

Formulation Characterization and *In-Vivo* Anti-ischemic activity of Ranolazine loaded Ethyl Cellulose Microspheres in Albino Wistar Rats

Gupta Jitendra*^{1,3}

Mohan Govind ¹

Prabakaran L.²

*^{1,3}NIMS Institute of Pharmacy,
NIMS University, Jaipur-303121,
Rajasthan, India

²Department of Pharmaceutical
Science, ASIA Metropolitan
University Batu-9, 43200-Cheras,
Selangor, Malaysia.

³Institute of Pharmaceutical
Research, GLA University,
Mathura-281406, U.P., India

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 characterization and *in-vivo* antiischemic activity of RZ loaded ethyl cellulose microspheres in albino wistar rats. RZ microspheres were developed by oil-in-water (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 subjected for characterization by scanning electron microscopy (SEM), percent yield, Fourier transformer infra red spectroscopy (FTIR), X-ray diffraction (XRD), percent entrapment efficiency and percent drug release. The size of microspheres formulations (F1 to F6) were in range of 20 ± 1.2 to $54\pm 1.7\mu\text{m}$, percent yield 78.21 ± 2.31 to $94.24\pm 1.21\%$, percent drug entrapment efficiency 53.25 ± 0.65 to $85.76\pm 0.78\%$ and percent drug release 56.87 ± 0.34 to $92.74 \pm 0.83 \%$ up to 12 hrs. XRD and IR studies showed no interaction between drug and polymer; no degradation during microspheres preparation and stable at storage conditions. Then compare *in-vivo* activity of optimized F2 microspheres formulation to standard drug in 120-200g of Albino wistar rats of either sex. The results of present study reflect that successfully prepared free flowing RZ loaded EC microspheres and showed a significant reduction in level of cardiac biomarker LDH and CK-MB enzyme for prolong period of time with respect to standard in isoproterenol induced myocardial infarction (MI) rats.

Keywords: Anti-ischemic, Ranolazine, Isoproterenole.

Corresponding Authors:

Email: smartjitu79@gmail.com

Introduction

Now a day 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 sustained 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 CC(=O)N1CCN(C1)C2=CC=C(C=C2)C3=CC=C(C=C3)C4=CC=C(C=C4)C5=CC=C(C=C5)C6=CC=C(C=C6)C7=CC=C(C=C7)C8=CC=C(C=C8)C9=CC=C(C=C9)C10=CC=C(C=C10)C11=CC=C(C=C11)C12=CC=C(C=C12)C13=CC=C(C=C13)C14=CC=C(C=C14)C15=CC=C(C=C15)C16=CC=C(C=C16)C17=CC=C(C=C17)C18=CC=C(C=C18)C19=CC=C(C=C19)C20=CC=C(C=C20)C21=CC=C(C=C21)C22=CC=C(C=C22)C23=CC=C(C=C23)C24=CC=C(C=C24)C25=CC=C(C=C25)C26=CC=C(C=C26)C27=CC=C(C=C27)C28=CC=C(C=C28)C29=CC=C(C=C29)C30=CC=C(C=C30)C31=CC=C(C=C31)C32=CC=C(C=C32)C33=CC=C(C=C33)C34=CC=C(C=C34)C35=CC=C(C=C35)C36=CC=C(C=C36)C37=CC=C(C=C37)C38=CC=C(C=C38)C39=CC=C(C=C39)C40=CC=C(C=C40)C41=CC=C(C=C41)C42=CC=C(C=C42)C43=CC=C(C=C43)C44=CC=C(C=C44)C45=CC=C(C=C45)C46=CC=C(C=C46)C47=CC=C(C=C47)C48=CC=C(C=C48)C49=CC=C(C=C49)C50=CC=C(C=C50)C51=CC=C(C=C51)C52=CC=C(C=C52)C53=CC=C(C=C53)C54=CC=C(C=C54)C55=CC=C(C=C55)C56=CC=C(C=C56)C57=CC=C(C=C57)C58=CC=C(C=C58)C59=CC=C(C=C59)C60=CC=C(C=C60)C61=CC=C(C=C61)C62=CC=C(C=C62)C63=CC=C(C=C63)C64=CC=C(C=C64)C65=CC=C(C=C65)C66=CC=C(C=C66)C67=CC=C(C=C67)C68=CC=C(C=C68)C69=CC=C(C=C69)C70=CC=C(C=C70)C71=CC=C(C=C71)C72=CC=C(C=C72)C73=CC=C(C=C73)C74=CC=C(C=C74)C75=CC=C(C=C75)C76=CC=C(C=C76)C77=CC=C(C=C77)C78=CC=C(C=C78)C79=CC=C(C=C79)C80=CC=C(C=C80)C81=CC=C(C=C81)C82=CC=C(C=C82)C83=CC=C(C=C83)C84=CC=C(C=C84)C85=CC=C(C=C85)C86=CC=C(C=C86)C87=CC=C(C=C87)C88=CC=C(C=C88)C89=CC=C(C=C89)C90=CC=C(C=C90)C91=CC=C(C=C91)C92=CC=C(C=C92)C93=CC=C(C=C93)C94=CC=C(C=C94)C95=CC=C(C=C95)C96=CC=C(C=C96)C97=CC=C(C=C97)C98=CC=C(C=C98)C99=CC=C(C=C99)C100=CC=C(C=C100)C101=CC=C(C=C101)C102=CC=C(C=C102)C103=CC=C(C=C103)C104=CC=C(C=C104)C105=CC=C(C=C105)C106=CC=C(C=C106)C107=CC=C(C=C107)C108=CC=C(C=C108)C109=CC=C(C=C109)C110=CC=C(C=C110)C111=CC=C(C=C111)C112=CC=C(C=C112)C113=CC=C(C=C113)C114=CC=C(C=C114)C115=CC=C(C=C115)C116=CC=C(C=C116)C117=CC=C(C=C117)C118=CC=C(C=C118)C119=CC=C(C=C119)C120=CC=C(C=C120)C121=CC=C(C=C121)C122=CC=C(C=C122)C123=CC=C(C=C123)C124=CC=C(C=C124)C125=CC=C(C=C125)C126=CC=C(C=C126)C127=CC=C(C=C127)C128=CC=C(C=C128)C129=CC=C(C=C129)C130=CC=C(C=C130)C131=CC=C(C=C131)C132=CC=C(C=C132)C133=CC=C(C=C133)C134=CC=C(C=C134)C135=CC=C(C=C135)C136=CC=C(C=C136)C137=CC=C(C=C137)C138=CC=C(C=C138)C139=CC=C(C=C139)C140=CC=C(C=C140)C141=CC=C(C=C141)C142=CC=C(C=C142)C143=CC=C(C=C143)C144=CC=C(C=C144)C145=CC=C(C=C145)C146=CC=C(C=C146)C147=CC=C(C=C147)C148=CC=C(C=C148)C149=CC=C(C=C149)C150=CC=C(C=C150)C151=CC=C(C=C151)C152=CC=C(C=C152)C153=CC=C(C=C153)C154=CC=C(C=C154)C155=CC=C(C=C155)C156=CC=C(C=C156)C157=CC=C(C=C157)C158=CC=C(C=C158)C159=CC=C(C=C159)C160=CC=C(C=C160)C161=CC=C(C=C161)C162=CC=C(C=C162)C163=CC=C(C=C163)C164=CC=C(C=C164)C165=CC=C(C=C165)C166=CC=C(C=C166)C167=CC=C(C=C167)C168=CC=C(C=C168)C169=CC=C(C=C169)C170=CC=C(C=C170)C171=CC=C(C=C171)C172=CC=C(C=C172)C173=CC=C(C=C173)C174=CC=C(C=C174)C175=CC=C(C=C175)C176=CC=C(C=C176)C177=CC=C(C=C177)C178=CC=C(C=C178)C179=CC=C(C=C179)C180=CC=C(C=C180)C181=CC=C(C=C181)C182=CC=C(C=C182)C183=CC=C(C=C183)C184=CC=C(C=C184)C185=CC=C(C=C185)C186=CC=C(C=C186)C187=CC=C(C=C187)C188=CC=C(C=C188)C189=CC=C(C=C189)C190=CC=C(C=C190)C191=CC=C(C=C191)C192=CC=C(C=C192)C193=CC=C(C=C193)C194=CC=C(C=C194)C195=CC=C(C=C195)C196=CC=C(C=C196)C197=CC=C(C=C197)C198=CC=C(C=C198)C199=CC=C(C=C199)C200=CC=C(C=C200)C201=CC=C(C=C201)C202=CC=C(C=C202)C203=CC=C(C=C203)C204=CC=C(C=C204)C205=CC=C(C=C205)C206=CC=C(C=C206)C207=CC=C(C=C207)C208=CC=C(C=C208)C209=CC=C(C=C209)C210=CC=C(C=C210)C211=CC=C(C=C211)C212=CC=C(C=C212)C213=CC=C(C=C213)C214=CC=C(C=C214)C215=CC=C(C=C215)C216=CC=C(C=C216)C217=CC=C(C=C217)C218=CC=C(C=C218)C219=CC=C(C=C219)C220=CC=C(C=C220)C221=CC=C(C=C221)C222=CC=C(C=C222)C223=CC=C(C=C223)C224=CC=C(C=C224)C225=CC=C(C=C225)C226=CC=C(C=C226)C227=CC=C(C=C227)C228=CC=C(C=C228)C229=CC=C(C=C229)C230=CC=C(C=C230)C231=CC=C(C=C231)C232=CC=C(C=C232)C233=CC=C(C=C233)C234=CC=C(C=C234)C235=CC=C(C=C235)C236=CC=C(C=C236)C237=CC=C(C=C237)C238=CC=C(C=C238)C239=CC=C(C=C239)C240=CC=C(C=C240)C241=CC=C(C=C241)C242=CC=C(C=C242)C243=CC=C(C=C243)C244=CC=C(C=C244)C245=CC=C(C=C245)C246=CC=C(C=C246)C247=CC=C(C=C247)C248=CC=C(C=C248)C249=CC=C(C=C249)C250=CC=C(C=C250)C251=CC=C(C=C251)C252=CC=C(C=C252)C253=CC=C(C=C253)C254=CC=C(C=C254)C255=CC=C(C=C255)C256=CC=C(C=C256)C257=CC=C(C=C257)C258=CC=C(C=C258)C259=CC=C(C=C259)C260=CC=C(C=C260)C261=CC=C(C=C261)C262=CC=C(C=C262)C263=CC=C(C=C263)C264=CC=C(C=C264)C265=CC=C(C=C265)C266=CC=C(C=C266)C267=CC=C(C=C267)C268=CC=C(C=C268)C269=CC=C(C=C269)C270=CC=C(C=C270)C271=CC=C(C=C271)C272=CC=C(C=C272)C273=CC=C(C=C273)C274=CC=C(C=C274)C275=CC=C(C=C275)C276=CC=C(C=C276)C277=CC=C(C=C277)C278=CC=C(C=C278)C279=CC=C(C=C279)C280=CC=C(C=C280)C281=CC=C(C=C281)C282=CC=C(C=C282)C283=CC=C(C=C283)C284=CC=C(C=C284)C285=CC=C(C=C285)C286=CC=C(C=C286)C287=CC=C(C=C287)C288=CC=C(C=C288)C289=CC=C(C=C289)C290=CC=C(C=C290)C291=CC=C(C=C291)C292=CC=C(C=C292)C293=CC=C(C=C293)C294=CC=C(C=C294)C295=CC=C(C=C295)C296=CC=C(C=C296)C297=CC=C(C=C297)C298=CC=C(C=C298)C299=CC=C(C=C299)C300=CC=C(C=C300)C301=CC=C(C=C301)C302=CC=C(C=C302)C303=CC=C(C=C303)C304=CC=C(C=C304)C305=CC=C(C=C305)C306=CC=C(C=C306)C307=CC=C(C=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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 (drugs) coated with an aqueous insoluble coat (polymer) by emulsion solvent diffusion evaporation technique for sustain release drug delivery system [10].

EC being insoluble in water extensively used for preparation of microcapsule serves as good candidate for water insoluble drug to achieve sustained release drug delivery systems. The study was previously performed using different solvents like dichloromethane, ethyl acetate and chloroform, employed in preparation of microcapsules of diclofenac sodium as a core material to coat with aqueous insoluble EC as a coat material to investigate the effects of solvent on drug release because such solvent enhance the both permeability and drug release profile from microcapsules [11-13].

Therefore, the objective of the present research work to formulation characterization and in-vivo antiischemic activity of RZ loaded ethyl cellulose microspheres in albino wistar rats. So we can

achieve modified sustained release drug profile by release rate retarding polymer and reduce the frequency of dose administration result in improve the patient compliance.

MATERIAL AND METHOD

Ranolazine as a gift sample was procured from MSN Laboratories Ltd. Hyderabad, India. Isoproterenol was procured from Unichem laboratories, 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 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 (table 1, 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].

Characterization of RZ loaded EC microspheres formulation

Percent Yield:

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

$$\% \text{ Yield} = \left[\frac{\text{Weight of microspheres}}{\text{Total weight of drug and polymer}} \right] \times 100$$

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 resulting mixture was sonicated and agitated on a mechanical shaker for one day, filtered through whatman filter (0.45 μ m), and then measured the absorbance using a UV/VIS double beam spectrophotometer (Shimadzu UV-1700, Japan) after suitable dilution at 274nm and calculate percent entrapment efficiency (%EE) by using following formula and each determination was made in triplicate [15-17].

$$\text{Entrapment Efficiency (\%)} = \left(\frac{A_d}{T_d} \right) \times 100$$

Where, A_d - Actual drug content, T_d - Theoretical 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[12].

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 vacuum 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.

Fourier Transformer Infrared (FTIR) spectroscopy 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 vacuum 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.

X-Ray Diffraction study

To investigate the effect of microsphere process on crystallinity of the drug carried out X-ray powder diffraction analysis. The XRD patterns of pure Ranolazine, ethyl cellulose and drug-loaded microspheres were recorded. Before scanning, samples were triturated and convert in to fine powder. Powder XRD patterns were determined by using X-ray diffraction (XRD), Philips Analytical X-RD (Model: PW 3710, Holland) using Ni-filtered, CuK α radiation, a voltage of 40 Kv voltages, and a current of 30 mA at room temperature. The samples were loaded on to the diffractometer and scanned over range of 2 θ values from 10° to 80° at a scan rate of 0.05°/0.4 sec.

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 \pm 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 [19].

***In Vivo* Anti-ischemic/Anti-anginal activity:**

Experimental animals:

The *in vivo* anti-ischemic/anti-anginal activity was performed by using isoproterenol induced myocardial necrosis. [20]. The protocol of the present work was approved by Institutional Animal Ethical Committee, Institute of Pharmaceutical Research, GLA University, Mathura, Uttar Pradesh, India(Ref.No.GLAUIPR/IAEC/1260/09/ac/CPCSEA). The animals were grouped and housed in standard poly acrylic cages (38x23x10 cms) with not more than four animals per cage and maintained standard laboratory conditions at room temperature (27±2°C; relative humidity 44-56%) with natural dark and light cycle (12 hr light-dark cycle). The rats were given a standard laboratory diet (Golden Feeds, India) and *ad libitum* for one week before and during the experiments. The animals were acclimatized one week before start the experiment.

Experimental Protocol and Biochemical Assay:

The animals were randomly selected divided into four groups and each group subdivided in to two

subgroups containing six Albino rats (wistar strain) of either sex of 6–8 weeks of age, each weighing 120+20g fasted over night. The experiments were performed at constant temperature. Care was taken that the animals have minimal stress [21,22,23]. The experiments were also performed daily between 9 AM to 14 PM to avoid effects of circadian rhythms [24].

Group I-a, Group I-b served as control and received normal saline, group II-a, group II-b served as a negative control and were administered Isoproterenol (85mg/kg body weight s.c.) at an interval of 24 hrs for two consecutive days to induce ischemia [20]. Group III-a and group III-b received Ranolazine (20mg/k body weight p.o.) [25] as a standard drug for 7 days and then injected with isoproterenol (85 mg/Kg, s.c.) on 6th and 7th day. Group IV-a, group IV-b served as treated group and administered optimized F2 microspheres formulation (108 mg/kg/day, p.o.) after dispersion in normal saline for 7 days and then injected with isoproterenol (85 mg/Kg, s.c.) on 6th and 7th day [26,27]. In each group the symptoms and mortality was recorded and then compared with negative control group. Rats were sacrificed at different sampling time interval by cervical decapitation, collected the blood samples via puncture of heart aorta using anticoagulant (Sodium citrate 3.8%w/v) and the serum was separated immediately in cold condition and used for estimation of biomarker enzyme. The biomarker enzyme Lactate dehydrogenase (LDH) was analyzed in serum employing standard kit of LDH, AUTOSPAN, Surat, India. The heart was excised immediately and washed with chilled isotonic saline. The homogenate of tissue with 0.1 M Tris-HCl buffer (pH 7.2) was prepared and employed for the assay of CK-MB clinical cardiac biomarker enzyme using

standard kit of CK-MB, AUTOSPAN, Surat, India [28,29,30]

Statistical analysis

The results of pharmacological studies were expressed as Mean \pm S.D. The total variations present in data were evaluated by using Graph Pad Prism 5 project software one way ANOVA (analysis of variance) followed by Dunnett's Test. The result were considered statistically significant when P value less than 0.05 ($P < 0.05$) vs control.

Stability Studies

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 $5 \pm 2^\circ\text{C}$, $25 \pm 2^\circ\text{C}/60 \pm 5\%$ RH and $40 \pm 2^\circ\text{C}/75 \pm 5\%$ RH to check the effects of temperature and RH on percent entrapment efficiency and physical appearance 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 and physical appearance [31-33].

Result and discussion

The various Ranolazine loaded EC microspheres formulations F1 to F6 were prepared by emulsion solvent evaporation diffusion technique. 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 $94.24 \pm 1.21\%$. Out of six formulations, F2 formulation showed highest yield ($94.24 \pm 1.21\%$). 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 $85.76 \pm 0.78\%$, result shown in table 2.

From the SEM investigation (fig 2) free flowing and spherical shape microspheres were found and indicate $20 \pm 1.2 \mu\text{m}$ particles size. The particle size of various microspheres formulations were depicted in table 2.

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.

For study of crystalline change of drug employed XRD analysis. XRD of pure RZ, drug loaded EC microspheres and EC polymer shown in Fig 4. The diffraction spectrum of pure RZ showed that the

drug was of crystalline nature as demonstrated by numerous characteristic prominent sharp peaks at 2θ of 10.1° , 10.40° , 12.26° , 14.36° , 15.00° , 16.5° , 19.34° , 21.41° , 23.44° , 24.65° , 25.45° , 27.26° , 30.21° , 31.26° and 43.72° etc. XRD patterns of pure drug compared to XRD patterns of drug loaded EC microspheres, found that the observe peaks of drug loaded EC microspheres formulation was similar to peak of pure drug but of low intensity, confirm the presence of drug in polymer matrix either entrapped or dispersed.

The *in-vitro* drug release profile of drug loaded EC microsphere formulations studied in different dissolution medium for dissolution study. 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 % (fig 5, table 2) but F2 formulation indicated highest drug release 92.74 ± 0.83 % up to 12 hrs 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. So F2 formulation considered as a best and further subjected for *in-vivo* study.

In vivo antiischemic/antianginal activity was performed by using isoproterenol induce myocardial necrosis. Figure 6 and 7 indicates levels of LDH and CK-MB in various treated experimental groups respectively. A significant enhancement in the level of LDH and CK-MB were found in isoproterenol induced rats. This may be due to metabolic damage of myocardium result in enhancing the release of LDH and CK-MB enzymes [34]. The specific marker enzymes are responsible for specific function of tissue. The myocardial damage releases the CK-MB enzyme so as well as increase the concentration of it in serum indicates decrease in activity of heart tissue

function [35]. Initially decrease in level of LDH, CK-MB as well as rapidly increase in concentration of standard drug in body in comparison to drug release from RZ loaded EC microspheres up to 2 hrs. After first half life, effect of standard drug was not higher due to decrease in concentration of drug in body. But gradually increase in concentration of drug due to sustain release of ranolazine from sustain release optimized F2 microspheres formulation up to 12 hrs showed significant reduction in level of cardiac biomarker LDH and CK-MB enzyme at 12 hrs with respect to standard in isoproterenol induced myocardial infraction (MI) rats. Isoproterenol induce myocardial necrosis reliable and acts as a standard MI model to analyzed the beneficial effects of many antianginal/antiischemic drugs and for function of heart because this model mimics the clinical conditions of MI due to ischemia in human [36].

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 and physical appearance of drug loaded EC microspheres formulations.

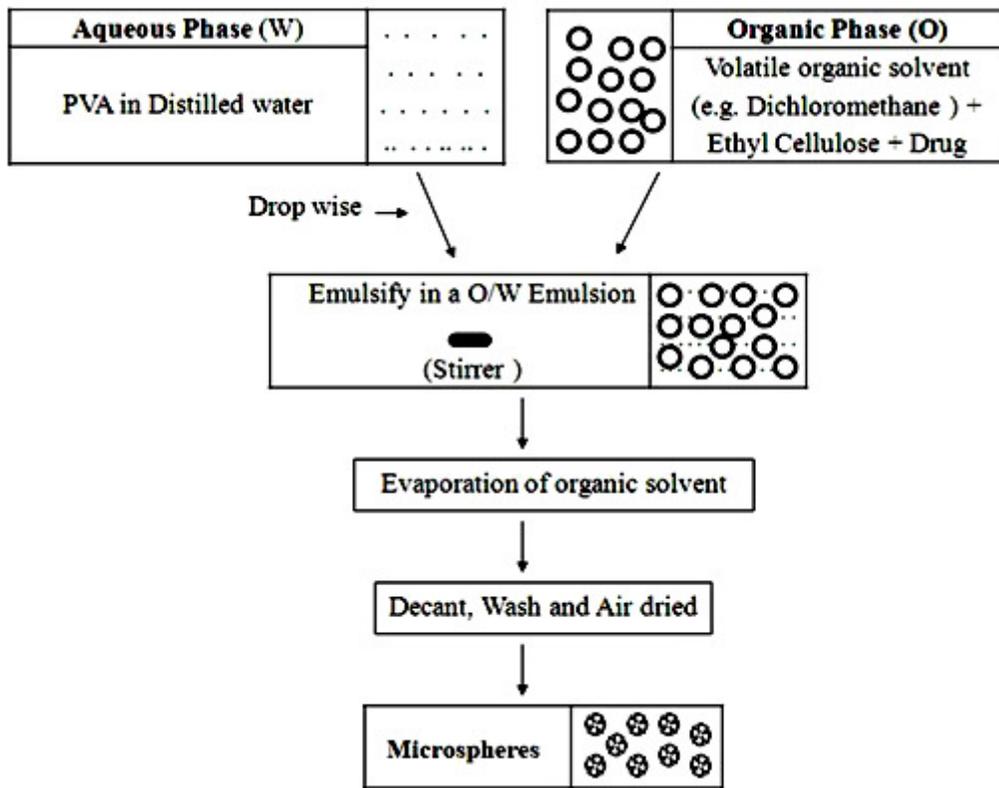


Figure 1: Schematic diagram of Oil-in-Water (o/w) emulsion solvent evaporation diffusion method for preparation of microspheres.

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

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

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

Table 2: Percentage yield and percent entrapment efficiency, mean particle size and percent cumulative drug release of various RZ loaded EC microspheres formulations

Formulation	Percent yield [#]	Entrapment Efficiency (%) [#]	Mean Particle Size (µm) [#]	Cumulative Drug Release (%) [#]
F1	F1	81.63±2.14	70.57±0.57	33±2.3
F2	F2	94.24±1.21	85.76±0.78	20±1.2
F3	F3	90.64±2.16	73.13±0.45	38±0.9
F4	F4	87.02±1.03	67.54±0.87	44±3.0
F5	F5	78.21±2.31	62.36±1.03	50±2.1
F6	F6	80.35±1.20	53.25±0.65	54±1.7

[#]N=3±S.D.



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

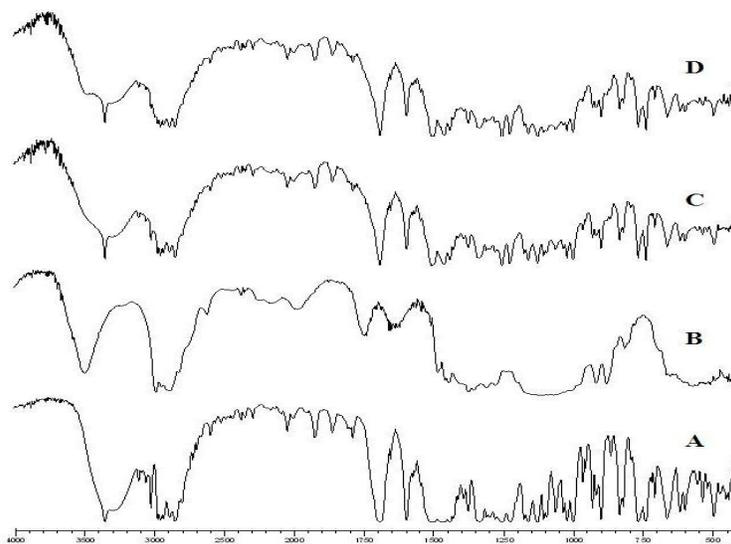


Figure 3: FTIR spectrum of pure RZ (A), EC polymer (B), Physical mixture of drug-EC polymer (C) and Drug loaded EC microsphere formulation (D)

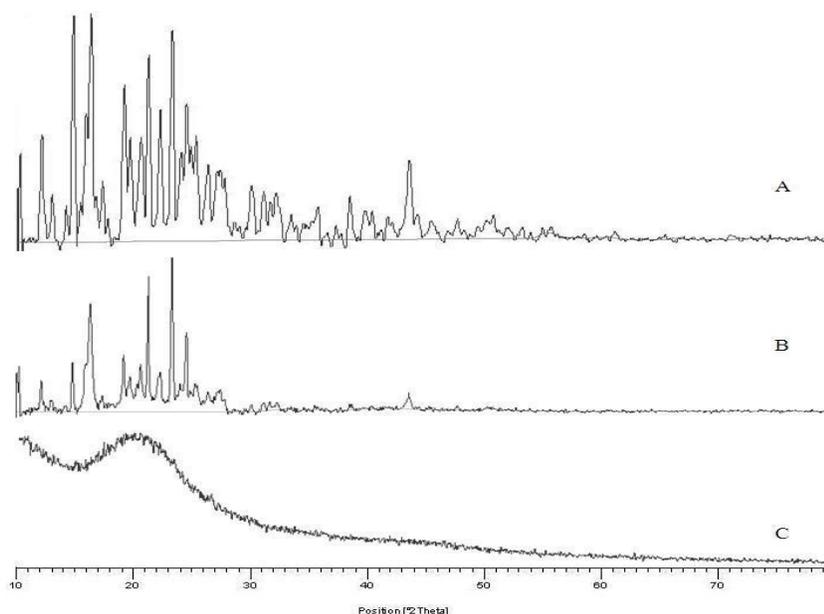


Figure 4: XRD spectra of pure RZ (A), RZ loaded EC microspheres (B), EC polymer (C)

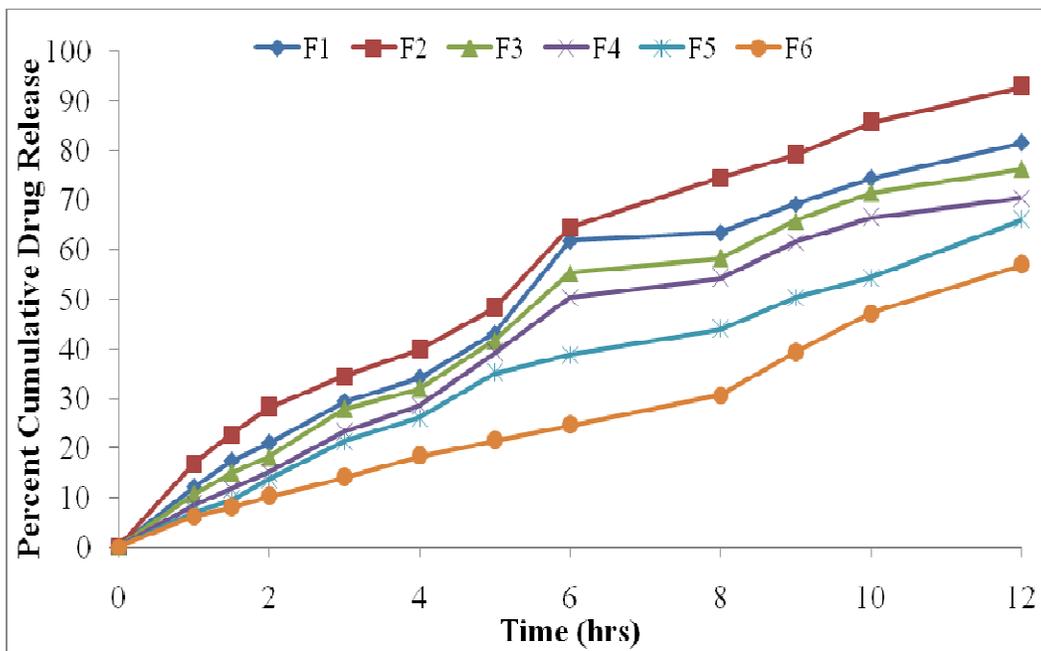
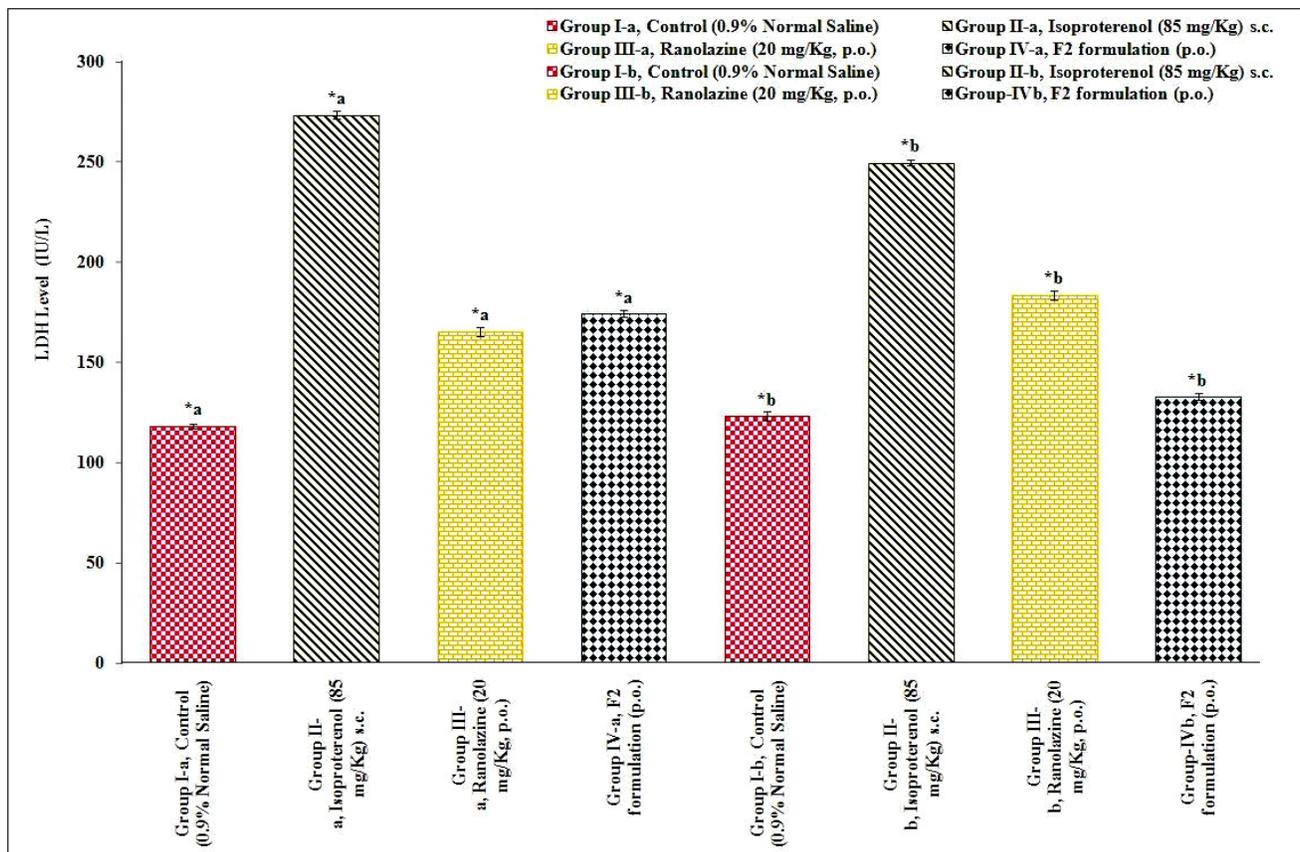
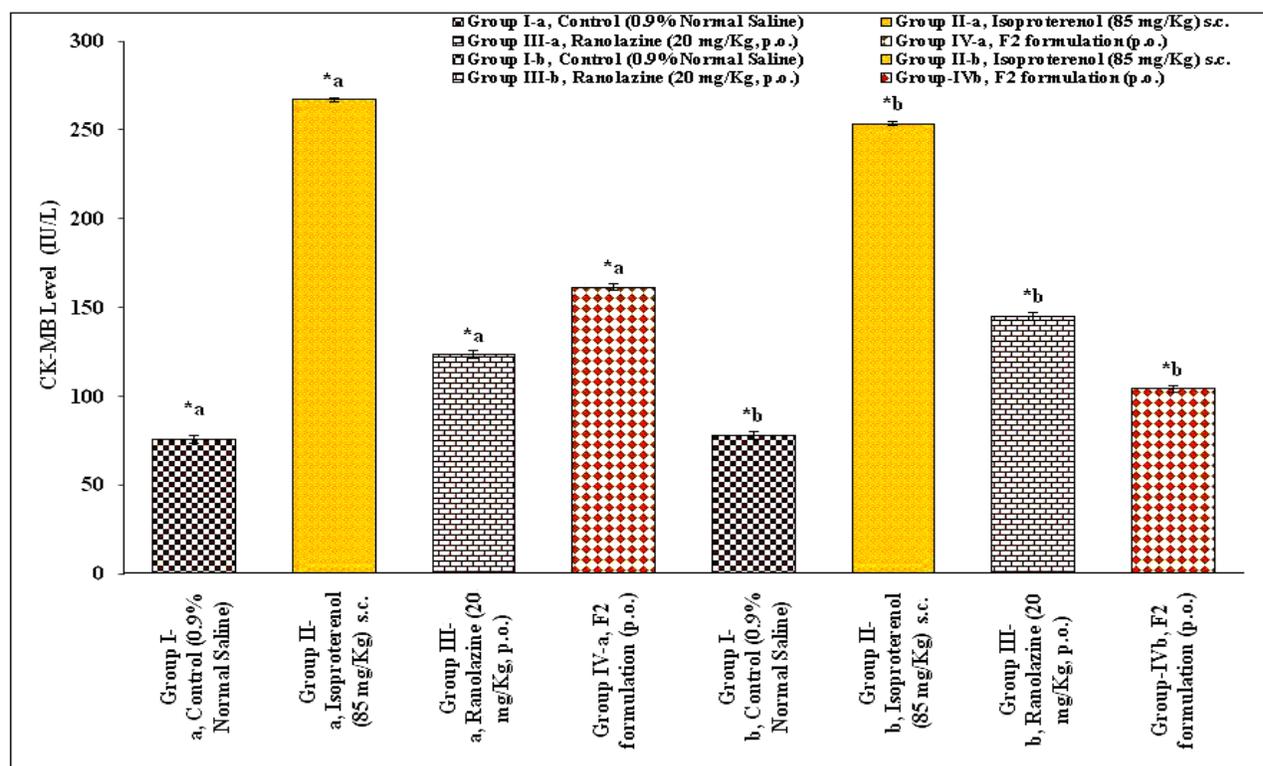


Figure 5: Comparative *in-vitro* percent cumulative drug release profile of various RZ loaded EC microspheres formulations.



#Mean \pm S.E.M., N=6, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ for comparison of treated groups vs control, a- LDH level at 2 hrs, b- LDH level at 12 hrs.

Figure 6. Effect of standard pure Ranolazine and optimized F2 microspheres formulation on LDH level biomarker enzymes of various experimental rats.



#Mean \pm S.E.M., N=6, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ for comparison of treated groups vs control, a- CK-MB level at 2 hrs, b- CK-MB level at 12 hrs.

Figure 7: Effect of standard pure Ranolazine and optimized F2 microspheres formulation on CK-MB cardiac marker enzymes of various experimental rats.

Conclusion

Among the six formulations, F2 microspheres formulation provided reliable, reproducible results when compare to other microspheres formulations with respect to percent entrapment efficiency, *in-vitro* release profile of drug for prolong period of time, stability study and also assured from output of results of *in vivo* anti-ischemic/antianginal activity of modified release RZ microspheres developed by emulsion solvent diffusion evaporation technique that shows a significant reduction in level of cardiac biomarker LDH and CK-MB enzyme for prolong period of time with respect to standard in isoproterenol induced myocardial infraction (MI) rats. This may result in reduce the frequency of dose administration and improve the patient compliance.

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