Original Article

Improvement of Bioavailability of Poorly Soluble Racecadotril by Solid Dispersion with Surface Adsorption Method: A Case Study

Abstract

Introduction: Biopharmaceutics classification system class II drugs show unpredictable bioavailability based on their solubility. Unfortunately, very few products were manufactured by this technique owing to their poor flowability and stability. The objective of the current investigation was used to improve the flowability by surface solid dispersion (SSD; SD with surface adsorption technology) and improve the absorption of racecadotril (RT) under low pH conditions (i.e., in stomach) to show anti-diarrheal effect by reducing water and electrolyte secretion into the intestine. **Materials and Methods:** SSDs and physical mixtures (PMs) were prepared using various ratios of hydrophilic carriers (polyethylene glycol 4000, polyethylene glycol 6000, and Gelucire 50/13) and an adsorbent (lactose monohydrate). Fourier-transform infrared spectroscopy, differential scanning calorimetry, X-ray diffractometry , and dissolution studies (*in vitro)* were conducted to characterize SSDs and PMs. **Results:** Phase solubility curves represent A_L type, indicating that the solubility of drug linearly increased with an increase in the concentration of carrier. Characterization studies indicated that no interactions between carrier and drug. Solid-state characterization showed a reduction in crystallinity that further supports increment in solubility and dissolution. The optimized formulation (SDG4) showed 99.84 ± 1.5% drug release in 15 min compared to RT plain drug (11.95 ± 1.72%). *In vivo* bioavailability studies of SDG4 revealed a significant ($P < 0.05$) increase in C_{max} 65.38 ± 1.34 µg/mL (1.75-fold) with increased relative bioavailability (180.22-fold) against the RT plain drug. **Conclusion:** Formulation of SD with surface adsorption method could enhance solubility, dissolution, and bioavailability of RT.

Keywords: *Bioavailability, flowability, gelucire, solubility, surface solid dispersion*

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Introduction

Poorly water-soluble drugs exhibit bioavailability problems, especially when they are orally administered. Dissolution is the rate-determining step for absorption of a drug to show therapeutic activity. Poorly water-soluble drugs show unpredictable absorption as compared to highly soluble drugs.[1]

Solid dispersion (SD) uses homogeneous dispersion of poor soluble drugs in a hydrophilic carrier to improve solubility and dissolution and thereby bioavailability.[2] The mechanism for enhancement of the dissolution of SD is solid-state transformation from crystalline to amorphous form,[3] molecule-level reduction in particle size, improvement of wettability, and solubility of a drug by hydrophilic carriers in the surrounding environment.[4-6] However, the obtained SD was so tacky and sticky and leads to a decrease in yield recovery. This problem will reflect in handling and subsequently in the processes of manufacturing.[7] It also affects the flow property and stability of the product.

Nowadays new approaches are used to get control of these problems and also improve the bioavailability of drug using SD with surface adsorption technique by adsorbing on the inert core of adsorbent.[8-10] This technology has been successfully used for a variety of drugs such as ibuprofen,[11] piroxicam,[12] meloxicam,[13] itraconazole,[14] aceclofenac,[15] and smvastatin.[16]

In all age group of people, the commonly affecting illness is diarrhea. It is associated with excessive loss of water and electrolyte.[17] Racecadotril (RT) is an enkephalinase inhibitor used to treat acute diarrhea.[18] It has an antisecretory effect by reducing intestinal motility and thereby reduces electrolyte and water secretion into the intestine.[19] It also decreases the abdominal pain and reduces the duration and frequency of acute diarrhea.[20,21]

RT comes under BCS (Biopharmaceutics classification system) class II drug with

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low bioavailability. The time of peak plasma concentration of conventional RT tablets is ~1 h.[22] But it needs a faster onset of action to prevent the excessive loss of fluid. Hence, an attempt has been made to develop a new RT dosage form to overcome this limitation.

In this present study, RT SD was prepared using carriers such as polyethylene glycol 4000, polyethylene glycol 6000, and Gelucire 50/13. Surface adsorbents further promote the flow property of SD, stability, and absorption of RT that improves bioavailability and drug's acceptability.

Materials and Methods

Materials

RT was obtained ex gratis by M/S Symed Laboratory Limited, (Hyderabad, India). PEG 4000 and 6000 were provided by Qualikems Fine Chemicals Private Limited (Vadodara, India), and Gelucire 50/13 was provided ex gratis by M/S Gattefosse Private Limited (Mumbai, India). Chemicals, reagents, and excipients were used of analytical grade.

Methods

RT phase solubility studies

The shake flask method was employed for carrying phase solubility studies to measure the solubility of RT.[23] An amount of RT, more than saturation, was placed in a test tube having different concentrations of polyethylene glycol 4000, polyethylene glycol 6000, and Gelucire 50/13 (0, 5, 10, 15, 20, 25, and 30% w/v) solution separately.[24] The tubes were sonicated for 15 min and stirred continuously on a shaker at room temperature for 48 h. After centrifugation, the supernatant of the suspensions was passed through a membrane filter (0.45 µm) and the content of RT was measured using ultraviolet-visible spectroscopy at 231 nm. Gelucire 50/13 does not show the absorbance at 231 nm.

Apparent stability constant at 1:1 (K_s) was determined using the phase solubility curve[25]

$$K_s = \frac{\text{Slope}}{S_o\left(1-\text{Slope}\right)} \quad (1)$$

where S_o is solubility of RT in water.

Aqueous solubility of RT was expressed by Gibbs transfer of free energy (ΔG^o_{tr}) and it was calculated by the following equation[26]:

$$\Delta G^o_{tr} = 2.303\ RT\ \log\frac{S_s}{S_o} \quad (2)$$

where S_s/S_o is the solubility ratio of RT in polymeric solution to water.

Preparation of SD with surface adsorption and physical mixtures

Preparation of SD with surface adsorption

SDs of RT were formulated in different ratios [Table 1] using a different drug to carrier ratio by melt method.[27] The carriers selected for the formulation of SD were polyethylene glycol 4000, polyethylene glycol 6000, and Gelucire 50/13 at a different drug to carrier ratio as given in Table 1. The carrier was taken on a Petri plate and melted by placing on a water bath. Then, the drug was incorporated by continuously stirring into a molten polymer. Then, the mixture was cooled to 25°C. Lactose monohydrate (adsorbent) was added to the molten mass during the cooling process and mixed continuously. The prepared SSDs were collected and sieved through 60 # and stored in desiccators.

Formulation of RT physical mixture

All physical mixtures (PMs) of RT were prepared by initially crushing all the carriers to fines using a mortar individually for 10 min [Table 1] in four ratios. PMs were prepared by triturating drug, carrier, and adsorbent in a mortar with pestle and passed through 60 # sieve to get a homogeneous mixture.

Table 1: Formulation of RT surface solid dispersions using various carriers

	Excipients (mg)					
Formulation code	**Racecadotril**	**PEG 4000**	**PEG 6000**	**Gelucire 50/13**	**Lactose monohydrate**	**Drug:carrier ratio**
SDP1/PMP1	100	100	–	–	500	1:01
SDP2/PMP2	100	200	–	–	500	1:02
SDP3/PMP3	100	300	–	–	500	1:03
SDP4/PMP4	100	400	–	–	500	1:04
SDS1/PMS1	100	–	100	–	500	1:01
SDS2/PMS2	100	–	200	–	500	1:02
SDS3/PMS3	100	–	300	–	500	1:03
SDS4/PMS4	100	–	400	–	500	1:04
SDG1/PMG1	100	–	–	100	2000	1:01
SDG2/PMG2	100	–	–	200	2000	1:02
SDG3/PMG3	100	–	–	300	2000	1:03
SDG4/PMG4	100	–	–	400	2000	1:04

SDP = surface solid dispersion with PEG 4000, SDS = surface solid dispersion with PEG 6000, SDG = surface solid dispersion with Gelucire 50/13, PMP = physical mixture with PEG 4000, PMS = physical mixture with PEG 6000, PMG = physical mixture with Gelucire 50/13

Evaluation of SD with surface adsorbent

Determination of drug content

SD with surface adsorbents (SSDs) was accurately weighed and dissolved in methanol. The samples were mixed in a bath sonicator for 10 min. The resulting samples were filtered through a membrane filter (0.45 µ). The clear solution was appropriately diluted with 0.1 N HCl and RT drug content was determined from the calibration curve. The calibration curve was prepared by dissolving the pure RT in 0.1 N HCl. The sample solutions (2 to 10 µg/mL) were prepared using 0.1 N HCl and analyzed by ultraviolet-visible spectroscopy at 231 nm.

Flow properties of SD with surface adsorbent

Flow properties of the powder blend were measured by determining the angle of repose and Carr's compressibility index by the following equation[28]:

$$\theta = \tan^{-1}\frac{H}{R} \quad (3)$$

where θ was angle of repose, and radius and height of pile were *R* and *H*, respectively. Carr's index was measured by

$$\text{Carr's index} = \frac{\rho_p - \rho_b}{\rho_p} \times 100 \quad (4)$$

where ρ_b is bulk density and ρ_p is tapped density.

In vitro dissolution and data treatment

In vitro dissolution studies of RT, SSDs, and PMs were carried out using USP paddle apparatus II (UV3000$^+$, Lab India Solutions, Mumbai, India) containing 0.1 N HCl (900 mL) at 37 ± 0.5°C for 50 rotations per minute. The amount of RT was equivalent to 100 mg in all formulations. An aliquot (5 mL) was removed at suitable time point and replaced by an equal amount of unused buffer. An aliquot was passed through membrane filters (0.45 µm) and the contents were spectrometrically analyzed at 231 nm. Mean values were reported by performing the studies in triplicate. Dissolution profiles were analyzed and compared for various parameters, cumulative percent drug release Q_{15} (in 15 min), MDT (mean dissolution time), and % DE (% dissolution efficiency) at 15 min.[29]

Characterization of SD with surface adsorbent

FTIR spectrum of plain RT, Gelucire 50/13, PMG4, and SDG4 was recorded on a FTIR spectroscopy (IRTracer-100, Shimadzu, Japan) between 400 and 4000 cm^{-1} by potassium bromide pellet method. A differential scanning calorimeter (DSC-60A, Shimadzu, Japan) was used to record the thermograms of RT, Gelucire 50/13, PM (PMG4), and optimized SSDs (SDG4). Approximately 5–7 mg sample was heated in an aluminum pan under the flow of nitrogen gas for a range of temperature of 0 to 400°C at 5°C/min rate. X-ray diffractograms of the samples (pure RT, Gelucire 50/13, SDG4, and PMG4) were recorded using X-ray diffractometry (Siemens D5000, TX, USA) by scanning at 2θ range of 2° to 50° by exposing to Cu radiation at 30 mA current of 40 kV voltage under a wavelength of 1.540 Å.

Stability studies

SDG4 (optimized) was stored for 6 months at 40 ± 2°C and 75 ± 5% RH (relative humidity). Drug content and % assay were determined to study the effect of conditions of storage on formulations.[30] The similarity index (F2) was determined to find out the stability of SSD.[31]

In vivo bioavailability studies

Bioavailability studies were planned and executed as per the approved protocol (IAEC No: VCOP/2018/13/1). In the present study, 12 albino rats weighing 190 to 210 g were used. A crossover design study was used. The animals (rats) were equally divided into two groups. The first group received optimized formulation (SDG4) and the second group received pure RT at an oral dose equivalent to 10 mg per kg of body weight. Optimized formulations and pure RT were dispersed in sodium carboxymethylcellulose and the resulted suspension was administered orally. After 24 h of washout period, optimized SDG4 was administered to the second group; whereas pure RT was administered to the first group. At different time points (0, 0.125, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 h), 0.5 mL of blood samples were periodically collected from retro-orbital vein in microcentrifuged tubes. After centrifugation of blood samples for 5 min at 5000 rpm, the plasma was stored at −40°C.

HPLC analysis of RT in plasma

RT concentration was quantitatively analyzed from the plasma by the high-performance liquid chromatography (HPLC) method.[32] The analysis was carried out using RP-HPLC [Shimadzu LC-20AD, rheodyne sample injection port with 20 µL loop, SPD-M20A Photodiode array detector (PDA), Shimadzu Corporation, Japan] equipped with Kromasil C18 (250 × 4.6 mm, 5 µm) column. The mobile phase consisted of 20 mM phosphate buffer (pH 3.5) and acetonitrile (60:40 v/v). The eluents were monitored at a wavelength of 230 nm at a flow rate of 1 mL/min.

Ninety microliters of plasma were transferred to a microcentrifuge tube and spiked with 10 µL of internal standard (10 µg/mL gemfibrozil solution) and vortexed for 2 min. Acetonitrile (400 µL) was added to precipitate the proteins and vortexed for 5 min. The mixture was centrifuged at 5000 rpm at 5 min. The supernatant was separated and filtered through 0.45 µm membrane filter and 20 µL of the solution was injected into the HPLC system.

Pharmacokinetic parameters

All the pharmacokinetic (PK) parameters were determined by PK Solver (trial version 2.0) using noncompartmental model analysis. T_{max} and C_{max} were obtained from the plasma concentration-time profile. The trapezoidal method was used to determine AUC and AUMC. The relative bioavailability of optimized formulation was calculated against pure RT using the following equation:

$$\% \text{ Relative bioavailability} = \frac{\text{AUC (SDG4)}}{\text{AUC (pure drug)}} \times \frac{\text{Dose (pure drug)}}{\text{Does (SDG4)}} \times 100 \quad 5$$

Statistical method of analysis

To investigate the differences between pure drug and optimized formulation of RT, the pharmacokinetic parameters were evaluated by paired *t*-test (at $P = 0.05$).[33]

Results and Discussion

Phase solubility studies of RT

The results of phase solubility studies are given in Table 2. Aqueous solubility of RT was observed as 0.00176 mg/mL and increased linearly with an increase in carrier concentration, indicating A_L-type [Figure 1A–C] of solubility diagram.[24] Significant improvement in solubility was observed in the presence of Gelucire 50/13 with 115-fold improvement at 30% w/v concentration compared to pure drug. The different solubility parameters were calculated and shown in Table 3. Stability constant values were found to be 285.52 mL/g for PEGs and 342.97 mL/g for Gelucire 50/13, indicating that stronger interactions between carriers and drug. The negative values of Gibb's free energy of transfer, $\Delta G°_{tr}$, indicate that solubilization was taking place spontaneously in aqueous polymeric solution.[25]

Formulation of SD with surface adsorbent (SSDs) and PM

SSDs and PMs of RT were formulated using various hydrophilic carriers and adsorbent [Table 1]. Pre-evaluation studies were conducted to select suitable adsorbent. These studies revealed that lactose monohydrate was found to be suitable compared to others adsorbents. For SDs of PEGs, 0.5 g of lactose monohydrate was added. Because of sticky nature of Gelucire, about 2 g of lactose monohydrate was added to get free flowing.

Evaluation of SD with surface adsorbent

Determination of drug content

Determination of RT content was performed by dissolving into a suitable media (0.1 N HCl). The RT content in the SDG4 was 99.25 ± 1.26% and found to be in the range (85–115%), indicating that the content uniformity of RT was in an acceptable limit.

Flow properties of SD with surface adsorbent

Plain RT has poor flow as its angle of repose value is 42.64 ± 0.86°. Without the surface adsorbent, all the formulations are sticky and showed poor flow properties. The formulations which are prepared using adsorbent showed angles of repose are less than 30°, indicating good flow properties [Table 4]. The compressibility of surface SDs was determined by Carr's index which was less than 18% for all formulations, indicating good flow property. The Carr's index and angle of repose values of optimized formulation were found to be 14.14 ± 0.52% and 26.38 ± 0.27°, respectively.

In vitro dissolution studies

The release patterns of RT from SSDs and PMs are shown in Figure 2A–D. The order of drug release from SSDs was Gelucire 50/13 > PEG 6000 > PEG 4000. SSDs prepared from Gelucire 50/13 (SDG4) (99.84 ± 1.53% in 15 min) showed faster dissolution (significantly improved $P < 0.05$) than a marketed tablet (20.28 ± 1.84% in 15 min) and pure drug (11.95 ± 1.72% in 15 min). Dissolution enhancement of RT with Gelucire may be attributed to the emulsifying nature of Gelucire 50/13[34] and increased wettability.[35,36] The increase in surface area of lactose monohydrate might also be contributed for the release of drug from SSD.[9,10] The enhancement of dissolution was further confirmed by a significant increase in Q_{15}, $DE_{15\%}$, and reduction in MDT [Table 5] for a formulation containing Gelucire 50/13 compared to marketed tablet and pure drug. The rates of drug release from PMs were also improved to a lesser extent compared to SSDs.

Table 2: Thermodynamic parameter (Gibb's free energy of transfer, $\Delta G°_{tr}$) of RT in PEG 4000, PEG 6000, and Gelucire 50/13 aqueous solutions (mean ± SD, $n = 3$)

Concentration of carrier (%, w/v)	$\Delta G°_{tr}$ (kJ/mol)		
	PEG 4000	PEG 6000	Gelucire 50/13
5	−8.05 ± 0.146	−7.68 ± 0.173	−8.72 ± 0.182
10	−8.36 ± 0.128	−8.36 ± 0.181	−9.18 ± 0.145
15	−9.84 ± 0.162	−9.24 ± 0.143	−9.92 ± 0.184
20	−10.49 ± 0.137	−10.69 ± 0.171	−11.04 ± 0.115
25	−10.69 ± 0.141	−11.04 ± 0.158	−11.49 ± 0.126
30	−11.07 ± 0.152	−11.23 ± 0.167	−11.77 ± 0.174

Table 3: Solubility parameters of RT in different hydrophilic carriers

Hydrophilic carrier	Slope	Stability constant	r^2
PEG 4000	5×10^{-3}	285.52	0.972
PEG 6000	5×10^{-3}	285.52	0.969
Gelucire 50/13	6×10^{-3}	342.97	0.978

Table 4: Flow properties of RT and formulations (mean ± SD, *n* = 3)

Formulation code	Angle of repose (°)	Carr's index (%)
SDP1	27.78 ± 0.63	15.94 ± 0.74
SDP2	29.41 ± 0.82	15.54 ± 0.63
SDP3	28.24 ± 0.57	14.99 ± 0.32
SDP4	28.62 ± 0.74	15.56 ± 0.83
SDS1	27.06 ± 0.79	15.95 ± 0.73
SDS2	29.51 ± 0.83	16.62 ± 0.61
SDS3	29.72 ± 3.15	15.28 ± 0.35
SDS4	27.28 ± 0.52	16.71 ± 0.58
SDG1	28.47 ± 0.93	15.94 ± 0.46
SDG2	27.35 ± 0.46	16.62 ± 0.18
SDG3	28.85 ± 0.53	16.80 ± 0.27
SDG4	26.38 ± 0.27	14.14 ± 0.52
Plain drug	42.64 ± 0.86	27.15 ± 0.62

Dissolution data treatment

The dissolution data were analyzed further for DE and MDT. The results showed that a significant improvement in DE of RT from SSDs containing Gelucire 50/13 was 62.12% (SDG4 formulation) compared to marketed tablet (13.17%) and pure drug (5.24%) [Table 5]. A significant reduction in MDT of RT from SSDs containing Gelucire 50/13 (5.67 min) was observed compared to all other formulations, indicating faster release of drug and faster onset of action.

Characterization of SSD

FTIR spectra of SDG4 SSDs were compared with a plain drug, Gelucire 50/13, and PMG4 [Figure 3]. FTIR spectra of RT are characterized by 3263.65 cm^{-1} (N–H stretch of amide), 1773.54 cm^{-1} (C = O ester group of stretching), 1539.25 cm^{-1} (C = C aromatic group of stretching), and 1278.85 cm^{-1} (C–S stretching). PM (PMG4) also exhibits similar types of peaks. The absence of extra new peaks, the presence of all drug peaks in an optimized formulation (SDG4), suggests that interaction is absent between drug and Gelucire 50/13.

Differential scanning calorimetry thermograms of RT showed an endothermic sharp peak at 81.76°C [Figure 4A] and Gelucire [Figure 4B] showed at 50.7°C corresponding to their melting points. In PM [Figure 4C] and optimized formulation [Figure 4D], the peak was broadened, indicating molecular dispersion of drug in carrier.

Figure 5 shows the X-ray diffractogram of plain RT, carrier, PMG4, and SDG4 formulation. The pattern of X-ray diffraction at 2θ angles of diffraction of RT showed sharp distinct peaks (i.e., 4°, 9°, 13°, 17°, 18° and 20°) compared to less intense peaks in PMG4 and SDG4 formulation. The PM [Figure 5C] shows some intense peaks, indicating that the drug completely may not undergo solid-state transition. The peaks intensity was decreased or disappeared in SDG4 formulation [Figure 5D], indicating a reduction in crystalline to amorphous drug form.

Stability studies

SDG4 formulation was studied for stability according to ICH and stored for 6 months. No significant differences [Table 6] in drug release and drug content were observed between stored formulation and freshly prepared formulations, indicating the prepared formulations were stable for 6 months.

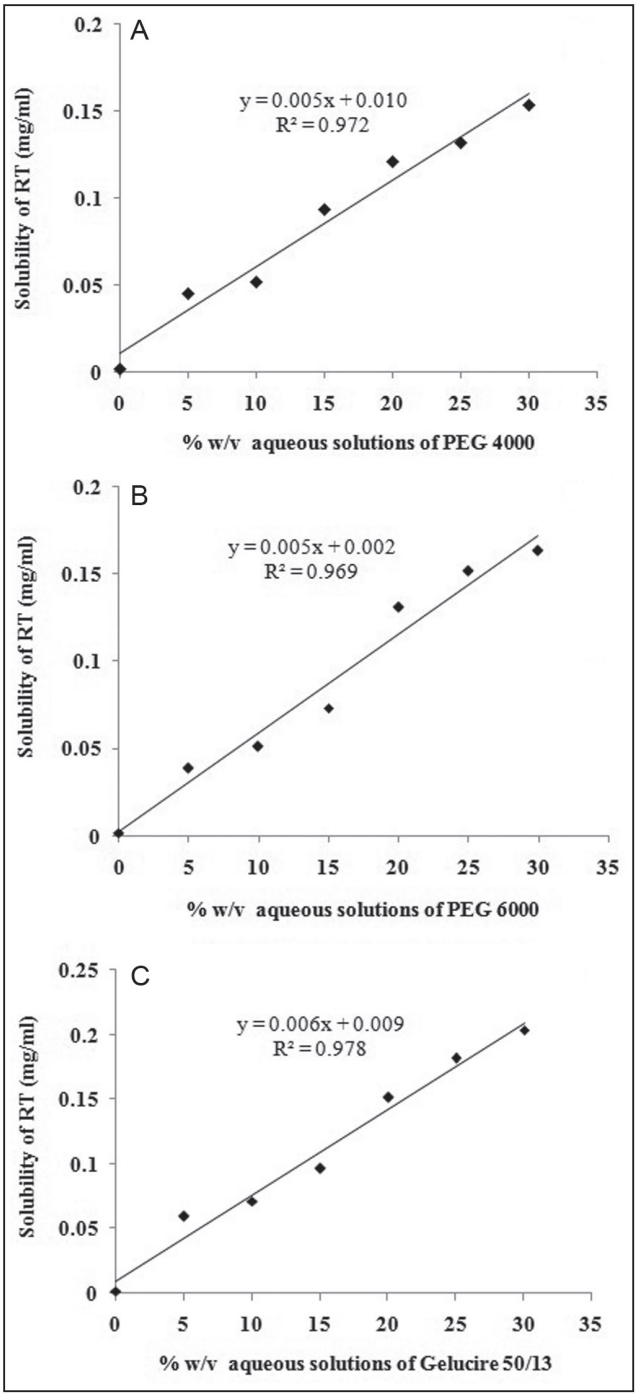

Figure 1: Phase solubility diagrams of RT in PEGs and Gelucire solutions at room temperature (*n* = 6) [(a) PEG 4000 (b) PEG 6000 (c) Gelucire 50/13]

Bioavailability studies

Mean RT plasma concentration profiles of SD with the surface adsorbent (formulation SDG4) and RT pure drug is showed in Figure 6. Various PK parameters are given in Table 7. Formulation SDG4 produced peak plasma concentration (C_{max}) 65.38±1.34 µg/mL at T_{max} of 0.5 h, in contrary to pure drug

Table 5: Dissolution parameters of RT from various formulations (mean ± SD, n = 3)

Formulation Code	Q_{15}	$\%DE_{15}$	MDT (min)
SDP1	23.52 ± 2.17	15.31	72.07
SDP2	29.63 ± 1.42	20.36	67.79
SDP3	42.46 ± 0.94	26.73	37.22
SDP4	58.25 ± 2.36	35.68	22.69
SDS1	28.52 ± 0.72	18.81	70.92
SDS2	35.63 ± 1.46	24.03	48.82
SDS3	47.46 ± 1.68	29.56	28.21
SDS4	63.25 ± 2.53	39.51	15.91
SDG1	48.52 ± 1.28	34.15	17.85
SDG2	75.63 ± 0.86	45.66	11.62
SDG3	82.46 ± 0.47	50.76	8.51
SDG4	99.84 ± 1.53	62.12	5.67
Marketed tablet	20.28 ± 1.84	13.17	73.61
Pure drug	11.95 ± 1.72	5.24	106.3

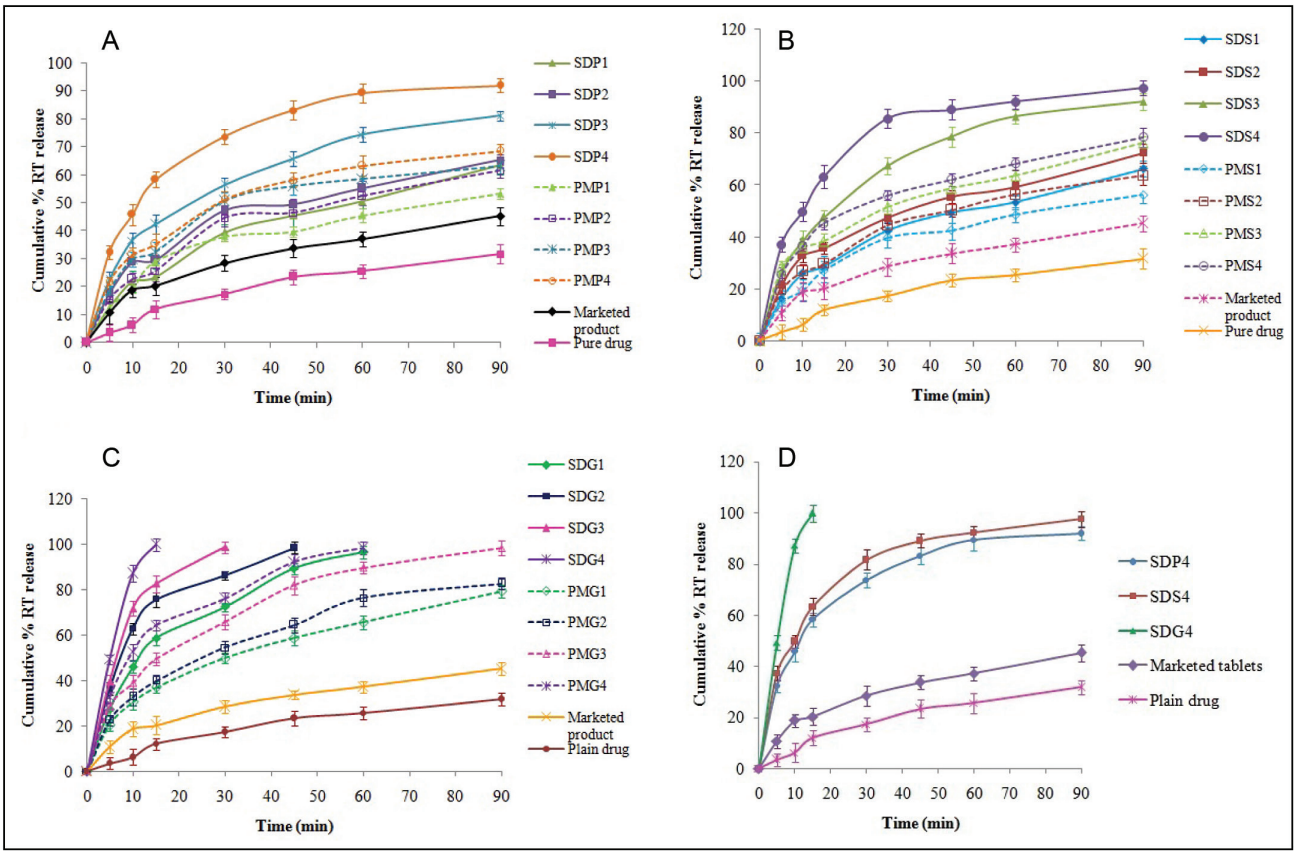

Figure 2: (A) Comparison of in-vitro RT release from PEG 4000 formulations (n = 6). (B) Comparison of in-vitro RT release from PEG 6000 formulations (n = 6). (C) Comparison of in-vitro RT release from Gelucire 50/13formulations (n = 6). (D) Comparison of in-vitro RT release from various formulations (n = 6)

C_{max} 37.29 ± 1.16 µg/mL at T_{max} of 1 h. The AUC of SDG4 formulation was found to be 242.31 ± 3.65 µg-h/mL and that of pure drug was 134.45 ± 2.14 µg-h/mL, respectively. Percentage relative bioavailability of optimized formulation SDG4 was 180.22% in comparison to pure drug.

The decreased t_{max} with significant improvement in the C_{max} of RT from SDG4 formulation compared to pure drug indicates a faster onset of action with improved dissolution and faster absorption rate. Similarly, significant improvement was observed in the AUC of optimized SDG4 formulation compared to pure drug. A significant change was observed in mean residence time of SDG4 (5.59 ± 0.14 h) and pure drug (4.65 ± 0.35 h). The faster onset of action is indicated with significant improvement in PK parameters (C_{max} and AUC), enhanced dissolution, and faster absorption that resulted in bioavailability improvement of RT. Hence, the developed SD with surface adsorbent can be a choice for improving solubility,

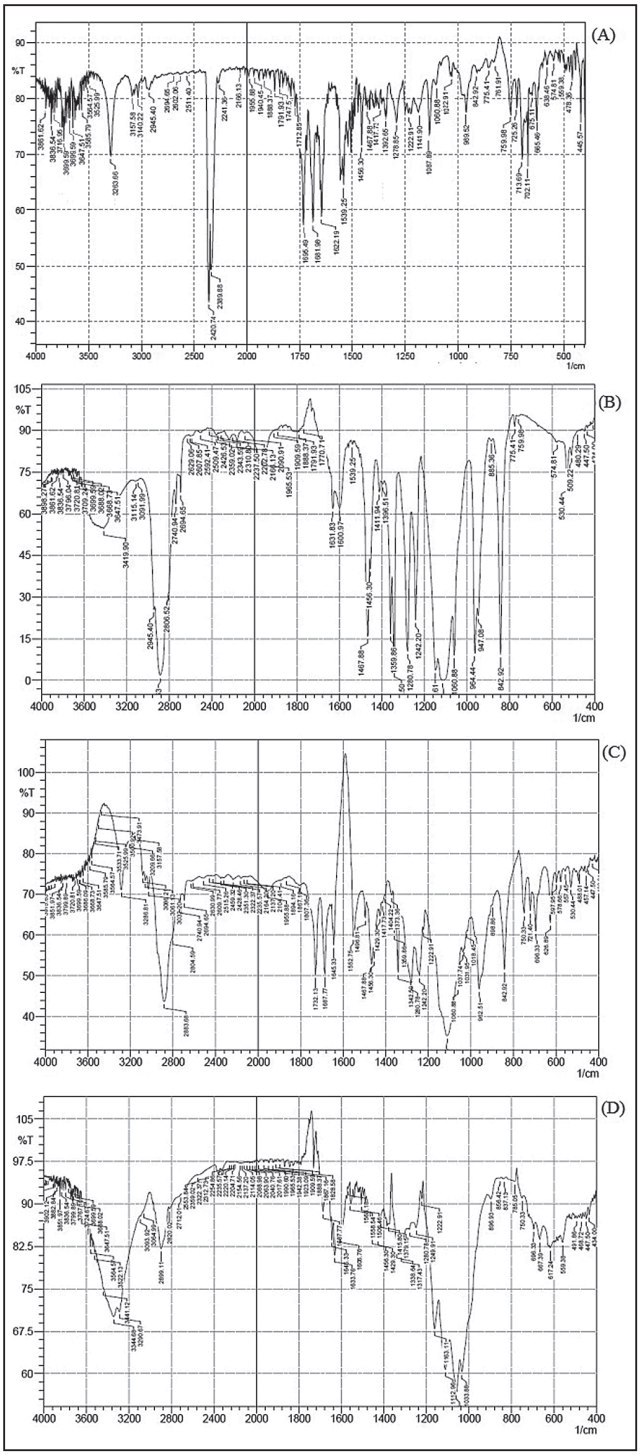

Figure 3: Fourier transform infrared spectrum of a) RT b) Gelucire 50/13 c) PMG4 Physical mixture d) SDG4 optimized formulation

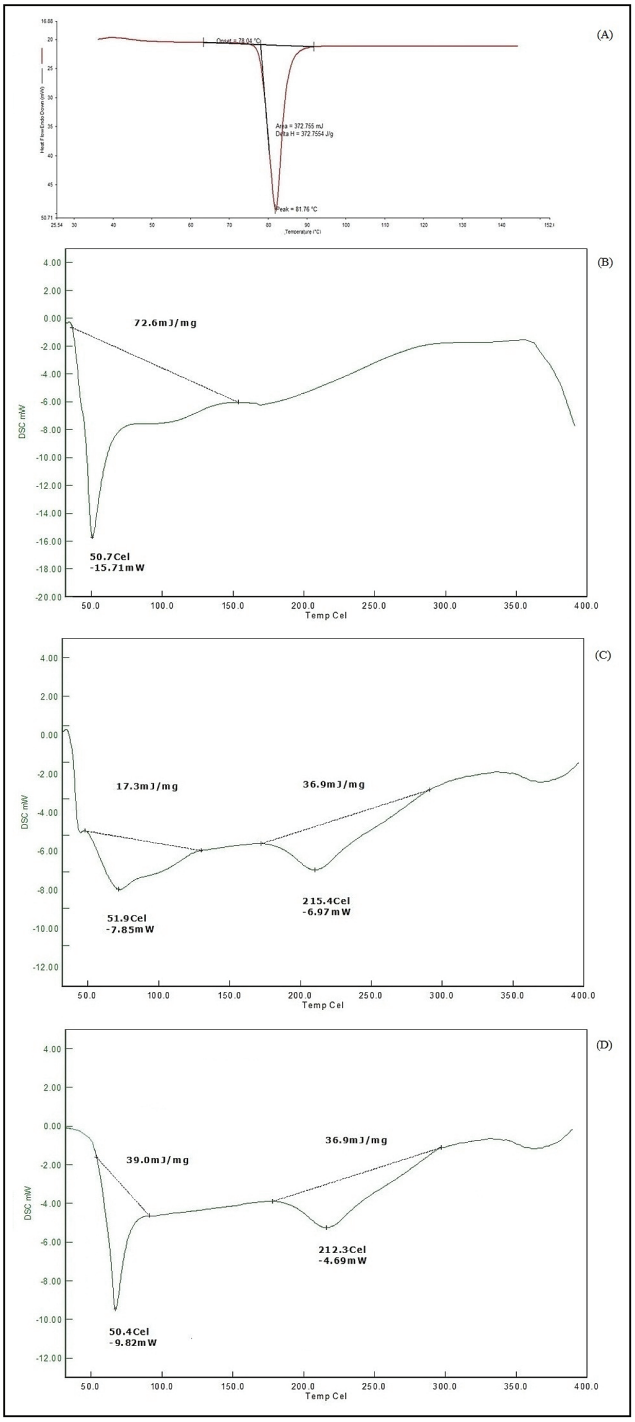

Figure 4: Differential scanning colorimeter thermograms of a) RT b) Gelucire 50/13 c) PMG4 physical mixture d) SDG4 optimized formulation

dissolution, and bioavailability of a poorly aqueous soluble drug, RT.

Conclusion

An effort was made to prepare SDs with surface adsorbents using polyethylene glycols and Gelucire as carrier to formulate RT SSDs, showing the faster drug release with improved flowable characteristics. The presence of Gelucire 50/13 showed significant enhancement of solubility and dissolution rate of poor aqueous soluble RT. *In vivo* bioavailability studies revealed that a considerable enhancement of oral bioavailability of RT from optimized SDG4 containing Gelucire 50/13 than pure drug. Thus, the use of SD with surface adsorbent is a promising method to promote the flow property, stability, and absorption of RT that improves the bioavailability of RT.

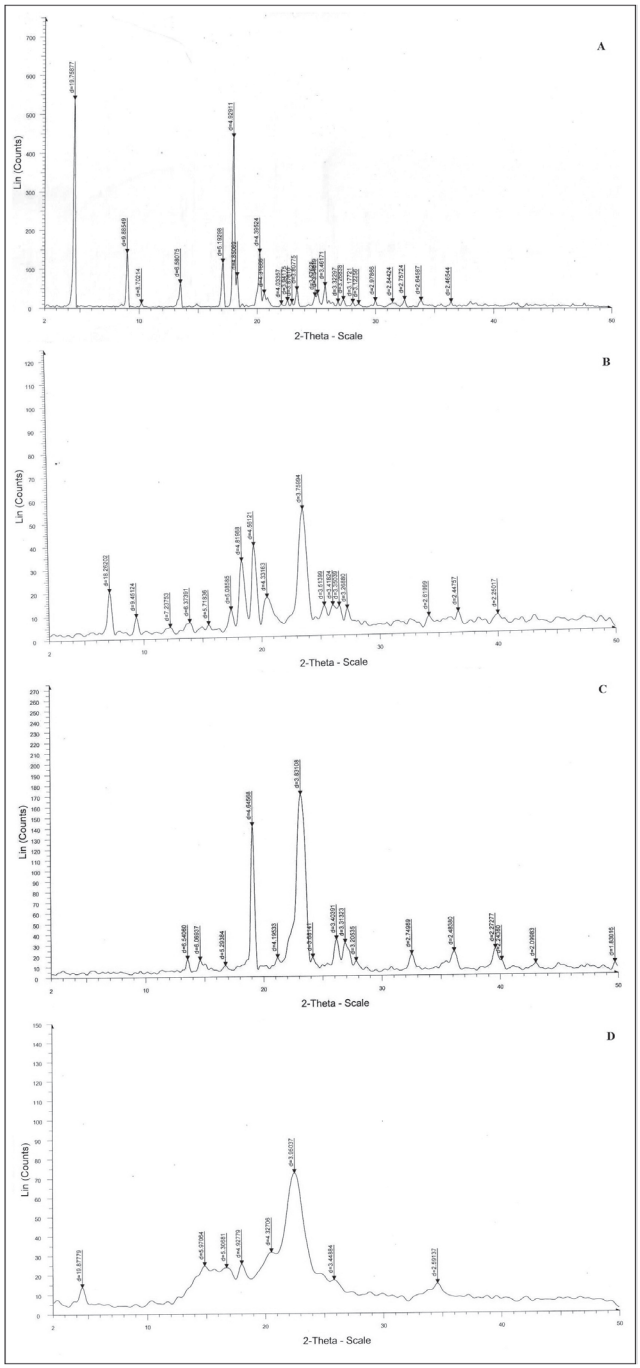

Figure 5: X-ray diffraction patterns of a) RT b) Gelucire 50/13 c) PMG4 Physical mixture d) SDG4 optimized formulation

Table 6: Stability studies of SDG4 optimized formulation ($n = 3$)

Time (min)	Cumulative % RT (mean ± SD)				Similarity factor (F2)
	Before storage	After 1 month of storage	After 2 months of storage	After 3 months of storage	After 6 months of storage	
5	49.18 ± 1.34	48.46 ± 1.73	47.37 ± 1.45	45.84 ± 1.38	42.37 ± 1.47	75.21
10	87.25 ± 1.82	85.14 ± 1.24	82.16 ± 1.72	80.74 ± 1.84	75.28 ± 1.63	
15	99.84 ± 1.53	99.53 ± 1.81	98.52 ± 1.34	98.42 ± 1.12	98.27 ± 1.32	
% Assay	99.25 ± 1.26	99.17 ± 1.34	99.13 ± 1.62	99.09 ± 1.32	99.03 ± 1.14	–

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Nil.

Table 7: PK parameters of RT pure drug and SDG4 formulation (Avg ± SD *n* = 12)

Parameters	RT pure drug	SDG4 formulation	*t*-test at 0.05 Level of Significance
C_{max} (µg/mL)	37.29 ± 1.16	65.38 ± 1.34	Significant
T_{max} (h)	1.00 ± 0.14	0.5 ± 0.12	Not significant
$t_{1/2}$ (h)	3.07 ± 0.21	3.14 ± 0.43	Not Significant
AUC $_{0-\infty}$(µg- h/mL)	134.45 ± 2.14	242.31 ± 3.65	Significant
AUMC$_{0-\infty}$ (µg-h^2/mL)	625.61 ± 11.26	1353.36 ± 13.53	Significant
MRT (h)	4.65 ± 0.35	5.59 ± 0.14	Significant
Relative bioavailability (%)	180.22		–

MRT = mean residence time

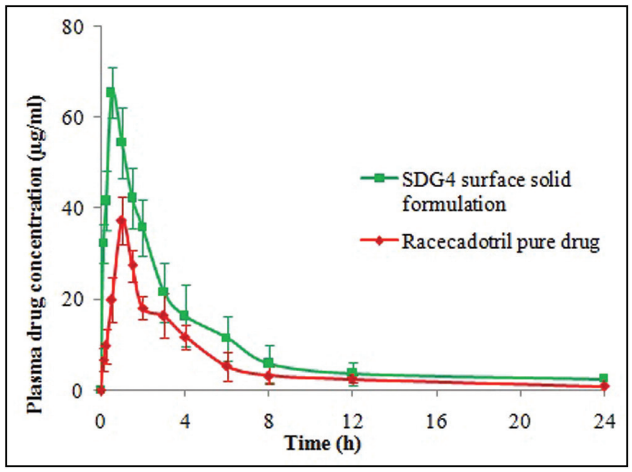

Figure 6: *In vivo* plasma concentrations-time profile of SDG4 formulation and pure RT (*n* = 6)

Conflicts of interest

There are no conflicts of interest.

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