Open Access Contents
Int. J. Drug Dev. & Res.
| October - December 2014 | Vol. 6 | Issue 4 | ISSN 0975-9344 |
www.ijddr.in

Full Length Original Research Paper

Formulation Development and Characterization of Modified Release Microspheres of Antianginal Drug

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Abstract:
Ranolazine (RZ) is an antiischemic/antianginal agent employed in therapy of cardiovascular diseases such as myocardial infarction, variant and exercise-induced angina and arrhythmias constipation, headache, nausea and dizziness are the most common side effects. So the aim of the present research work was to formulation development and characterization of modified release RZ loaded EC microspheres by o/w emulsion solvent diffusion evaporation technique with different ratio of drug and ethyl cellulose as a polymer in order to achieve high entrapment efficiency and prolonged release characteristics. The prepared microspheres were characterized by Scanning electron microscopy (SEM), percent yield, micrometrics properties, Fourier transformer infra red spectroscopy (FTIR), percent entrapment efficiency and percent drug release characteristics. The size of microspheres formulations (F1 to F6) were in range of 20±1.2 to 54±1.7µm, percent yield 78.21±2.31 to 94.24±1.21%, percent drug entrapment efficiency 53.25±0.65 to 85.76±0.78% and percent drug release 56.87 ± 0.34 to 92.74 ± 0.83 % up to 12 hrs. IR study showed no interaction between drug and polymer; no degradation during microspheres preparation and stable at storage conditions. All microsphere formulations showed various drug releases kinetic but F2 formulation followed first order drug release kinetics and 92.74 ± 0.83% drug release for prong period of time. From the study, it was investigated that free flowing spherical microspheres of RZ could be prepared successfully by solvent diffusion evaporation technique with high entrapment efficiency and prolong release profile characteristics.

Keywords: Ranolazine, Ethyl Cellulose, Anti-ischemic/Anti-anginal.

Introduction

The main goal of any drug therapy to gain a steady-state plasma drug concentration or tissue concentration, nontoxic and therapeutically effective for prolong time period. Many demerits of conventional drug therapy are overcome by modified release drug delivery systems such as controlled release drug delivery system, site specific release drug delivery system, sustained release drug delivery system and delayed release drug delivery system [1]. The merits of sustain release drug delivery therapy like easily administered, enhanced the bioavailability, reduced the side effects, minimized the drug toxicity, increased patient compliance, and enhanced reliability of drug therapy [2].

Ranolazine (RZ), chemically ([(+)*N*-(2,6-dimethylphenyl)-4 (2-hydroxy-3-(2-methoxy phenoxy) -propyl)-1-piperazine acetamide dihydrochloride]), effective antiischemic/ antianginal agent employed in therapy of cardiovascular diseases such as myocardial infarction, variant and exercise-induced angina and arrhythmias. Through intracellular metabolic alterations it regulates myocardiac ischemia and useful in chronic stable angina and other cardio metabolic disorder. Its terminal half life range 1.4 to 1.9 hours of immediately release RZ and a 10 times peak difference with 240 to 400 mg TID. RZ sustain release (Ranexa) formulation showed prolong absorption phase with Cmax 4 to 6 hours after administration, terminal elimination half-life

approximate 7 h, attain peak plasma concentration within 2–5 hrs when prescribed in multiple dosing (500 mg twice daily), may enhance up to 1 g BID [3-7]. After oral administration effectively absorbed and rapidly clear so need frequent administration and causes gastrointestinal, pancreatic, hepatic, endocrine, nervous, renal, cardiac and hematological disorders but constipation, headache and dizziness are the most common side effects [8]. So to obtain maximum therapeutic efficacy with a low risk of adverse effects, necessary to develop sustain released drug delivery system [9].

One of the novel techniques, microencapsulation used for retarding the drug release from dosage forms and reduced the adverse effects, increased the patient compliance. In this technique, aqueous insoluble core coated with an aqueous insoluble coat by emulsion solvent diffusion evaporation technique for sustain release drug delivery system [10]. Ethyl cellulose (EC) being insoluble in water extensively used for preparation of microspheres serves as good candidate for water insoluble drug to achieve sustained release drug delivery systems. [11-13].

Therefore, the objective of the present research work was to formulation design optimization and investigation of RZ loaded EC microspheres by oil-in-water (o/w) emulsion solvent diffusion evaporation technique. So we can achieve sustain release drug profile by release rate retarding polymer for per oral route of administration.

MATERIAL AND METHOD

Ranolazine as a gift sample was procured from MSN Laboratories Ltd. Hyderabad, India. Ethyl cellulose and Poly vinyl alcohol of A.R. grade were used as purchased from CDH, Mumbai. All other reagents and solvents employed were of analytical grade.

Method of preparation of RZ loaded EC microsphere:

Emulsion solvent diffusion-evaporation technique was employed to prepare Ranolazine (RZ) loaded EC microsphere. EC (250mg) and drug (250mg) were dissolved in dichloromethane (10 ml, DCM) as an internal phase. The polymeric solution of drug was then added slowly drop wise manner under stirring in to previous prepared a solution of polyvinyl alcohol (100 ml, 0.5%w/v PVA) in water as an external phase (fig. 1). The both phase initially forms a milky white emulsion and the resultant mixture was stirred constantly with a propeller type agitator up to 3 hours until complete volatile organic solvent DCM evaporated. The emulsion breaks down to formed tiny microspheres and allowed for settle down. The resulting microspheres were collected after filtration, rinsing thrice with excess of water and then dried overnight at room temperature [14]. In the same way, several microspheres formulations were prepared by varying the parameters mention in table 1.

Characterization of RZ loaded EC microspheres formulations:

The percentage yield of different microsphere formulations was determined gravimetrically on the basis of polymer and drug recovery.

% Yield= [Weight of microspheres / Total weight of drug and polymer] x100

Percent Incorporation efficiency:

The drug content in various microsphere formulations were estimated by extracting RZ in 7.4 pH phosphate buffer solution (PBS) after dissolving the microspheres (100mg) in 25 mL methanol and adjusted the volume up to 100 ml using pH 7.4 PBS in glass stopper conical flask. The

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resulting mixture was sonicated and agitated on a mechanical shaker for one day, filtered through whatman filter (0.45µm), and then measured the absorbance using a UV/VIS double beam spectrophotometer (Shimadzu UV-1700, Japan) after suitable dilution at 272nm and calculate percent entrapment efficiency (%EE) by using following formula and each determination was made in triplicate [15].

Entrapment Efficiency (%) = $(A_d/T_d) \times 100$

Where, T_d -Theoretical drug content, A_d actual drug content.

Particle size analysis and Scanning Electron Microscopy (SEM) study:

The particle size of microspheres were determined using Scalar-USB Digital scale ver. 1.1 E-Photomicroscope, attached with canon camera (Japan) system based on mean diameter and then calculated size distribution [16].

The surface morphology and shape of microspheres were analyzed by a Scanning Electron Microscopy (SEM, Hitachi Model S-3000H, CECRI, Karaikudi, Tamilnadu, India). During the SEM examination, a drop of microspheres dispersion to be examined was mounted over a SEM stub and dried in desicator. Microspheres were coated with very thin coat of gold employing a vaccum evaporator to make electrically conductive. Then the size of the microspheres was recorded under SEM at a magnification ranging from 500X to 3000X and operated at an accelerating voltage of 20 kV.

Micromeritics study:

Bulk density and Tapped density:

The sample poured in 10 ml of graduated cylinder, tapped mechanically 50 times and then noted down tapped volume. The experiment was repeated three times for reproducibility of results [17-19].

Bulk density (BD) = Mass / Bulk volume (1)

Tap density (TD) = Mass / Tapped volume (2)

Carr's index (CI)

Carr's index or Compressibility index (CI) value of microspheres was calculated according to the following equation.

Percent Carr's Index = [(TD – BD) / TD] x 100 (3)

Hausner's ratio (HR):

Hausner's ratio of different microspheres formulations were calculated using following formula when compared the tapped density to bulk density.

Hausner's ratio (= (TD / BD) (4)

Flow property:

For study of flow behavior, weight amount of powder samples to be analyzed poured through the funnel ensure 2.5 cm height of its tip until formed a conical pile on the flat surface of graph and observe the height and radius of pile of base then calculate the tangent of the angle of repose by using following formula-

$\theta = \tan^{-1}(h / r)$

Where, θ = Angle of repose, r = Radius of the base of the pile, h = Height of pile

Fourier Transformer Infrared (FTIR) spectral study:

Infrared (I.R.) spectrum of drug, physical mixture of drug-polymer and RZ loaded microsphere gives information about the group present in that particular compound. Before I.R. spectra studies, ranolazine, physical mixture of drug-polymer and RZ loaded microsphere were dried in vaccum for 12 hours. Potassium bromide (KBr) 200mg in 3mg test sample was used to prepared discs, scan under the range 4000 – 400 wave number (cm^{-1}) and % Transmittance employing Perkin Elmer (USA). The above experiments were performed in triplicate manner to confirm the results.

Differential Scanning Calorimetry (DSC) study:

The thermal behavior of RZ, physical mixture of drug-polymer and drug-loaded microspheres were investigated employing differential scanning calorimeter (DSC-60 Instruments, Shimadzu Corporation, Japan). The samples (5mg) were accurately weighed, sealed hermetically into aluminum pans and heating run for each sample kept from 50˚C- 300˚C at a heating rate of 10˚C per min, using in atmosphere of air as blanket gas

In vitro Drug Release Profile:

The *in vitro* dissolution studies were carried out in 0.1 N HCl (pH 1.2) and phosphate buffer solution (PBS, pH 7.4), 900 mL, maintained at 37 ± 0.5°C temperature thermostatic controlled water bath, 100 rpm by employing basket-type dissolution apparatus (United States Pharmacopeia XXIV) of eight station (Electro-lab, Mumbai, India). Weighing amount of microsphere suspended in to the dissolution medium and withdrawn the sample (5ml) at predetermined time interval over a period of 12 hours, filtered through a 0.45 mm membrane filter, diluted suitably, and assessed for drug release at 272 nm for RZ by using a UV spectrophotometer (Shimadzu UV-1700, Japan). After each withdraw, immediately supplemented an equal amount of fresh PBS. Each determination was performed thrice and the percent cumulative drug release plotted as the percent drug release in dissolution media Vs time [20].

Kinetics and mechanism of drug release study:

The *in-vitro* drug release data were analyzed to understand the drug release mechanism employing various mathematical models such as zero-order kinetics, first-order kinetics, Hixson Crowell's Model and Higuchi model [21-24].

$A_t = K_0 t$ (1)

Where, K_0 - Release rate constant of Zero order, A_t - Amount of drug release at time (t).

$\ln(A_0-A_t) = \ln A_0 - K_1 t$ (2)

Where, K_1- Release rate constant First order, A_0 - Initial amount of drug release, A_t - Amount of drug release at time (t),

$W_o^{1/3} - W_t^{1/3} = K_c t$ (3)

Where, K_c - Release rate constant of Hixson Crowell's cube root, W_o - Initial weight ,W_t - Weight remaining at time (t),

$A_t = K_H.\sqrt{t}$ (4)

Where, A_t - Amount of drug release at time (t), K_H - Release rate constant of Higuchi, Square root of time (SQRT) ($\sqrt{t}$)

$A_t / A_\infty = K_p t^n$ (5)

Where, A_t/A_∞ - Fraction of drug released at time (t), A_t and A_∞ - Amount of drug released at time (t) and time (∞) respectively, K_p - Korsmeyer-Peppas power law constant comprising the structural and geometric characteristics of the microspheres, n - Diffusion exponent .

The following graph were plotted for Zero-order kinetic model- $\%A_t$ vs t, First-order kinetic model- log% unreleased vs t, Hixson Crowell's cube root model- $(W_o^{1/3} - W_t^{1/3})$ vs t, Higuchi model- $\%A_t$ vs $\sqrt{t}$, and Korsmeyer-peppas model- Log percent drug release vs Log t.

In order to define a model, the *in-vitro* drug dissolution data was evaluated by Korsmeyer-peppas mathematical equation represents a best fit for the formulation. The correlation coefficient (R^2) was calculated by least square linear regression method of the above plots and also determine release rate constant of various kinetic models and diffusion exponent [25-27].

Determination of similarity and difference factor study:

A model independent approach based on determination of difference factor (f_1) and similarity factor (f_2) were evaluated for compare the dissolution profiles. The *in-vitro* drug release data of RZ loaded EC microspheres formulations

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were compared with marketed formulation (MF) Ranolazine-Caroza, Zydus Cadila Healthcare Ltd using a statistical tool to investigate the difference factor (f_1) and the similarity factor (f_2) by the following equation-

$$f_1 = \{(\sum_{=1}^{n} | R_t - T_t |) (\sum_{=1}^{n} R_t)\} \times 100 \quad (6)$$

Where, n – No. of samples; R_t and T_t - Drug release data of reference and test sample at the same time point (t) respectively.

The difference factor (f_1) investigates the percent difference between drug release profiles of curves of test and reference samples at the same time and is a measurement of the relative error. If the (f_1) factor between drug release profiles of curves is zero, indicates the identical *in-vitro* dissolution profile.

The similarity factor (f_2) is measurement of the similarity in the percent *in-vitro* dissolution between the test and reference sample profiles by analyzing the average sum of squares. It calculated by using the following formula:

$$f_2 = 50 \times \text{Log} \{(1+ (1/n) \sum_{=1}^{n} (R_t - T_t)^2)^{-0.5} \times 100\} \quad (7)$$

The f_2 value (50 to 100 ranges) ensures similarity of the *in-vitro* dissolution profile of test and reference samples [28-31].

Stability Studies

To find the stable product stability studies were performed under storage conditions. As per ICH guidelines, optimized drug loaded microspheres formulation subjected to stability studies and stability protocol was designed to find the effect of percent RH (relative humidity) and temperature. Optimized drug loaded microspheres formulations in hermetically sealed tubes were exposed at 5±2°C, 25±2°C/60±5% RH and 40±2°C/75±5% RH to check the effects of temperature and RH on percent entrapment efficiency and percent drug release profiles for a period of six months at 2 months interval. At the end of prescribed time period, the microspheres evaluated for determination of percent encapsulation efficiency, percent drug release and physical appearance [32-34].

Result and discussion

The various RZ loaded EC microspheres formulations F1 to F6 were prepared by emulsion solvent evaporation diffusion technique (fig. 1, table 1). In which EC employed as a polymer and RZ as a core material used in therapy of antiischemic/antianginal activity.

The percent yield of all microspheres formulations F1 to F6 was found to be 78.21±2.31 to 94.24±1.21% and entrapment efficiency 53.44±1.19 to 84.87±1.89%. Out of six formulations, F2 formulation showed highest yield (94.24±1.21%). The reason behind that concentration of coat increased the percentage yield increased as well as further increased in coat concentration, decreased in percentage yield. In the similar way, highest percent entrapment efficiency of F2 microspheres formulation was found to be 85.76±0.78% result shown in table 2.

From the SEM investigation (fig 2) free flowing and spherical shape microspheres were found and indicate 20±1.2µm particles size. The particle size of various microspheres formulations were depicted in table 3.

All microspheres formulations subjected for study of various micromeritics parameters result shown in table 3. The bulk density, tapped density of all microspheres formulations F1 to F6 were found to be 0.327±0.04 to 0.387±0.05 and 0.373±0.05 to 0.465±0.04 g/cm^3 respectively but F2 showed 0.327±0.04 and 0.373±0.05g/cm^3 respectively. For

study of flow property determined the angle of repose, Hausner's ratio and Carr's index. All F1 to F6 microspheres formulation showed angle of repose 19.34±0.41^0 to 37.45±0.27^0, Carr's index 12.332±0.28 to 16.774±0.41% and Hausner's ratio 1.141±0.003 to 1.202±0.004 respectively but F2 microspheres formulation indicates excellent flow behaviour.

FTIR analysis study was used for interaction between the drug and polymer. I.R. spectra of pure RZ, physical mixture of drug-polymer and RZ loaded EC microspheres shown in fig. 3. I.R. spectra of pure RZ showed the prominent characteristic peaks at 3331.07 nm indicating the NH– stretching, two peaks at 3277.06 nm indicate –OH stretching, peak at 1685.79 nm indicate C=O stretching, peak at 1647.21 nm indicating C=O stretching of –COOH, peak at 1298.09 nm indicating C-N stretching, peak at 1436.97 nm indicating Aromatic –C=C stretching, peaks at 1458.18 nm indicate –C=C stretching and another peaks at 1253.73 nm indicate C-O stretching respectively. I.R. spectra of drug loaded microspheres showed the prominent characteristic peaks of pure ranolazine that confirms the presence of drug in microsphere without any interaction with polymer [35].

DSC demonstrated a possible interaction between drug and execipient and also provided information on the physical properties of sample and its crystalline or amorphous nature. DSC thermograms showed characteristic sharp endothermic peak of pure RZ at 122.26˚C, which corresponded to its melting point (M.P. 122˚C). DSC thermograms of physical mixture of drug-polymer showed M.P. at 122.32˚C and drug loaded microspheres showed peak at 116.74˚C due to uniform dispersion of drug in microsphere and higher amount of EC. The melting endotherms indicate no considerable change in melting point of drug loaded EC microspheres as compared to drug and indicate no interaction between drug and polymer, result shown in fig. 4. So F2 formulation considered as an ideal formulation, subjected for *in vitro* and stability studies [36].

The in vitro drug release profile of drug loaded EC microsphere formulations studied in different dissolution medium and simultaneously investigated MF for dissolution study. So that compare the *in vitro* dissolution profile of drug loaded EC microspheres formulation to MF and determine the similarity between the formulations. There was no significant amount of drug release at pH 1.2. In PBS, all microspheres formulation (F1 to F6) showed drug release 56.87 ± 0.34 to 92.74 ± 0.83 % (table 3) but F2 formulation indicated highest drug release 92.74 ± 0.83 **%** up to 12 hrs (fig. 5) as well as concentration of polymer increased, decreased in percent drug release. It reveals that polymer concentration prominent factor that responsible for the drug release profile. MF showed the *in vitro* drug release 89.13±0.20 up to 12 hrs (table 4, fig. 6) near to similar F2 optimized formulation.

In order to study the mechanism of RZ release from the RZ loaded EC microspheres, the *in-vitro* drug release data of various drug to polymer ratio for EC microspheres were analyzed by using various mathematical model to describe drug release, i.e. zero order, first order, Higuchi model and Hixson Crowell's cube root model. The correlation coefficients (R^2) of all release kinetic models were determined, results shown in table 5, fig. 7-11. From table 5, in first order model, the R^2 of various F1, F2, F3 and F5 microsphere formulations were obtained 0.982, 0.972, 0.992 and 0.993 respectively and in Zero model obtained 0.971,

983 of F4 respectively. The various microsphere formulations containing different drug to polymer ratio were obtained the highest correlation coefficient in first order model than Zero order followed by Higuchi order. The optimized F2 microsphere formulation found correlation coefficient (R^2=0.972) of first order release plot. It confirmed that rate of drug release depend upon amount of drug present in microspheres. The diffusion exponent (n) value from Peppas model was found 0.698-0.899 range for different drug to polymer ratio (1:0.5 to 1:3) indicating that all microsphere formulations follow non Fickian (Anomalous transport) diffusion controlled release. Amongst the all microsphere formulations, the highest correlation coefficient containing formulation gives idea about model best fitted to the release data. The *in vitro* drug release profile of MF as a reference standard and F2 optimized microsphere formulation as a test sample was compared, result shown in Fig. 6. The similarity factor (f_2) was determined by the equation (6) between MF and F2 optimized microsphere formulation as reported earlier. It was observed that optimized microspheres F2 formulation have similarity factor more than 70 and confirmed the similarity of dissolution profiles with that of MF. If F2 optimized microsphere formulation as a reference sample to compare with other drug loaded EC microsphere formulations as test samples individually, the similarity factor were obtained between 26.84 to 56.14 and difference factor 13.54 to 52.82 respectively.

In order to make stable sustained product, tubes were evaluated at the end of prescribed time interval. There was no significant difference observe in their percent entrapment efficiency, percent drug release profiles and physical appearance of drug loaded EC microspheres formulations, result shown in table 6.

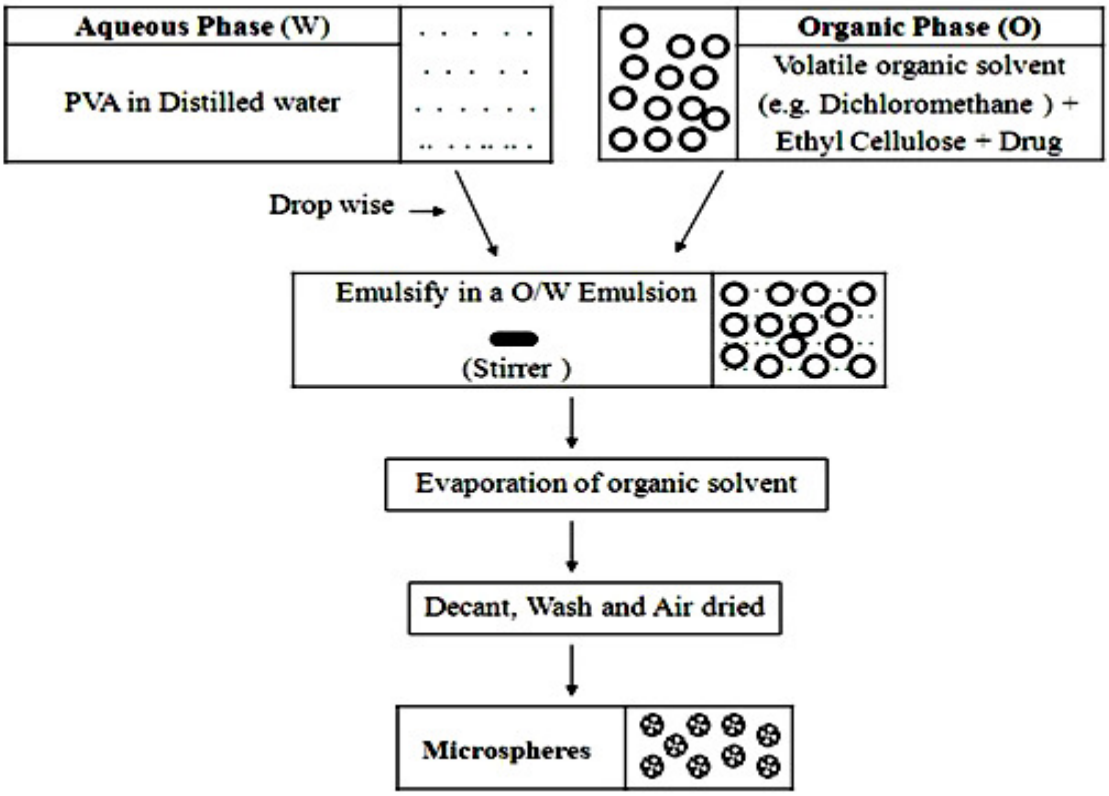

Figure 1: Oil-in-Water (o/w) emulsion solvent evaporation diffusion method for preparation of microspheres.

Table 1- Composition of various RZ loaded EC microsphere formulations.

Formulation Code	Drug : Polymer	EPV (ml)	IPV (ml) (DCM)	PVA (%w/v)
F1	1:0.5	100	10	0.5
F2	1:1.0	100	10	0.5
F3	1:1.5	100	10	0.5
F4	1:2.0	100	10	0.5
F5	1:2.5	100	10	0.5
F6	1:3.0	100	10	0.5

EPV- External Phase Volume, IPV- Internal Phase Volume (ml), PVA- Poly vinyl alcohol
DCM- Dichloro methane,

Table 2: Percentage yield and percent entrapment efficiency of various formulations of RZ loaded EC microspheres.

Formulation Code	Drug : Polymer	Percent yield#	Entrapment Efficiency (%)#
F1	1:0.5	81.63±2.14	70.57±0.57
F2	1:1.0	94.24±1.21	85.76±0.78
F3	1:1.5	90.64±2.16	73.13±0.45
F4	1:2.0	87.02±1.03	67.54±0.87
F5	1:2.5	78.21±2.31	62.36±1.03
F6	1:3.0	80.35±1.20	53.25±0.65

#N=3±S.D.

Table 3: Micromeritic properties and percent drug release of various drug loaded EC microspheres formulations.

Formulation Code	Bulk Density (g/cm^3)#	Tapped Density (g/cm^3)#	Hausner's Ratio#	Carr's Index (%)#	Angle Repose (^{0})#	Particle Size (µm)#	Cumulative Drug Release (%)#
F1	0.349±0.03	0.404±0.02	1.158±0.004	13.614±0.52	21.13±0.27	33±2.3	84.53 ± 0.45
F2	0.327±0.04	0.373±0.05	1.141±0.003	12.332±0.28	19.34±0.41	20±1.2	92.74 ± 0.83
F3	0.356±0.02	0.413±0.03	1.160±0.006	13.801±0.41	24.12±0.32	38±0.9	74.61 ± 0.32
F4	0.367±0.05	0.43±0.01	1.172±0.005	14.651±0.22	29.47±0.53	44±3.0	66.45 ± 0.29
F5	0.373±0.03	0.444±0.06	1.190±0.002	15.991±0.34	33.21±0.54	50±2.1	63.13 ± 0.15
F6	0.387±0.05	0.465±0.04	1.202±0.004	16.774±0.41	37.45±0.27	54±1.7	56.87 ± 0.34

#N=3± S.D.

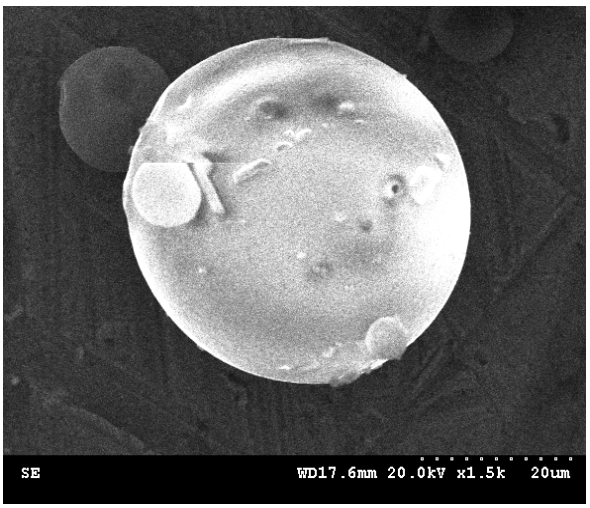

Figure 2: Scanning electron micrograph of RZ loaded EC microsphere.

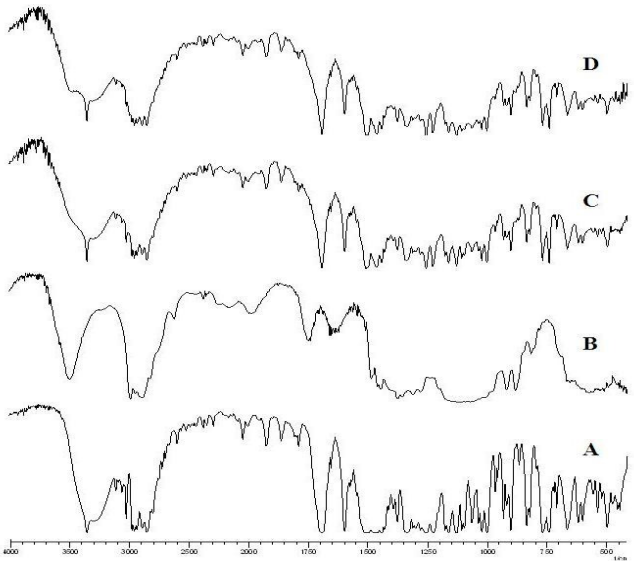

Figure 3: FTIR spectrum of pure RZ (A), EC polymer (B), Physical mixture of drug-EC polymer (C) and Drug loaded EC microsphere formulation (D)

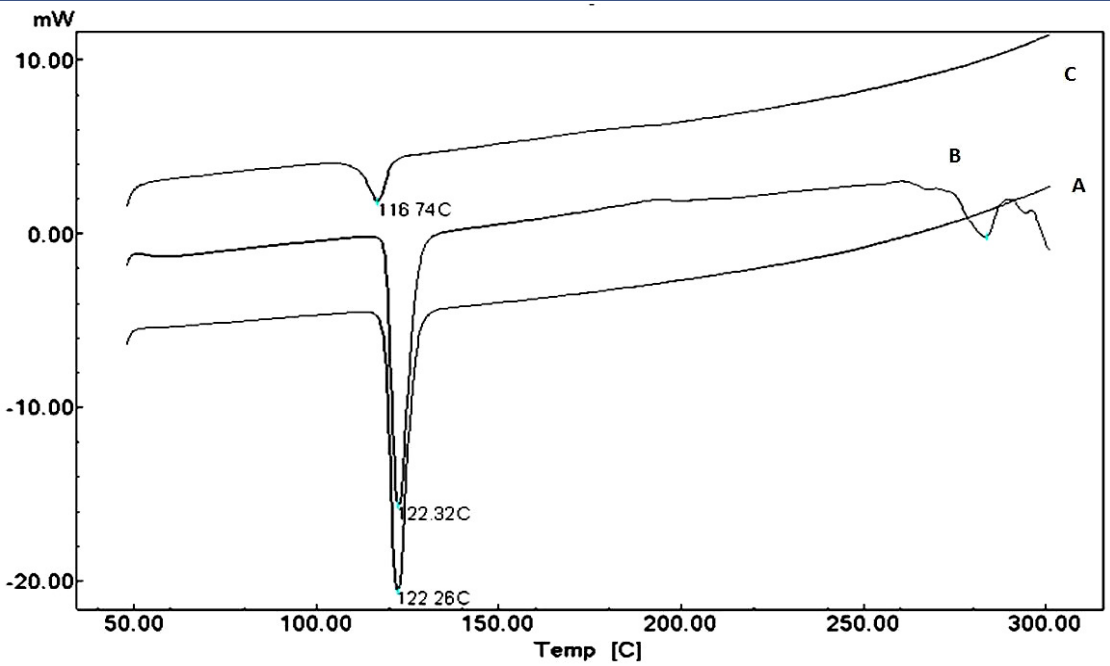

Figure 4: Comparative DSC thermogram of Pure RZ (A), Physical mixture drug-polymer (B), RZ loaded EC microspheres (C).

Table 4: *In-vitro* percent cumulative drug release of F2 microsphere formulation (Test sample) and marketed product (MP as a Reference sample)

Time (h)	Percent drug release of Test sample (T_t)#	Percent drug release of Reference sample (R_t)#
0	0	0
1	16.80±0.21	14.17±0.42
1.5	22.79±0.43	20.11±0.37
2	28.13±0.54	26.45±0.11
3	34.47±0.13	31.86±0.18
4	39.83±0.22	37.74±0.23
5	48.26±0.65	45.57±0.53
6	64.34±0.28	63.45±0.33
8	74.42±0.56	72.78±0.21
9	79.12±0.17	75.63±0.45
10	85.58±0.25	83.92±0.14
12	92.74±0.59	89.13±0.20

#N=3± S.D.

Table 5: Drug release kinetic parameters of different RZ loaded EC microspheres formulations.

Formulation Code	Zero order		First order		Higuchi		Hixson Crowell		Korsmeyer–Peppas	
	R^2	K0	R^2	K1	R^2	Kh	R^2	Khc	R^2	n
F1	0.962	6.841	0.982	-0.06	0.956	26.07	0.691	-0.257	0.984	0.773
F2	0.970	7.588	0.972	-0.072	0.969	28.96	0.665	-0.259	0.989	0.698
F3	0.969	6.51	0.991	-0.048	0.957	24.74	0.705	-0.256	0.990	0.822
F4	0.971	6.192	0.967	-0.049	0.948	23.39	0.732	-0.258	0.991	0.898
F5	0.984	5.314	0.993	-0.03	0.989	23.3	0.734	-0.245	0.990	0.899
F6	0.983	4.442	0.948	-0.027	0.889	16.13	0.775	-0.231	0.986	0.864

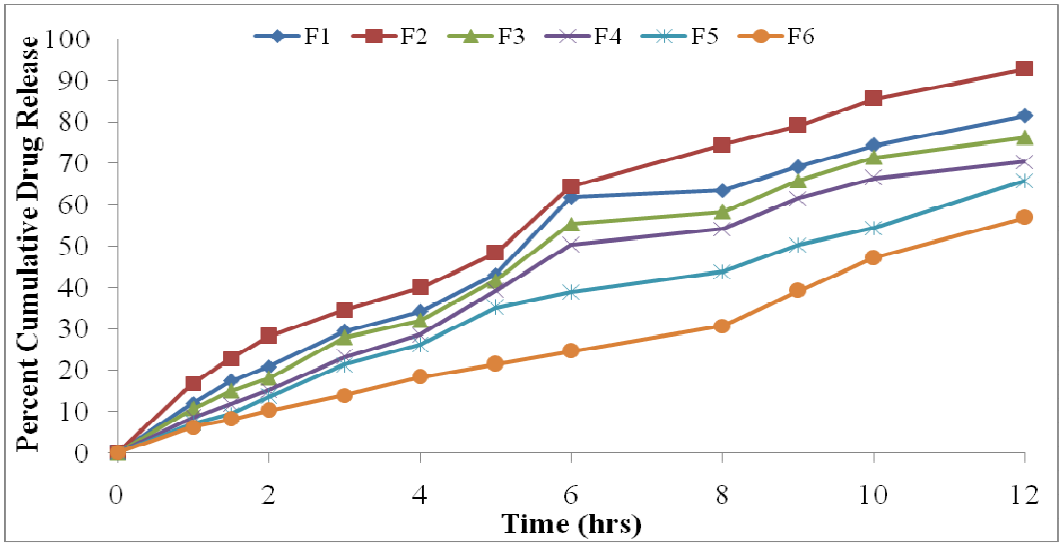

Figure 5: Comparative *in vitro* percent cumulative drug release profile of various RZ loaded EC microspheres formulations

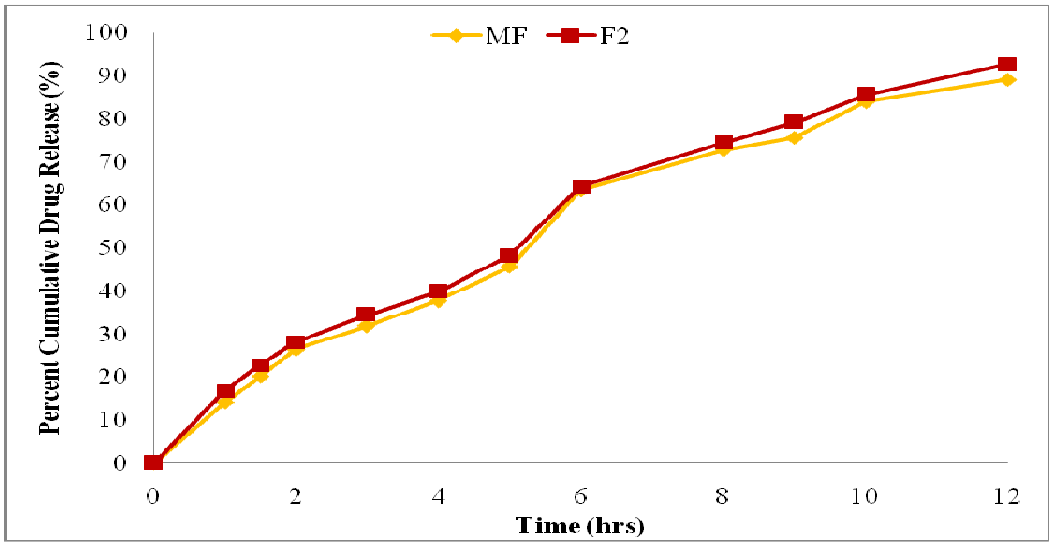

Figure 6: Comparative *in-vitro* dissolution study of F2 optimized microspheres formulation and MF.

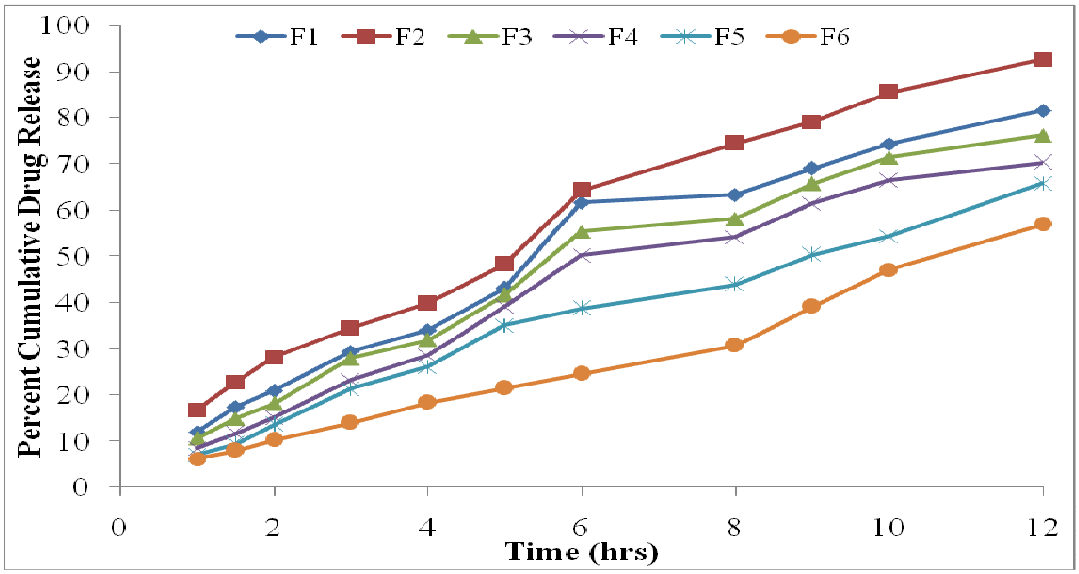

Figure 7: Zero order release model of RZ from RZ loaded EC microspheres.

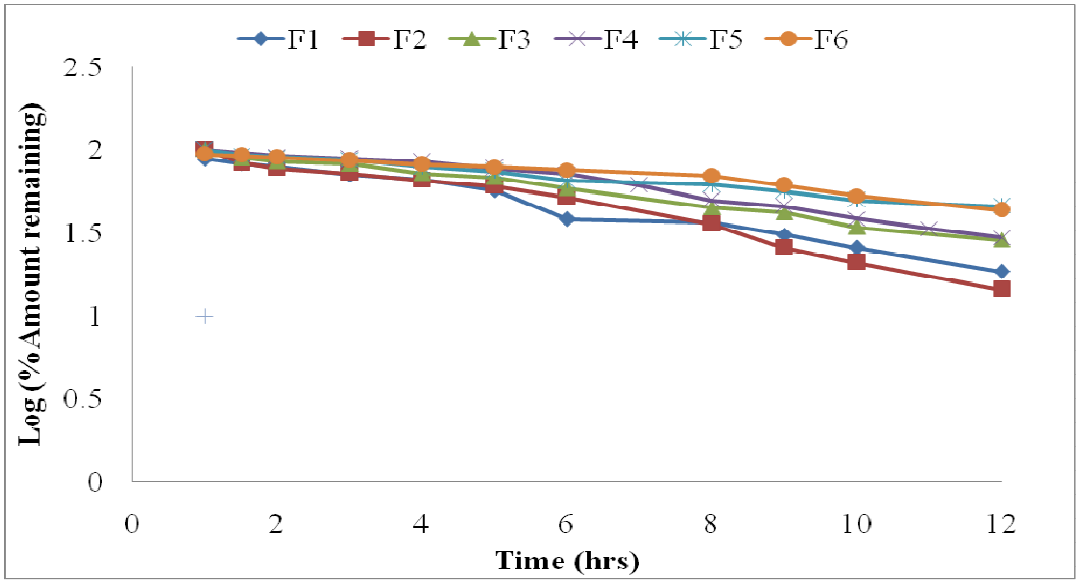

Figure 8: First order release model of RZ from RZ loaded EC microspheres.

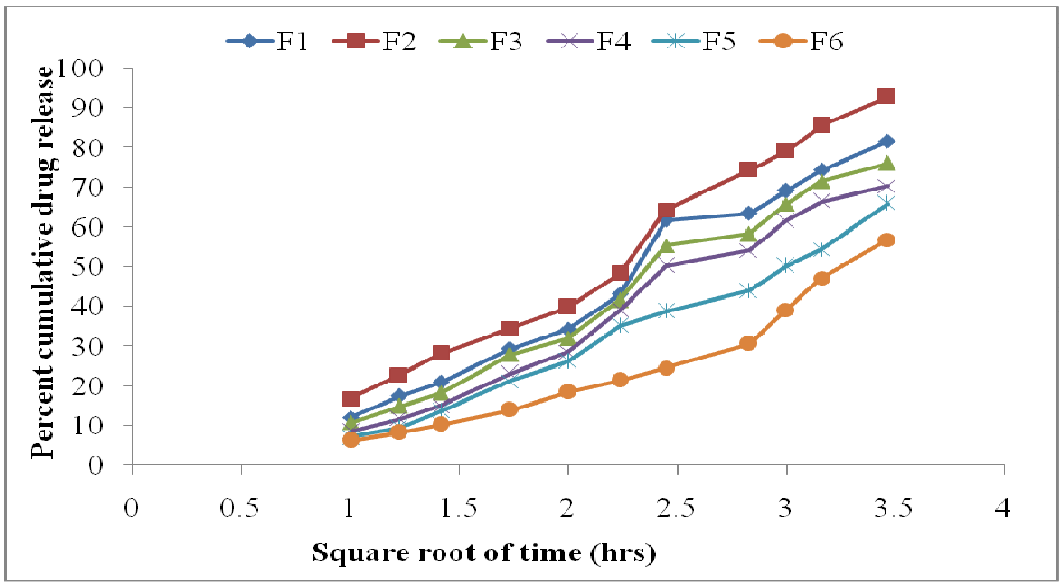

Figure 9: Higuchi release model of RZ from RZ loaded EC microspheres.

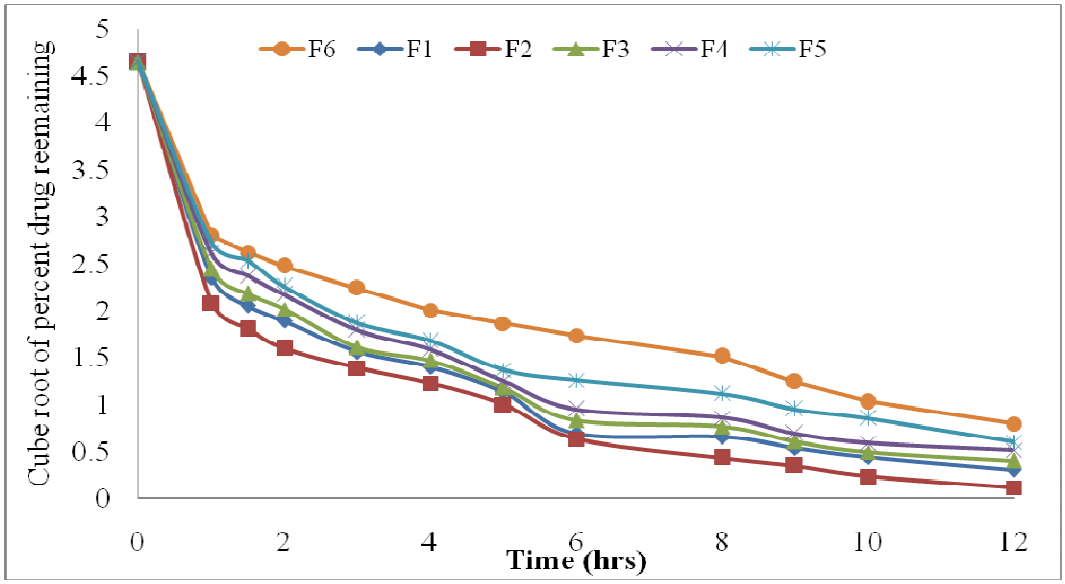

Figure 10: Hixson-Crowell cube root release model of RZ from RZ loaded EC microspheres.

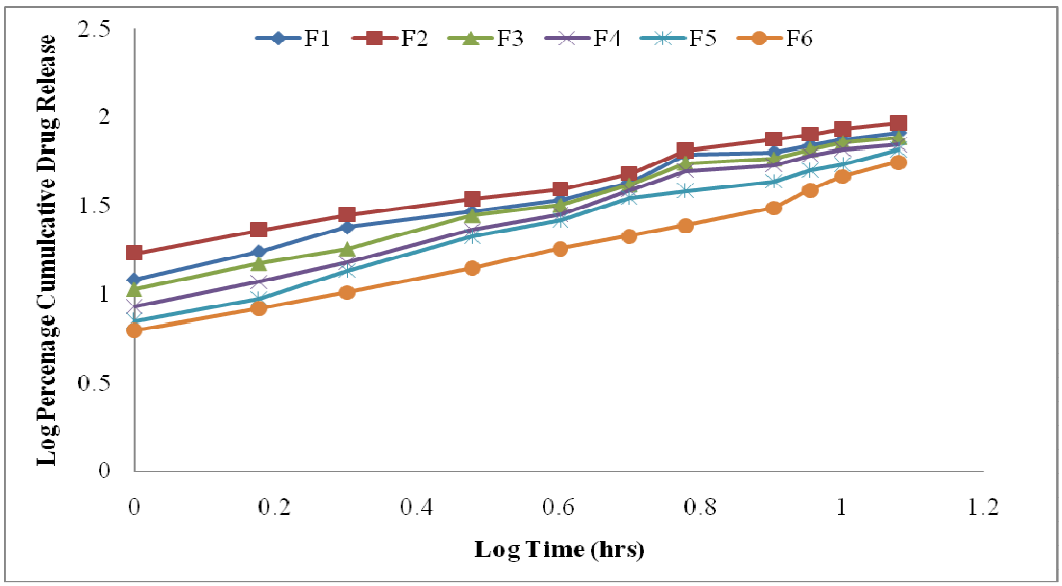

Figure 11: Korsmeyer-Peppas release model of RZ from RZ loaded EC microspheres.

Table 6: Stability data for optimized ACF loaded EC microspheres formulation.

Time Period (Months)	% Entrapment Efficiency#			% Drug Release (at 12 hrs)#			Physical appearance#		
	5± 2°C	25±2°C, 60±5% RH	40±2°C, 75±5% RH	5± 2°C	25±2°C, 60±5% RH	40±2°C, 75±5% RH	5± 2°C	25±2°C, 60±5% RH	40±2°C, 75±5% RH
0	85.76 ±0.78	85.76 ±0.78	85.76 ±0.78	92.74 ±0.83	92.74 ±0.83	92.74 ±0.83	-	-	-
2	85.41 ±0.05	85.38 ±0.03	85.32 ±0.03	92.49 ±0.18	94.47 ±0.39	92.45 ±0.30	-	-	-
3	85.25 ±0.03	85.29 ±0.05	85.27 ±0.02	92.37 ±0.32	94.29 ±0.31	91.95 ±0.21	-	-	-
4	85.10 ±0.04	85.11 ±0.04	85.01 ±0.05	92.30 ±0.43	91.91 ±0.77	91.72 ±0.32	-	-	-
6	85.03 ±0.05	84.77 ±0.02	84.51 ±0.04	92.09 ±0.24	91.73 ±0.03	90.87 ±0.07	-	+	+

N=3, (-) No change, (+) Slight change

Conclusion

Among the six formulations, F2 microspheres formulation provided reliable, reproducible results when compare to other microspheres formulations and MF with respect to percent entrapment efficiency, *in-vitro* release profile of drug for prolong period of time and stability study and also assured from output of results of kinetics of drug release employing EC polymer is suitable for preparing RZ microspheres by emulsion solvent diffusion evaporation technique which provides first order drug release kinetics. So the present oil-in-water emulsion diffusion solvent evaporation method significantly employed to develop microspheres of modify (retard) *in vitro* drug release. This may result in reduce the frequency of dose administration and improve the patient compliance.

Acknowledgement

The author thanks to GLA University for providing necessary facility to accomplish the research work, Central Electrochemical Research Institute (CECRI) Karaikudi, Tamil Nadu, India for instrumental facility and The author hearty thanks to Dr. Ranga Reddy, MSN Laboratories Ltd. Hyderabad, India for providing Ranolazine.

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Article History: ----------

Date of Submission: 17-08-2014

Date of Acceptance: 20-09-2014

Conflict of Interest: NIL

Source of Support: NONE