



SOLUBILITY ENHANCEMENT OF REGORAFENIB VIA SOLID DISPERSION STRATEGY USING HYDROPHILIC CARRIERS

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ABSTRACT

The present study investigated the molecular interactions governing the solid dispersion behavior of BCS Class-II drug Regorafenib using hydrophilic carriers, with the aim of enhancing its solubility. Solid dispersions at 1:1 and 1:2 drug-to-carrier weight ratios were prepared using PEG 4000 and PVP K90 by kneading method. Fourier-transform infrared (FTIR) spectroscopy was employed to investigate functional-group interactions and structural modifications associated with solubility enhancement, while saturation solubility and dissolution profiles were evaluated using USP Apparatus II. Distinct shifts and broadening of characteristic absorption bands, including N–H/O–H stretching at approximately 3400 cm⁻¹, C=O stretching at 1718–1720 cm⁻¹, Amide II vibration around 1550 cm⁻¹, and C–O–C stretching at 1200–1250 cm⁻¹, indicated hydrogen-bonding interactions between Regorafenib and the polymer matrices. Comparative analysis revealed greater amorphous character in PVP K90-based systems than in PEG 4000-based systems. These findings demonstrate the important role of polymer–drug hydrogen bonding in modulating the solubility and structural characteristics of Regorafenib in solid dispersions. Pure RGF exhibited extremely slow dissolution owing to its poor aqueous solubility. In contrast, all SDs showed a significant enhancement in the dissolution rate. The dissolution parameter analysis confirmed that F4 (RGF:PVP K90, 1:2 ratio) was the optimized formulation, exhibiting the shortest T50, highest DE, and greatest RDR. Overall, the study confirms that the solid dispersion technique can be effectively employed to enhance the solubility and dissolution of poorly soluble drug Regorafenib.

KEYWORDS: Regorafenib, Solid dispersions, PVP K90, PEG 4000, FTIR, Solubility studies.

INTRODUCTION

Solubility plays an important role in drug disposition, since the maximum rate of passive drug transport across a biological membrane, is the product of permeability and solubility. Poor solubility has been identified as the cause of numerous drug development failures. For drugs that have very poor aqueous solubility, the rate at which the drug dissolves (dissolution) are often the slowest step and therefore exhibits a rate limiting effect on drug bioavailability.^[1] Therefore, one of the major current challenges of the pharmaceutical industry is related to strategies that improve the water solubility of drugs. Consequently, great efforts have been made to improve oral bioavailability of poorly water-soluble drug by increasing their dissolution rate through various techniques.^[2]

Solid dispersion formulation represents one of the most effective and practical strategies for enhancing the solubility and oral bioavailability of poorly water-soluble drugs.^[3] As defined by Chiou and Riegelman,^[4] a solid dispersion system is “a solid-state dispersion of one or more active substances within an inert carrier or matrix, prepared through fusion, solvent evaporation, or melting–solvent techniques.” In these systems, the matrix is typically hydrophilic, while the drug is hydrophobic. Depending on the method of preparation and the interaction between components, solid dispersions can exist in various forms, including simple eutectic mixtures, solid or glass solutions, glass suspensions, amorphous precipitates in crystalline carriers, and complex or compound forms.^[5,6] Many approaches have been employed for preparing solid

dispersions (SDs), such as the melting method, hot melt extrusion, solvent evaporation process, fusion and kneading method, spray drying technique, co-grinding and freeze drying, supercritical fluid technology, etc. A wide variety of hydrophilic materials such as PEGs, Gelucires, Poloxamers, PVP, Sugar, Urea etc., are available as carriers, which are employed in the formulation of solid dispersions. By reducing drug particle size to the absolute minimum, and hence improving drug wettability, bioavailability may be significantly improved.

A novel API, regorafenib monohydrate (RGF) is a small molecule non-biologic anticancer drug based on

effectiveness and safety profile and preferentially administered by gastrointestinal (GI) route⁷. Recently approved by the US FDA in 2012, as well as by the Japan and European Medicines Agency (EMA) in 2013, it is employed in the treatment of metastatic colorectal cancers and advanced gastrointestinal tumors (GIST)⁸. The model drug belongs to class II compound (low solubility, high permeability), according to the Biopharmaceutics Classification System (BCS) and has been approved for the treatment of metastatic colorectal cancer by the FDA in 2012⁹. Hence, the current investigation was aimed to enhance the solubility of RGF using polyethylene glycol (PEG) 4000 and PVP K90 as hydrophilic carriers through solid dispersion technique.

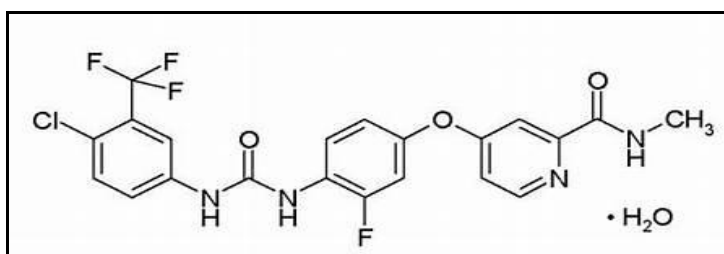


Fig. 1: Chemical structure of RGF.

MATERIAL AND METHODS

Materials

The pure sample of Regorafenib monohydrate (RGF MH) was obtained from well reputed research laboratory. All reagents, solvents used were of analytical grade (SD Fine Chemicals, Bengaluru, India). Double distilled water was used throughout the experiment.

Determination of absorption maxima (λ max) and calibration curve

100 mg of RGF was dissolved in 100 ml of methanol. 1 ml of this solution was diluted serially with pH 6.8 to get

desired concentration (10 μ g/ml) and subjected for UV scanning in the range of 200-400 nm using double beam UV-VIS spectrophotometer. The absorption maxima for RGF were obtained at 266.5 nm with a characteristic peak as shown in Figure 2. Then, a standard curve was prepared in the concentration range of 2-10 μ g/ml. The optical density values of resulting solutions measured at 266.5 nm. The concentration versus optical density values is plotted and shown in the Figure 3.

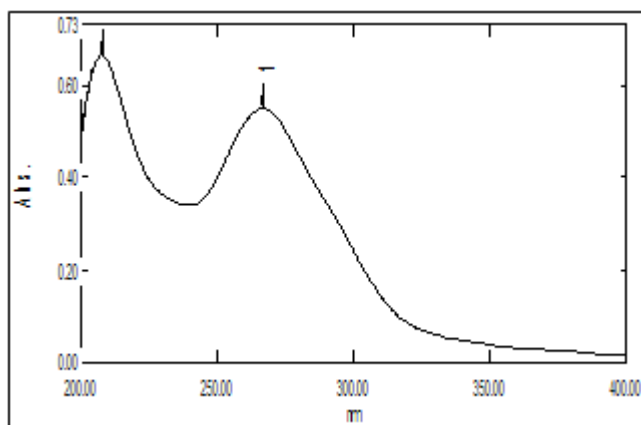


Fig. 2: Absorption maxima of RGF in pH 6.8

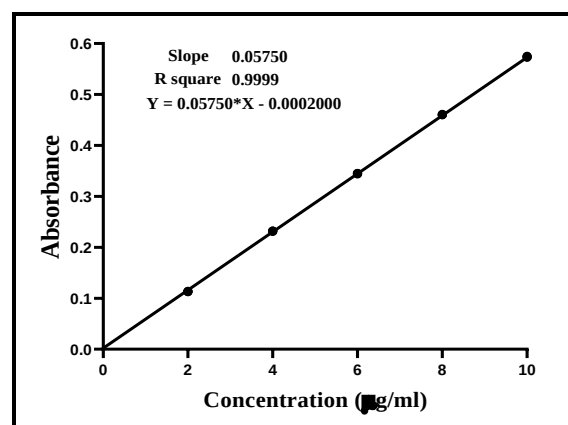


Fig. 3 Calibration curve of RGF

Preparation of physical mixtures (PMs)

The physical mixtures were prepared in the ratio of 1:1 and 1:2 w/w of drug to carrier. Accurately weighed quantities of RGF with PEG 4000 and RGF with PVP K90 were blended continuously for 5 -10 min using a

glass mortar and pestle. They were passed through 120-mesh sieve and kept in desiccators for other studies.

Preparation of solid dispersion (SDs)^[10]

Kneading method (KM) was used for the preparation of RGF solid dispersion in the ratio of 1:1 and 1:2 w/w of

drug to carrier as shown in Table 1. Accurately weighed quantities of RGF with PEG 4000 and RGF with PVP K90 were taken in glass mortar with small volume of solvent blend of ethanol and water. The thick slurry was

kneaded for 1h and then dried at 45°C until dryness. The dried mass was pulverized and sieved through sieve no.120 and stored in desiccator for further evaluation.

Table 1: Formulae of RGF SDs.

Batch code	Formulation	RGF:Carrier	Method
F1	RGF:PVP K90	1:1	Physical mixture
F2	RGF:PEG 4000	1:1	Physical mixture
F3	RGF:PVP K90	1:1	Kneading method
F4	RGF:PVP K90	1:2	Kneading method
F5	RGF:PEG 4000	1:1	Kneading method
F6	RGF:PEG 4000	1:2	Kneading method

Drug content uniformity

In each case PMs and SDs, sample equivalent to 10 mg of RGF was accurately weighed and transferred to 100 ml volumetric flask and extracted in methanol. The volume was made up to 100 ml with pH 6.8. From this 1 ml is subsequently diluted to 10 ml with buffer and assayed for drug content by measuring at 266.5 nm using pH 6.8 buffer as blank. The RGF content was calculated from the calibration curve. The experiments were conducted in triplicate.

Saturation solubility studies

Pure RGF (20 mg), PMs, SDs equivalent to 20 mg of RGF were added to 15 ml of pH 6.8 containing in a series of 25 ml stoppered conical flasks. The mixtures were shaken for 24 h in rotary flask shaker at room temperature $37^{\circ}\text{C} \pm 1^{\circ}\text{C}$. Appropriate aliquots were withdrawn and filtered through 0.45 μm membrane filter, suitably diluted and filtrate so obtained was analyzed spectrophotometrically at 266.5 nm. Shaking was continued until three consecutive estimations were the same. All solubility measurements were performed in triplicate.

Fourier transform infrared spectrometry (FT-IR)

Solid samples were prepared by the potassium bromide disc method and scanned for absorbance from 400–4000 cm^{-1} . The spectra were obtained on a Perkin Elmer 1600 series, (USA) for pure RGF, and solid dispersions of RGF with PEG 4000 and PVP K90.

In vitro dissolution studies

The in vitro dissolution studies of pure RGF, PMs and SDs were performed using the dissolution test apparatus (USP XXII Type II) by the powder dispersion method i.e., powder samples were spread over the dissolution medium. RGF 10 mg or physical mixture or SDs equivalent to 10 mg of drug was used in each test. The dissolution studies were carried out using 900 ml of pH 6.8, maintained at $37 \pm 0.5^{\circ}\text{C}$ with paddle rotation maintained at 50 rpm. The release of RGF was measured by withdrawing 5 ml aliquot at regular time intervals, filtered, suitably diluted and assayed spectrophotometrically at 266.5 nm. Fresh medium was added to maintain a constant volume after each sampling. All dissolution experiments were conducted in triplicate.

Dissolution results of drug alone, PMs and SDs were computed by using dissolution software PCP DISSO V3.

Statistical analysis

Statistical analysis was performed to assess the dissolution of RGF from PMs, and SDs using Graph Pad Instat V9.0. The percent dissolution efficiency (DE_{30}) values obtained from dissolution studies of SDs were compared with one-way ANOVA at 95% confidence interval using Dunnett multiple comparison test. A significance level of $P < 0.05$ was used to denote statistical significance in all cases.

RESULTS AND DISCUSSIONS

Solid dispersions of RGF were prepared using hydrophilic carriers such as PVP K90 and PEG 4000 in different drug-to-carrier ratios (1:1 and 1:2) by physical mixture and kneading methods. The percentage yield of SDs was in the range of 95 to 98 % of the initial amounts taken. The prepared formulations (F1–F6) were further evaluated for solubility enhancement and dissolution behavior for selected formulations based on the solubility improvement. All prepared SDs of RGF with PVP K90 and PEG 4000 were found to be fine and free flowing.

Drug Content Uniformity

The percentage drug content results of PMs and all SDs of RGF with both carriers were found to be in the range of 95.56 to 98.74 %. Low standard deviation (SD) values (i.e., < 1) indicated uniform drug distribution in all prepared batches.

Solubility Studies

Solubility of pure drug, PMs and SDs was determined at $37^{\circ}\text{C} \pm 1^{\circ}\text{C}$, in pH 6.8. The results are displayed in the Table 2. The aqueous solubility of pure RGF was found to be 0.005 ± 0.005 mg/mL, confirming its highly hydrophobic nature and BCS Class II characteristics. Preparation of physical mixtures with PVP K90 and PEG 4000 produced only a slight improvement in solubility indicating that simple blending was insufficient to markedly enhance drug dissolution. In contrast, SDs significantly improved the solubility of RGF. Among the PVP K90-based formulations, solubility increased to 0.670 ± 0.003 mg/mL at a 1:1 drug-to-polymer ratio (F3) and further to 1.610 ± 0.006 mg/mL at a 1:2 ratio (F4).

Similarly, PEG 4000-based SDs improved solubility to 0.262 ± 0.003 mg/mL (F5) and 0.477 ± 0.003 mg/mL (F6) for the 1:1 and 1:2 ratios, respectively. These findings demonstrate that increasing the polymer concentration enhanced the solubility of RGF, with PVP K90 exhibiting a greater solubilizing effect than PEG 4000.

The superior performance of PVP K90 can be attributed to its excellent hydrophilicity, high aqueous solubility, strong hydrogen-bonding capability, and ability to inhibit drug crystallization, thereby maintaining RGF in an amorphous, readily dissolving state.^[11] Consequently, formulation F4 (RGF:PVP K90, 1:2) exhibited the highest solubility (1.610 mg/mL), representing an approximately 322-fold increase compared with pure RGF.

Table 2: Solubility of pure drug RGF, PMs and SDs.

Batch	Type	Carrier	Ratio	Solubility (mg/mL)	Mean $\pm$ SD
RGF	Pure drug	—	—	0.005	0.005 ± 0.005
F1	PM	PVP K90	1:1	0.055	0.055 ± 0.004
F2	PM	PEG 4000	1:1	0.036	0.036 ± 0.002
F3	SD	PVP K90	1:1	0.670	0.670 ± 0.003
F4	SD	PVP K90	1:2	1.610	1.610 ± 0.006
F5	SD	PEG 4000	1:1	0.262	0.262 ± 0.003
F6	SD	PEG 4000	1:2	0.477	0.477 ± 0.003

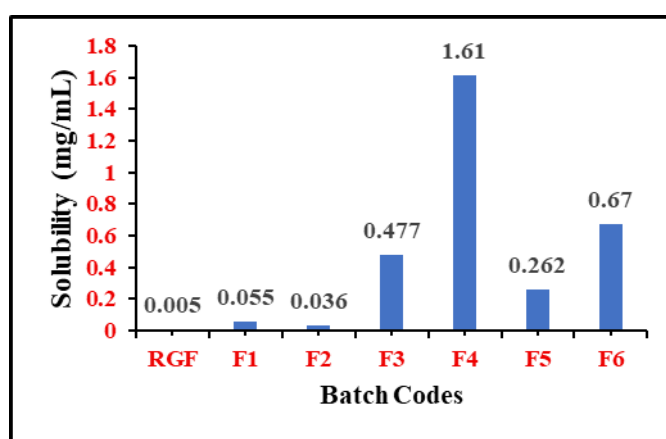


Fig. 4: Solubility profile of pure drug RGF, PMs and SDs.

Fourier transform infrared spectrometry (FT-IR)

To study the possible interactions between the pure drug RGF with polymers in the solid state, IR spectra of RGF-PEG 4000 and RGF-PVP K90 SDs were compared with the drug alone, as shown in Figure 5. The IR spectrum of RGF exhibited characteristic peaks for amide (C=O, N-H) at 1718 cm^{-1} and 1545 cm^{-1} , aromatic system (C=C,

C-H) at $1600\text{--}750\text{ cm}^{-1}$, ether (C-O-C) at $1200\text{--}1250\text{ cm}^{-1}$, halogen substitution (C-F, C-Cl) at 1040 cm^{-1} and 650 cm^{-1} , aliphatic and aromatic C-H at $2950\text{--}3020\text{ cm}^{-1}$ and hydrogen-bonded N-H/O-H at $3500\text{--}3250\text{ cm}^{-1}$. Both polymers modify the microenvironment around aromatic and amide functionalities of RGF.

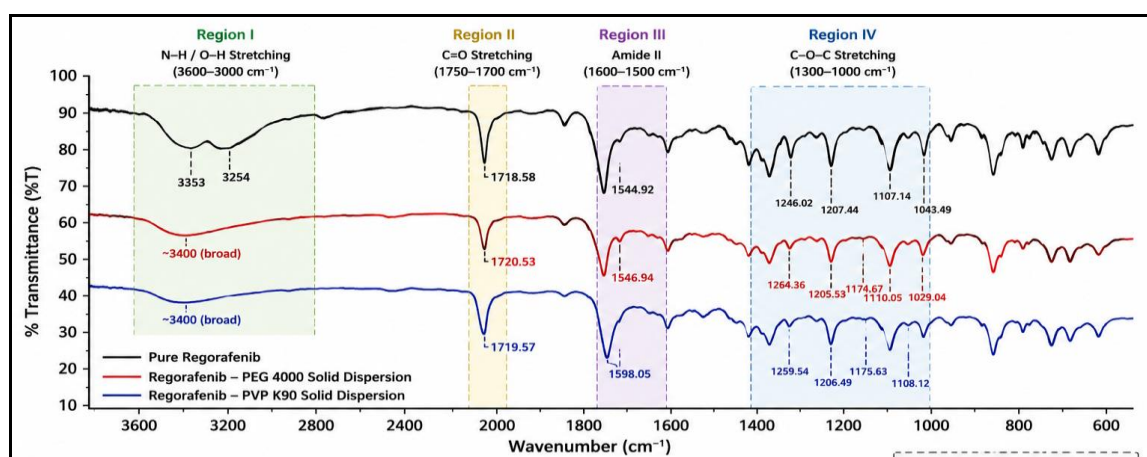


Fig. 5: Comparative FTIR Analysis of RGF SDs with pure Drug.

Table 3: Comparative FTIR peak shifts and functional group assignments of RGF in PEG 4000 and PVP K90 SDs.

Region	Vibrational Assignment	Pure RGF (cm ⁻¹)	PEG 4000 SD (cm ⁻¹)	PVP K90 SD (cm ⁻¹)	Observation / Interpretation
I (3600-3000 cm ⁻¹)	N-H / O-H stretching	3353, 3254	~3400 (broad)	~3400 (broad)	Broadening indicates hydrogen bonding with polymer
II (1750-1700 cm ⁻¹)	C=O stretching	1718.58	1720.53	1719.57	Slight shift confirms drug-polymer interaction
III (1600-1500 cm ⁻¹)	Amide II (N-H bending + C-N stretching)	1544.92	1546.94	1598.05	More pronounced shift in PVP SD indicates stronger interaction
IV (1300-1000 cm ⁻¹)	C-O-C stretching (ether region)	1246, 1207, 1107, 1043	1264, 1175, 1029	1259, 1206, 1176, 1108	Increased intensity confirms polymer incorporation

The FTIR spectrum of the RGF: PVP K90 SDs retained the characteristic peaks of RGF with slight shifts and reduced peak intensities as shown in figure 5. The slight broadening and reduction in peak intensity may be attributed to hydrogen-bonding interactions between the carbonyl groups of PVP K90 and the functional groups of RGF. Similarly, the RGF:PEG 4000 SDs exhibited all the characteristic peaks of RGF with only minor shifts in peak positions and reduced intensities. No new absorption bands or disappearance of major characteristic peaks were observed, indicating the absence of any chemical incompatibility or degradation during formulation. However, FTIR analysis showed greater broadening and attenuation of the characteristic RGF peaks in the PVP K90 formulations, indicating stronger hydrogen-bonding interactions and a higher degree of molecular dispersion compared to PEG 4000

formulations. These spectroscopic observations correlated well with the solubility and dissolution studies.

Dissolution behaviour of SDs: When the goal of preparing SDs is to improve solubility and dissolution rate of the drug in question, the results of dissolution test experiments are of prime importance in assessing the success of the objective. All SDs were tested for dissolution properties and compared with the pure RGF to assess the benefits of preparing SDs. Pure RGF exhibited slow dissolution, with $14.099 \pm 0.91\%$ released at 90 min. In contrast, dissolution study indicated a marked improvement of dissolution rate of RGF in SDs as shown in table 4.

Table 4: In Vitro Dissolution Data of RGF and SDs.

Time (min)	RGF	F3	F4	F5	F6
10	2.167 ± 0.45	33.209 ± 1.57	45.730 ± 1.57	23.818 ± 1.57	28.513 ± 1.57
20	5.048 ± 1.57	45.914 ± 1.57	58.505 ± 1.56	34.906 ± 1.56	39.627 ± 1.57
30	6.641 ± 1.56	58.689 ± 1.55	71.349 ± 1.57	46.055 ± 1.57	50.803 ± 1.55
45	9.808 ± 1.56	68.404 ± 1.56	81.133 ± 1.57	55.700 ± 1.56	60.474 ± 1.57
60	11.427 ± 1.57	78.170 ± 1.57	87.839 ± 1.56	62.267 ± 1.57	68.632 ± 1.58
90	14.099 ± 0.91	87.989 ± 1.57	94.580 ± 1.54	73.564 ± 1.57	78.398 ± 1.59

Among the formulations, F4 (RGF:PVP K90, 1:2) exhibited the highest dissolution rate, achieving approximately 94-95% cumulative drug release within 90 min. This was followed by F3 (RGF:PVP K90, 1:1), which released nearly 88-89% of the drug during the

same period. The PEG 4000-based formulations also enhanced the dissolution of regorafenib, with F6 (RGF:PEG 4000, 1:2) and F5 (RGF:PEG 4000, 1:1) exhibiting cumulative drug releases of approximately 78% and 73%, respectively.

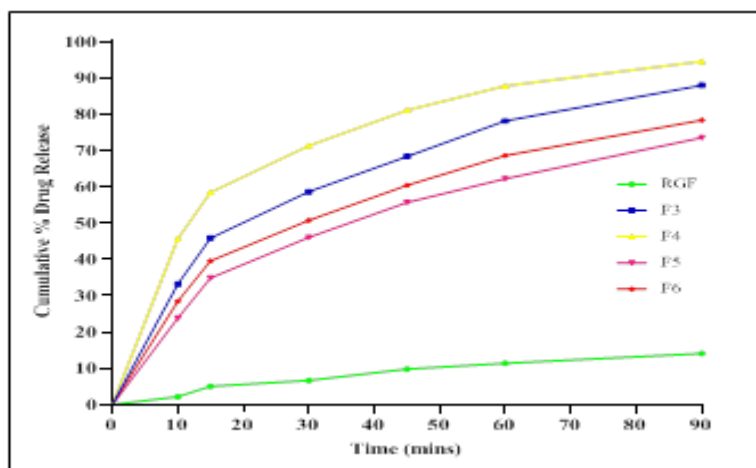


Fig. 6: Comparative dissolution profile of pure RGF and SDs.

The dissolution parameters, including T_{50} , Dissolution Efficiency (DE_{10} , DE_{30} , DE_{60}), Mean Dissolution Time (MDT_{30}), and Relative Dissolution Rate (RDR_{30}), were calculated to compare the dissolution performance of pure RGF and SDs and displayed in the table 5. Pure RGF exhibited a T_{50} value of 314.6 min, indicating its extremely slow dissolution owing to its poor aqueous solubility. In contrast, all SDs showed a remarkable

reduction in T_{50} , demonstrating a significant enhancement in the dissolution rate. Among the formulations, F4 (RGF:PVP K90, 1:2) exhibited the lowest T_{50} (12.1 min), followed by F3 (23.2 min), F6 (31.5 min), and F5 (39.2 min). The substantial reduction in T_{50} confirms that the incorporation of RGF into hydrophilic polymer matrices markedly accelerated drug dissolution.

Table 5: Various dissolution parameters of RGF, SDs of F3-F6.

Parameter	RGF	F3	F4	F5	F6
T_{50} (min)	314.6	23.2	12.1	39.2	31.5
DE_{10} (%)	1.08	16.6	22.86	11.91	14.26
DE_{30} (%)	3.51	36.16	46.64	27.25	31.8
DE_{60} (%)	6.47	52.29	63.5	41.09	45.64
MDT_{30} (min)	14.14	11.52	10.39	12.25	11.59
RDR_{30}	1.0	10.3	13.28	7.76	9.05

The DE values further supported these findings. The DE_{10} of pure RGF was only 1.08%, whereas the SDs showed values ranging from 11.91% to 22.86%. Similarly, the DE_{30} increased from 3.51% for the pure drug to 27.25–46.64% for the SDs, while the DE_{60} increased from 6.47% to 41.09–63.50%. Among all formulations, F4 consistently exhibited the highest DE at all sampling intervals (DE_{10} = 22.86%, DE_{30} = 46.64%, and DE_{60} = 63.50%), demonstrating its superior dissolution performance.

The MDT_{30} further confirmed the improved dissolution behavior of the SDs. Pure RGF exhibited an MDT of 14.14 min, whereas SDs showed lower MDT values ranging from 10.39 to 12.25 min. Formulation F4 exhibited the lowest MDT (10.39 min), indicating the fastest dissolution among all formulations, while F3 (11.52 min) and F6 (11.59 min) also demonstrated rapid dissolution. Lower MDT values indicate that the drug dissolves more rapidly from the formulation, which is desirable for improving the oral absorption of poorly water-soluble drugs.

The RDR_{30} also showed a marked improvement over the pure drug. Formulation F4 exhibited the highest RDR_{30} value (13.28), indicating that it dissolved approximately 13.2 times faster than pure RGF during the initial 30 min. The remaining formulations also demonstrated enhanced dissolution rates, with RDR_{30} values of 10.30 (F3), 9.05 (F6), and 7.76 (F5).

The enhanced dissolution characteristics of the PVP K90-based formulations may be attributed to the strong hydrogen-bonding interactions between RGF and PVP K90, improved wettability, reduced particle aggregation, inhibition of drug recrystallization, reduced drug particle size, increased effective surface area, thereby stabilizing RGF in a molecularly dispersed state within the polymeric matrix.^[12]

Although PEG 4000 also improved dissolution by enhancing wettability, its effect was comparatively less pronounced than that of PVP K90. These observations are consistent with the FTIR, solubility, and dissolution profile results, all of which identified PVP K90 as the more effective carrier for enhancing the dissolution of RGF. Further, the rate of dissolution increases as the

concentration of PVP K90 increases in SDs. The higher polymer concentration provided better molecular dispersion of the drug and enhanced the wettability of drug particles, resulting in faster dissolution.^[13,14]

Overall, the dissolution parameter analysis confirmed that F4 (RGF:PVP K90, 1:2) was the optimized formulation, exhibiting the shortest T_{50} , highest DE, and greatest RDR. These findings demonstrate that increasing the concentration of PVP K90 significantly enhanced the dissolution behavior of RGF and justified its selection for further incorporation into mucoadhesive microspheres in the present study.

CONCLUSION

Solid dispersions provided a substantial improvement in the aqueous solubility and dissolution of RGF compared with the pure drug and corresponding physical mixtures and SDs. PVP K90 produced greater enhancement than PEG 4000, and increasing the carrier ratio from 1:1 to 1:2 further improved performance. The RGF:PVP K90 1:2 formulation (F4) showed the highest saturation solubility (1.610 ± 0.006 mg/mL), approximately 322-fold higher than pure RGF, together with the most rapid and efficient dissolution profile. Further, FTIR findings indicated retention of the characteristic drug bands without evidence of major chemical incompatibility.

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CONFLICT OF INTEREST: The Authors declare no conflict of interest.

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