Evaluation of *in vitro* Dissolution Profile and Physicochemical Characterization of Polymer Based Formulations of Sparingly Soluble Rosuvastatin

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ABSTRACT: Rosuvastatin (RVT) is a BCS class II antilipidemic crystalline drug, which exhibits low bioavailability due to its very poor aqueous solubility; therefore, it is challenging to develop a proper formulation of RVT. To enhance solubility and bioavailability of this API, an attempt has been made by implementing solid dispersion technique. Solid dispersion (SD) technique is a solubility enhancing technique where one or more active entities are dispersed in an inert medium (matrix or carrier) at solid state. In this study, different ratios of Kollicoat® IR (KIR) and Kollidon® 90F (KF90) polymers were used with API to prepare various formulations by physical mixing (PM) and SD approaches; here solvent evaporation technique was used whereas methanol was used as solvent which was completely evaporated from the homogenously dispersed system by placing in a water-bath at 60-65°C and then in oven for 30 minutes at 50 °C. Among the formulations, RVT-KF90 SD formulations showed the most promising result in *in-vitro* study in terms of drug release profile (78.04 – 99.21%) in comparison to pure RVT (63.1%) and physical mixing of RVT with those polymers. USP dissolution apparatus type II was used at 37°C ± 0.5°C with 50 rpm to conduct the *in-vitro* experiment. The experiment also unraveled that the dissolution of RVT improved with increasing the amounts of polymers. Subsequently, stability of the developed formulations was conducted by Fourier transforms infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) as well as scanning electron microscopy (SEM). The results obtained from FTIR ensured no involvement of any significant drug-excipient interaction. Moreover, the DSC study signified thermal stability at high temperature. Besides, the SEM micrograph illustrated homogenous distribution of RVT in the polymer and transformation of crystal-like RVT into amorphous formulations.

Key words: Rosuvastatin, low solubility, physical mixing, solid dispersion, solvent evaporation.

INTRODUCTION

Formulating suitable dosage form is highly challenging for drugs which possess low aqueous solubility.[1] The drug's water solubility has a significant impact on its oral dissolution rate. Orally administered medicines' dissolving rate, absorption, and bioavailability are all limited by their water solubility.[1,2] Biopharmaceutical classification system (BCS) categorizes drug substrates into four categories, poorly water soluble drugs fall into the second and fourth category.[2,3] The Noyes-Whiteny equation describes that dissolution rate of a API is directly proportionate to its solubility properties.[4] Among the other factors to improve drug release, solubility is the most important factor to be concerned of.[5-7] Several attempts have been made to upsurge the solubility of poorly soluble APIs from BCS class II group such as- salt formation, nanotechnology, co-crystallization, co-solvency, chemical modification, pH adjustment, hydrotropic,

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solubilizing agents, particle size reduction, physical modification, nanosuspension micronization, alteration of the crystal habit, self-microemulsifying drug delivery system, usage of complexing agents, by different surfactants, microemulsions, dispersion in carriers e.g. solid solution, solid dispersion.[3,8]

Solid dispersion (SD) system refers to the dispersed system where one or more active entities are dispersed in an inert medium (carrier or matrix) at solid state.[9,10] Sekiguchi and Obi in their experiment used hot-melt method to prepare their system and urea as carrier excipient.[9] Although later on hot-melt method became less popular due to some limitations such as active component and carrier must be miscible in molten form, active ingredient and carrier must be also thermo stable in high temperature etc.[9] That's why solvent evaporation method became more popular.[7] Fusion method, milling/co-grinding, spray-drying, supercritical fluid processing, and so on are also some approaches to prepare solid dispersion system in small or large scale.[13] SD system has an advantage over the conventional tablet/capsule as it reduces the crystal properties of drug substrates which cause immediate dissolution of the SD formulated tablet in the gastrointestinal fluid.[11,12]

Rosuvastatin Calcium (RVT) was approved by the US drug regulation authority, USFDA in 2003 as the seventh member of the statin family.[14,15] In early stage of cholesterol biosynthesis, 3-hydroxy-3 methylglutaryl CoA (HMG-CoA) gets converted into mevalonate with the help of HMG-CoA reductase.[14-16] It is hypothesized that the statin family members reduce the cholesterol level by inhibiting HMG-CoA reductase.[14-16] RVT is a fully synthetic statin compound which was discovered by screening a series of pyrimidine-substituted dihydroxy-6-heptenoates consisting of a sulphonyl functional group incorporated to decline lipophilicity and thus increase selectivity for the liver.[15]

RVT is a sparingly soluble crystalline BCS class II drug which is widely used for its antilipidemic activity.[14,17,18] Due to low solubility in water (0.33 mg/ml), this antilipidemic drug demonstrates poor bioavailability (20%) when it is taken orally.[19] To improve the oral bioavailability of RVT hitherto several strives have been made. Among them self-nanoemulsifying drug delivery system[20-23], microparticle based drug delivery system[24-27], liquisolid technology[28,29], solid dispersion technique[30] are some notable approaches.

Kollicoat® IR (KIR) is a graft copolymer of polyethyleleglycol (PEG)-polyvinlylpyrrollidon (PVP) which was introduced by BASF Chemical Co. (Ludwigshafen, Germany) to design an immediate release dosage form.[31] KIR is recommended for preparing SD system because of its interesting non-ionic hydrophilic characteristics as well as along with gastrointestinal tract, its solubility does not change.[32-34] Moreover, it has surface-active characteristics and former studies showed that KIR is effective for SD system preparation which improves bioavailability of some BCS Class II APIs.[32-36] Kollidon® 90F (KF90) is a commercial grade of polyvinylpyrroydone polymer series which is usually used as a binder.[19,37] Potentiality of the aforementioned polymers were first time explored with RVT to enhance dissolution rate preparing SD formulations, since the available data is not enough to justify the polymer combinations required to enhance the dissolution rate of highly valuable drug molecule RVT.

The present study was focused on the enhancement of *in vitro* dissolution rate of RVT by a solid dispersion (SD) system, here solvent evaporation technique was used. The formulations were prepared with two different polymers as carrier, KIR and KF90. The system was further assessed by Fourier transform infrared (FTIR) spectroscopy for compatibility study, differential scanning calorimetry (DSC) for thermal stability checking, and scanning electron microscopy (SEM) for checking the surface morphology of the formulation. Moreover, *in vitro* dissolution studies of SD formulations were compared with the physical mixtures (PMs) which had the same ratio of active and polymers as in SDs as well as with the pure drug.

MATERIALS AND METHODS

Materials. Rosuvastatin calcium (RVT), Kollicoat® IR (KIR) and Kollidon® 90F (KF90) were purchased from BASF, Germany. Sodium dihydrogen phosphate, sodium phosphate dibasic dihydrate, methanol, sodium hydroxide were bought from Merck, Germany. Other chemical agents and distilled water were collected and prepared from the Biopharmaceutics laboratory, Department of Pharmaceutical Technology, University of Dhaka, Bangladesh.

Methods

Preparation of physical mixing formulations (PMs). Pure active RVT and polymers (KIR and KF90) were weighed accurately by four-digit digital balance (Mettler Toledo, Switzerland). The measured RVT was mixed and triturated separately with KIR and KF90 in a properly cleaned mortar at different ratios of 1:1, 1:2, 1:3, and 1:4 to ensure homogenous mixture. Then the mixtures were sieved (36-micron test sieve, 300 x 75 mm) to get the uniformity of the particles in the mixtures. Finally, the mixing formulations were named as F1, F2, F3, F4, F5, F6, F7 and F8 and kept in a desiccator at ambient temperature before further analysis **(**Table 1**)**.

Preparation of SD formulations by solvent evaporation technique. Methanol was used as solvent to prepare solid dispersion system in this method. Properly weighed RVT-KIR mixture (1:1, 1:2, 1:3, 1:4) and RVT-KF90 mixture (1:1, 1:2, 1:3, 1:4) were taken into a beaker, and sufficient amount of methanol was added to dissolve the mixture. Subsequently, the mixture was stimulated for sufficient time to ensure a homogenous dispersion. In order to evaporate the solvent completely, the homogenously dispersed system was placed in a water-bath (placed in a closed environment) at 60-65°C. The resultant dried residue was then kept in oven for 30 minutes at 50 °C to confirm complete removal of solvent and moisture. The moisture content of SD formulations was determined by moisture analyzer (Mettler Toledo, Switzerland) and was found less than 1% for all the formulations. Finally, the prepared SDs were persevered in a desiccator for 24 hours followed by named as S1, S2, S3, S4, S5, S6, S7 and S8. Before further analysis, SDs were crushed and sized uniformly using different sieve fractions and stored in desiccator **(**Table 1**)**.[38]

Table 1. Rosuvastatin (RVT) formulations by physical mixing (PM) and solid dispersion (SD) techniques.

Formulation Codes	Ingredients			
	Rosuvastatin Calcium (RVT) (mg)	Kollicoat® IR (KIR) (mg)	Kollidon® 90F (KF90) (mg)	Methanol
F1	10	10	-	Q.S.
F2	10	20	-	Q.S.
F3	10	30	-	Q.S.
F4	10	40	-	Q.S.
F5	10	-	10	Q.S.
F6	10	-	20	Q.S.
F7	10	-	30	Q.S.
F8	10	-	40	Q.S.
S1	10	10	-	Q.S.
S2	10	20	-	Q.S.
S3	10	30	-	Q.S.
S4	10	40	-	Q.S.
S5	10	-	10	Q.S.
S6	10	-	20	Q.S.
S7	10	-	30	Q.S.
S8	10	-	40	Q.S.

Determination of the wavelength (λ_{max}). Firstly, 10 mg of pure RVT was dissolved in 100 ml of methanol, which was the primary stock solution (100 µg/ml). Then 10 µg/ml solution was prepared from the stock solution by adding distilled water. After preparing the stock solution, absorbance was measured by UV spectrophotometer (Shimadzu-1700, Shimadzu Corp, Kyoto, Japan) at the range of 200- 400 nm, and sharp peak was found at 242 nm.[39]

Preparation of pH 6.8 buffer medium. Sodium dihydrogen phosphate (3.1202 g) and sodium phosphate dibasic dihydrate (2.8392 g) were weighed correctly and dissolved in 800 ml distilled water. Cyberscan 500 pH meter, Singapore was used to check and adjust the pH at 6.8 using sodium hydroxide and 0.1 N hydrochloric acid. Then the amount of the medium was adjusted to 1000 ml after obtaining the desired pH.[39]

Calibration curve of RVT. A series of concentration of 0, 4, 8, 12 and 16 µg/ml of RVT was prepared through dilution with phosphate buffer of pH 6.8 from the stock solution of pure RVT of concentration 100 µg/ml. Then spectrophotometric analysis was performed by UV spectrophotometer at 242 nm **(**Figure 1**)**.

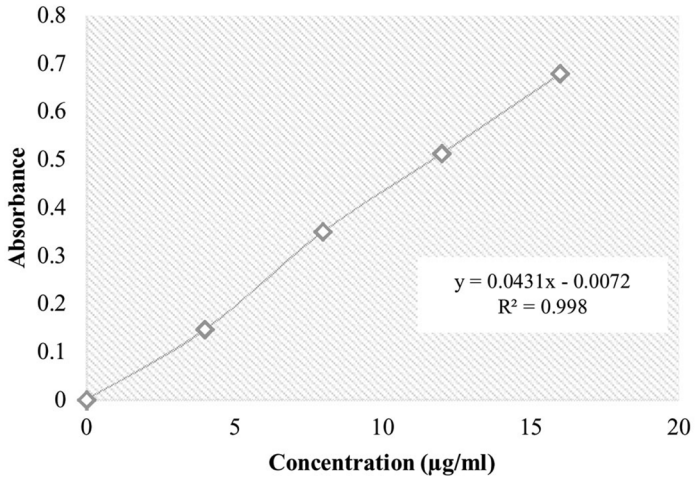

Figure 1. Calibration curve of RVT in phosphate buffer medium.

Dissolution studies of pure RVT, PMs and SDs. USP Type II dissolution apparatus (Erweka, Germany) stabled at 37±0.5°C and 50 rpm was employed in this experiment to study the release kinetics of pure RVT, PMs and SDs system.[18] 900 ml phosphate buffer was used as dissolution medium and at every 10 minutes' interval, 5 ml sample was withdrawn followed by filtration with Filter Paper No. 41 (Whatman plc, UK) and analyzed at 242 nm by UV-Visible spectrophotometer. To maintain the sink condition, dissolution medium was replenished simultaneously with 5 ml of buffer media immediately after each sample withdrawal.[18]

Drug release kinetics and statistical analysis. Release of drug from its relevant dosage form is a major factor for evaluating its pharmacological effect. Therefore, estimation of drug release kinetics has an importance in pharmaceutical science. Different kinetics models such as zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models were used to know the RVT release pattern from PMs and SDs formulations. One-way analysis of variance (ANOVA) was also performed to dictate how drug release varies among these formulations.[40]

Fourier transform infrared spectroscopic (FTIR) analysis. RVT, KIR, KF90 and their optimized PMs and SDs formulations were scanned by FTIR (FTIR Spectrum Two TM L160000T of Perkin Elmer, USA) in a range of 4000-400 cm^{-1} with the scanning resolution of 1 cm^{-1}.

Thermal stability analysis by differential scanning calorimetry (DSC). DSC thermograms of RVT, KIR, KF90 and their optimized PMs and SDs formulations were obtained by DSC-60 thermal analyzer (Shimadzu corporation, Japan). 2.28–2.95 mg prepared samples were taken for the analysis and scanning was performed at a heating rate of 10°C/min from 25°C - 500°C.

Surface morphology analysis by scanning electron microscope (SEM). Scanning Electron Microscope SEM-8100FM (Shimadzu, Japan) was used to analyze the surface of pure RVT, PMs and SDs by 2000X to 5500X magnification.

Results and Discussion

Drug release from PMs formulation of RVT. After performing dissolution studies, release rate of pure RVT was observed 63.1% in 60 minutes **(**Figure 2a**)**. The formulations prepared by physical mixing with polymers KIR and KF90 showed an improved drug release rate than that of pure RVT. After 60 minutes, formulations F1, F2, F3 and F4 showed a drug release rate of 68.11%, 70.51%, 76.44% and 78.39% respectively (Figure 2a). Whether the formulations F5, F6, F7 and F8 showed a release rate of 71.38%, 74.44%, 82.39% and 84.14% respectively in 60 minutes **(**Figure 2a**)**. These two polymers, KIR and KF90, which were used in the PMs are hydrophilic polymers. KIR has been applied in different SD formulations to boost the dissolution rate of indomethacin and also to increase the dissolution rate of clonazepam by solvent evaporation technique due to wetting ability. KF90 increases the dissolution rate of various poorly aqueous soluble drugs formulated using solid dispersion techniques such as lovastatin, itraconazole and repaglinide.[41-45]

Drug release study from RVT SD formulations prepared by solvent evaporation method. RVT solid dispersion (S1 to S8) formulations were prepared by solvent evaporation technique. Here also 1:1, 1:2, 1:3 and 1:4 ratios were considered for preparing SD formulations. *In vitro* dissolution study was accomplished for 60 minutes. SD formulations, S1, S2, S3 and S4 exhibited cumulative drug release rate of 83.39%, 92.8%, 98.23% and 98.97% respectively whereas S5, S6, S7 and S8 formulations displayed cumulative drug release rate of 78.04%, 83.47%, 96.66% and 99.21% after 60 minutes. All the eight SD formulations showed much better release pattern than the pure RVT **(**Figure 2b**)**.

Optimization of the formulations. Among the PM formulations made by KIR and KF90, F4 and F8 gave better cumulative percent drug release (78.39% and 84.14% respectively) compared to their respective other PM formulations whereas S4 and S8 had given the best cumulative percent of drug release (98.97% and 99.21% respectively) after 60 minutes among the respective SD formulations. Their cumulative percent of drug releases were compared to the pure RVT as well as PM formulations and found that S8 was the optimized formulation on the basis of cumulative percent drug release (Figure 2c). Though S8 was the best among all the formulations, however all other SD formulations maintained the USP mentioned drug release limit criteria after 60 minutes (Figure 2b).

RVT is crystalline in nature and there might be several reasons for better release rate in SD formulations with the water-soluble polymer KIR and KF90. This might be due to the reduction in crystallinity or its physical conversion into an amorphous shape. This might have somehow attributed to a reduction in particle size and an upsurge in the surface area thus resulting in a better dissolution rate.[46]

From cumulative percent of drug release pattern, among the PMs, F4 and F8 gave better drug release percent but S4 and S8 had given the best cumulative percent of drug release after 60 minutes (Figure 2c). Increasing the concentration of KIR and KF90 upturn the solubility of RVT both in PMs and SDs. From the comparison it also revealed that the release rate from different formulation prepared by different techniques increasing order would be SDs using KF90> SDs using KIR > PMs using KF90> PMs using KIR (Figure 2c).

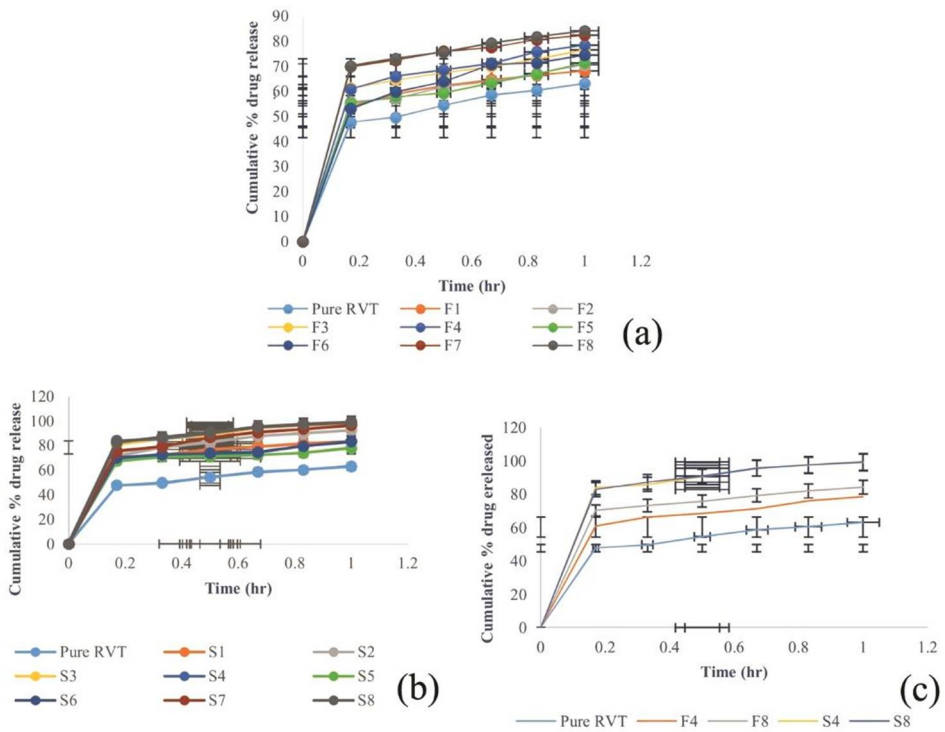

Figure 2. Comparison of cumulative percent drug release of pure RVT with (a) PM formulations (F1 to F8), (b) SD formulations (S1 to S8) prepared by solvent evaporation technique and (c) Comparison of formulations of SDs, PMs and pure RVT.

Drug release kinetic study and statistical analysis. Drug release kinetic study was achieved by different kinetic models like, zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas model. All the PM formulations were well fitted to the Higuchi model compared to other models and among the formulations F6 was the best fitted, where the R^2 value was 0.8922 (Table 2). As Higuchi model was established for the study of water soluble and low soluble drugs in semisolid or solid matrices, it indicates that the formulations had developed solubility after physical mixing. Furthermore, SD formulations were fitted with the first order kinetics where S7 was the best fitted formulation with R^2 value of 0.9473 (Table 2). However, according to the Korsmeyer-Peppas Model, all the formulations as well as the pure RVT followed the Super Case-II transport system as the value of n was greater than 0.85 (Table 2).

To further inspect the effect of concentration of experimented polymers (KIR and KF90) on the dissolution profile of RVT, one-way ANOVA (analysis of variance) was performed to determine whether there were any statistically significant differences between the means of two groups. Results revealed that the p-values were <0.005 for all the formulations which indicate the significant difference of the formulations. So, it supports that all the formulations showed the increased cumulative percent of drug release, when the concentrations of polymers were increased accordingly (Table 3).

Fourier transform infrared spectroscopy (FTIR). To assure compatibility of pure RVT with the experimented excipients, FTIR assays were conducted. Prominent peaks of the untreated active ingredient were found at 3417.86 (alcohol group), 2927.94 (O-H stretching carboxylic acid), 1550.77 (carbonyl group), 1151.50 (sulfone group) and 964.41 (aromatic C-H bending) cm^{-1} (Figure 3A).[47,48]

Additionally, in physical mixtures of KIR and KF90 with pure RVT, prominent peaks of RVT were found at almost the same position (KIR: 3429.43, 2926.01, 1548.84 cm^{-1}; KF90: 3427.51, 2936.52, 1548.84 cm^{-1}) which ensure pure drug remained unchanged and no interaction with the polymers occurred in the physical mixture formulations (Figures 3D, 3E). The spectra of the solid dispersion systems, RVT-KIR, RVT-KF90 solid dispersion system also maintained consistency with the pure RVT spectrum **(**KIR: 3427.51, 2924.09 cm^{-1}; KF90: 3429.33, 2926.01, 1548.91 cm^{-1}; Figures 3F, 3G). The findings confirm that there was no significant modification took place while the pure drug was dispersed in the polymers utilizing solvent evaporation solid dispersion technique. As there was no stability issue, these polymers could be used readily to improve the dissolution profile RVT in large-scale production.

Table 2. **Drug release kinetic of pure RVT, PMs and SDs formulations.**

Formulation Codes	Drug: Polymer	Zero Order		First Order		Higuchi Model		Hixson- Crowell Model		Korsmeyer-Peppas Model	
		R^2	K_0	R^2	K_1	R^2	K_h	R^2	K_{HC}	R^2	n
F1	1:1	0.5694	50.502	0.6864	-0.3928	0.8327	64.046	0.6448	-1.1379	0.8608	1.0297
F2	1:2	0.5889	51.795	0.7229	-0.4134	0.8404	64.908	0.6755	-1.1858	0.8604	1.0309
F3	1:3	0.5652	55.286	0.7182	-0.4845	0.8238	70.025	0.6628	-1.3398	0.8567	1.0509
F4	1:4	0.5902	58.002	0.7630	-0.5330	0.8439	72.757	0.7018	-1.4476	0.8610	1.0591
F5	1:1	0.6011	52.127	0.7399	-0.4185	0.8458	64.870	0.6915	-1.1977	0.8614	1.0298
F6	1:2	0.6542	58.149	0.8123	-0.5030	0.8922	71.241	0.7594	-1.4007	0.8762	1.0519
F7	1:3	0.5236	58.814	0.6936	-0.5873	0.7928	75.922	0.6291	-1.5399	0.8490	1.0728
F8	1:4	0.5396	60.534	0.7321	-0.6312	0.8049	77.561	0.6601	-1.6268	0.8513	1.0771
S1	1:1	0.4878	53.526	0.6026	-0.4726	0.7613	70.150	0.5586	-1.3005	0.8519	1.0773
S2	1:2	0.5218	58.227	0.6918	-0.5808	0.7861	74.973	0.6281	-1.5222	0.8620	1.1045
S3	1:3	0.5962	72.519	0.9346	-1.2753	0.8499	90.832	0.8345	-2.6149	0.8535	1.1181
S4	1:4	0.5347	71.588	0.9374	-1.7046	0.8922	71.241	0.8179	-2.9767	0.8518	1.1217
S5	1:1	0.5389	60.465	0.7253	-0.6254	0.8059	77.570	0.6556	-1.6177	0.8430	1.0554
S6	1:2	0.5937	69.724	0.8859	-0.9850	0.8498	87.510	0.7876	-2.2363	0.8469	1.0692
S7	1:3	0.5532	72.120	0.9413	-1.5525	0.8175	91.970	0.8224	-2.8724	0.8611	1.1131
S8	1:4	0.5502	73.265	0.9034	-2.0066	0.8130	93.434	0.9046	-3.8799	0.8510	1.1202
RVT	-	0.6309	48.063	0.7462	-0.3493	0.8725	59.295	0.7065	-1.0384	0.8704	1.0072

Differential scanning calorimetry (DSC) analysis. DSC study demonstrated that the melting point of the pure RVT, KIR, and KF90 was in 86.38°C, 115.49°C, and 154.13°C respectively (Figure 4A, 4B, 4C). Increase in melting point was observed for RVT-KIR PM formulations whereas the RVT-KF90 PM formulations remained stable up to 152.03°C (Figure 4D, 4E). DSC thermogram of PM formulations displayed different sharp endothermic peaks from the pure RVT which is due to the crystallinity form change of this drug.[47] In case of SD formulations, the melting point was in between pure RVT and KIR for RVT-KIR SD formulations, and a decrease in melting point was observed for the RVT-KF90 SD formulations (Figure 4F, 4G). The peaks of the pure RVT were disappeared in the DSC curve of SD formulations due to the conversion of RVT crystal structure to the amorphous state.[47]

Scanning electron microscopic (SEM) analysis. Surface morphology of the pure RVT, PMs and SDs have been inspected by performing SEM analysis. The micrograph provides a detailed illustration of drug particle state before and after the treatment with excipients. Untreated pure RVT crystal appeared to be with rough surfaces where crystals of PM of KIR with RVT displayed shiny

surfaces (Figure 5A, 5B). Reduced crystallinity was observed for the PM of KF90 (Figure 5C). The feature explains better dissolution properties of the F5, F6, F7, and F8 formulation corresponding to the F1, F2, F3, and F4 formulation respectively. Furthermore, in SD of KIR with RVT, the pure drug particles were found to be dispersed in the excipient (Figure 5D). On the other hand, SD of KF90 with RVT was in amorphous state **(**Figure 5E). Herein, the excipient and the pure drug content formed a homogenous dispersion system and obtained a better dissolution profile than other formulations.

Table 3. **ANOVA analysis of PMs and SDs (solvent evaporation method) formulations of RVT with two polymers in different ratios.**

Formulation Codes	Drug: Polymer	Source of Variation	SS	Df	Ms	F	P-value	F_{crit}
F1	1:1	Between Groups	1923.252	1	1923.252	3.680	0.079	4.747
		Within Groups	6271.361	12	522.613			
F2	1:2	Between Groups	1973.744	1	1973.744	3.740	0.077	4.747
		Within Groups	6332.943	12	527.745			
F3	1:3	Between Groups	2917.458	1	2917.458	5.005	0.045	4.747
		Within Groups	6994.697	12	582.891			
F4	1:4	Between Groups	3171.938	1	3171.938	5.271	0.040	4.747
		Within Groups	7220.782	12	601.732			
F5	1:1	Between Groups	1911.082	1	1911.082	3.637	0.081	4.747
		Within Groups	6306.207	12	525.517			
F6	1:2	Between Groups	2392.333	1	2392.333	4.216	0.062	4.747
		Within Groups	6809.059	12	567.422			
F7	1:3	Between Groups	4418.688	1	4418.688	6.692	0.024	4.747
		Within Groups	7923.964	12	660.330			
F8	1:4	Between Groups	4606.109	1	4606.109	6.852	0.022	4.747
		Within Groups	8067.088	12	672.257			
S1	1:1	Between Groups	4594.145	1	4594.145	6.838	0.023	4.747
		Within Groups	8061.748	12	671.812			
S2	1:2	Between Groups	6155.114	1	6155.114	8.071	0.015	4.747
		Within Groups	9150.976	12	762.581			
S3	1:3	Between Groups	7981.174	1	7981.174	9.490	0.010	4.747
		Within Groups	10091.81	12	840.9839			
S4	1:4	Between Groups	8488.484	1	8488.484	9.826	0.008	4.747
		Within Groups	10366.9	12	863.908			
S5	1:1	Between Groups	3594.888	1	3594.888	5.865	0.032	4.747
		Within Groups	7355.074	12	612.923			
S6	1:2	Between Groups	4274.56	1	4274.560	6.543	0.025	4.747
		Within Groups	7839.36	12	653.280			
S7	1:3	Between Groups	6972.322	1	6972.322	8.678	0.012	4.747
		Within Groups	9641.446	12	803.454			
S8	1:4	Between Groups	8388.317	1	8388.317	9.794	0.009	4.747
		Within Groups	10277.3	12	856.442			

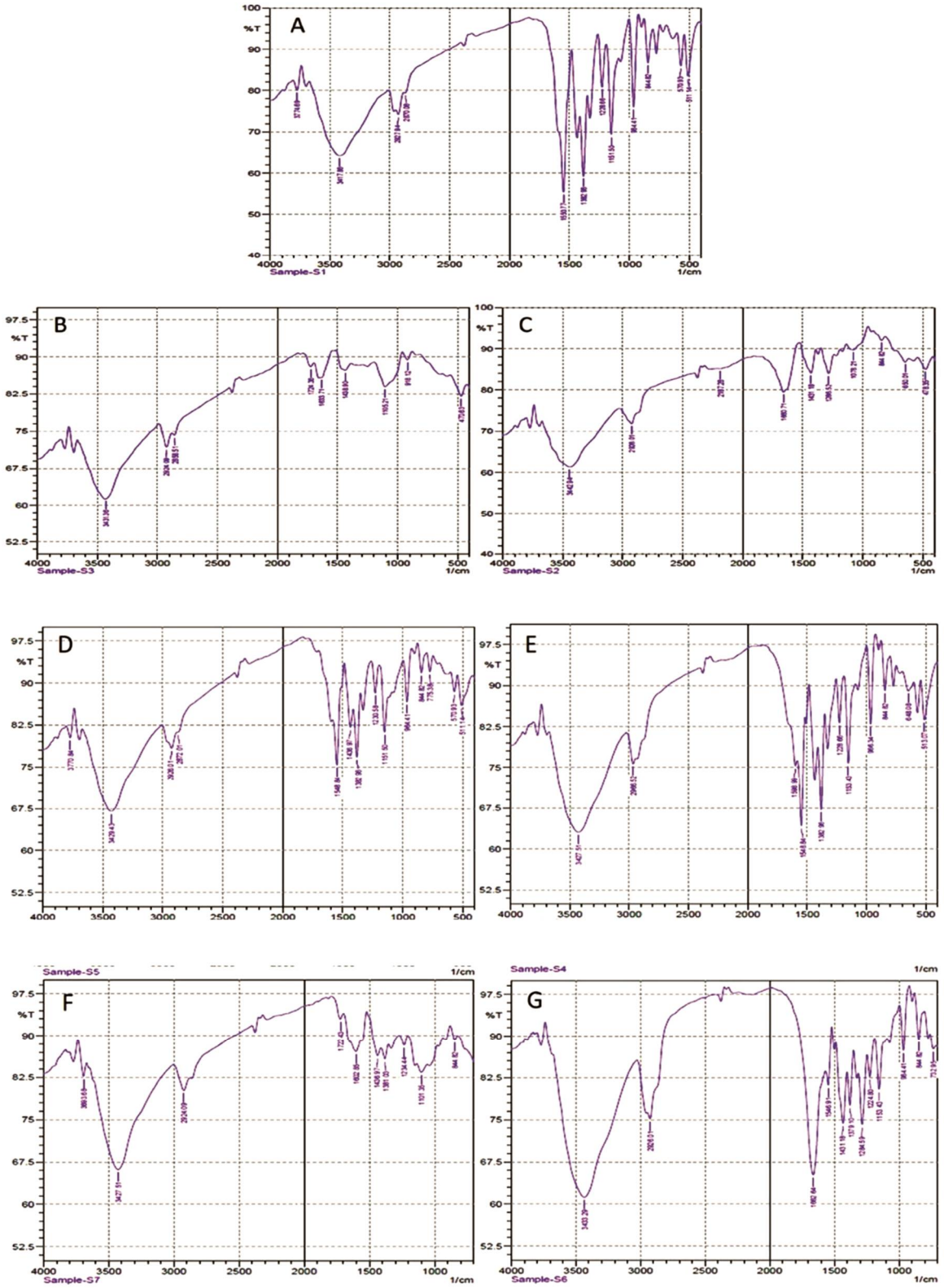

Figure 3. FTIR spectrum of (A) RVT, (B) KIR, (C) KF90 (D) PM of RVT with KIR, (E) PM of RVT with KF90, (F) SD of RVT with KIR, (G) SD of RVT with KF90.

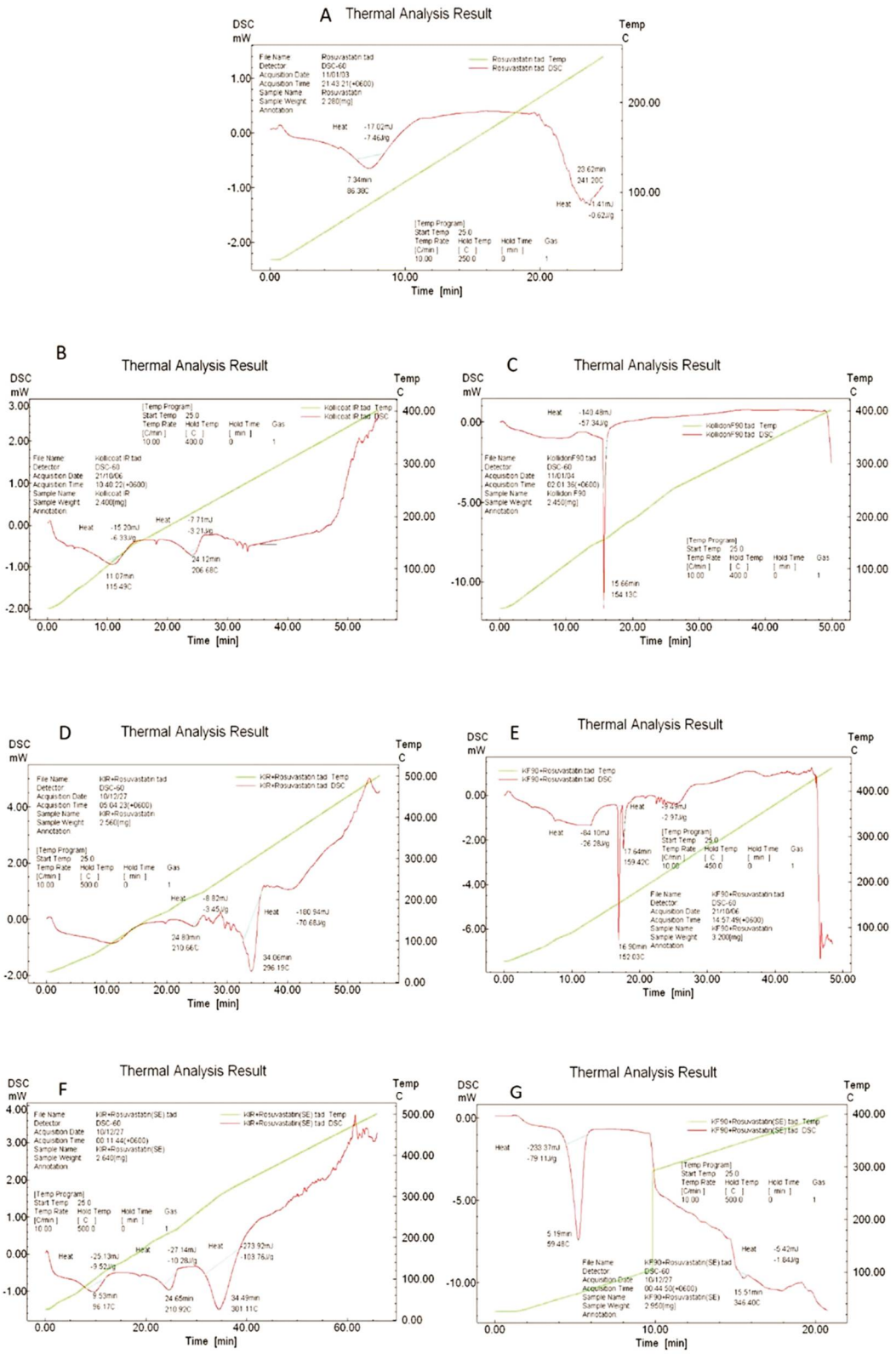

Figure 4. DSC thermogram of (A) RVT, (B) KIR, (C) KF90 (D) PM of RVT with KIR, (E) PM of RVT with KF90, (F) SD of RVT with KIR and (G) SD of RVT with KF90.

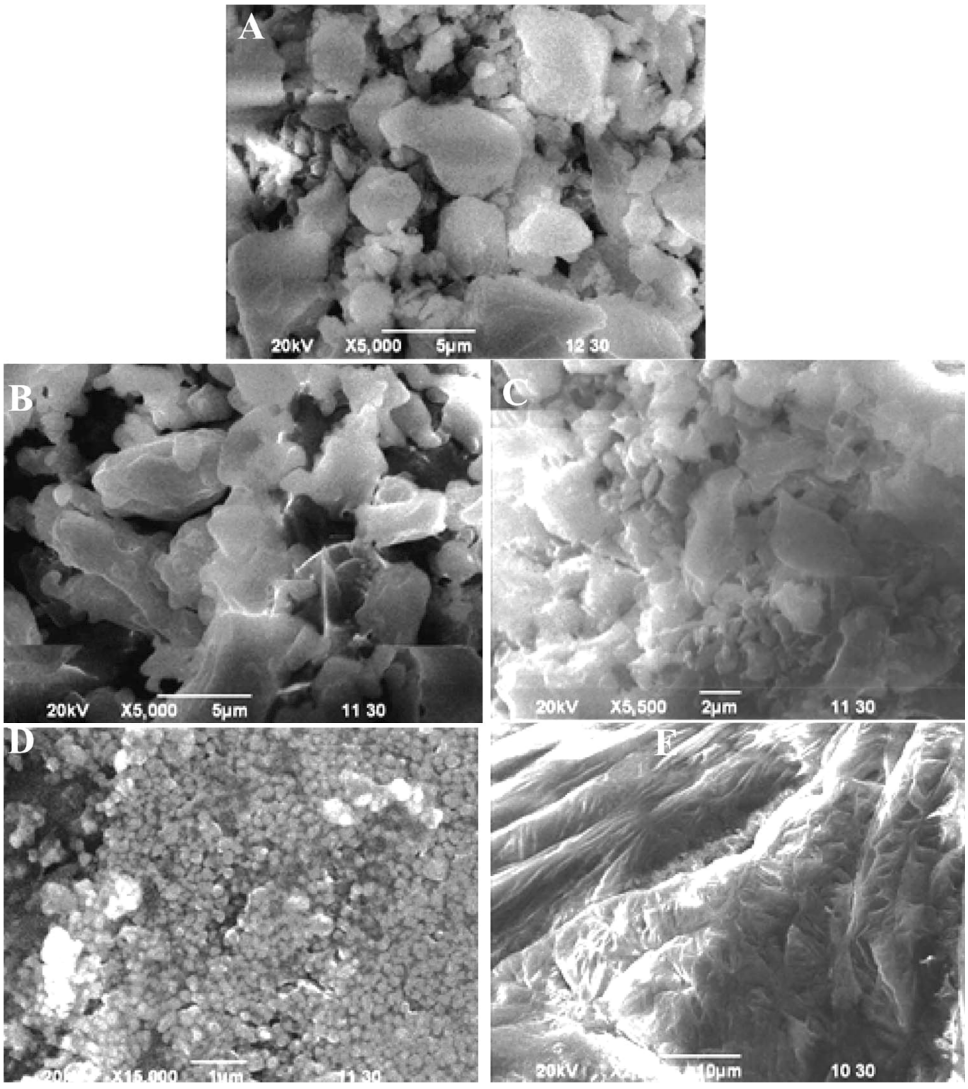

Figure 5. SEM of (A) RVT at 5000 magnifications, (B) PM of RVT with KIR at 5000 magnifications, (C) PM of RVT with KF90 at 5500 magnifications, (D) SD of RVT with KIR at 15000 magnifications and (E) SD of RVT with KF90 at 2000 magnifications.

CONCLUSION

Current study investigated that how the dissolution profile of sparingly soluble RVT can be improved by KIR and KF90 using a solid dispersion (SD) approach (solvent evaporation technique). Among the prepared formulations, S8 had given the best cumulative percent drug release after 60 minutes. This revealed that increasing concentration of KIR and KF90 improved the dissolution of RVT both in PMs and SDs. From the comparison, it is also demonstrated that the release rate from different prepared formulations, increasing order would be SDs using KF90> SDs using KIR> PMs using KF90> PMs using KIR. The physicochemical stability and amorphous characteristics of these formulations were also supported by FTIR, DSC and SEM data. No significant peak deviations were observed in FTIR results for PMs and SDs of KIR with RVT in comparison to the pure RVT spectrum. Reduced crystallinity of RVT was also obtained in PM formulations and SD formulations through SEM analysis, where it was illustrated that the RVT in KF90 dispersion system almost transformed into amorphous state which was responsible for better dissolution profile. The study suggested that KF90 is a potential drug carrier for RVT SD system to

improve the dissolution of pure RVT, and the optimized ratio for the RVT to KF90 was found 1:4. However, further study is needed for ensuring more precise SD formulations and *in vivo* assays for manufacturing SD RVT tablet dosage form.

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