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Design And Evaluation Of Self Emulsifying Mouth Dissolving Film Of Ranolazine By Solvent Casting Method

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ABSTRACT

A novel self-emulsifying mouth dissolving film (SEMDF) containing ranolazine (RZ) is being produced in the current study with the aid of a mouth dissolving film (MDF) mixed with self-emulsifying components. Using a solvent casting process, the films for ranolazine were made from the water-soluble polymer HPMC K15M. Ethyl oleate was used as the oil phase, Tween 80 as the surfactant, PEG 400 as the co-surfactant, and distilled water as the solvent to create the pseudoternary phase diagram (aqueous phase). There are ten different possible surfactant mixture to oil combinations with different Km values for the phase diagram investigation of RZ SEDDS (1, 2, 3, and 4 were employed). The phase diagram at Km value 3 shows better microemulsion existence zones when compared to Km values 1, 2, and 4. In this study, a 3^2-factorial design was used to evaluate two factors at each of three levels, and experimental batches were conducted in all conceivable combinations. In testing of their physical characteristics, such as uniformity of weight, thickness, folding durability, drug content uniformity, surface pH, and tensile strength, the developed mouth-dissolving films functioned satisfactorily. The formulations underwent disintegration, *in-vitro* drug release testing, and stability studies. The FTIR and DSC analyses showed no physicochemical interaction between the excipients and the medicine. F5 showed a maximal drug release of 93.85% at 5 minutes. Studies on stability demonstrated the dependability of the modified formulation. When a dosage form must have a quicker onset of action and be suitable for administration, ranolazine self-emulsifying mouth dissolving film (SEMDF) might be viewed as an anti-anginal formulation.

Keywords: Ranolazine, Self-emulsifying, Mouth dissolving film, Pseudo ternary phase Factorial design, Solvent casting method

INTRODUCTION

More than 40% of recently developed chemical entities are essentially insoluble in water. To be absorbed, the medication needs to be present in solution form at the absorption site. Solubility, then, represents a considerable challenge for formulation scientists[1]. Poor solubility and ineffective medication absorption contribute to low bioavailability, which also jeopardises the product's efficacy and safety[2]. The complex structure, size, high molecular weight, high lipophilicity, compound H-bonding to solvent, intramolecular H-bonding, intermolecular H-bonding (crystal packing), crystallinity, polymorphic forms, ionic charge status, pH, and salt form of drugs are a few physicochemical factors that contribute to their poor solubility[3]. To improve their solubility, dissolution rate, and absorption, various methods have been used, including particle size reduction, nanonization, Co-solvency, Hydrotropy, pH adjustment, so no-crystallization, the supercritical fluid (SCF) process, solid dispersion, inclusion complexation, self-emulsifying or self-micro emulsifying systems, liquid-solid methods, etc.[4]. Self-emulsifying drug delivery systems are a popular and economically sound formulation choice for tackling these problems. SMEDDs can dramatically improve the oral bioavailability and solubility of medications that are only marginally water soluble[5]. The primary elements of SMEDDS are drug, oil, surfactant, co-surfactant, and co-solvents. This dosage form's basic concept is to interfere with drug absorption to increase bioavailability by forming microscopic oil-in-water (o/w) microemulsions with light agitation after aqueous phase dilution[6, 7]. Mouth dissolving film (MDF) is a convenient dosage form that dissolves in the mouth without chewing in a few minutes, enhancing the onset of therapeutic action and increasing treatment efficacy. The objective of this work was to develop a novel self-emulsifying mouth dissolving film (SEMDF) based on an MDF with integrated self-emulsifying components. Quick drug release, great potential for improving oral dissolution and bioavailability of poorly water-soluble drugs, no need for water during administration, the potential for taste masking, the absence of choking risk, high patient compliance, flexibility and portability for ease of handling, and the avoidance of first past metabolism are all advantages of SEMDF[8]. An anti-anginal medication called ranolazine (RZ) is used to treat a number of cardiovascular conditions. The biochemical classification system places it in class II, which is characterised by low solubility and high permeability. Due to its low solubility in biological fluids, the drug's poor oral bioavailability is one of its key problems. Ranolazine poor dissolution and limited solubility reduce its bioavailability. Therefore, it is critical to improve ranolazine solubility and water dissolution for medicinal purposes. Ranolazine aqueous solubility and dissolution can be improved by formulating it in SEDDS[9].

MATERIALS AND METHODS

Materials

We received a complimentary sample of ranolazine from Unichem Laboratories Ltd. in Goa, India. The following ingredients were purchased from Loba Chemie Pvt. Ltd., Mumbai: ethyl oleate, PEG 400, PEG 600, isopropyl myristate, and tween 80. The supplier of the hydroxy propyl methyl cellulose (K 15M) was Colorcorn Asia Pvt. Ltd. in Verna, Goa. From Molychem Pvt. Ltd., Mumbai, we acquired citric acid and propylene glycol. From Mumbai's Hi Media Pvt. Ltd., aspartame was purchased.

Methods

Determination of saturation solubility of ranolazine in oils, surfactants and co-surfactants

Oils such as oleic acid, ethyl oleate, isopropyl myristate, and castor oil, as well as surfactants like Tween 80, Tween 20, and Span 20, and cosurfactants like PEG 200, PEG 400, and PEG 600, were all used to test ranolazine saturation solubility. Excess RZ was added to a vial holding 2mL of each selected solvent. Following sealing, the liquid was vortexed using a cyclomixer for 10min to make sure that the vehicles and ranolazine were properly mixed. Mixtures were kept at room temperature for 72hours to attain equilibrium in an orbital shaking incubator before being centrifuged at 2000 rpm for 15 minutes. Mixtures were kept at room temperature for 72 hours to attain equilibrium in an orbital shaking incubator before being centrifuged at 2000 rpm for 15 minutes and filtered through a membrane filter (0.45 mm). After aliquots of supernatant were diluted with methanol, the drug concentration was assessed using a UV-visible double beam spectrophotometer (Jasco V-630) against methanol as a blank solution at max 272 nm. Three measurements were taken for each measurement[10, 11].

Pseudo-ternary phase diagram

Using the water titration method at room temperature, the homogenous liquid mixture of oil, surfactant, and co-surfactant was added drop by drop to produce the pseudo-ternary phase diagrams. Based on the outcomes

of solubility tests and excipients screening, ethyl oleate, tween 80, and PEG 400 were selected as the oily phase, surfactant, and co-surfactant, respectively. The appropriate mixture (Smix), corresponding to the chosen surfactant to co-surfactant ratio (Km), was formed. At the necessary Km values (1:1, 2:1, 3:1, and 4:1), Smix and oil were blended in a test tube at the following ratios: 0.5:1, 1:1, 1.5:1, 2:1, 2.5:1, 3:1, 3.5:1, 4:1, 4.5:1, and 5:1. (Table V and Fig.1 a-d). Double distilled water was gradually added to the resulting mixtures until the first sign of turbidity appeared in order to ascertain the endpoint and equilibrium. The water addition was then restarted if the system became clear. Visual inspection of the combinations' ability to flow and exhibit distinct phases was performed once perfect equilibrium had been reached[12].

Preparation of liquid self-emulsifying drug delivery system (SEDDS)

The phase diagrams were created using a variety of Km values, and the Km value that produced the largest microemulsion area was selected for further study. Four formulations were selected from this microemulsion zone and used in additional evaluation experiments. Calculations were made to determine the proportions of water, oil, and surfactant/co-surfactant concentration in each formulation. Weighing out the proper proportions of oil, surfactant, and co-surfactant, they were then combined with gentle stirring. According to its solubility in the formulation amount, ranolazine was dissolved into the mixture of oil and surfactants. The ranolazine was then thoroughly dissolved by combining the components at 37ºC were using a combination of gentle stirring and vortex mixing. After sealing the glass vial, the solution was added there and stored until required[13].

Evaluation of liquid self-emulsifying drug delivery system (SEDDS)

Dilution and self-emulsification study

In this study, selected formulations were diluted in distilled water at several ratios (1: 10, 1:50, and 1:100), and the formulations were then rated visually. The SEDDS's emulsification time was calculated using the USP Dissolution Test Apparatus Type II. 300 mg of each formulation were added drop wise to 500 ml of pure water that had been boiled to 37°C. A simple dissolving paddle made of stainless steel that rotated at 50 rpm offered light agitation. A visual measurement of emulsification time was made[14].

Thermodynamic stability study of SEDDS

Using freeze-thaw, the formulations' stability was evaluated. Three to four cycles of freezing and thawing, including a 24-hour period of freezing at - 4°C and a 24-hour period of thawing at 40°C, were performed on the formulations. At 3000 rpm, 5 minutes of centrifugation were completed. The formulations were then examined for evidence of phase separation. For subsequent research, only formulations that could tolerate phase separation were chosen[15]. **Globule size determination**

Using the lesser light scattering method, the Malvern zetasizer was utilised to gauge the microemulsions average droplet size, size distribution, and polydispersity index[16] (Nano-ZS, Malvern Instruments, and U. K).

Zeta potential analysis

By using electrophoretic mobility in a Malvern Zetasizer device (Malvern Instruments, UK) outfitted with the appropriate software and calibrated with the provided standard, the zeta potential of the Microemulsion droplet surface was ascertained. At 25ºC three measurements are made back-to-back with a constant cell drive of 150 mV. Using the dielectric constants and viscosity of the dispersion medium, the Smoluchowsky equation transforms the electrophoretic mobility into zeta potential values[16].

Preparation of self emulsifying mouth dissolving film

The solvent casting method was used to create the ranolazine mouth dissolving film. Cold water was used to dissolve water-soluble polymers, such as HPMC K15M, and create a homogeneous viscous solution while being simultaneously stirred at 1000 rpm. The viscous mixture is maintained at room temperature. Following this, an emulsion comprising the API ranolazine, the plasticizer glycerol, and other chemicals such as aspartame was added. It was combined with a flavoring agent (orange flavor) and citric acid. For defoaming, the final film solution was cast on a typical petri dish. For three hours, it was dried in the hot air oven at 40° C. The film was carefully taken out of the petri dish, examined for flaws, and sliced to the proper size ($2x2cm^2$) per strip to administer the prescribed dose. The samples were placed in a desiccator until further analysis[17] Table III.

Factorial design

In this work, a 3^2-factorial design was employed to examine two factors at each of three levels, and experimental batches were run in all possible combinations. Tensile strength and cumulative% drug release were chosen as dependent variables, whilst HPMC K4M (X1) and glycerol (X2) amounts were chosen as independent factors. In PCP Disso 2.08, 3-D response surface methodology was applied to the data to ascertain the impact of the types and concentrations of polymers on the various dependent variables Table I displays the whole factorial experimental design arrangement. Table II shows the values of the variables in a 3^2Factorial Design. The responses were computed using a statistical model with interactive and polynomial terms.

$Y=b_0+b_1X_1+b_2X_2+b_{12}X_1X_2+b_{11}X_1X_1+b_{22}X_2X_2+\epsilon$

In the equation above, Y is the dependent variable, and b0 is the arithmetic mean response of the nine trials. Bi (b1, b2, b12, b11, and b22) is the estimated coefficient for the corresponding factor Xi (X1, X2, X1X2, X12, and X22), which represents the average result of changing one factor at a time from its low to high value. The interaction term demonstrates how the answer changes when two factors are changed at once (X1X2). The polynomial terms (X1X1 and X2X2) are provided to analyse the nonlinearity. The symbol ϵ denotes random error [18].

Table I: Full factorial experimental design layout

Trials	Variable levels in coded form	
	X1	X2
1	-1	-1
2	-1	0
3	-1	+1
4	0	-1
5	0	0
6	0	+1
7	1	-1
8	1	0
9	1	+1

Table II: Amount of variables in a 3^2 factorial design

Coded Level	-1	0	+1
HPMC K15M (X1)	175	225	275
Glycerol (X2)	1	1.25	1.50

Table III: Formulation of self emulsifying mouth dissolving film

Components	F1	F2	F3	F4	F5	F6	F7	F8	F9
RZ Emulsion (mL)	5	5	5	5	5	5	5	5	5
HPMC K 15 (mg)	175	175	175	225	225	225	275	275	275
Glycerol (mL)	1	1.25	1.50	1	1.25	1.50	1	1.25	1.50
Citric acid (mg)	50	50	50	50	50	50	50	50	50
Aspartame (mg)	10	10	10	10	10	10	10	10	10
Water (mL)	10	10	10	10	10	10	10	10	10
Orange colour (mg)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Orange flavour (mg)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Characterization of self-emulsifying mouth dissolving films

The physical parameters of the prepared self emulsifying mouth dissolving films such as weight variation, thickness, tensile strength, folding endurance and surface pH of the film were calculated and reported[19,20].

Drug content uniformity

The four corners and the centre of the moulded film (n = 3) were sliced into three film strips (2 × 2 cm^2). A separate conical flask containing 100 mL of distilled water was used for each film strip. For two hours, the flasks were shaken in a mechanical shaker. In a UV-Visible spectrophotometer, all of the solutions were filtered and examined at a wavelength of 272 nm[19, 20].

***In-vitro* disintegration test**

A petri plate disintegration test was conducted. Each batch's film sample (2×2 cm^2) was put in 10mL of simulated saliva. A film begins to shatter or dissolve at the disintegration time (n=3) [19, 20].

***In-vitro* dissolution studies**

Utilizing a USP dissolving apparatus I (basket device) in 300mL of simulated saliva fluid (pH 6.8) held at 37±0.5°C and agitated at 50 rpm, the dissolution investigation was conducted. The film was divided into patches measuring (2 × 2 cm^2). At intervals of 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, and 5 minutes, 2 mL samples were taken, filtered, and subjected to spectrophotometric analysis at 272 nm in a UV Spectrophotometer[19,20].

FTIR (Fourier transform infrared spectroscopy)

In order to identify any potential interactions between the API and the excipients used, FTIR experiments were conducted. Using the KBr dispersion method, a Fourier transform infrared spectrophotometer (Jasco V-530 model) was used to obtain the IR absorption spectra of ranolazine. In a nutshell, 2 mg of the sample was fully ground with previously dried KBr at 120°C for 30 minutes. The drug sample was then uniformly mixed with the ground sample and maintained in the sample holder, and spectra were recorded over the wave number 400-4000 cm-1. The infrared Spectra of the Optimised batch, physical mixture of formulation, and API were recorded[19, 20].

Differential scanning calorimetry (DSC)

Thermograms of the physical combination and the Optimized formulation were acquired using an intracooler-equipped DSC (Pyris Diamond TG/DTA, Make-Perkin Elmer). Alpha alumina powder and a platinum crucible are used as a standard for calibrating the DSC temperature and enthalpy scale. The 2-10 mg powder samples were hermetically sealed in an aluminum pan and heated steadily to 10°C[19, 20].

Scanning electron microscopy (SEM)

Using a 20 kV SEM from JEOL in Japan, the exterior macroscopic structure (morphology) of the Film was examined. The sample was glued to a SEM stub before a small layer of gold or platinum was applied[19, 20].

Stability studies

In the present study, stability studies were carried out for a specific time period up to 30 days for selected formulations, ambient temperature and humidity 40°C ± 2°C/75% ± 5%RH in stability chamber for 30 days. After 30 days sample were removed and characterized for tensile strength, % drug content and cumulative % drug release of optimized formulation[9,19,20].

RESULTS AND DISCUSSION

Selection and screening of potential emulsion components (surfactant, co surfactant and oil), from solubility data (Table IV), Ethyl oleate shows good solubilizing power for ranolazine (46.96 mg/mL) amongst other oils investigated. In case of surfactant, Tween 80 has more solubilizing capacity (48.094 mg/mL) of drug followed by PEG 400 (36.65 mg/mL).

Table IV: Solubility of RZ in oils, surfactants and co-surfactants

Type of oil	**Solubility (mg/mL)***
Oleic acid	42.653 ± 0.025
Ethyl oleate	46.960 ± 0.007
Isopropyl myristate	16.830 ± 0.019
Castor oil	42.248 ± 0.017
Type of surfactants	
Tween 80	48.094 ± 0.023

Tween 20	34.804 ± 0.034
Span 20	36.344 ± 0.019
Type of co-surfactants	
PEG 400	36.65 ± 0.022
PEG 200	25.286 ± 0.017
PEG 600	23.376 ± 0.013
Propylene glycol	24.58 ± 0.007

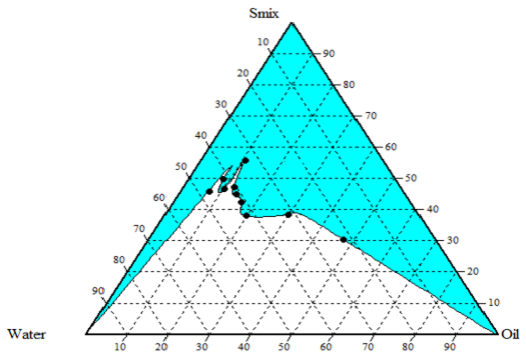
*Indicates average triplicates ±SD (n=3)

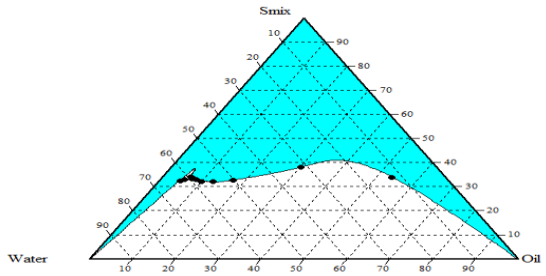
Construction of pseudoternary phase diagram

Oil, a surfactant, and a co-surfactant were chosen for microemulsion formulation based on the findings of solubility investigations. The phase diagram analysis of RZ SEDDS utilised ten alternative combinations of surfactant mixture to oil at various Km values (1, 2, 3, and 4) (Table V). Oil-in-water (o/w) and water-in-oil (w/o) did not clearly convert into one another. Each phase diagram revealed the o/w microemulsions boundary layer (Fig.1 a-d).

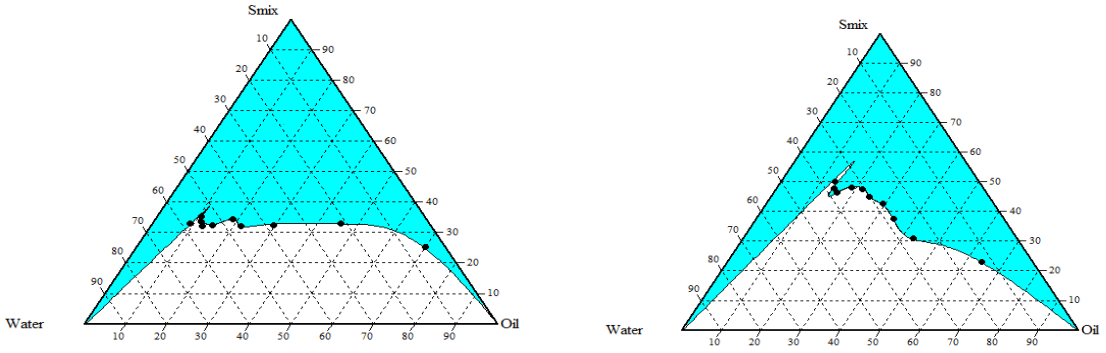
Table V: Composition of ethyl oleate/tween 80 /peg 400/water at Km=1,2,3,4

Sr. No.	Smix (mL)	Oil (mL)	Water(mL)			
			Km=1	**Km=2**	**Km=3**	**Km=4**
1	0.5	1	0.4	0.2	0.1	0.3
2	1	1	0.9	0.9	0.7	0.9
3	1.5	1	1.8	2.5	1.9	1.2
4	2	1	2.1	3.7	3.1	1.4
5	2.5	1	2.5	4.9	3.7	1.8
6	3	1	2.8	5.8	5.3	2.1
7	3.5	1	3.5	6.7	6.5	2.6
8	4	1	2.6	7.5	7.1	3.5
9	4.5	1	4.1	9.1	7.5	3.8
10	5	1	5.6	10.5	9.5	3.9





1.a) Pseudoternary phase diagram at Km=1 1.b)Pseudoternary phase diagram at Km=2



1.c) Pseudoternary phase diagram at Km=31.d) Pseudoternary phase diagram at Km=4
Fig.1: Pseudoternary phase diagram

All the combinations of km i.e. surfactant and co-surfactant ratio in certain different concentrations were taken and constructed as pseudo ternary phase diagram. But the diagram shows highest water absorption i.e. wider self micro emulsifying region was considered to be a better combination (Km) in terms of self-micro emulsification efficiency. The phase diagram at Km value 3 show better microemulsion existence regions than 1, 2 and 4 and value didn't show further increase in microemulsion existence region which shown in Fig. 2. So, Km 3 system was selected as final formulation of SEDDS.

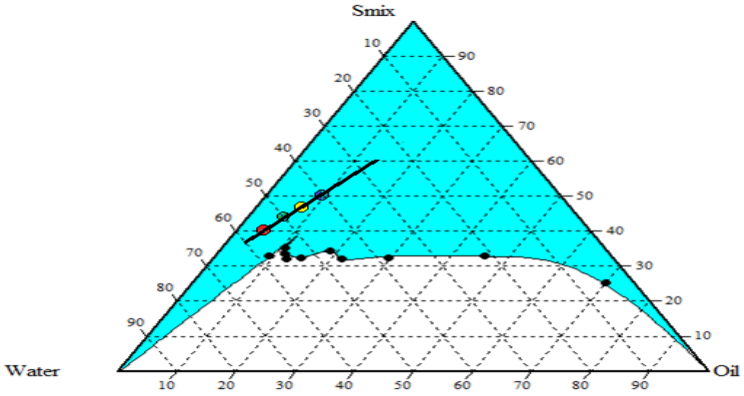


Fig. 2: Selected composition of formulation RZ 1 to RZ 4

Evaluation of liquid self emulsifying drug delivery system (SEDDS)
Dilution & self emulsification study
The self-emulsification of SEDDS in 100mL double distilled water at 37°C with gentle agitation was evaluated visually. After two hours of storage, as indicated in Table VI, all solid SEDDS batches displayed spontaneous emulsification and showed no indication of phase separation or phase inversion of microemulsion. The grade of the optimized batch was A, indicating quick formation of a clear microemulsion with a 20-second self-microemulsion formation time.

Table VI: Dilution & self-emulsification time study of solid SEDDS batches

Sr. No.	Batch code	Dilution study			Emulsification time (S)
		1:10	1:50	1:500	
1	RZ 1	B	A	A	50
2	RZ 2	B	A	A	35
3	RZ 3	A	A	A	20
4	RZ 4	B	A	A	22

Thermodynamic stability study of SEDDS

RZ 1, RZ 2, RZ 3 showed better results but in case of RZ 4 there was slightly precipitation occurred after centrifugation. Liquid SEDDS formulation showed good storage stability at different temperature shown in Table VII (+ Phase separation, + + Drug precipitation, - No phase separation, -- No precipitation)

Table VII: Thermodynamic stability study of SEDDS

Sr. No.	Batch code	Thermodynamic Stability		
		at 4°C	at 40°C	After centrifugation
1	RZ 1	-,--	-,--	-,--
2	RZ 2	-,--	-,--	-,--
3	RZ 3	-,--	-,--	-,--
4	RZ 4	-,--	-,+	-,++

Globule size determination

Because it affects both drug release and absorption, the droplet size of the emulsion is a key component in how well it performs self-emulsification. Additionally, it has been suggested that the emulsion droplets' lower particle size may promote quicker absorption and increase bioavailability (Table VIII).

Table VIII: Globule size of SEDDS formulation

Sr. No.	Batch Code	Mean particle size (nm)	Polydispersibility index (PDI)
1	RZ 1	21.50	0.177
2	RZ 2	16.79	0.315
3	RZ 3	14.72	0.277
4	RZ 4	18.76	0.278

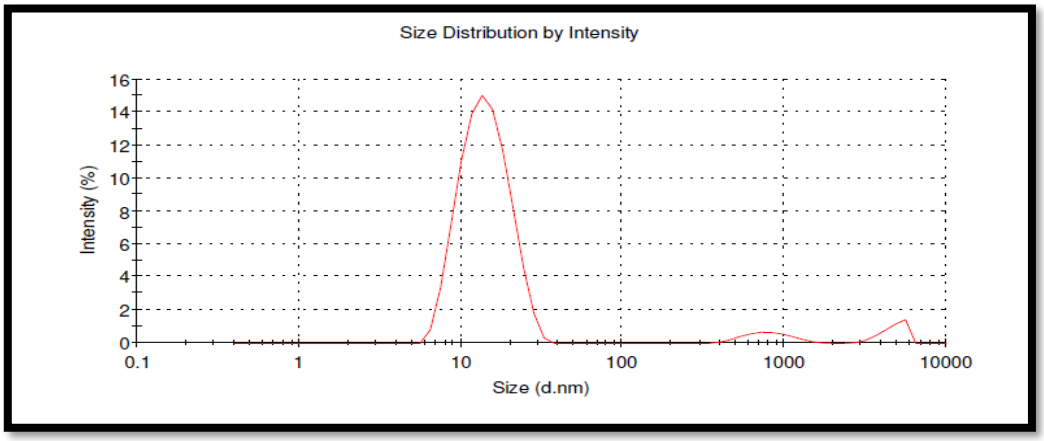


Fig. 3: Particle size distribution of optimized formulation RZ 3

The globule size determination study was used to calculate the mean particle size and polydispersity index. It was discovered that the optimised batch RZ 3 illustrated in Fig. 3 had dimensions of 14.72 nm and 0.277, respectively. All of the reconstituted SEDDS had extremely small average droplet sizes, all of which were in the nanometer range (<100 nm). Globules with a size in the nano- or micron range are more transparent and have a larger surface area, which is important for dividing drugs between oil and water. Results for droplet size are shown in Table VIII. All formulations have polydispersibility indices that are less than 1, which indicates that globules are distributed uniformly throughout the formulation.

Zeta potential analysis

Table IX displays the zeta potential values of the diluted SEDDS formulations. The examined SEDDS formulations zeta potential showed a large, substantial variance. All SEDDS batches, with the exception of RZ 3, had zeta potential values that ranged from -0.3 to -0.4 mV. RZ 3 was the only batch to have a mean zeta potential of -38.21 mV, indicating that it was more stable than the other batches.

Table IX: Zeta potential of SEDDS formulation

Sr. No.	Batch code	Mean zeta potential (mV)
1	RZ 1	-0.411
2	RZ 2	-0.365
3	RZ 3	-38.21
4	RZ 4	-0.441

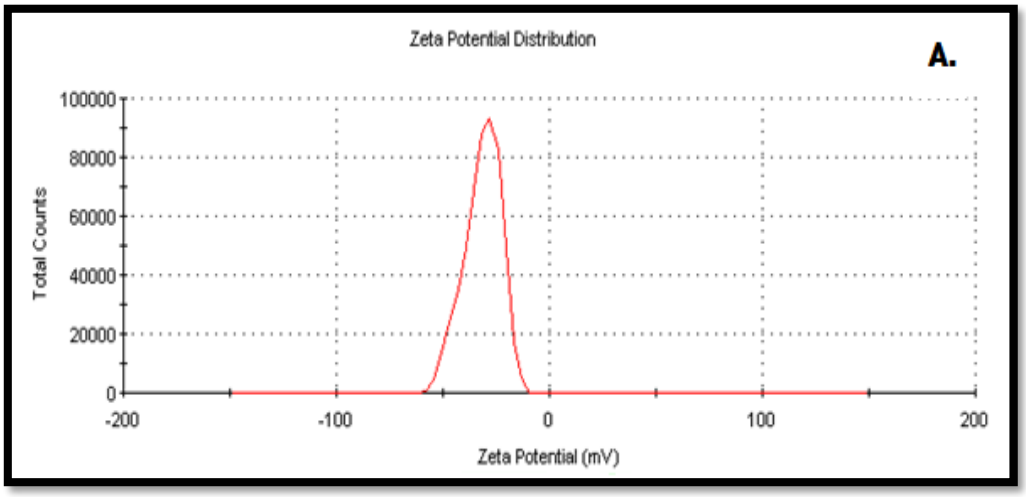


Fig. 4: Zeta potential of optimized batch RZ 3

Characterization of self emulsifying mouth dissolving films

The weight of the film increases together with the weight of the polymer. The films from F1 through F9 ranged in weight from 162mg to 277mg. The F3 formulation had the lightest weight of the film, and the F7 formulation had the heaviest weight of the film, as stated in Table X. The homogeneous weight of the films is indicated by the low standard deviation figures. The film's thickness was discovered in ascending sequence. As polymer concentration rises, the film's thickness rises as well, as illustrated in Table X. The range of 0.405-0.926 mm was obtained for the film thickness of formulations F1-F9. It was discovered that formulation F5 was 0.688 mm thick. The film's physical consistency is indicated by the low standard deviation numbers. The F5 formulation's folding resistance was measured at 305. The films' folding endurance values were discovered to be at their maximum, and as a result, they displayed good physical and mechanical qualities. All of the films' surfaces had pH values that fell within the range of salivary pH. There was no discernible variation in the surface pH of any films. All of the formulations measured surface pH values were found to be near to neutral, reducing their propensity to irritate the buccal mucosa and indicating that they should be tolerable. The film's tensile strength was determined to be between 11.90 and 50.00 N/mm^2. It was discovered that formulation F5 had a tensile strength of 50.00 N/mm^2. It is evident from the surface response plot that the tensile strength increases when the amount of HPMC K15M is increased; this could be the result of hydrogen bonds between the medication and the polymer. The drug content of ranged between 91.39 and 98.00%, as reported in Table X. 98.00% of the drug was discovered in formulation F5. As can be observed, the fact that it is significantly closer to 100% indicates that there was no drug loss during the production of the film. The disintegration time was discovered to be between 20 to 30 seconds, as stated in Table X. The disintegration time for formulation F9 was determined to be the slowest, at 30 seconds, and the fastest, at 20 seconds for F5.

Table X: evaluation of mouth dissolving film formulation batches F1 to F9

B. code	Weight variation (mg)*	Thickness (mm)*	Folding endurance	Surface pH	Tensile strength (N/mm^2)*	Drug content uniformity (%)	Disintegration time (sec)*
F1	163 ± 0.02	0.405 ± 0.02	260 ± 0.03	7.1 ± 0.05	11.90 ± 0.2	96.52 ± 2.32	22 ± 0.4
F2	167 ± 0.05	0.524 ± 0.05	270 ± 0.02	7.0 ± 0.03	22.91 ± 0.05	95.21 ± 1.30	22 ± 0.6
F3	162 ± 0.03	0.574 ± 0.07	273 ± 0.05	6.9 ± 0.05	17.50 ± 0.2	95.41 ± 1.32	23 ± 0.4
F4	189 ± 0.07	0.678 ± 0.03	276 ± 0.02	7.0 ± 0.02	16.06 ± 0.3	96.41 ± 2.30	24 ± 0.4

F5	**199 ± 0.06**	**0.688 ± 0.02**	**305 ± 0.05**	**6.8 ± 0.05**	**50.00 ± 0.2**	**98.00 ± 1.34**	**20 ± 0.2**
F6	206 ± 0.02	0.690 ± 0.08	293 ± 0.07	7.1 ± 0.07	26.31 ± 0.05	96.01 ± 0.75	25 ± 0.4
F7	277 ± 0.03	0.711 ± 0.07	280 ± 0.02	7.0 ± 0.03	34.21 ± 0.1	93.56 ± 0.25	26 ± 0.1
F8	247 ± 0.05	0.734 ± 0.05	281 ± 0.09	6.9 ± 0.09	33.3 ± 0.10	92.85 ± 1.85	28 ± 0.2
F9	251 ± 0.05	0.926 ± 0.03	287 ± 1.27	7.2 ± 0.02	36.36 ± 0.2	91.39 ± 0.39	30 ± 0.2

*****All readings are average ± SD (n=3)

***In-vitro* dissolution studies**

To know the release at varied polymer concentrations, the drug release at various time intervals was computed and determined. The collected values were translated to % drug release. In Table XI & Fig. 5, the percentage cumulative release was displayed.

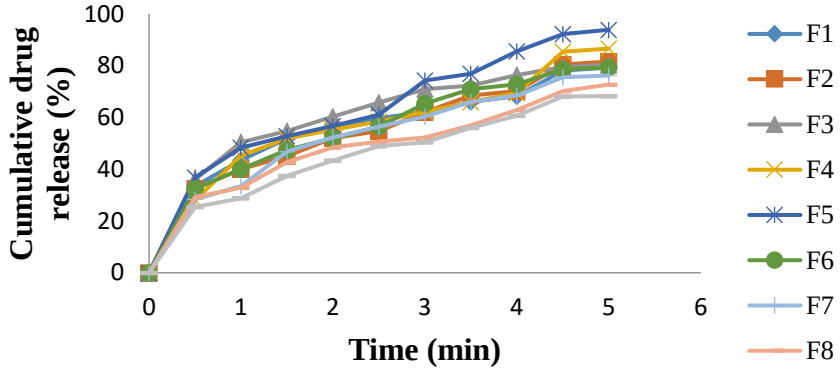


Fig. 5: Dissolution profile of formulations

Table XI: Percent cumulative release of formulations

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	**0**	0	0	0	0
0.5	33.45	32.48	36	28	**36.82**	32.45	28.34	29.3	25.45
1	43.54	40.01	50.4	45.18	**48.34**	40.01	33.45	32.79	28.81
1.5	51.87	45.05	54.76	51.87	**52.76**	47.4	46.8	42.68	37.45
2	56.37	52.04	60.24	55.24	**56.75**	52.04	52.24	48.45	43.31
2.5	59.74	54.79	65.75	58.47	**60.98**	56.48	56.47	50.64	48.86
3	62.14	62.03	70.94	62.14	**74.25**	65.34	60.26	52.31	50.38
3.5	66.04	68.47	72.29	66.04	**76.85**	70.98	65.93	56.98	56.02
4	68.25	70.15	76.35	69.48	**85.49**	72.84	68.45	62.87	60.68
4.5	78.12	80.45	79.45	85.45	**92.2**	78.65	75.49	70.24	68.1
5	79.25	81.6	80.36	86.59	**93.85**	79.36	76.2	72.69	68.25

Differential scanning calorimetry (DSC)

The physical condition of the medication in the formulation was investigated using a DSC investigation. We assessed the physical mixture, formulation F5, and pure medication. Fig. 6 displays the thermograms for ranolazine, HPMC K15M, the physical combination, and the Optimized formulation (F5).

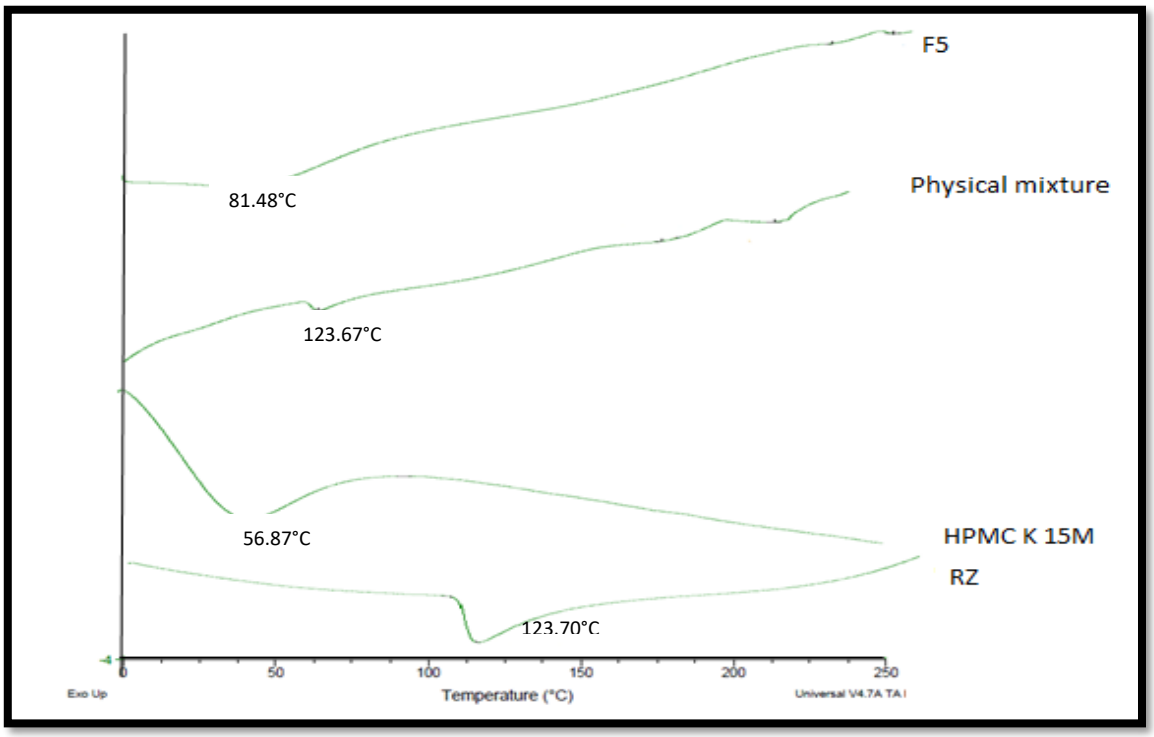


Fig. 6: Overlain DSC of RZ, HPMC K 15M, physical mixture and optimized formulation F5

Ranolazine, when taken in its purest form, produces an endothermic peak that corresponds to melting at 123°C, demonstrating its crystalline nature. The endothermic peak in the DSC of the physical combination does not significantly change. The DSC data showed that there was no specific alteration in the melting endothermic peak, indicating that there was no interaction between the medication and the employed polymers.

Powder X-ray diffraction analysis (PXRD)

The physical mixture and formulation batch diffractograms showed complete amorphism of the drug and excipients. No sharp peak, as seen in Fig. 7 was noticed.

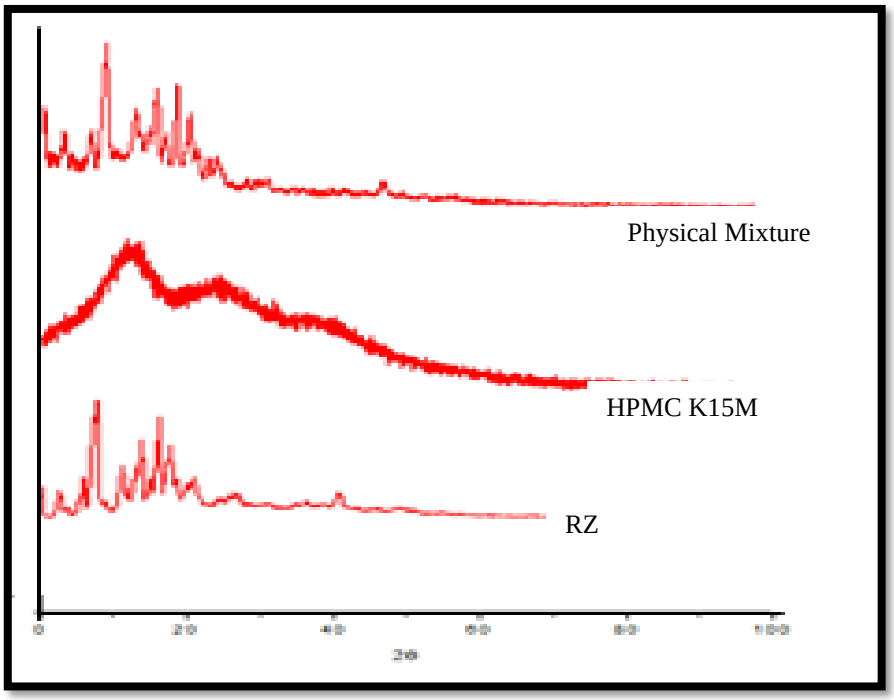


Fig. 7: Overlain of PXRD of pure RZ, HPMC K 15M and physical mixture

Scanning electron microscopy (SEM)

Investigations using a SEM revealed that the surface structures of the SEMDF varied. Fig.8 depicts typical characteristics of the MDF surface with visible cellulose fibres. Self-emulsifying components in SEMDF that contain oils, surfactants, and co-surfactants tightened up on the surface and were entirely contained by the cellulose fibre surface.

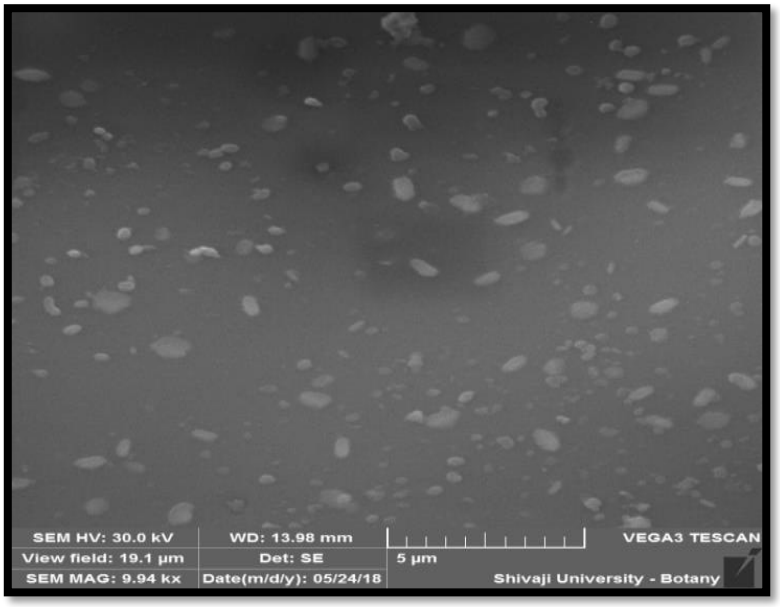


Fig. 8: SEM of optimized formulation F5

The self-emulsifying elements on the surface of SEMDF may quickly self-emulsify in water and contribute significantly to the rapid commencement of action of ranolazine.

Stability studies

The formulations underwent a stability assessment for 30 days at 40°C with a 1°C temperature fluctuation and 75% relative humidity. The samples drug content was determined using different time intervals, and it is clear that there were minor variations, as indicated in Table XII.

Table XII: Evaluation of optimized formulation F5 after stability period

Parameters	Time period	
	Before	After 30 days
Tensile strength (N/mm^2)	50 ± 0.2	50 ± 0.1
% Drug release	93.85	93.16
Drug content (%)	98.0 ± 01.34	98.23 ± 0.02

CONCLUSION

In order to achieve greater therapeutic effectiveness with enhanced bioavailability and better patient compliance, the present study demonstrated that the SEMDF of ranolazine could be successfully manufactured by solvent casting process. For the phase diagram analysis of RZ SEDDS, ten distinct possible surfactant mixtures to oil combinations at various Km values (1, 2, 3, and 4) were employed. Compared to Km values 1, 2, and 4, the phase diagram at Km value 3 displays better microemulsion existence zones. Km 3 system was ultimately chosen as the SEDDS formulation. Additionally, it was determined that formulation F5 had the best physicochemical and mechanical characteristics out of all the other formulations. Additionally, the new formulation's stability analysis validated SEMDF's increased shelf life. The current study thus illustrates the enormous potential of SEMDF for improving patient comfort and compliance by expediting the commencement of action and avoiding hepatic first-pass metabolism, especially in pediatric and geriatric patients.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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