International Journal of Pharmacy and Pharmaceutical Sciences

Vol 2, Issue 2, 2010

Research Article

FORMULATION AND IN-VITRO EVALUATION OF OSMOTIC DRUG DELIVERY SYSTEM OF METOPROLOL SUCCINATE

MOTHILAL M*, DAMODHARAN N, LAKSHMI K.S, SHARANYA V.BARATHARAJ, SRIKRISHNA T

Department Of Pharmaceutics, SRM College of Pharmacy, SRM University, Kattankulathur- 603203, India. E-mail:mothipharma78@gmail.com

Received: 21 Dec 2009, Revised and Accepted: 20 Jan 2010

ABSTRACT

Controlled release delivery system provides a uniform concentration of drug at the absorption site and thus after absorption allow maintenance of plasma concentration within a therapeutic range, which minimizes side effects and also reduces the frequency of administration. An appropriately designed osmotically controlled oral drug delivery system (ODDS) can be a major breakthrough. Drug delivery from these systems is not influenced by the different physiological factors within the gut lumen. The main objective of this is to formulate ODDS for metoprolol Succinate that can provide prolonged effect to better patient compliance. Metoprolol is a β^1- receptor blocking agent. ODDS formulations of metoprolol succinate were prepared using different concentrations of mannitol, by wet granulation technique. The tablets were coated by dip coating with cellulose acetate. Stainless steel drill pins were used to make an orifice on the tablets. Tablet thickness, hardness, weight variation and drug content analysis, drug release study were performed. Orifice diameter was examined using scanning electron microscopy (SEM). With increase in osmogen content and bore size, rate of drug release were found to be increasing an optimum concentration of osmogen and bore size to give a zero order release was identified.

Keywords: Osmotic drug delivery system, Metoprolol succinate, Wet granulation, Osmogen, Scanning electron microscopy.

INTRODUCTION

In conventional oral drug delivery systems, there is little or no to control over release of the drug, and effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses[1]. Moreover, the rate and extent of absorption of drug from conventional formulations may vary greatly, depending on factors such as physico chemical properties of the drug, presence of excipients, various physiological factors such as the presence or absence of food, pH of the gastrointestinal tract, GI motility, and so on. Uncontrolled rapid release of drug may also cause local GI (or) systemic toxicity[2]. Among controlled-release devices, osmotically driven systems hold a prominent place because of their reliability and ability to deliver the contents at predetermined zero-order rates for prolonged periods. Osmotic pumps (OP) are standard dosage forms for a constant-rate drug delivery[3]. Osmosis is an aristocratic biophenomenon, which is exploited for development of delivery systems with every desirable property of an ideal controlled drug delivery system. Osmosis refers to the process of movement of solvent from lower concentration of solute towards higher concentration of solute across a semi permeable membrane[4]. Osmotic pumps essentially contain a drug and semi permeable membrane, if drug itself acts as an osmogen (Eg: KCl pumps). If the drug does not possess any osmogenic property, the osmogenic salt and other sugars can be incorporated in the formulation[5]. Osmogens are freely water soluble and capable of producing osmotic pressure. Osmotic pump has an orifice in order to release the active material[6]. When the system happens to be inside the gastrointestinal tract, the fluid enters the core through the membrane and dissolves the active material[7]. The osmotic pressure generated in the core induces release of the drug in solution at a slow but constant rate. To gain the advantages of pH and agitation independent release performance leading to similar *in vitro/in vivo* delivery, osmotically active drug delivery systems have been extensively investigated[8]. Metoprolol is an anti-hypertensive agent. It has a relatively short biological half-life and suffers from the hazards of adverse gastro-intestinal reactions. Therefore, the development of oral sustained (or) controlled release formulations of this drug is highly desirable. Many efforts have been made towards achieving sustained release formulations of Metoprolol. Hence, the present work was aimed to design, develop and evaluate an oral osmotic delivery system of Metoprolol.

MATERIALS

Metoprolol succinate was used as a model drug obtained as a gift samples from Madras Pharmaceuticals, Chennai, Dicalcium phosphate, Mannitol, Isopropyl alcohol were obtained as a gift samples from Rankem chemicals Pvt.Ltd, Starch, PEG 6000, Cellulose acetate were purchased from Sisco research laboratories Pvt.Ltd, Magnesium stearate was obtained from Loba Chemie Pvt. Ltd.

Preparation of tablets

Granules were prepared by wet granulation by using 2% starch paste as binding agent. The wet granules subjected to drying at 60^{o}C in hot air oven for 30min.These dried granules were passed through sieve no.14.Then mixed with lubricants and subjected to punching with CADMACH rotary 16 stations punching machine. Various formulations of ODDS were made as given table 1.

After this tablets were coated with cellulose acetate. Stainless steel drill pins of various diameters Viz. 0.3, 0.45, 0.8, 0.9mm were used for making orifice in the tablets.

Physical properties of Metoprolol succinate tablet

Hardness

This is the force required to break a tablet in diametric compression. Hardness of the tablets is determined by Monsanto hardness tester which consists of a barrel with a compressible spring[9]. The pointer moving along the gauge in the barrel at which the tablet fractures.

Tablet size and Thickness

The size and thickness of the tablets were measured by using Vernier Calipers scale[10].

Weight variation

Ten tablets were selected at random and average weight was determined. Then individual tablets were weighted and the individual weight was compared with an average weight. Not more than two of the individual weights deviate from the official standard (limit ± 5%)[11].

Drug content analysis

It was done by spectrophotometric method[12]. Three tablets were taken and powered. From the powder an accurately weighed amount equivalent to 100mg of Metoprolol was weighed and dissolved in distilled water. The solution was suitably diluted and dilute solution was then assayed for the drug content by measuring the absorbance at 222nm using UV – Visible spectrophotometer[13].

In vitro drug release

The drug release studies were carried out using USP type-II dissolution (Disso 2000) apparatus[14]. The dissolution vessels filled with 900ml of 0.1N HCl using basket rotation of 100rpm and temperature was kept constant at 37 ± 0.5°C. The time of sampling was every 1 hrs up to 6 hrs[15]. 5ml of sample was withdrawn and an equal amount of 0.1N HCl was replaced to maintain sink conditions and after the first hour was replaced with p^H 7.4 phosphate buffer and the dissolution was continued for 6 hours[16]. Samples are directly analyzed by using U.V Spectrophotometer without any dilution. Concentration of the drug was calculated from standard equation obtained from standard curve. Cumulative percentage drug release and percentage drug unreleased was calculated and respective graphs were plotted as shown in Fig.1 – 4.

SEM analysis

The diameters of the orifice were examined with scanning electron microscope. SEM photos of orifice were taken with X50 & X100 magnifications. The photos are given in Fig.5 – 8.

RESULTS AND DISCUSSION

Physical characteristics like hardness, tablet size, thickness and weight variation was determined.Invitro drug release also determined by using 900ml of 0.1N HCL using basket rotation of 100rpm at 37 ± 0.5°C.The drug release of metoprolol was determined by using release kinetics and the drug release correlation coefficient values for each drug release kinetics was listed in Table No.7. The dosage form developed was designed as a tablet core coated with a rate-controlling membrane. Tablet core consists of drug along with osmogent, and other conventional excipients to form the core compartment.

Table 1: Formulation composition

Ingredients	F_A	F_B	F_C	F_D
Metoprolol succinate	100	100	100	100
Dicalcium phosphate	210	195	180	165
Mannitol	-	15	30	45
Starch	8	8	8	8
Talk	3	3	3	3
Magnesium stearate	3	3	3	3

Table 2: Evaluation of tablets

S.No	Formulation	Hardness	Weight variation	Thickness	Amount of drug(mg)
1	F_A	4.8	356	5.2	95.22
2	F_B	4.7	327	5.4	95.76
3	F_C	4.7	352	5.4	96.45
4	F_D	4.7	333	5.5	97.37

Table 3: Drug release from ODDS with different orifice diameter (F_A)

S.No	Time (hr)	0.3mm	0.45mm	0.8mm	0.9mm
1	0	0	0	0	0
2	0.5	8.12	15.58	18.21	32.67
3	1	12.80	19.52	22.47	36.96
4	2	15.55	21.03	24.87	39.8
5	3	18.58	24.06	28.90	41.82
6	4	20.62	26.11	31.93	44.83
7	5	23.66	29.17	33.96	47.85
8	6	25.70	31.23	36.00	50.86

Table 4: Drug release from ODDS with different orifice diameter (F_B)

S.No	Time (hr)	0.3mm	0.45mm	0.8mm	0.9mm
1	0	0	0	0	0
2	0.5	8.59	12.94	12.06	17.33
3	1	12.62	14.41	18.14	21.74
4	2	14.17	18.76	22.18	25.42
5	3	16.21	20.79	26.220	29.46
6	4	19.27	24.82	30.25	33.50
7	5	20.33	28.85	32.29	36.56
8	6	23.38	30.89	36.34	40.62

Table 5: Drug release from ODDS with different orifice diameter (F_C)

S.No	Time (hr)	0.3mm	0.45mm	0.8mm	0.9mm
1	0	0	0	0	0
2	0.5	8.17	15.5	16.21	22.77
3	1	12.83	18.48	19.47	26.34
4	2	14.45	22.23	22.84	28.08
5	3	16.54	24.23	25.90	31.00
6	4	18.77	26.11	30.87	34.44
7	5	20.22	28.12	33.93	38.85
8	6	22.25	30.26	35.08	40.83

Table 6: Drug release from ODDS with different orifice diameter (F D)

S.No	Time(hr)	0.3mm	0.45mm	0.8mm	0.9mm
1	0	0	0	0	0
2	0.5	5.5	13.9	15.04	19.68
3	1	6.66	16.41	17.12	23.74
4	2	8.17	19.76	22.18	27.44
5	3	12.21	22.79	26.24	30.78
6	4	16.68	24.65	28.8	35.55
7	5	18.33	26.85	30.25	38.52
8	6	20.45	28.01	34.28	42.64

Table 7: Correlation co-efficient for drug release

S.No.	Formulation	Orifice Diameter (mm)	Zero order		First order		Kosermayer plot		
			r	k	r	k	r	k	n
1	FA	0.3	0.9405	3.665	0.9548	0.0414	0.9927	12.331	0.391
2	FA	0.45	0.8702	3.92	0.8984	0.0483	0.9851	18.492	0.267
3	FA	0.8	0.8673	4.597	0.9007	0.0575	0.9935	21.677	0.273
4	FA	0.9	0.7756	5.672	0.8373	0.0829	0.9832	35.892	0.173
5	FB	0.3	0.9223	3.136	0.9371	0.0345	0.9862	11.857	0.341
6	FB	0.45	0.9354	4.26	0.9541	0.0506	0.9796	13.963	0.427
7	FB	0.8	0.9354	5.1	0.9572	0.0644	0.9949	17.579	0.385
8	FB	0.9	0.9138	5.384	0.9443	0.0713	0.9925	20.844	0.348
9	FC	0.3	0.9091	3.012	0.9244	0.0345	0.9840	12.246	0.309
10	FC	0.45	0.8586	3.786	0.8862	0.0460	0.9982	18.365	0.266
11	FC	0.8	0.9059	4.758	0.9332	0.0598	0.9883	18.706	0.348
12	FC	0.9	0.8495	4.972	0.8912	0.0667	0.9690	24.831	0.253
13	FD	0.3	0.9813	3.195	0.9853	0.0345	0.9694	6.039	0.676
14	FD	0.45	0.8778	3.665	0.9018	0.0437	0.9980	16.255	0.304
15	FD	0.8	0.9099	4.555	0.9394	0.0552	0.9926	17.139	0.374
16	FD	0.9	0.8883	5.318	0.9352	0.0737	0.9879	22.698	0.325

The core compartment is surrounded by a membrane consisting of a semipermeable membrane-forming polymer, water-soluble pore-forming additives, and at least 1 plasticizer capable of improving film forming properties of the polymers. The semipermeable membrane-forming polymer is permeable to aqueous fluids but substantially impermeable to the components of the core. In operation, the core compartment imbibes aqueous fluids from the surrounding environment across the membrane and dissolves the drug. The dissolved drug is released through the pores created after leaching of water-soluble additive(s) in the membrane. The diameter of orifice was determined by using scanning electron microscope. There is an increase in percent of drug release with an increase in orifice diameter. From these results it is obvious that orifice diameter selected for the controlled release formulations appears to be a major factor in determining the release of the drug. The release pattern was found to be faster in the formulations containing higher percentage of osmogen. The results obtained for in-vitro drug release study is given in Table No. 3-6. By careful analysis of the dissolution profile of the formulations F_A, F_B, F_C, F_D it was evident that the formulation B with orifice diameter 0.8mm was the best formulation since the percentage release within the first hour was only 8% and the rate of release was found to be constant and sustained over the six hour period.

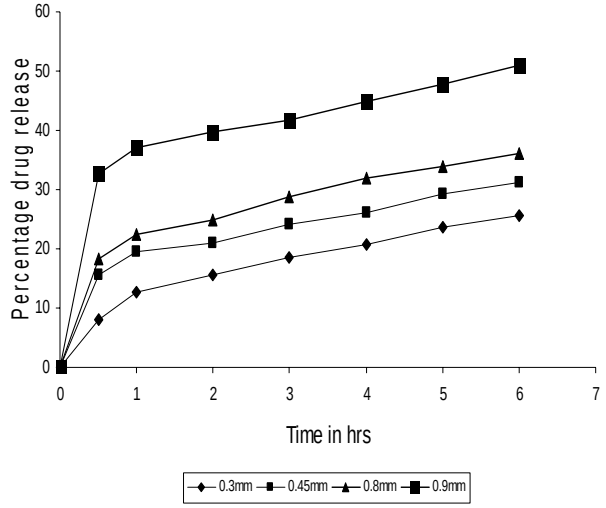

Fig. 1: Drug release from ODDS with different orifice diameter (F_A)

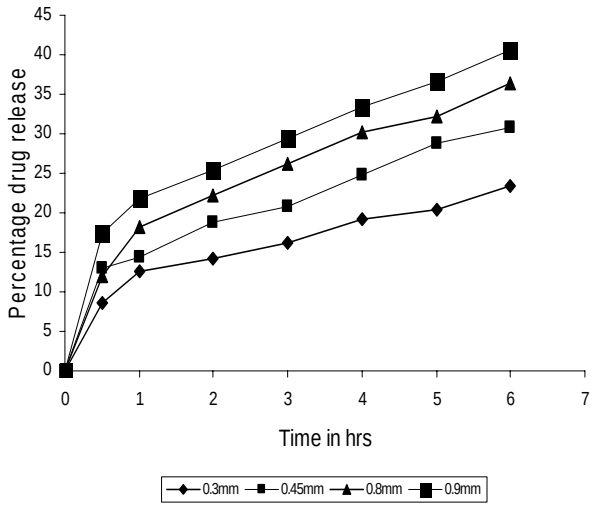

Fig. 2: Drug release from ODDS with different orifice diameter (F_B)

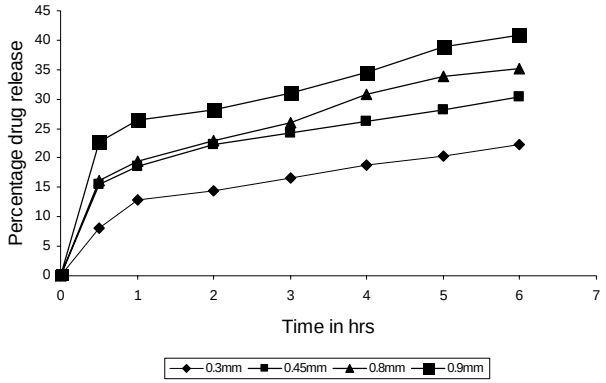

Fig. 3: Drug Release from ODDS with Different Orifice Diameter (F_C)

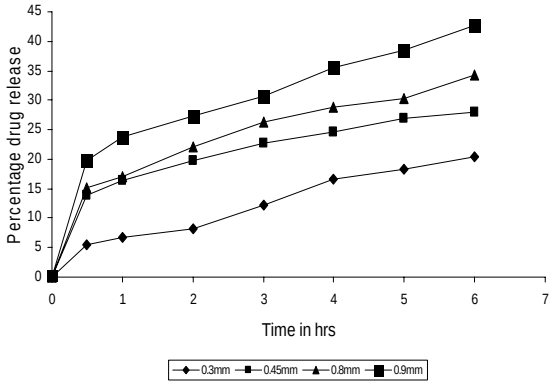

Fig. 4: Drug release from ODDS with different orifice diameter (F_D)

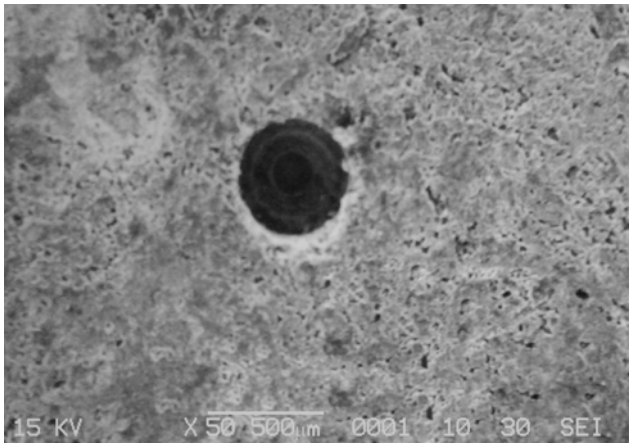

Fig. 5: SEM photograph of ODDS with 0.3mm orifice diameter

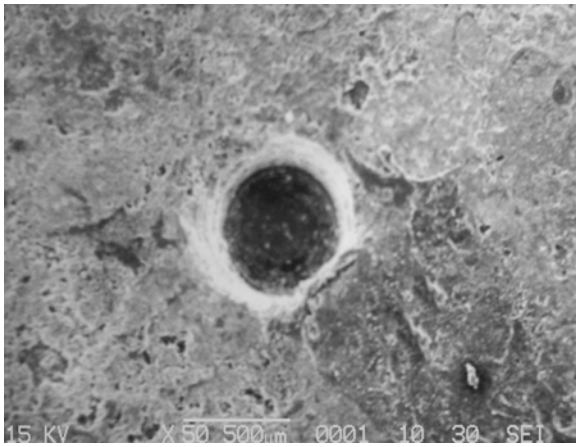

Fig. 6: SEM photograph of ODDS with 0.45mm orifice diameter

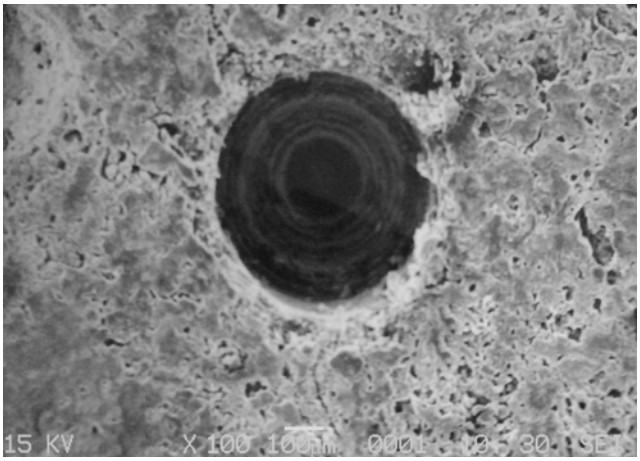

Fig. 7: SEM photograph of ODDS with 0.8mm 0rifice diameter

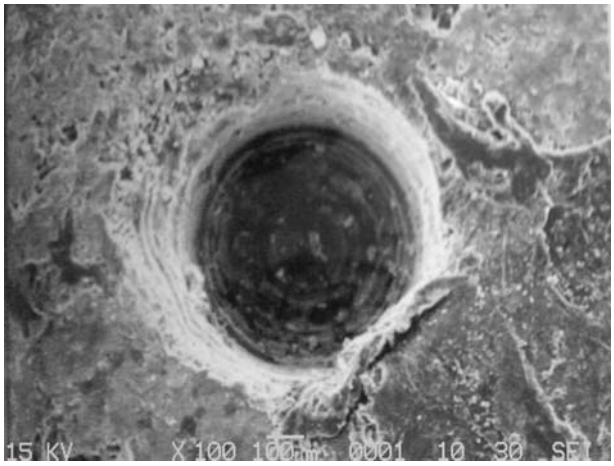

Fig. 8: SEM photograph of ODDS with 0.9mm Orifice Diameter

CONCLUSION

Oral osmotic pumps are being attempted on certain drugs with a view to provide constant release of the drug to achieve the desired therapeutic efficacy in clinical disorders. The results obtained with osmotic pump of Metoprolol succinate that was developed and evaluated in the present study are encouraging. The formulation B with orifice diameter 0.8mm chosen in the study has given the expected results. The delivery rate was found to increase at a constant rate throughout the dissolution study. The percentage release was found to be 36% at the end of the six hour study was found to be satisfactory. Metoprolol is a potential drug in curing angina, hypertension, and a constant release formulation like an osmotic pump on this drug can be considered as a suitable alternative to currently available formulations of Metoprolol. A detailed experimental and clinical investigation on the osmotic pump of Metoprolol succinate may throw light on its viability for human use.

ACKNOWLEDGEMENTS

The authors are thankful to emeritus Prof. K. S. Lakshmi, principal, SRM College of Pharmacy, Kattangulathur, Chennai for providing all the necessary facilities for the project and also our sincere thanks to m/s Madras Pharmaceuticals Ltd., Chennai for giving the gift sample of drug.

REFERENCES

1. Salsa T, Veiga F, Pina ME. Oral controlled release dosage forms I. Cellulose ether polymer in hydrophilic matrices. Drug Dev Ind Pharm 1997; 23**:** 929–938.
2. Eckenhoff B, Theeuwes F, Urquhart J. Osmotically activated dosage forms for rate controlled drug delivery. Pharm Technol 1981; 5: 35–44.
3. Eckenhoff B, Yum SI. The osmotic pump; novel research tool for optimizing drug regimens. Biomaterials 1981; 2: 89–97.
4. Bindschaedler C, Gurny R, Doelker E. Osmotically controlled drug delivery systems produced from organic solutions and aqueous dispersions of cellulose acetate. J Controlled Release 1986; 4: 203–212.
5. Verma RK, Mishra B, Garg S. Osmotically controlled oral drug delivery. Drug Dev Ind Pharm 2000; 26: 695–708.
6. Verma RK, Krishna DM, Garg S. Formulation aspects in the developments of osmotically controlled oral drug delivery system. J Controlled Release 2002; 79: 7–27.
7. Schultz P, Kleinebudde P. A new multiparticulate delayed release system. Part I: Dissolution properties and release mechanism. J Controlled Release 1997; 47: 181-189.
8. Herbig SM, Cardinal JR, Korsmeyer RW, Smith KL. Asymmetric-membrane tablet coatings for osmotic drug delivery. J Controlled Release 1995; 35: 127-136.
9. Zentner GM, Rork GS, Himmelstein KJ. Osmotic flow through controlled porosity films: An approach to delivery of water soluble compounds. J Controlled Release 1985; 2: 217-229.
10. Thombre AG, Cardinal JR, DeNoto AR, Herbig SM, Smith KL. Asymmetric membrane capsules for osmotic drug delivery I. Development of a manufacturing process. J Controlled Release 1999; 57: 55-64.
11. Liu L, Wang X. Solubility modulated monolithic osmotic pump tablet for atenolol delivery. Eur J Pharm Sci 2008; 68 Suppl 2: 298-302.
12. Jensen JL, Appel LE, Clair JH, Zentner GM. Variables that affect the mechanism of drug release from osmotic pumps coated with acrylate/methacrylate copolymer latexes. J Pharm Sci 1995; 84 Suppl 5: 530-533.
13. Ramakrishna N , Mishra B. Plasticizer effect and comparative evaluation of cellulose acetate and ethyl cellulose-HPMC combination coatings as semi permeable membranes for oral osmotic pumps of naproxen sodium. Drug Dev Ind Pharm 2002; 28: 403–412.
14. Skelly JP, Yamamoto LA, Shah V P, Yau MK, Barr WH. Topographical dissolution characterization for controlled release products: new technique. Drug Dev Ind Pharm 1986; 12: 1159–1175.
15. Ramadan MA, Tawashi R. Effect of hydrodynamic conditions and delivery orifice size on the rate of drug release from elementary osmotic pump system (EOP). Drug Dev Ind Pharm 1987; 13: 235–248.
16. Santus G, Baker WR. Osmotic drug delivery: a review of patent literature. J Controlled Release 1995;35:1-21.