World Journal of Pharmaceutical research

Volume 2, Issue 4, 1122-1140. Research Article ISSN 2277 – 7105

DEVELOPMENT AND EVALUATION OF SWELLABLE CONTROLLED POROSITY OSMOTIC PUMP TABLETS OF METOPROLOL SUCCINATE AND RAMIPRIL

Padma priya S[1] ∗, Ravichandran V[1],Suba V[2]

[1]Vels college of pharmacy, Velan nagar, Pallavaram, Chennai-600 117, Tamilnadu, India.

[2]National Institute of siddha,Tambaram sanitorium,Chennai 600047, Tamilnadu, India.

Article Received on
23 April 2013,

Revised on 15 May 2013,
Accepted on 30 June 2013

***Correspondence for Author:**

Padma priya S
Vels college of pharmacy,
Velan nagar, Pallavaram,
Chennai-600 117, Tamilnadu,
India.
sppriya11@yahoo.co.in

ABSTRACT

Swellable controlled porosity osmotic pump (SEOP) utilizes the osmotic pressure and polymer-swelling force to deliver drugs to the GI tract in a reliable and reproducible manner. Metoprolol and ramipril are one of the combinations indicated in the management of hypertension in patients with heart failure and post myocardial infarction. This combination was selected to develop SEOP to release the drugs continuously for a period of 24hrs and the release is controlled by swellable polymer and the osmogen.SCPOP tablets of Metoprolol and Ramipril were prepared using additives like Mannitol MCC, talc, magnesium stearate , aerosol with varying concentrations of osmopolymers(PEO,Carbopol and PVAand SCMC) coating of cellulose acetate as semi permeable membrane ,Dibutyl phthalate as plasticizer. An orifice was made on one face of the tablet mechanically. Effects of different concentrations of PEO (MRSC1-MRSC3) carbopol (MRSC4-MRSC6) PVAand SCMC(MRSC7-MRSC9) on the *in vitro* release were studied. On comparing *in vitro* release of formulations (MRSC1-MRSC6), *the* release rate decreased with the increased concentrations of polymers The decreased release rate was due to due to solubility-modulating properties of the polymers. Among the formulations, MRSC7 shown optimum drug release rate 99.98%and 92.32% for metoprolol and ramipril respectively at the end of 24 hours. The optimized formulation was independent of the agitation intensity, pH of the medium, stable and delivers Metoprolol and Ramipril at a zero order rate for 24 hrs.

KEYWORDS: Swellable controlled porosity osmotic pump, Metoprolol tartrate, Ramipril, Osmogent, Cellulose acetate, Osmopolymers

INTRODUCTION

Hypertension is one of the chronic disorders affecting a large number of populations in the world and it is an important cardiovascular risk factor[1]. The seventh Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure (JNC 7) recommends appropriate treatment of hypertension and the need for combination therapy to achieve and maintain the goal blood pressure[2.] Usage of fixed dose combinations in cardiovascular diseases have many advantages such as reduction in cost, adverse effects and dose, ease of use by patients, improved patient compliance and medication adherence. They also offer the possibility of combining agents with different pharmacological profiles to achieve additive effects with enhanced tolerability[3] .A number of two-drug fixed combinations is available for clinical use. These include Angiotensin converting enzyme (ACE) inhibitor /thiazide diuretic, Angiotensin receptor blockers (ARB)/ thiazidediuretic, βblocker/thiazidediuretic, ACEinhibitor/(CCB), ARB/ CCB, β-blocker/ ACE inhibitor, β blocker/CCB combinations…. etc[4] **.**

ACEIs and β-blockers are indicated in the management of hypertension in patients with heart failure and post myocardial infarction. In these patients, treatment with these combination shown to improve symptoms and reduce the risk of death and worsening heart failure. Metoprolol and Ramipril are one of the combinations showed reduction in morbidity and mortality in appropriately selected patients with heart failure[5].

Metoprolol[6] is a prototype β-1 anti adrenergic drug, which has the potency to decreases the force and rate of the heart's contractions, which lowers blood pressure. It is used in the treatment of hypertension and angina pectoris. Ramipril is a potent and specific angiotensin-converting enzyme (ACE) inhibitor that catalyzes the conversion of angiotensin-I to vasoconstrictor substances. Angiotensin-II also stimulates the secretion of aldosterone by adrenal cortex leading to vasopressor activity. Thus role of the ACE inhibiting is to inhibit the last step of the biosynthesis of angiotensin-II and therefore causing a general vasodilatation and lowering of blood pressure. It is also used in the treatment of hypertension and angina pectoris [7.] These combinations are available as film coated uncoated, sustained and extended delivery systems. Still these systems offer disadvantages which are overcome by the development of oral osmotic drug delivery system. This system utilizes the principle

of osmotic pressure for the delivery of drugs. Drug release from this system is not influenced by different physiological environment within the gut lumen (surface tension, viscosity of the GIT and intestinal fluids, GIT and intestinal motility) and showed improved safety profile, stable drug concentration, reduced dosing frequency which enhance patient compliance and convenience[8, 9, 10]

Among the system, SCPOP is selected in which drug is released through a delivery through the pores formed on the surface of the membrane due to dissolution of the pore formers present on them. When the pump is in operation, both drug and osmogent imbibe water across the membrane, swelling the osmogent simultaneously forming a suspension in the drug layer. The swelling of the osmotic layer "pushes" against the drug solution or suspension to flow out of the orifice at a controlled rate. This mechanism of operations suitable for the delivery of slightly/insoluble drugs [11,12,13]. In this study, swellable controlled porosity osmotic pump (SCPOP) of Metoprolol and Ramipril were formulated with an objective to investigate and explore the effect of formulation variables and release kinetics in the drugs release profile of swellable controlled porosity osmotic pump of Metoprolol and Ramipril tablets.

MATERIALS AND METHODS

Materials

Metoprolol succinate and Ramipil , a kind gift sample from Kniss Pharmaceuticals private Limited, Chennai, India. Cellulose acetate, PEO, Carbopol and DBP were obtained from Loba Chemie, Mumbai, India. Mannitol, MCC, Talc, Magnesium stearate and Aerosil were obtained from Otto Chemicals & Reagents. Pvt. Ltd, India. All other solvents and chemicals used were of the analytical grade.

Methods

Drug-excipients compatibility study[14,15]

Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the preformulation stage during the development of dosage form. Infra red spectrum and Differential Scanning Calorimeter allow the evaluation of possible incompatibilities between the drug and excipients. The IR spectrum and DSC thermo grams of pure drugs Metoprolol and Ramipril, osmotic agent (mannitol,), plasticizer (Dibutylpthalate) , osmopolymers (Polyethylene Oxide, Carbopol,) and other excipients alone and in a mixture with drugs used in formulation were recorded.

Analysis of API[16]

UV determination was carried out for drugs content uniformity and measure quantity of Metoprolol and Ramipril during dissolution test. The response of the sample solution was measured at 209.5 and 222nm. The amount of Metoprolol and Ramipril present in the sample solution were determined by fitting the responses into the regression equation.

Preparation of swellable controlled porosity osmotic pump[17]

The swellable controlled porosity osmotic pump tablets contained Metoprolol, Ramipril, mannitol (osmotic agent) PEO ,carbopol and PVAand SCMS (swellable polymer) surrounded by a semi permeable membrane CA with Dibutylpthalate as plasticizer. The drug was mixed with all the excipients and passed through sieve of aperture size 250 µm. The blend was mixed for 5-10min in a polythene bag to get a uniform mix. Magnesium stearate, talc and aerosil were added and blended for 2 min and were compressed in a rotary tablet-punching machine (Cadmac, India) fitted with 14/32 inch deep concave punches. Core tablets were coated in a conventional laboratory coating pan (Cipweka, India). Coating solution was prepared by dissolving cellulose acetate and dibutylpthalate in a binary solvent mixture of acetone and water. The components of coating solution were added to solvent mixture in sequential manner. The component added first was allowed to dissolve before next component was added. Before starting coating, tablets were warmed at 40° ± 5°c for 10 minutes and then coating solution was applied at a constant spray rate of 4-5 ml/min.Coating process was done on a batch of 100 tablets. Pan speed was maintained at 20 rpm and hot air inlet temperature was kept at 40° ± 5°c. Coating was continued until desired percentage of coat weight (2%) was obtained on the core tablets.

Evaluation of swellable controlled porosity osmotic pump

Pre and post compression characteristics[18, 19]

The blends were evaluated for precompression parameters like angle of repose, bulk density, tap density, carr's index and hausner's ratio and the core tablets were evaluated for the post compression parameters like appearance, shape, thickness, hardness, friability weight variation,

Drugs content uniformity[20]

Accurately weighed 20 tablets (of all batches) were dissolvedin 500 ml of distilled water [19]. The samples were sonicated for 30 min. and filtered through membrane filter. The

filtered samples, after appropriate dilution ,the samples were analyzed spectrophotometrically at 209.5 and 222nm.

***In vitro* release study**

The formulations (MRSE1-MRSE6) were subjected to release studies using USP-II dissolution apparatus (Electrolab, India) at 50 rpm. Dissolution medium used was distilled water (pH 7.4, 900 ml) maintained at $37^0 \pm 0.5^0$C. The samples (5ml) were withdrawn at 1, 2, 4, 6, 8, 10, 12, 16, 20, 24 hrs intervals and replaced with an equivalent amount of fresh medium. The dissolution sample after filtration through 0.45 µm cellulose acetate filters was analyzed using a validated UV spectrophotometric method at 209.5 and 222nm for Metoprolol and Ramipril respectively and a plot of cumulative percentage of drugs release versus time was made.

Effect of type and level swellable polymers[21]

To study the effect of different concentrations of swellable polymer in the release profile, six formulations (MRSE1-MRSE6) were prepared with varying concentration of PEO and carbopol and the *in vitro* drugs release was studied.

Determination of swelling index[22]

To study the effect of swellable polymer on drug release, swelling index of developed formulations (MRSE1-MRSE6) was determined in 900 ml of distilled water (pH 7.4) at 37 °C. At every hour upto 6hrs, tablets were withdrawn from dissolution fluid and weight of swollen tablets were calculated.. The swelling index (SI) was determined from the following equation.

$$SI = \frac{(Wt - Wo)}{Wt} \times 100$$

Where, Wt is the weight of the swollen tablet at each time interval t,

Wo is the initial weight of the tablet

Performance evaluations of optimized formulations[24]

Effect of pH

To study the effect of pH and to assure a reliable performance of the optimized formulations, *in vitro* release studies was conducted in media of different p^H. The release media was pH 1.2, pH 6.8, and pH 7.4 The percentage of drugs released were determined for a period of 24 hrs.

Effect of agitation intensity

In order to study the effect of agitation intensity , release studies was performed for optimized formulations in dissolution apparatus at various rotational speeds of 50, 100 and 150 rpm and the *in vitro* release studies of the tablets were conducted. The percentages of drugs released were conducted.

Release kinetic studies[25]

Drug-release data from the optimized formulation was fitted to various kinetic models like zero-order, first-order and higuchi models to elucidate the mechanism and kinetics of drug release. Best goodness of fit test (R2) was taken as criteria for selecting the most appropriate model. The model with the highest correlation coefficient was considered to be the best fitting one.

Stability study of optimized formulations as per ICH guidelines[25]

The optimized formulation was subjected to stability studies as per ICH guidelines, 25ºC/60%RH, 30ºC/60%RH and 40ºC/75%RH. Samples were withdrawn at time intervals of 0, 1, 2 and 3 months. The samples were evaluated for appearance, drug content and *in vitro* release profile.

Desired drug release profile

The purpose of this study was to develop a SCPOP for Metoprolol and Ramipril which can deliver the drug in a controlled manner for 24 hrs. The dose, the delivery time and the dosing interval are the key features for any temporal controlled release system. Taking different pharmacokinetic parameters of both drugs into consideration, a zero-order based delivery strategy was designed to produce the desired plasma levels. The dosage form developed consists of a tablet core of Metoprolol and Ramipril along with other excipients. The core compartment is surrounded by a membrane consisting of a semi permeable membrane-forming polymer, with one plasticizer capable of improving film forming properties of the polymers and a pore forming sgents for the release of the drugs.The semi permeable membrane-forming polymer is permeable to aqueous fluids but substantially impermeable to the components of the core. In operation, the core compartment swells and imbibes aqueous fluids from the surrounding environment across the membrane and dissolves the drug. the dissolved drugs are released continuously through the pores formed on the surface of the spm due to dissolution of the pore forming agents.

Drug-excipients compatibility study

IR study was performed on the physical mixture of Metoprolol, Ramipril and different tablet excipients In IR study, the characteristics spectral bands of Metoprolol and Ramipril were not significantly affected in the physical mixture of drugs and excipients. All the characteristics bands of the drugs were retained at their respective positions in the IR spectra of drugs-excipients physical mixtures showed no interaction between Metoprolol and Ramipril and excipients in the physical mixtures showed that the selected tablet excipients used in final formulations were compatible.

Analysis of API

A linear correlation was obtained between peak areas versus concentration of metoprolol and ramipril in the range of 4-120 µg/ml and 4-20 µg/ml respectively. The slope of regression equation and correlation coefficient for metoprolol and ramipril were within the limits.

Formulation and evaluation of controlled porosity osmotic pump

Preparation of controlled porosity osmotic pump

Three formulations (MRSC1-MRSC9) were prepared with different concentrations of swellable polymers(PEO ,carbopol and PVA and SCMC) and coated with the CA (3%) solvent mixture containing dibutyl pthalate sorbitol and evaluated for precompression, post compression and *in vitro* drugs release study.

Evaluation of controlled porosity osmotic pump

Pre and post compression characteristics

The bulk density of powder blend of CPOP of MPT and excipients were found between 0.581±0.020 gm/cc to 0.628±0.025 gm/cc and tapped density was found between 0.712±0.015 gm/cc to 0.738±0.035 gm/cc and these values were found to be within the limits. The angle of repose of all, formulations was less than 30^{o} which indicates that material had excellent flow property. The measurement of free flowing powder can also be done by carr's index. The Carr's index for formulations MRSC1-MRSC9 was found to be between 12.34% ± 0.048 to 14.89% ± 0.064. which indicates that the blends had good flow property. Hausner's ratio was also found to be well within the limits. All these results indicate that the blends possess satisfactory flow properties and compressibility. Tablet thickness, hardness, friability, weight variation and drug content of different formulations were found to be satisfactory. (Table 3)

***Invitro* drug release study**

Osmotic pumps per se are suitable for delivery of drugs having intermediate water solubility. In order to get the desired release from the developed systems, swellable polymer PEO/carbopol /PVA and SCMC was added in core formulation to modulate the solubility and release characteristics of Metoprolol and Ramipril within the core. Inclusion of PEO is expected to control the release of Metoprolol and Ramipril from the osmotic system. *In-vitro* release profiles of SIX batches (MRSCI-MRSC9) in comparison are clearly indicated that the concentration of swellable polymers has indirect effect on drug release. With increase in concentration of polymers within the core there was decrease drug release and increase in swelling index of the formulations due to higher internal pressure generated by the polymers. The lag time was correlated with parameters like osmogents, swellable polymers and membrane thickness. The membrane permeability, swelling nature and the osmotic pressure of the core composition are mainly controlling the tablet hydration kinetics[27.28].

Effect of type and level swellable polymers

The *in-vitro* release of the formulations (MRSC1-MRSC9) studied did not show any significant time lag before the start of the drugs-release phase. An increased drug: osmopolymer ratio delayed the release rate of both the drugs in terms both time and cumulative percentage. This could be due to the fact that release of drug was dependent upon the viscosity of hydrophilic polymers. Increment in the viscosity impedes the movement of drug molecules within the system as well as lesser permeation power of water generates weak osmotic pressure. As increase in the osmo polymer concentration increases the viscosity of the gel as well as the formation of gel layer with longer diffusional path. This could cause a decrease in the effective diffusion co-efficient of drug and therefore reduction in drug release rate from MRSC1 to MRCS9.

On comparing the rate amount of the of drugs release from the **swellable controlled porosity osmotic pump tablets** Metoprolol succinate and Ramipril formulations containing PEO (MRSC1- MRSC3)and carbopol(MRSC4-MRSC6) ,it was clearly showed that the release was more with PEO and delayed with the carbopol due to hydrophobic nature of the polymer whereas combinations of PVAand SCMC produced steady slow and controlled release for a period of 24 hrs.

The optimal release was further suggested by due to higher swelling of CMC in higher concentration in the dissolution medium results in more suspension of the drug in the

dissolution media which led to removal of gel layer on the tablet surfaces. Further the aim of controlling the drug release was not achieved both with high concentration of PEO(**MRSC3)** and also with lower concentration of carbopol (**MRSC4)** ,showed more than 24 hrs drug release for Ramipril due to increased swelling ,hydration and diffusion of the drugs from the matrix and polymer characteristics .Hence in the formulations (MRCS7-MRCS9), the release was controlled for a period of 24 hrs with a lag time of 1 hrs due to swelling of PVA in lower pH followed by SCMC swelling results in complete release of the drugs**(MRSC7).**

Thus **MRSC7 (**99.98%and 92.32% for metoprolol and ramipril respectively) was considered as a suitable formulation for further study. Thus in an osmotic system (SCPOP) a combination of hydrophilic and hydrophobis nature of polymer results in producing a controlled drug delivery OF DRUGS with the osmotic ,swelling and erosion mechanisms
Thus among the formulations (MRSC7- MRSC9), **MRSC7** ($t_{90\%}$ at 19hrs, $t_{90\%}$at 24 hrs) **formulation contains 2%weight of coated tablets with3%CA ,10%DBP and 40% sorbitol** was optimized with a suitable 1:0.5 drug: osmopolymer ratio for controlling the release rate of the drugs for a period of 24 hrs.

Determination of swelling index

In all the formulations swelling index was increased with increase in the concentration of the swellable polymers. Thus on comparing swelling index of all the formulations, it was concluded that swelling was increased both with the time and concentration as the polymer gradually absorbed water and swollen and had an indirect effect on the drug release profile of formulations MRSC1-MRSC9 .The order of swelling was PVAand SCMC>> Carbopol >> PEO.The order of release was found to be PVAand SCMC<< Carbopol << PEO. The finding was supported by Parakh et al, who explained that water absorption rate increases as the viscosity of the polymer increases and at the end of experiment, polymer of the higher viscosity showed the maximumabsorption with decreased drug release. (Table6)

Performance evaluations of optimized formulation

Effect of pH

The optimized formulations were subjected to *in vitro* release studies in buffers with different pH showed no significant difference in the release profile, demonstrating that the developed formulations showed pH-independent release.

Table 1: FORMULATION OF SWELLABLE CONTROLLED POROSITY OSMOTIC PUMPTABLETS METOPROLOL AND RAMIPRIL

Coating solutions		**MRSC1**	**MRSC2**	**MRSC3**	**MRSC4**	**MRSC5**	**MRSC6**	**MRSC7**	**MRSC8**	**MRSC9**
S.No	**Ingredients**									
	Metoprolol Succinate	95	95	95	95	95	95	95	95	95
	Ramipril	10	10	10	10	10	10	10	10	10
	Mannitol	105	105	105	105	105	105	105	105	105
	Polethylene oxide	52.5	105	157.5	--	--	---	----	----	----
	Carbopol	----	----	-----	52.5	105	157.5	-----	-----	----
	PVA and SCMC (1:1)	--	-----	-----	----	----	-----	52.5	105	157.5
	Microcrystalline Cellulose	227.5	175	122.5	227.5	175	122.5	227.5	175	122.5
	Magnesium Stearate	4	4	4	4	4	4	4	4	4
	Talc	4	4	4	4	4	4	4	4	4
.	Aerosil	2	2	2	2	2	2	2	2	2

MRSC1, MRSC2, MRSC3 corresponds to formulations containing Drugs: PEO ratio of 1:0.5,1:1,1:1.5

MRSC4, MRSC5, MRSC6corresponds to formulations containing Drugs: Carbopol ratio of 1:0.5,1:1,1:1.5

MRSC7, MRSC8, MRSC9 corresponds to formulations containing Drugs : PVA AND SCMC ratio of 1:0.5,1:1,1:1.5

TABLE 2 : PRE COMPRESSION PARAMETERS OF GRANULES OF SWELLABLE CONTROLLED OSMOTIC PUMP OF METOPROLOL AND RAMIPRIL

S.No	Formulations	Angle of repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's ratio
	MRSC1	29°.06±0.231	0.60 ±0.032	0.73 ± 0.025	14.80 ±0.371	1.26 ±0.112
	MRSC2	29°.49±0.226	0.60 ±0.014	0.73 ±0.037	14.64 ±0.024	1.20±0.077
	MRSC3	29°.08±0.474	0.62 ± 0.025	0.72 ± 0.032	14.89 ±0.064	1.16 ±0.070
	MRSC4	27°.03±0.206	0.60 ±0.034	0.73 ± 0.027	13.21 ±0.370	1.26 ±0.110
	MRSC5	27°.37±0.06	0.62 ±0.018	0.73 ±0.035	13.06 ±0.042	1.17 ±0.142
	MRSC6	27°.26±0.105	0.61 ± 0.025	0.74 ± 0.036	13.56 ±0.045	1.21±0.140
	MRSC7	27° .33±0.103	0.58 ±0.017	0.72 ± 0.035	12.34 ±0.048	1.24 ±0.145
	MRSC8	27° .26±0.107	0.58 ± 0.020	0.72 ±0.015	12.45 ±0.396	1.24 ±0.055
	MRSC9	26°.38±0.242	0.60 ± 0.020	0.71 ±0.015	12.55 ±0.396	1.04 ±0.018

TABLE 3 : POST COMPRESSION PARAMETERS OF SWELLABLE CONTROLLED OSMOTIC PUMP TABLETS OF METOPROLOL AND RAMIPRIL

S.No	Formulations	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight Variation (mg)	Drug content (%)	
						METO	RAM
1	MRSC1	4.32 ± 0.110	5.53 ±0.114	1.31 ± 0.104	499.00 ± 1.002	100.19 ± 0.970	100.49 ± 2.400
2	MRSC2	4.47 ± 0.132	5.50 ± 0.175	1.34 ± 0.152	499.33 ± 2.08	99.19 ± 0.512	98.53 ± 1.917
3	MRSC3	4.35 ± 0.170	5.47 ± 0.302	1.35 ± 0.077	499.00 ± 2.045	98.42 ± 1.015	101.23 ± 0.090
4	MRSC4	4.15 ± 0.054	5.40 ± 0.178	1.25 ±0.052	500.33 ±2.510	97.77 ± 1.267	99.60 ± 0.045
5	MRSC5	4.48 ± 0.050	5.20 ± 0.260	1.24 ± 0.023	500.33 ± 2.300	97.53 ± 1.826	100.44 ± 0.940
6	MRSC6	4.53 ± 0.285	5.37 ± 0.205	1.28 ± 0.068	499.33 ± 1.522	99.82 ± 0.330	99.91 ±1.443
7	MRSC7	4.54 ± 0.185	5.13 ± 0.056	1.10 ± 0.121	501.67 ± 1.150	100.55 ± 0.581	98.63 ± 1.442
8	MRSC8	4.50 ± 0.124	5.17 ± 0.204	1.12 ± 0.103	499.33 ± 1.522	100.25 ± 2.943	98.40 ±1.790
9	MRSC9	4.41 ± 0.250	5.33 ± 0.050	1.12 ± 0.100	500.67 ± 1.150	99.40 ± 0.940	98.86 ±1.965

TABLE 4: *INVITRO* DISSOLUTION PROFILE OF SWELLABLE CONTROLLED POROSITY OSMOTIC PUMP TABLETS Of METOPROLOL AND RAMIPRIL EFFECT OF TYPE AND LEVEL OF SWELLABLE POLYMER (PEO)

S.No	Time (hrs)	MRSC1		MRSC2		MRSC3	
		METO	RAM	METO	RAM	METO	RAM
1	0	0.00	0.00	0.00	0.00	0.00	0.00
2	2	29.12±0.145	22.11±0.025	26.24±0.015	18.48±0.015	24.22±0.147	15.02±0.001
3	4	47.51±0.012	35.20±0.014	41.60±0.012	33.57±1.025	36.33±0.013	26.01±0.003
4	**6**	58.10±0.045	47.64±0.235	54.25±0.045	43.59±0.025	49.40±0.012	39.04±0.015
5	8	**66.12**±0.315	**56.89**±0.155	**62.40**±1.024	**50.24**±1.021	**56.78**±0.025	**48.05**±0.048
6	10	83.13±0.125	67.78±0.123	74.98±0.036	62.26±0.025	66.46±0.046	57.58±0.087
7	12	90.12±0.245	79.01±0.145	83.60±0.085	74.15±0.245	78.49±0.078	71.45±0.058
8	16	98.13±0.341	90.45±0.168	92.33±0.240	83.35±0.123	86.78±0.089	80.65±0.094
9	20	101.21±0.211	92.46±0.014	98.47±0.360	90.44±0.456	92.69±0.047	88.25±0.125
10	24	103.54±0.011	96.58±0.169	101.68±0.135	94.28±0.025	100.54±0.022	92.60±0.268

TABLE 5:*IN VITRO* DISSOLUTION PROFILE OF SWELLABLE CONTROLLED POROSITY OSMOTIC PUMPTABLETS Of METOPROLOL AND RAMIPRIL EFFECT OF TYPE AND LEVEL OF SWELLABLE POLYMER (CARBOPOL)

S.No	Time (hrs)	MRSC4		MRSC5		MRSC6	
		METO	RAM	METO	RAM	METO	RAM
1	0	0.00	0.00	0.00	0.00	0.00	0.00
2	2	21.25±0.014	15.13±1.023	18.77±0.014	12.21±1.006	15.25±0.001	10.02±0.048
3	4	34.36±0.056	24.45±0.025	29.150.025±	20.31.0046±	25.48±0.003	18.31±0.098
4	6	40.14±0.035	36.85±0.014	38.24±1.026	28.25±0.005	36.69±0.005	23.05±0.074
5	8	52.27±0.314	41.79±0.036	49.22±0.002	38.14±0.007	46.66±0.001	33.14±0.064
6	10	64.87±0.140	54.46±0.019	61.33±0.003	48.40±0.002	59.55±0.016	42.06±0.035
7	12	72.94±0.015	63.24±0.025	68.86±0.0478	59.84±0.004	64.77±0.014	54.14±0.034
8	16	80.58±0.016	70.39±0.018	79.90±0.003	67.96±0.006	76.44±0.025	62.01±0.012
9	20	92.68±0.014	83.58±0.036	88.68±0.221	76.58±1.001	85.32±0.035	71.77±0.078
10	24	99.49±0.045	90.66±0.017	95.22±0.019	88.47±1.002	92.80±0.049	84.88±0.005

TABLE 6 :*IN VITRO* DISSOLUTION PROFILE OF SWELLABLE CONTROLLED POROSITY OSMOTIC PUMPTABLETS Of METOPROLOL AND RAMIPRIL EFFECT OF TYPE AND LEVEL OF SWELLABLE POLYMER (PVA AND SCMC)

S.No	Time (hrs)	MRSC7		MRSC8		MRSC9	
		METO	RAM	METO	RAM	METO	RAM
1	0	0.00	0.00	0.00	0.00	0.00	0.00
2	2	24.25±0.054	18.25±0.003	22.45±0.045	16.78±0.004	20.25±0.003	14.27±0.047
3	4	31.36±0.049	26.46±1.003	29.69±1.023	24.96±0.008	27.39±1.004	22.48±0.058
4	6	40.48±0.036	34.97±1.045	38.58±0.354	32.35±0.001	36.47±0.005	30.69±0.694
5	8	52.97±0.014	46.24±0.004	50.46±0.025	44.48±0.021	48.58±0.064	42.33±0.046
6	10	63.56±0.025	59.36±0.006	61.35±0.368	57.97±0.014	59.69±0.045	55.44±0.358
7	12	76.94±0.004	70.12±0.254	74.78±0.047	68.64±0.057	72.45±0.047	66.57±0.347
8	16	84.79±0.058	81.36±0.147	82.47±0.058	78.31±0.047	80.62.±0.069	76.69±0.358
9	20	92.02±0.040	87.38±0.058	90.22±0.690	84.33±0.360	88.32±0.014	82.18±0.481
10	24	99.98±1.024	92.32±0.369	96.45±1.002	90.71±0.088	94.11±0.004	88.22±0.252

TABLE 7: DETERMINATION OF SWELLING INDEXAND RELEASE KINETICS OF OPTIMISED FORMULATION

S.No	Optimised formulation	Mean of Swelling Index(%)at 24 th hour	Release kinetics (Zero order-r^2)	Stability study (3months)	
				Drug content(%)	Invitro release of Metoprolol and Ramipril
1	MRSC7	98.64.34±.0.020	0.991	98.25±0.015	98.88±0.010& 91.27±0.021

Effect of agitation intensity

The optimized formulation was subjected to *in-vitro* release studies in different speeds and can be seen that there is no significant difference in the release profile, demonstrating that the optimized formulation showed a release profile, fairly independent of the hydrodynamic conditions of the body.

Release kinetic studies

Based on the results of the release kinetic study, the data of optimized formulations fit well into the zero order kinetics. The compatible fit of the zero order kinetics indicated that the drugs release is controlled by a concentration independent release mechanism. (Table6)

Stability studies of optimized formulation

The results showed that there was no change in the physicochemical parameters of the formulations during three months of stability study. (Table6)

CONCLUSIONS

In the present study, SCPOP of Metoprolol and Ramipril was developed and evaluated. Drug release from the developed ormulations was independent of pH and agitation intensity of the release media, assuring the release to be fairly independent of pH and hydrodynamic conditions of the absorption site. Metoprolol and Ramipril release from developed SCPOP was inversely proportional to the level of swellable polymer .Drug release data from MRSC7 formulation fitted well into zero-order kinetics. Developed formulations were found to be stable during six months of storage at acceleratedstability condition.

REFERENCES

1. Sica D. A current concept of pharmacotherapy in hypertension. *J.Clin.Hypertension.* 2000;3:322-327.
2. JNC VI. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Int Med.* 1997; 157: 2413-446.
3. Shammas E, Dickstein K. Drug selection for optimal treatment of hypertension in the elderly. *Drugs Aging.* 1997;11:19-26.
4. Beevers DG. Introduction: control of blood pressure by combination therapies. *J Hum Hypertens.* 1991;5(2): 1-2.
5. Chobanian AV, Bakris GL, Black HR. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003; 42:1206-52.
6. Barar F.S.K. Essentials of Pharmacothearpeutis, S.Chand and companyLtd., New Delhi, 1985, 215-46.
7. AHFS; Drug Information, American society of Health-system Pharmacists, Inc. 72 Wisconsin Avenue, Bethseda, MD 20814. 2005:1869–75.
8. Verma R.K, Krishna D.M, and Garg S. Formulated aspects in the development of osmotic controlled oral drug delivery system. *J. Controlled Release* 2002;79:7-27.
9. Verma R.K, Mishra B, and Garg S. Osmotic controlled oral drug delivery. *Drug. Dev. Ind. Pharm*. 2000;26:695-708.
10. Appel LE., Thombre AG, Chidlaw MB, Daugherity PD, Dumont F, Evans LAF and Sutton SC. Swellable core technology for osmotic drug delivery. *Journal of Controlled Release*. 2004;94:75– 89.
11. Javad Shokri, Parinaz Ahmad, Parisa Rashidi, Mahbobeh Shahsavari, Ali Rajabi-Siahboomi and Ali Nokhodchi. Swellable elementary osmotic pump (SEOP). *European Journal of Pharmaceutics and Biopharmaceutics.* 2008;6:289–297.
12. Nokhodchi A, Momin MN, Shokri J, Shahsavari M, Rashidi PA. Factors affecting the release of nifedipine from a swellable controlled porosity osmotic pump. Drug delivery. 2008;15(1):43-48.
13. Shokri J, Ahmadi P, Rashidi P, Shahsavari M, Rajabi-Siahboomi A, Nokhodchi. A Swellable elementary osmotic pump (SEOP): An effective device for delivery of poorly water-soluble drugs. *Eur J Pharm Biopharm.* 2008; 68(2): 289-97.

14. Mothilal M, Damodharan N, laksmi.K.S and Sharanya V. Formulation and in vitro evaluation of osmotic drug delivery systems of metoprolol succinate. *International journal of pharmacy and pharmaceutical sciences.* 2010; 2: 2-6.
15. Wei L, Li J, Guo L, Nie S, Pan W, Sun P, Liu H. Investigations of a novel self-emulsifying osmotic pump tablet containing carvedilol. *Drug Dev Ind pharm.*2007;33(9):990-8.
16. Suresh Kumar K., Ravi Kumar R., Rajasekaran A., Ravichandran V., Simultaneous spectrophotometric determination of metoprolol tartrate and ramipril. Digest Journal of Nanomaterials and Biostructures. 2010;5(1):173-176.
17. Appel LE, Thombre AG, Chidlaw MB, Daugherity PD, Dumont F, Evans LAF, and Sutton SC. Swellable core technology for osmotic drug delivery. *Journal of Controlled Release*. 2004; 94:75– 89.
18. Subhash Chand Dadarwal, Sarika Madan, Shyam Sunder Agrawal. Formulation and evaluation of delayed-onset extended-release tablets of metoprolol tartrate using hydrophilic-swellable polymers. *Acta Pharm.* 62 (2012) 105–114.
19. Shokri J, Ahmadi P, Rashidi P, Shahsavari M, Rajabi-Siahboomi A, Nokhodchi A Swellable elementary osmotic pump (SEOP): An effective device for delivery of poorly water-soluble drugs. *Eur J Pharm Biopharm.* 2008;68(2):289-97.
20. Strubing S, Metz H, Mader K. Mechanistic analysis of drug release from tablets with membrane controlled drug delivery. *Eur J Pharm Biopharm*. 2007; 66:113–119.
21. Tuntikulwattana S, Sinchaipanid N, Ketjinda W, Williams DB, Mitrevej A. Fabrication of chitosan--polyacrylic acid complexes as polymeric osmogents for swellable micro/nanoporous osmotic pumps. *Drug Dev Ind pharm.* 2011;37(8):926-33
22. Sourabh Jain, SK Yadav and UK Patil Preparation and Evaluation of Sustained Release Matrix Tablet of Furosemide using Natural Polymers. *Research J. Pharm. and Tech.* 2008;1(4): 374-376
23. Rani M, Surana R, Sankar C, Mishra B. Development and biopharmaceutical evaluation of osmotic pump tablets for controlled delivery of diclofenac sodium. *Acta Pharm.* 2003;53:263–73
24. Okimoto K, Ohike A, Ibuki R, Aoki O, Ohnishi N, Rajewskib RA et al. Factors affecting membrane-controlled drug release for an osmotic pump tablet (OPT) utilizing (SBE) -b-CD as both a 7m solubilizer and osmotic agent. *J Control Release.* 1999;60:311-9.
25. Strubing S, Metz H, Mader K. Mechanistic analysis of drug release from tablets with membrane controlled drug delivery. *Eur J Pharm Biopharm*. 2007; 66:113–119.

26. Shivanand Pandey, Paridhi Shukla: Formulation and Evaluation of Osmotic Pump Delivery of Oxybutynin. *International Journal of PharmTech Research.* Oct – Dec 2009; 1: 1638-1643.
27. Jamzad S, Fassihi R. Development of a controlled release low dose class II drug-Glipizide.*Int.J.Pharm.* 2006(7); 312(1-2):24-32.
28. Gazzaniga A, Palugan L, Foppoli A, Sangalli ME. Oral pulsatile delivery systems based on swellable hydrophilic polymers.*Eur J PharmBiopharm.* 2008; 68(1):11-8.
29. Emara L H, Taha N F, Badr R M, Mursi N M. Development of an osmotic pump system for controlled delivery of diclofenac sodium.*Drug DiscovTher.* 2012; 6(5):269-77.
30. Gul Majid Khan, Zhu Jiabi. Formulation and in vitro evaluation of ibuprofen- carbopol 974PNFcontrolled release matrix tablets III: influence of co-excipientson release rate of the drug. Journal of Controlled Release .54; (1998) :185–190.