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Development and Evaluation of Swellable Elementary Osmotic Pump Tablets of Metoprolol Succinate and Ramipril

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Abstract: Swellable elementary 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 combinationsindicated 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.SEOP tablets of Metoprolol and Ramipril were preparedusing additives likeMannitol MCC, talc, magnesium stearate, aerosol with varying concentrations ofswellable polymers(PEO,Carbopol) 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 differentconcentrations of PEO (MRSE1-MRSE3) and carbopol (MRSE4-MRSE6)and various orifice size (MRSE7-MRSE10) on the *in vitro* release were studied. On comparing *in vitro* release of formulations (MRSE1-MRSE6), *the* release rate decreased with the increasedconcentrations of polymers and directly proportional to the orifice size. Thedecreased release rate was due to solubility-modulating properties of the polymer. Among the formulations, MRSE3 shown optimum drug release rate 97.54% and 89.6% for Metoprolol and Ramipril respectivelyat the end of 24 hours. The optimized formulations was independent of the agitation intensity, pH of the medium, stable and deliverMetoprolol and Ramipril at a zero order rate for 24 hrs.

Key words: Swellable elementary osmotic pump · Metoprolol tartrate · Ramipril · Osmogent · Cellulose acetate · Swellable polymers

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, ACE inhibitor/ (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

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angina pectoris.Ramiprilis a potent and specific angiotensin-converting enzyme (ACE) inhibitor that catalyzes the conversion of angiotensin-I to vasoconstrictor substances. Angiotensin-I² 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. Stillthese 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 [8-10].

Among the system, SEOP is selected in which drug is releasedthrough a delivery orifice in the form of a very fine dispersion ready for dissolution and absorption. 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 [11-13]. In this study, swellableelementary osmotic pump (SEOP) 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 swellableelementary osmotic pumpof Metoprolol and Ramipriltablets.

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 LobaChemie, Mumbai, India. Mannitol, MCC, Talc, Magnesiumstearate and Aerosil were obtained from Otto Chemicals and 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 andRamipril, osmoticagent (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 andRamipril during dissolution test. The response of the sample solution was measured at 209.5 and 222nm. The amount of Metoprolol andRamipril present in the sample solution were determined by fitting the responses into the regression equation.

Preparation of Swellable Elementary Osmotic Pump [17]: The swellable elementary osmotic pump tablets contained Metoprolol, Ramipril, mannitol (osmotic agent) PEO and carbopol (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 mixedfor 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 12/32 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. An orifice was made on one of the surface of the tablet mechanically (0.3mm).

Evaluation of Swellable Elementary 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 Contentuniformity [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 spectrophotometricallyat 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° ± 0.5°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 222nmfor Metoprolol and Ramipril respectively and a plot of cumulative percentage of drugs release versus time was made.

Effect of Type and Level Swellablepolymers [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 determinedin 900 ml of distilled water (pH 7.4) at 37 °C. At every hour upto 6hrs, tablets were withdrawn from dissolution fluid and weight ofswollen 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,

Wois the initial weight of the tablet

Effect of Orifice Size [23]: To demonstrate the effect of orifice size, coated tablets were drilled with different orifice size (0.3mm-0.9mm) and the formulations (MRSE7-MRSE10) were subjected to *in vitro* release studies.

Performance Evaluations of Optimized Formulations [24]

Effect of pH: To study the effect of pHand to assure a reliable performance of the optimized formulations, *in vitro* release studies was conducted in media of differentpH. The release media werepH1.2,pH 4.5,pH6.8,pH7.2 and pH7.6The percentage of drugs released and statistical analysis of data of dissolution profiles were determined.

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 SEOP 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 an orifice was made mechanically on one face of the tablets. 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 orifice in fine dispersion.

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 Ramipriland 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 andramipril in the range of 4-120µg/ml and 4-20 µg/ml respectively. The slope of regression equation and correlation coefficient for metoprolol andramipril were within the limits.

Formulation and Evaluation of Controlled Porosity Osmotic Pump

Preparation of Controlled Porosity Osmotic Pump: Three formulations (MRSE1-MRSE6) were prepared with different concentrations of swellablepolymers(PEO and carbopol) and coated with the CA (3%) solvent mixture containing dibutylpthalate 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 0.65±0.152g/cc to 0.67±0.211. True density was found between 0.72±0.210g/cc to 0.75±0.015g/cc and these values were under the limits of USP standards. The angle of repose of all formulations was less than 30° 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 MRSE1-MRSE6was found to be between 13.14±0.602 % to 13.88±0.601% 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).

Table 1: Formulation Of Swellable Elementary Osmotic Pump Tablets Of Metoprolol And Ramipril

S.NO	Ingredients	MRSE1	MRSE2	MRSE3	MRSE4	MRSE5	MRSE6
1.	Metoprolol Succinate	95	95	95	95	95	95
2.	Ramipril	10	10	10	10	10	10
3.	Mannitol	105	105	105	105	105	105
4.	Polyethylene oxide	52.5	105	157.5	----	----	-----
5.	Carbopol	----	----	-----	52.5	105	
6.	Microcrystalline Cellulose	227.5	175	122.5	227.5	175	122.5
7.	Magnesium Stearate	4	4	4	4	4	4
8.	Talc	4	4	4	4	4	4
9.	Aerosil	2	2	2	2	2	2
Coating solutions							
1.	CelluloseAcetate (%)	3	3	3	3	3	3
2.	Dibutyl phthalate(ml)	6	6	6	6	6	6

Mrse1, Mrse2, Mrse3 Corresponds To Formulations Containing Drugs: Peo Ratio Of 1:0.5,1:1,1:1.5

Mrse4, Mrse5, Mrse6 Corresponds To Formulations Containing Drugs: Carbopol Of 1:0.5,1:1,1:1.5

Table 2: Pre Compression Parameters Of Granules Of Swellable Elementary Osmotic Pump Of Metoprolol And Ramipril

S.No	Btches	Angle Of Repose (°)	Bulk Density (G/Ml)	Tapped Density (G/Ml)	Carr's Index (%)	Hausner's Ratio
1.	Mrse1	27.05±0.021	0.65±0.021	0.72±0.210	13.88±0.601	1.24±0.161
2.	Mrse2	27.49±0.062	0.65±0.152	0.73±0.022	13.14±0.602	1.22±0.051
3.	Mrse3	27.98±0.241	0.66±0.310	0.73±0.111	13.31±0.080	1.22±0.021
4.	Mrse4	28.21±0.110	0.67±0.211	0.74±0.020	13.46±0.401	1.21±0.022
5.	Mrse5	28.43±0.121	0.67±0.120	0.74±0.200	13.54±0.020	1.19±0.070
6.	Mrse6	28.51±0.212	0.67±0.030	0.75±0.015	13.28±0.300	1.19±0.052

Table 3: Postcompression Parameters Of Swellable Elementary Osmotic Pump Tablets Of Metoprolol And Ramipril

S.No	Batches	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Weight Variation (mg)	Drug content (%)	
						Metoprolol	Ramipril
1	MRSE1	4.48±0.110	6.10±0.170	1.24±0.051	501±0.142	99.39±0.105	98.24±0.120
2	MRSE2	4.44±0.022	6.07±0.302	1.21±0.042	500±0.121	100.22±0.010	99.25±0.021
3	MRSE3	4.42±0.151	6.20±0.121	1.13±0.031	499±0.012	101.07±1.021	99.54±0.214
4	MRSE4	4.38±0.140	6.57±0.250	1.14±0.150	499±0.012	99.53±0.025	100.20±0.120
5	MRSE5	4.47±0.313	6.37±0.204	1.02±0.020	500±0.042	99.22±0.125	100.01±0.014
6	MRSE6	4.43±0.121	6.83±0.052	1.09±0.013	500±0.150	100.21±0.110	99.48±0.014

Table 4: Invitro Dissolution Profile Of Swellable Elementary Osmotic Pumptablets Of Metoprolol And Ramipril Effect Of Type And Level Of Swellable Polymer (Peo)

S.No	Time (hrs)	MRSE1		MRSE2		MRSE3	
		METO	RAM	METO	RAM	METO	RAM
1	0	0.00	0.00	0.00	0.00	0.00	0.00
2	2	26.12±0.145	19.11±0.025	24.24±0.015	15.48±0.015	20.22±0.147	11.02±0.001
3	4	44.51±0.012	32.20±0.014	39.60±0.012	28.57±1.025	31.33±0.013	21.01±0.003
4	6	55.10±0.045	44.64±0.235	48.25±0.045	39.59±0.025	42.40±0.012	33.04±0.015
5	8	63.12±0.315	53.89±0.155	56.40±1.024	46.24±1.021	49.78±0.025	41.05±0.048
6	10	79.13±0.125	64.78±0.123	68.98±0.036	57.26±0.025	61.46±0.046	52.58±0.087
7	12	87.12±0.245	76.01±0.145	73.60±0.085	70.15±0.245	69.49±0.078	63.45±0.058
8	16	96.13±0.341	87.45±0.168	85.33±0.240	73.35±0.123	79.78±0.089	71.65±0.094
9	20	100.21±0.211	90.46±0.014	96.47±0.360	86.44±0.45	88.69±0.047	80.25±0.125
10	24	102.54±0.011	92.48±0.169	100.68±0.135	91.78±0.025	97.54±0.022	89.60±0.268

***In vitro* 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 thedeveloped systems, swellable polymer PEO/carbopol was added in core formulation to modulate the solubility of Metoprolol and Ramipril within the core. Inclusion of PEO is expected to control the release of Metoprolol and Ramipril from the EOP *In-vitro* release profiles of SIX batches (MRSE1-MRSE6) in comparison is 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 (MRSE1-MRSE6) studied did not show any significant time lag before the start of the drugs-release phase. There was a decrease in drugs release rate with increased concentration PEO in the core. This may be due to solubility-modulating properties of the polymer. The cores of the PEO produce better drug release profile than carbopol showed better suspending properties of the polymer and the drugs were uniformly suspended in the core when water imbibes [29,30]. A microenviroment occurs in which both osmogent and orifice played a role in controlled drug delivery.Thus MRSE3 was considered as a best one with release rate of 97.54% and 89.6% for metoprolol and ramipril respectively. (Tables 4,5)

Determination of Swelling Index: In all the formulations swelling index was increased with increase in the concentration of the swellable polymers (Table 6).

Effect of Orifice Size: From the results, it was found that release was increased with increase in orifice diameter of the formulations (Table 7).

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 5: *In vitro* Dissolution Profile Of Swellable Elementary Osmotic Pumptablets Of Metoprolol And Ramipril Effect Of Type And Level Of Swellable Polymer (Carbopol)

		MRSE4		MRSE5		MRSE6	
S.No	Time (hrs)	METO	RAM	METO	RAM	METO	RAM
1	0	0.00	0.00	0.00	0.00	0.00	0.00
2	2	17.25±0.014	10.13±1.023	15.77±0.014	9.21±1.006	13.25±0.001	8.02±0.048
3	4	29.36±0.056	19.45±0.025	26.150.025±	17.31.0046±	23.48±0.003	15.31±0.098
4	6	36.14±0.035	26.85±0.014	33.24±1.026	23.25±0.005	30.69±0.005	20.05±0.074
5	8	48.27±0.314	36.79±0.036	45.22±0.002	33.14±0.007	43.66±0.001	30.14±0.064
6	10	59.87±0.140	46.46±0.019	57.33±0.003	42.40±0.002	55.55±0.016	40.06±0.035
7	12	66.94±0.015	57.24±0.025	62.86±0.0478	53.84±0.004	60.77±0.014	51.14±0.034
8	16	78.58±0.016	65.39±0.018	76.90±0.003	62.96±0.006	74.44±0.025	60.01±0.012
9	20	86.68±0.014	76.58±0.036	84.68±0.221	71.58±1.001	81.32±0.035	69.77±0.078
10	24	94.49±0.045	86.66±0.017	91.22±0.019	83.47±1.002	90.80±0.049	82.88±0.005

Table 6: Determination Of Swelling Indexand Release KineticsOf Optimised Formulation

				Stability study (3months)	
S.No	Optimised formulation	Mean of Swelling Index(%)	Release kinetics (Zero order-r^2)	Drug content(%)	Invitro release of Metoprolol and Ramipril
1	MRSE3	35.34±0248	0.994	99.25±0.004	96.99±0.001 and 88.65±0.047

Table 7: Invitro Dissolution Profile Of Swellable Controlled Porosity Osmotic Pump Tablets Of Metoprolol And Ramipril Effect Of Concentration Of Oriice Size (0.3mm-0.9mm)

		MRSE7		MRSE8		MRSE9		MRSE10	
S.No	Time (hrs)	METO	RAM	METO	RAM	METO	RAM	METO	RAM
1	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	2	20.22±0.147	11.02±0.001	24.24±0.148	19.24±0.004	26.77±1.004	24.01±0.002	28.45±0.004	28.77±1.004
3	4	31.33±0.013	21.01±0.003	40.56±0.006	29.50.0058±	42.88±1.025	36.25±0.004	44.14±0.006	39.56±0.005
4	6	42.40±0.012	33.04±0.015	49.48±0.025	34.78±0.025	53.59±1.054	41.48±0.045	56.55±0.069	45.88±0.009
5	8	49.78±0.025	41.05±0.048	58.78±0.014	43.96±1.006	64.46±0.098	50.99±0.086	67.04 ±0.003	58.44±0.014
6	10	61.46±0.046	52.58±0.087	66.69±0.036	55.45±0.004	71.58±0.096	63.87±0.053	75.06±0.004	69.58±0.065
7	12	69.49±0.078	63.45±0.058	74.47±0.058	61..96±0.048	80.12±0.034	72.66±0.006	84.25±0.009	78.89±0.034
8	16	79.78±0.089	71.65±0.094	81.46±0.248	78.33±0.058	90.32±0.058	84.25±0.004	93.36±0.007	88.69±0.058
9	20	88.69±0.047	80.25±0.125	89.47±0.069	84.44±0.007	98.69±0.024	89.14±0.006	99.25±0.006	92.36±0.079
10	24	97.54±0.022	89.60±0.268	99.89±0.047	91.58±0.004	101.11±0.047	92.08±0.003	102.08±0.070	94.47±0.046

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 (Table 6).

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 (Table 6).

CONCLUSIONS

In the present study, SEOP of Metoprolol and Ramipril was developed and evaluated. Drug release from the developed ormulations was independent of pH and agitation intensityof the release media, assuring the release to be fairly independentof pH and hydrodynamic conditions of the absorptionsite. Metoprolol and Ramiprilrelease from developed SEOP was directly relatedto the level of orifice size but inversely proportional tothe level of swellable polymer. Drug release data from TRH formulations fitted well intozero-order kinetics. Developed formulations werefound to be stable during six months of storage at acceleratedstability condition.

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