/mL tapped density 0.50-0.53 g/mL and percentage compressibility index 18-24% as shown in the Table 2. The uncoated tablets were white in colour, circular and biconvex in shape. The coated tablets were pink in colour, circular and biconvex in shape. They were glossy and elegant in appearance. Hardness of the uncoated formulations was found to be within 5-6 Kg/cm^2 thickness 3.4-3.5 mm and the diameter was 10 mm , where as the coated tablets had hardness, thickness and diameter of 7-8 kg/cm^2, 3.6-3.8 mm and 10 mm respectively. Friability of all formulations was less than 1% and weight variation within the acceptable limits as per I.P. The drug content of the uncoated tablets was found to be between 98.19% and 100.69%. The drug content of the coated tablets was found to be between 98.42% and 100.41% ensured the uniform distribution of drug in the formulation. The results are shown in Tables 2, 3 and 4.

Table 2: Physico-chemical evaluation of granules

Parameter	Formulation code									
	SA	**SB**	**SC**	**HA**	**HB**	**HC**	**MA**	**MB**	**MC**	**C**
Bulk density (g/mL)	0.533	0.537	0.535	0.536	0.534	0.533	0.553	0.542	0.545	0.543
Tapped density (g/mL)	0.582	0.566	0.594	0.585	0.594	0.592	0.607	0.604	0.588	0.605
Compressibility index (%)	8.33	7.92	10	8.33	10.17	10	8.92	10.17	7.27	10.34
Angle of repose φ	24.98	24.48	25.64	25.64	24.70	25.20	25.64	25.14	25.20	24.70
Drug content (%)	101.9	100.6	99.6	100.8	100.3	100.8	99.7	100.2	100.8	99.5

Limit : The drug content should not be less than 90% and not more than 110% w/w (USP Limit)

Percentage weight increase

The percentage weight increase due to coating was found to be between 4.87 and 5.67%. All the values were found to be within the USP limits (± 10%). The results are shown in the Table 3.

Orifice diameter

The orifice diameter was measured using optical microscope. The tablets having orifice diameter of tabulated value ± 0.01% (Average ± SEM) were selected for further studies.

Table 3: Physico-chemical evaluation

Formulation code	Thickness (mm)			Hardness (mm)		Friability (%)	Weight variation	
	Coated	Uncoated	Membrane	Coated	Uncoated	Uncoated	Coated	Uncoated
SA	3.7	3.5	0.2	7-8	5-6	0.012	294-302	311-317
SB	3.7	3.5	0.2	7-8	5-6	0.21	293-302	307-316
SC	3.7	3.5	0.2	7-8	5-6	0.037	293-299	308-316
HA	3.7	3.5	0.2	7-8	5-6	0.024	294-300	310-317
HB	3.6	3.4	0.2	7-8	5-6	0.072	296-301	311-316
HC	3.7	3.5	0.2	7-8	5-6	0.010	292-308	310-317
MA	3.7	3.5	0.2	7-8	5-6	0.048	292-302	311-317
MB	3.6	3.4	0.2	7-8	5-6	0.128	292-302	309-316
MC	3.7	3.5	0.2	7-8	5-6	0.018	295-301	311-317
C	3.7	3.5	0.2	7-8	5-6	0.013	295-301	311-316

In vitro dissolution studies[1,19]

The *invitro* release studies showed that the release profiles of different formulations varied according to the orifice diameter and the type and concentration of polymers. The results are shown in the Fig. 2-11.

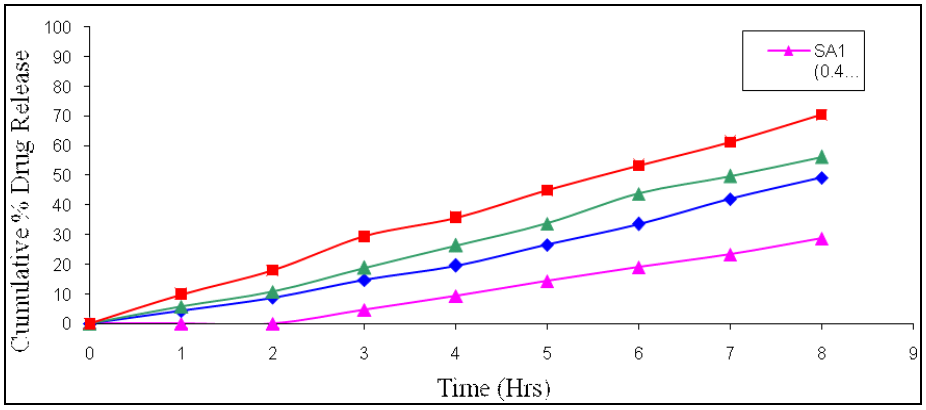


Fig. 2: *In vitro* dissolution studies of EOP-SA (CMC 15%)

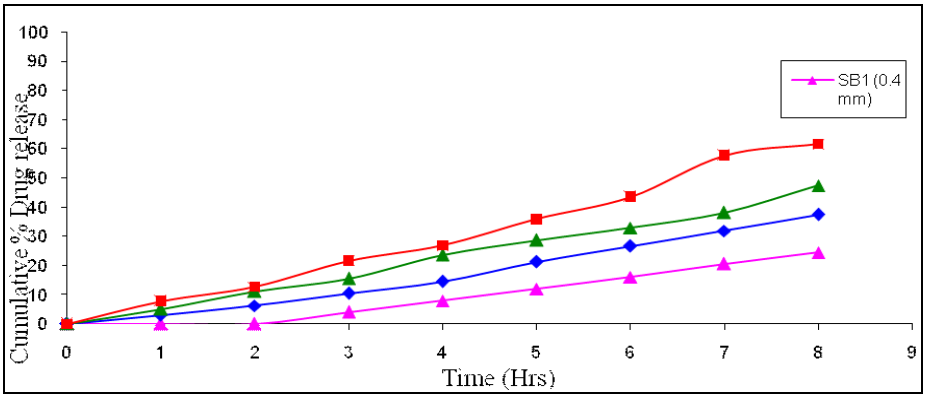


Fig. 3: *In vitro* dissolution studies of EOP-SB (CMC 25%)

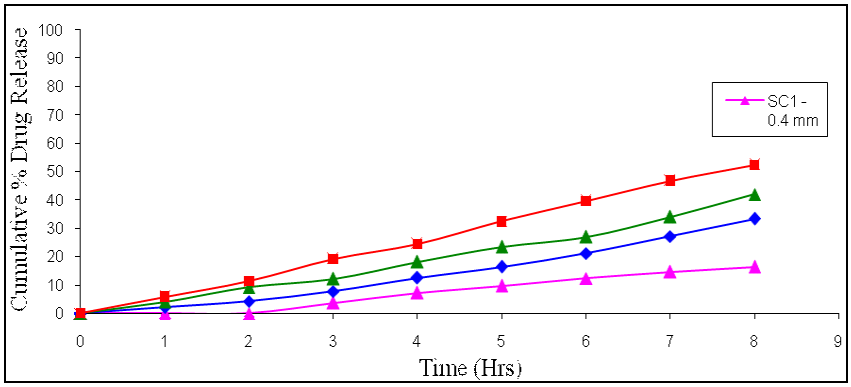


Fig. 4: *In vitro* dissolution studies of EOP-SC (CMC 50%)

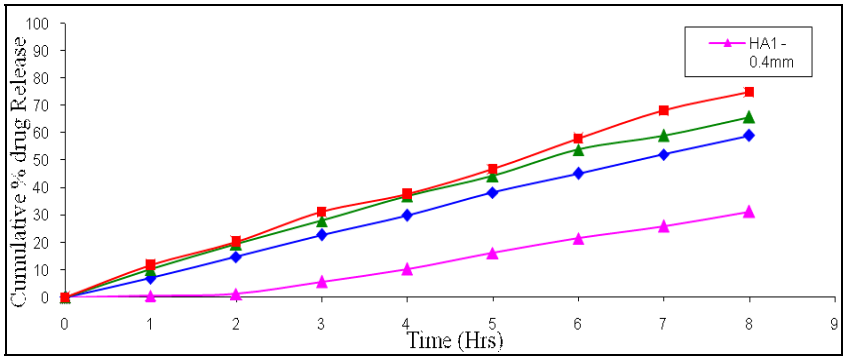


Fig. 5: *In vitro* dissolution studies of EOP-HA (HPMC 15%)

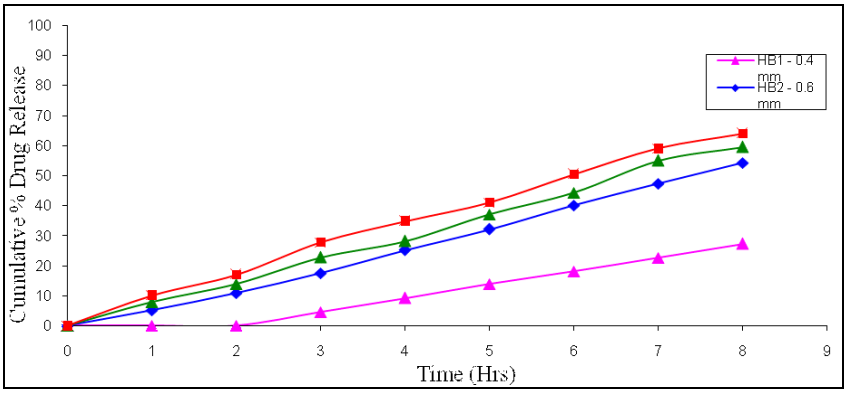


Fig. 6: *In vitro* dissolution studies of EOP-HB (HPMC 25%)

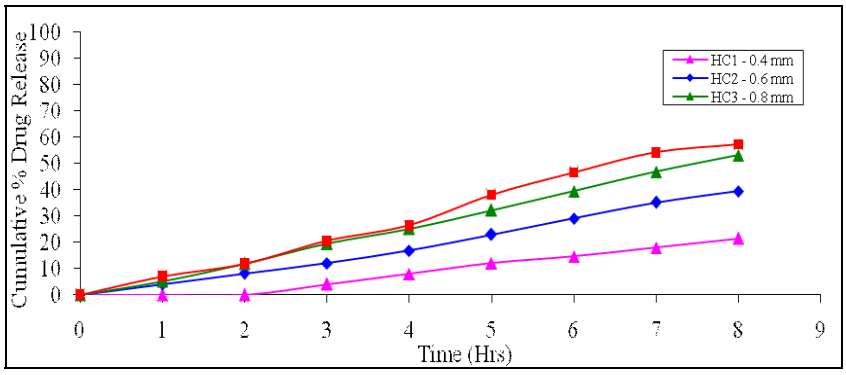


Fig. 7: *In vitro* dissolution studies of EOP-HB (HPMC 25%)

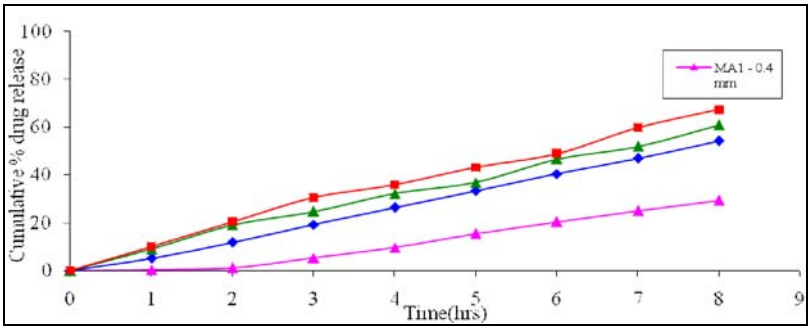


Fig. 8: *In vitro* dissolution studies of EOP-MA (MC 15%)

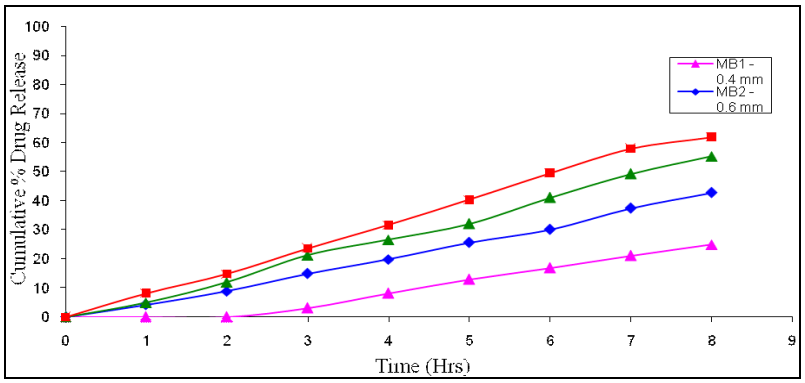


Fig. 9: *In vitro* dissolution studies of EOP-MB (MC 25%)

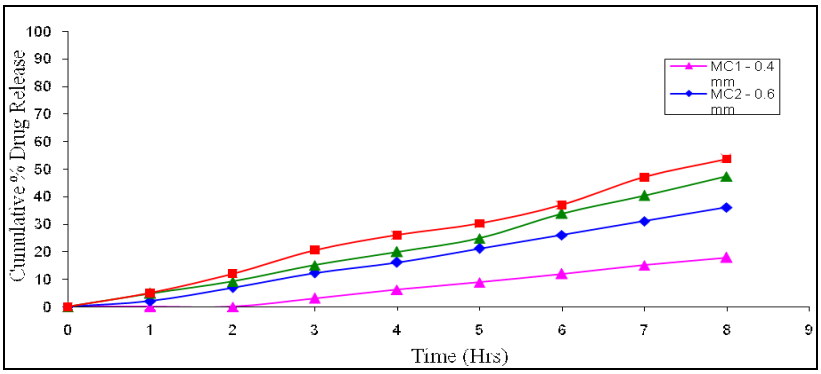


Fig. 10: *In vitro* dissolution studies of EOP-MC (MC 50%)

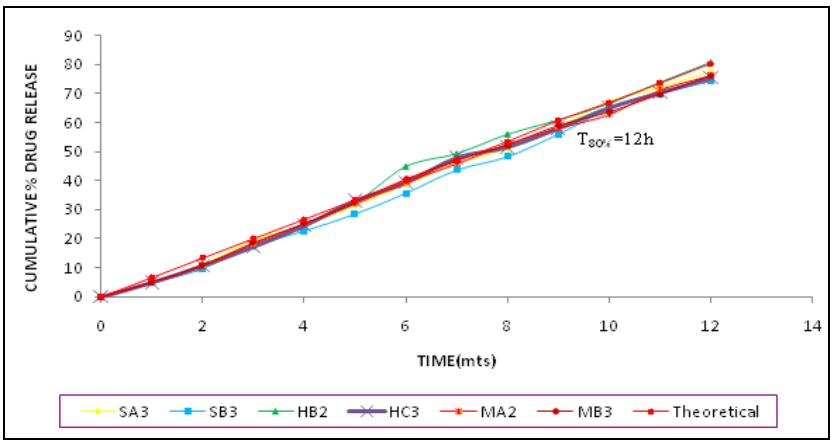


Fig. 11: Comparison of *in vitro* dissolution profile of the best formulatios with the oretical release

Effect of orifice diameter

The cumulative percentage drug release of formulations with 0.4 mm orifice diameter at the end of 8 hours was found to be 16.33% to 28.75% for SCMC (SA1, SA2, SA3, SA4), 21.49% to 31.42% for HPMC (HC1, HC2, HC3, HC4) and 17.9% to 29.24% for MC (MA1, MA2, MA3, MA4) and control C1-95%, (at the end of 6th hour). All the four formulations had a lag time of 2 hours. This may be attributed to the fact that the drug granules in suspension may occlude such a small orifice, thus affecting the drug release [17].

The orifice diameter of 0.6 mm showed drug release of 33.18% to 49.29% for SCMC, (SA5, SA6, SA7, SA8), 29.12% to 54.14% for HPMC (HC5, HC6, HC7, HC8) and 36.14% to 54.10%, for MC (MA5, MA6, MA7, MA8) and control C2 - 97.09%, (at the end of 5th hour) while 0.8 mm orifice delivered 42% to 57% (SCMC) (SA9, SA10, SA11, SA12), 54% to 65% (HPMC) (HC9, HC10, HC11, HC12), 47% to 55% (MC) (MA9, MA10, MA11, MA12) and 97% (control –C3) of drug].

Table 4: Drug content

Formulation code	Uncoated		Coated	
	Amount (mg)	Percentage (%)	Amount (mg)	Percentage (%)
SA	75.14	100.18	73.96	98.61
SB	73.64	98.19	75.27	100.36
SC	75.21	100.28	74.77	99.69
HA	75.31	100.41	75.27	100.36
HB	75.29	100.38	73.81	98.42
HC	75.04	100.05	74.66	99.55
MA	74.27	99.02	74.94	99.92
MB	75.48	100.64	75.15	100.2
MC	75.52	100.69	75.15	100.2
C	74.64	99.52	75.31	100.41

Limit : The drug content should not be less than 90% and not more than 110% w/w (USP Limit)

The formulations with 1 mm orifice diameter was able to deliver a maximum of 70% (SCMC) (SA13, SA14, SA15, SA16), 75% (HPMC) (HC13, HC14, HC15, HC16) 68% (MC) (MA13, MA14, MA15, MA16) and 98% (control –C4). This may be due to the result of more diffusion from the bigger orifice[18].

The formulations with orifice diameter 0.6 and 0.8 mm had a slower and controlled release when compared to other formulations and the effect of polymers of the selected formulations was studied by comparing with the theoretical release profile.

Comparison of dissolution studies with theoretical release profile

The theoretical release was calculated as $t_{80\%}$ in 12 hours[19]. The release profile of the formulations with orifice diameter of 0.6 mm and 0.8 mm were compared with the theoretical release profile and two

formulations from each polymer were selected (based upon the f_2 value). The formulations showing f_2 value greater than 50 were subjected to 12 hour dissolution studies. The results are shown in the Table 5.

Table 5: Similarity factor

S. No.	Formulation	Similarity factor
1	SA3 (SCMC 15% - 0.8 mm)	80
2	SB3 (SCMC 25% - 0.8 mm)	64
3	HB2 (HPMC 25% - 0.6 mm)	87
4	HC3 (HPMC 50% - 0.8 mm)	91
5	MA2 (MC 15% - 0.6 mm)	92
6	MB3 (MC 25% - 0.8 mm)	87

Effect of polymers

It was found that the retarding capacity of the polymers was decreased in the following order:

SCMC > MC > HPMC

The desired release rate of SCMC was achieved at low polymer concentration and large orifice diameter (15% polymer and 0.8 mm orifice diameter). This may be due to the greater rate of polymer swelling (volume expansion) than the rate of swelled polymer departure through the orifice. It also produces a highly viscous solution after the exposure to dissolution medium which may block the orifice of the device[20]. The retarding capacity of Methyl cellulose is intermediate between SCMC and HPMC. The HPMC is comparatively less retarding than the other two polymers which is evident from the higher polymer concentration (HPMC 50%) required to achieve the expected drug release.

Kinetics of drug release[1]

All the formulations found to exhibit zero order kinetics which is evident from the highest Correlation coefficient (R^2) value. This confirms that the drug release from all the selected formulations was found to be independent of drug concentration. The results are shown in the Table 6.

Table 6: Release kinetics of the selected formulations

Formulation code	Zero order		First order		Higuchi		Hixson-Crowell	
	R^2	K_0 (h^{-1})	R^2	K_1 (h^{-1})	R^2	k_H ($h^{-1/2}$)	R^2	k_{HC} ($h^{-1/3}$)
SA3	0.9982	6.7068	0.9688	0.1126	0.9141	24.607	0.8229	0.2785
SB3	0.9963	6.4308	0.9661	0.1048	0.9036	23.645	0.8366	0.278
HB2	0.9925	7.0395	0.9873	0.1191	0.9156	25.648	0.8269	0.2856
HC3	0.997	6.7044	0.9854	0.1105	0.9208	24.25	0.8206	0.2781
MA2	0.9979	6.5635	0.9912	0.1066	0.9203	24.171	0.8195	0.2769
MB3	0.9976	6.6284	0.9916	0.1082	0.9252	24.105	0.8142	0.276

Scanning electron microscopy[12]

It was found that there was no significant difference in the membrane structure and orifice diameter before and after dissolution studies and there were no pores in the membrane. The surface morphology of the membrane appeared similar before and after the dissolution studies. It also confirms that there was no blockade of delivery orifice during drug delivery. The results are shown in the Fig. 12 (a,b); 13 (a,b); 14 (a,b); 15 (a,b); 16 (a,b).

Scanning electron microscopy

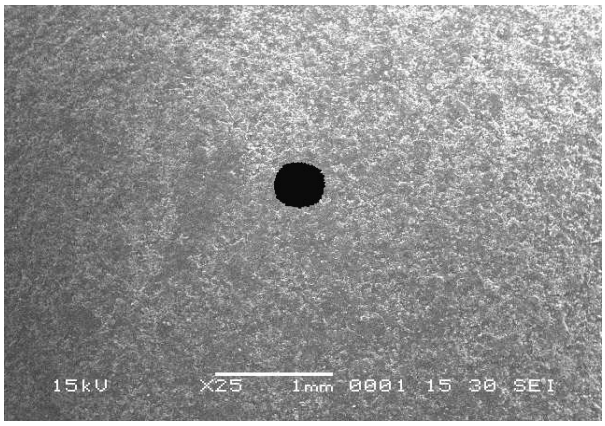


Fig. 12a: 0.4 mm - Before dissolution

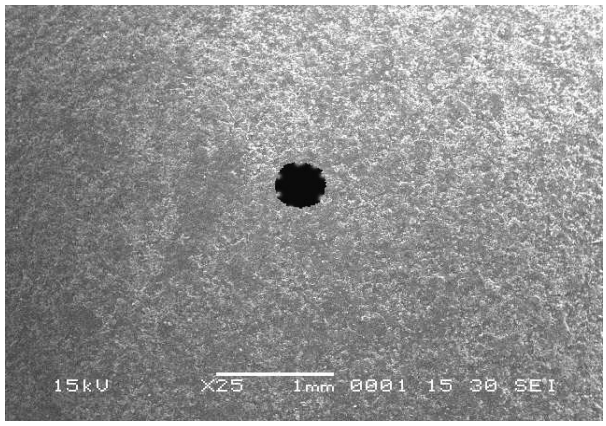


Fig. 12b: 0.4 mm – After dissolution

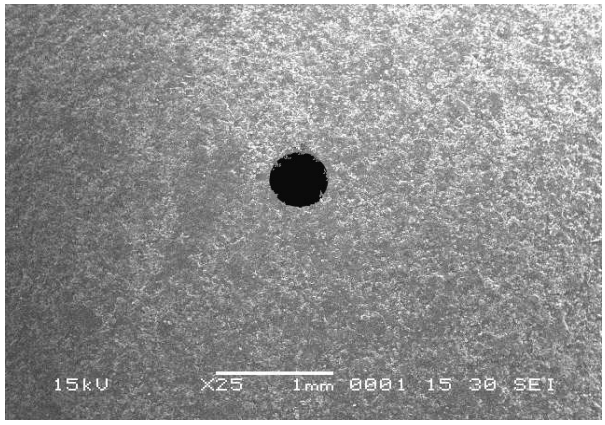


Fig. 13a: 0.6 mm – Before dissolution

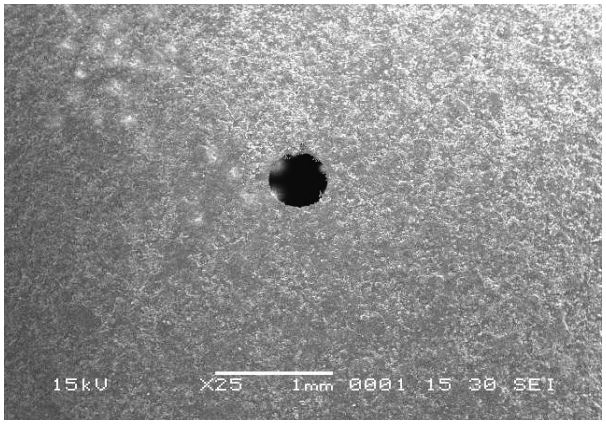


Fig. 13b: 0.6 mm – After dissolution

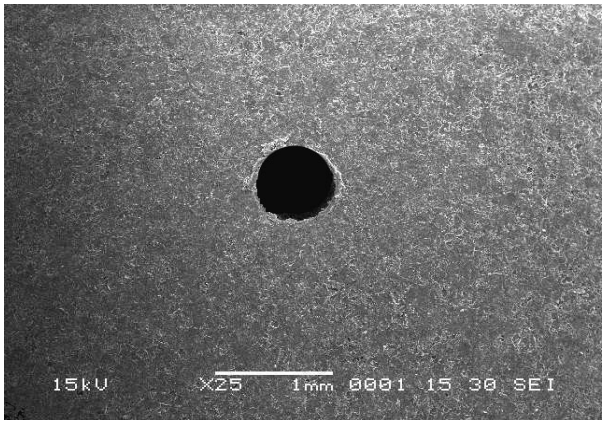


Fig. 14a: 0.8 mm – Before dissolution

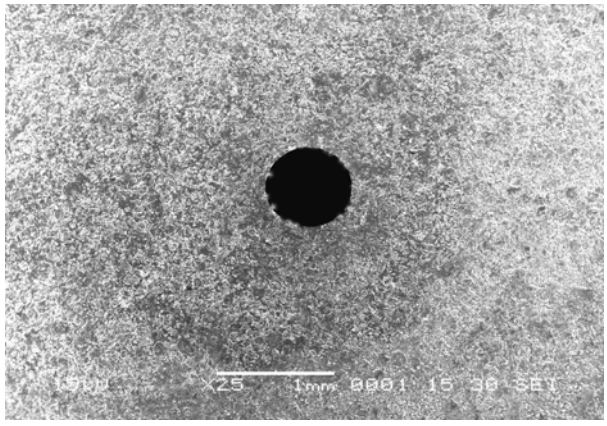


Fig. 14b: 0.8 mm – After dissolution

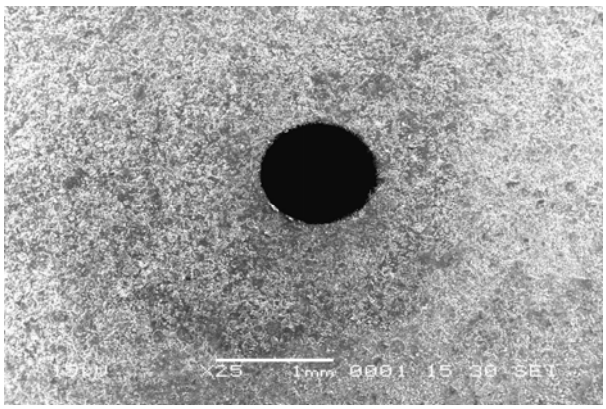


Fig. 15a: 1 mm – Before dissolution

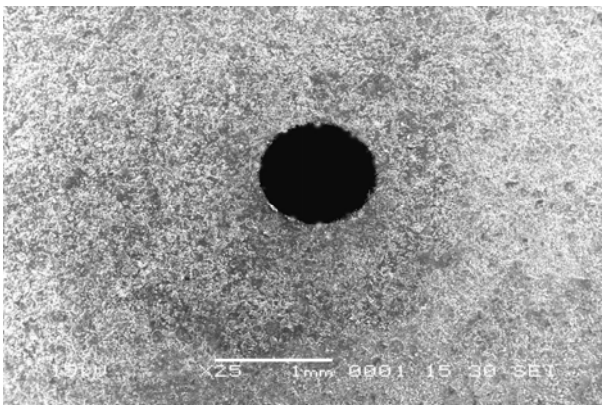


Fig. 15b: 1 mm – After dissolution

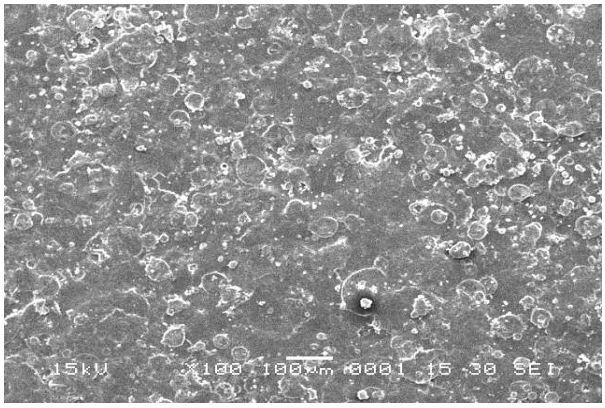


Fig. 16a: Coating membrane – Before dissolution

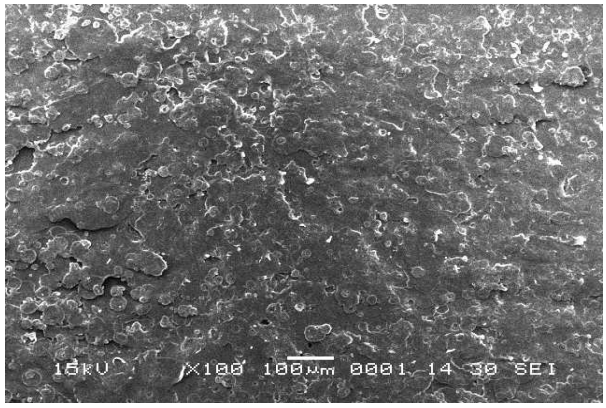


Fig. 16b: Coating membrane – after dissolution

Stability studies[14-16]

There was no significant change in the physical appearance and drug content of the formulations. This shows that the formulations remained stable during the process of storage. The results are presented in the Table 7 and 8.

Table 7: Drug content analysis of the formulations during stablilty studies

Sample with drawal period	% Drug content of the formulations									
	SA (CMC 15%)		SB (CMC 25%)		SC (CMC 50%)		HA (HPMC 15%)		HB (HPMC 25%)	
	Ambient Temp.	40ºC/ 75% RH	Ambient Temp.	40ºC/ 75% RH	Ambient Temp.	40ºC/ 75% RH	Ambient Temp.	40ºC/ 75% RH	Ambient Temp.	40ºC/ 75% RH
0th day	99.23	99.34	101.80	103.98	99.13	102.81	101.52	101.98	100.67	101.32
15th day	99.43	99.16	98.99	101.20	101.54	102.11	102.56	100.64	98.54	102.20
30th day	99.84	101.54	103.98	100.23	101.13	102.32	100.34	99.67	99.67	99.54
45th day	99.98	99.66	103.52	99.99	97.82	100.01	102.67	98.59	98.99	101.14
60th day	101.56	100.21	100.67	98.73	98.54	99.98	102.43	101.63	100.73	100.20
75th day	98.54	100.01	101.72	96.54	99.32	99.65	99.76	100.03	101.20	100.97
90th day	100.00	99.34	99.56	100.32	101.17	100.90	101.23	99.87	100.31	100.03

Table 8: Drug content analysis of the formulations during stablilty studies

Sample with drawal period	% Drug content of the formulations									
	HC (HPMC 50%)		MA (MC 15%)		MB (MC 25%)		MC (MC 50%)		C (Control)	
	Ambient Temp.	40ºC/ 75% RH	Ambient Temp.	40ºC/ 75% RH	Ambient Temp.	40ºC/ 75% RH	Ambient Temp.	40ºC/ 75% RH	Ambient Temp.	40ºC/ 75% RH
0th day	100.54	101.65	103.20	100.54	97.54	99.82	101.54	101.98	100.67	101.32
15th day	101.66	99.23	101.54	99.87	100.34	101.34	100.98	100.64	99.13	102.20
30th day	99.12	97.34	102.29	101.21	101.54	100.91	99.87	96.54	99.67	98.163
45th day	98.12	99.87	99.87	99.89	101.67	99.56	100.91	98.59	98.87	100.04
60th day	98.38	98.89	101.34	100.36	100.56	100.01	99.71	98.87	100.73	100.20
75th day	99.19	99.76	100.76	99.34	101.10	98.56	100.65	99.10	101.63	99.87
90th day	101.11	98.87	101.78	100.90	99.76	97.54	99.65	99.87	100.31	100.03

CONCLUSION

The above results clearly indicates the feasibility to develop swellable elementary osmotic pumps of highly water soluble drugs exempting the complex tableting technology associated with the two-compartment osmotic tablets. The drug release from these systems is influenced by the factors such as solubility and osmotic pressure of the core compound (s), membrane nature and size of delivery orifice, which can be easily optimized to get the desired release rate.

Further extension of detailed experimental and clinical investigations on swellable osmotic pumps may throw light on its viability for human use.

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