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Characterization and *In vitro* Dissolution Assessment of Pitavastatin-polyvinyl Pyrrolidone and Kollicoat®IR Solid Dispersions Prepared by Solvent Evaporation and Fusion Methodologies

Ishtyaque Mikrani[1], Kazi Milenur Rahman Prattay[2], Md. Raihan Sarkar[1], K.M. Yasif Kayes Sikdar[1], Mashiur Rahman[3] and Md. Abdus Samadd[4]

[1]Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka
Dhaka-1000, Bangladesh
[2]Department of Clinical Pharmacy and Pharmacology, Faculty of Pharmacy, University of Dhaka
Dhaka-1000, Bangladesh
[3]Bangladesh Reference Institute for Chemical Measurements (BRiCM), Dhaka-1205, Bangladesh
BCSIR Laboratories, BCSIR, Dhaka-1205, Bangladesh
[4]Department of Pharmacy, School of Pharmaceutical Sciences, State University of Bangladesh
Dhaka-1205, Bangladesh

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Abstract

Pitavastatin (PTV) is a potent lipid lowering drug that acts on hepatocytes by blocking the 3-hydroxy-3-methylglutaryl-CoA reductase enzyme. As a Biopharmaceutical Classification System (BCS) Class II drug, PTV possesses very low water solubility; hence, poor bioavailability leads to poor drug delivery to the target organ. The study aims to develop various PTV solid dispersion (SD) formulations and to investigate the release profile of PTV SD systems. Different PTV physical mixing and SD formulations were prepared using polyvinylpyrrolidone (Kollidon®90F) and Kollicoat®IR hydrophilic polymers by fusion and solvent evaporation approaches. The efficacy of the formulations was evaluated by *in vitro* PTV release studies. Subsequently, the characterization of SD formulations was performed using thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), and scanning electron microscopy (SEM). The *in vitro* release studies confirmed that all the developed formulations showed a comparatively better release percentage (75.31–98.45%) than the pure PTV (61.76%) after 60 min. Additionally, the outcomes showed that raising the concentration of both polymers improved PTV's ability to dissolve. In comparison to physical mixing formulations, SD formulations made using fusion and solvent evaporation processes performed better during dissolution. The TGA, DSC, and FTIR studies confirmed that the tested SD formulations (1:2, 1:3 ratios) were stable at high temperatures with a reduction in crystallinity and no notable interaction between the drug and polymers. The SEM analysis showed that the PTV was evenly spread out in the carriers and that the crystal-like structure of the PTV had changed into an amorphous form.

Key words: Pitavastatin, solid dispersions, dissolution, Kollicoat®IR, Kollidon®90F.

Introduction

Solubility is one of the key factors in achieving the preferable concentration of active pharmaceutical ingredient (API) in the systemic blood circulation that worthwhile produces a desirable therapeutic effect (Tambosi *et al*., 2018). Low scale aqueous solubility of API is a challenging issue for drug absorption and bioavailability and requires a higher dose than usual to achieve pharmacological action after oral administration (Messa and Ampati, 2016; Tambosi *et al*., 2018). The Biopharmaceutical Classification System (BCS) is the scientific approach that allows

Corresponding author: Md. Raihan Sarkar, E-mail: raihan.rezvi@du.ac.bd
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the classification of drugs based upon two parameters i.e. solubility and permeability and it comprise of four classes (Arrunátegui *et al*., 2015). BCS Class-II drugs possess characteristics of low aqueous solubility and high intestinal permeability (Nair *et al.*, 2012). There are various techniques to upturn the solubility of BCS Class-II drugs such as reduction of particle size, micro-emulsion, pH adjustment, solid dispersion, co-solvency, micellar solubilization, prodrugs etc. are considered as traditional approaches whereas, nano suspension, salt formation, micronization, self-emulsifying systems, spray drying are classified as advance or newer approaches (Kansara *et al.*, 2015). Among these, water-soluble molecular complexes, solid dispersion, micronization, lyophilization, co-precipitation and microencapsulation etc. are of the most significant formulation techniques that have been used to improve the water solubility and dissolving properties of BCS class II medications (Kapure *et al*., 2013; Nikghalb *et al*., 2012). Solid dispersion approach has some clear advantages over other techniques such as easiness of dosage form preparation, simplicity of optimization, and ease of reproducibility etc. (Chiou and Riegelman, 1971; Nikghalb *et al.*, 2012). The solid dispersion technique successfully reduces the particle size of the drug and converts the state of an API from one state to another, i.e., from a crystalline to a shapeless amorphous state (Nikghalb *et al*., 2012). In order to improve the solubility/dissolution properties and oral bioavailability of BCS class II molecules, a number of carriers, including various grades of polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methylcellulose, sugar, mannitol, polyvinylpyrrolidone, gelucires, natural gums, urea, hydroxypropyl methylcellulose phthalate, chitosan, eudragits are scrutinized (Nikghalb *et al.*, 2012; Prajapati *et al*., 2007; Singh *et al*., 2011).

Pitavastatin (PTV) is a statin class drug that lowers the level of cholesterol in the body by dropping the production of cholesterol in the liver (Figure 1) (Mukhtar *et al*., 2005).

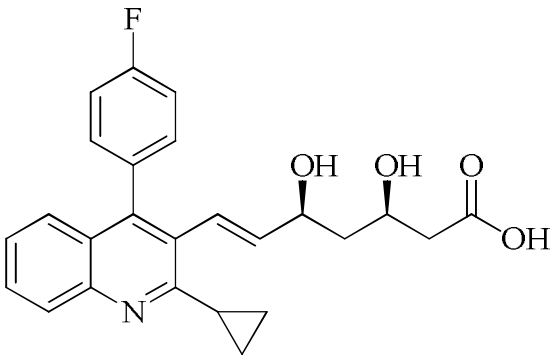

Figure 1.The structure of pitavastatin (PTV).

Pitavastatin (PTV) possesses poor aqueous solubility and high permeability being a characteristic of a BCS class-II drug. To enhance the water solubility of PTV various approaches has been carried out such as formulation of novel lipid-based delivery systems, creation of unique liquid-solid processes, creation of nano particulate PTV suspensions, etc. (Anuhya and Seetha Devi, 2014; Kumar and Baig, 2014; Parashar *et al*., 2016). Additionally, solid dispersions of PTV with mannitol and polyethylene glycol 6000 was formulated to improve the dissolution profile of this poorly aqueous soluble API (Messa and Ampati, 2016; Nirmala *et al*., 2016). In previous PTV formulation study, hydrophilic polymers such as poloxamer 407 and HPMC were used in SD systems by fusion and solvent evaporation technique which have higher dissolution profile than the pure PTV and physical mixture (Mikrani *et al*., 2022). However solid dispersion of PTV with other polymers such as Kollidon 90, Kollicoat IR, Lutrol, PVK30 has yet to be explored. Kollidon® 90, Kollicoat®IR were successfully used to enhance the *in vitro* dissolution profile of rosuvastatin, lovastatin and atorvastatin solid dispersion formulations etc. (Sarkar *et al*., 2020; Sarkar *et al*., 2021; Sikdar *et al*., 2021). So, these two polymers may boost the water solubility of PTV *in vitro* dissolution.

This study's objective was to investigate *in vitro* disintegration time of PTV by using various techniques such as physical mixing (PM) and solid dispersion (SD) (fusion and solvent evaporation technique) with two hydrophilic polymers Kollicoat® IR and Kollidon® 90F and a carrier polymer

polyethylene glycol 6000 (PEG-6000) for the formulations prepared by fusion approaches. Furthermore, SEM, TGA and FTIR analyses were carried out to ascertain about the physical stability and reasons for improving solubility of PTV by SD formulations.

Materials and Methods

Pitavastatin (PTV), Kollicoat® IR, PEG 6000 and Kollidon® 90F were provided as generous gift sample from Aristopharma (Bangladesh) Ltd. Sodium Phosphate Dibasic Dehydrate, Sodium Dihydrogen Phosphate, Hydrochloric acid, Sodium Hydroxide, Methanol were purchased from local vendor.

Preparation of a physical mixture of PTV and polymers: Initially, an accurate amount of PTV was taken with polymers (Kollicoat® IR and Kollidon® 90F) in a ratio of 1: 2 and 1: 3. After that, the drug and specific polymer were mixed well in mortars by pestles for around 10 min (Mikrani *et al.*, 2022; Sarkar *et al.*, 2021). The drug-polymer combinations were then kept at room temperature in a desiccator until further testing and coded as PKT1 (1:2; Kollicoat® IR), PKN2 (1:2; Kollidon® 90F), PKT3 (1:3; Kollicoat ®IR), PKN4 (1:3; Kollidon® 90F) (Table 1).

Table 1. PM, fusion, and solvent evaporation-based solid dispersion formulations.

Ingredients	Formulations											
	PKT1	PKN2	PKT3	PKN4	FKT1	FKN2	FKT3	FKN4	SKT1	SKN2	SKT3	SKN4
PTV (mg)	4	4	4	4	4	4	4	4	4	4	4	4
Polyethylene glycol (PEG 6000) (mg)	-	-	-	-	25	25	25	25	-	-	-	-
Kollicoat IR (mg)	8	-	12	-	8	-	12	-	8	-	12	-
Kollidon 90F (mg)	-	8	-	12	-	8	-	12	-	8	-	12

(-): no activity.

Preparation of SD by fusion process: Molten PEG 6000 was used as a melting-solvent to dissolve both PTV and polymers (Kollicoat® IR and Kollidon® 90F) (Mikrani *et al*., 2022; Minhaz *et al*., 2012; Sarkar *et al*., 2021; Shirke *et al*., 2015). Precisely weighed amount of (PEG 6000; 25 mg) was placed in a beaker and heated on a hot plate at a mild temperature around 55°- 60°C. 25 mg PEG was found enough to dissolve both PTV and polymers. PTV: PEG 6000: Polymers (either Kollicoat® IR or Kollidon® 90F) ratios were taken 1:6.25:2 and 1:6.25:3, respectively for individual polymer. When PEG 6000 started to melt then the weighted amount of drug and polymer were added to it and stirred continuously to do homogenous mixing. The formed mixture was then set aside to cool to ambient temperature and solidify into a bulk. The combination was then processed through a 30-mesh filter after being ground in a mortar and pestle to create a powder of consistent size of solid dispersion (SD). Before usage, the powder was kept at room temperature in a desiccator. The formulas had a code of FKT1 (1:6.25:2; Kollicoat® IR), FKN2 (1:6.25:2; Kollidon® 90F), FKT3 (1:6.25:3; Kollicoat® IR), and FKN4 (1:6.25:3; Kollidon® 90F) (Table 1).

Preparation of SD by solvent evaporation method: PTV and Kollicoat IR and Kollidon 90F (polymers) were accurately weighed to make in ratio 1:2 and 1:3 for each of the polymers. These determined amounts of drug and polymer were placed in a beaker, and then the required amount of methanol (about 15 mL) was introduced to thoroughly dissolve the drug and polymer and create a homogeneous mixture. In order to create a homogenous solid mass, the mixture was heated to a moderate temperature of roughly 50 °C while surface airflow was continuously and vigorously stirred to create a solid mass that is uniform. The solid mass was crushed and sized uniformly using a 30-mesh sieve to generate a uniform size powder of formulations. Following that,

the uniformly sized powder was kept under vacuum for 24 hours in a desiccator. The mixture was labeled as SKT1 (1:2; Kollicoat® IR), SKN2 (1:2; Kollidon® 90F), SKT3 (1:3; Kollicoat® IR), and SKN4 (1:3; Kollidon® 90F) (Table 1) (Mikrani *et al*., 2022; Minhaz *et al*., 2012; Sarkar *et al*., 2021).

Drug stability analysis by Fourier Transform Infrared Spectroscopy (FTIR): Shimadzu IR Prestige 21 (Kyoto, Japan) FTIR Spectrophotometer was used to scan PTV, optimized SDs, and PMs with Kollicoat® IR and Kollidon® 90F at a resolution of 1 cm^{-1} over a range of 600-4000 cm^{-1} (Mikrani *et al*., 2022). The detail method was described at previous study (Mikrani *et al*., 2022).

Differential scanning calorimetry (DSC): PTV, Kollicoat® IR, Kollidon® 90F, ideal PMs and SDs were analyzed through DSC method using DSC 60 (Shimadzu, Japan). Starting at 25 °C, the temperature was raised at a rate of 10 °C/min, and the hold temperature was set at 500 °C (maximum temperature was set 300 °C for pure PTV analysis).

Thermogravimetric analysis (TGA): Thermal stability of PTV and optimized SDs were analyzed by using TGA-50H (TGA-50 Shimadzu Thermogravimetric Analyzer). The supplied samples were warmed to 600 °C in open aluminum pans. 10 ml/min of nitrogen gas was employed as the purge gas. The specific procedure was already explained (Mikrani *et al*., 2022).

Morphological characterization analysis by Scanning Electron Microscope (SEM): The SEM-8100FM scanning electron microscope was used for the investigation of the scanning electron micrographs (Shimadzu, Japan). By using a 2000 X magnification, the surface of PTV and its improved SD formulations were examined. The specific approach was reported previously (Sikdar *et al*., 2021).

Wavelength (λ_{max}) determination, curve for PTV calibration in distilled water: The λ_{max} of PTV was determined using standard method at 200-400 nm range by UV Spectrophotometer (Shimadzu-1700, Shimadzu Corp, Kyoto, Japan) in which 0.1 N HCl was utilized as a reference solution (Mikrani *et al*., 2022; Minhaz *et al*., 2012; Shirke *et al*., 2015). The λ_{max} was found at 245 nm. Prepared phosphate buffer (pH 6.8) and distilled water was used to make different standard concentrations (0, 2, 4, 8, 12, 16, 20 µg/ml) of PTV to construct a calibration curve by measuring absorbance through UV Spectro-photometer at 245 nm (Figure 2) (Mikrani *et al*., 2022).

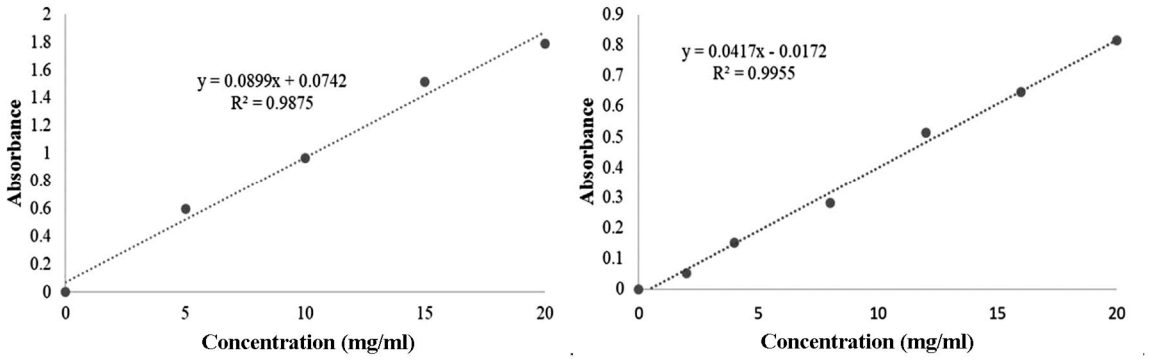

Figure 2. PTV calibration curves in (A) pure water and (B) phosphate buffer.

In vitro dissolution studies: Pure PTV, PMs, and SDs *in vitro* dissolution assays were accomplished in pH 6.8 buffer media at temperature 37°C ± 0.5°C, employing a paddle revolving at 50 rpm and a USP dissolving type II equipment (Erweka, Germany) (Chowdary and Rao, 2000; Fouad *et al*., 2011; Mikrani *et al*., 2022). Aliquots (5 ml) were withdrawn from dissolution media at a predetermined

time and 5 ml buffer media was replaced at the same time to sustain the sink condition. The collected samples were evaluated spectrophotometrically at 245 nm after being filtered via Filter Paper No. 41 (Whatman plc, UK).

Kinetics of drug release and statistical analysis: The release of a PTV from the formulations is an important factor in determining it's therapeutically outcome. As a result, drug release kinetics has been playing a significant role for developing new drug formulation design for upcoming future. To determine the drug release type from PMs and SDs formulations, multiple kinetics approaches such as zero order, first order, Higuchi, and Hixson-Crowell models were applied (Chowdary and Rao, 2000; Mikrani *et al*., 2022). ANOVA (One-way analysis of variance) was also accomplished to check how other drug formulations differ from either of these preparations (Mikrani *et al*., 2022).

Results and Discussion

PTV drug release study from PMs: The release rate of pure PTV was found 61.76% in 1h (Figure 3) (Mikrani *et al*., 2022). While the PM formulations PKT3 (Kollicoat IR) and PKN4 (Kollidon 90F) containing slightly high amount of polymer displayed a release rate of 80.21 ± 4% and 85.67 ± 2%, respectively in 60 min (Figure 3). In the past Kollicoat IR has been used in different physical mixture and solid dispersion formulations to enhance the rate at which clonazepam and indomethacin dissolve due to its' wetting ability (Minhaz *et al*., 2012; Shirke *et al*., 2015). Kollidon 90F upturns the dissolution profile of weakly water soluble APIs including itraconazole and lovastatin prepared via physical mixture and solid dispersion techniques (Chowdary and Rao, 2000; Sarkar *et al*., 2021). The current study findings agreed with previous studies and suggested that the PM formulations of PTV with these polymers could be suitable to some extent to enhance PTV's rate of dissolution.

Study of PTV drug release from SD formulations:

Fusion method: After successful improvement of PM formulations dissolution of PTV with Kollicoat IR and Kollidon 90F, solid dispersion (SD) formulations were made by fusion method. As the dissolution release rate obtained with a ratio of 1:2 and 1:3 (drug: polymer) with physical mixing formulations was promising. To create SD formulations, these ratios were also taken into account. *In vitro* dissolution technique was applied to carry out the drug release study for 60 min where dissolution media was phosphate buffer system. SD formulations of PTV with PEG 6000 in ratios of (1:6.25:2) and (1:6.25:3) using the fusion method and the cumulative percent drug release were compared with pure PTV (Figure 3). The formulations FKT1 and FKN2 showed an improved release rate of 87.26 ± 4.2% and 93.4 ± 0.83%, respectively. Whereas higher release rates were measured for FKT3 and FKN4 formulations 97.10 ± 5.02% and 96.31 ± 2.35%, respectively. So, SD formulations containing larger amount of hydrophilic polymer also gave better drug release than pure PTV and PM formulations (Figure 3b).

Solvent evaporation method: Another solid dispersion manufacturing method known as the solvent evaporation technique was also used to create PTV solid dispersion (SD) formulations. SD formulations (1:2 and 1:3 ratios) were prepared. SD formulation formulations SKT1 and SKN2 presented a cumulative drug release rate of 82.29 ± 3% and 87.1 ± 4%, respectively whereas SKT3 and SKN4 formulations having cumulative release rate of 89.42 ± 0.52% and 92.37 ± 5.62% in 60 min. The release profiles of all four formulations made using the solvent evaporation method were higher than those of pure PTV (Figure 3c). The cumulative percent release of pure PTV was compared with the highest release formulations of PMs, SDs using first order kinetics (Figure 3d), Higuchi (Figure 4a) and Hixson-Crowell model (Figure 4b).

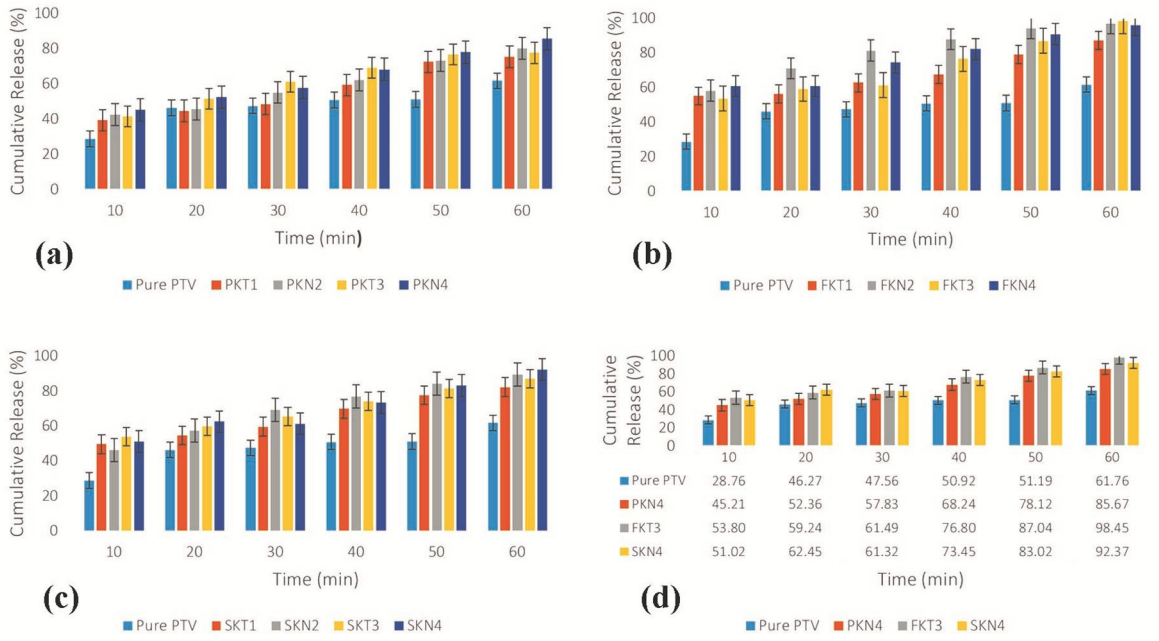

Figure 3. The cumulative percent API release of pure PTV with (a) PM formulations (PKT1, PKN2, PKT3 and PKN4), (b) SD formulations (FKT1, FKN2, FKT3 and FKN4) prepared by fusion method, (c) SD formulations (SKT1, SKN2, SKT3 and SKN4) formulated by solvent evaporation and (d) Comparison among optimized formulations of PMs, SDs and pure PTV.

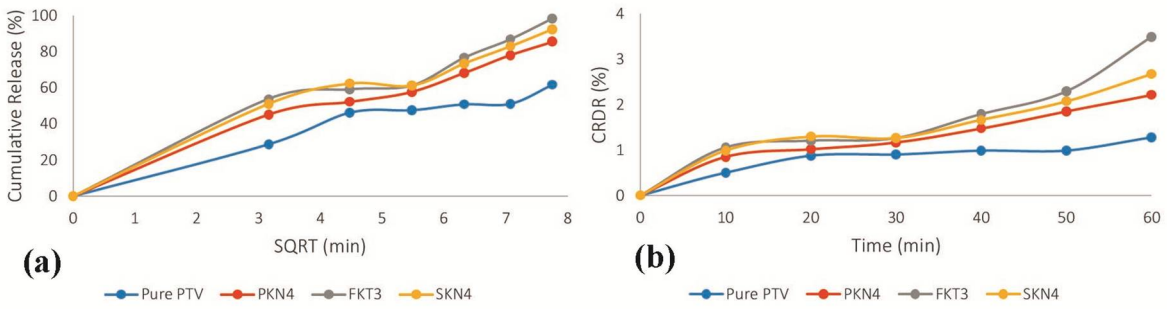

Figure 4. Comparison of drug release of pure PTV with the highest releasing formulations developed through PMs and SDs methods using (a) Higuchi model (b) Hixson-Crowell model. SQRT= Square root of time, CRDR+ Cubic root of drug release.

Fourier transform infrared spectroscopy: To identify any physicochemical interactions between PTV, Kollicoat IR, and Kollidon 90F in the form of PM and SDs, FTIR spectroscopy analysis was carried out. Pure PTV, PTV with Kollidon 90F by solvent evaporation, PTV with Kollidon 90F by fusion method, PTV with Kollicoat IR by solvent evaporation, and PTV with Kollicoat IR by fusion method were all used in the analysis. Noticeable peaks of the pure active ingredient PTV were detected at 3431.31, 2928.01, 1602.04, 1428.25 and 1204.38 cm^{-1} (Figure 5A) (Mikrani *et al*., 2022). When PTV mixed with Kollicoat IR and Kollidon 90F was analyzed in the form of PM and SDs by fusion and solvent evaporation methods, spectra were discovered in nearly identical locations. No significant changes in peaks were observed (Figure 5). These may indicate that there weren't any significant interactions between the PTV and polymers either before or after formulation.

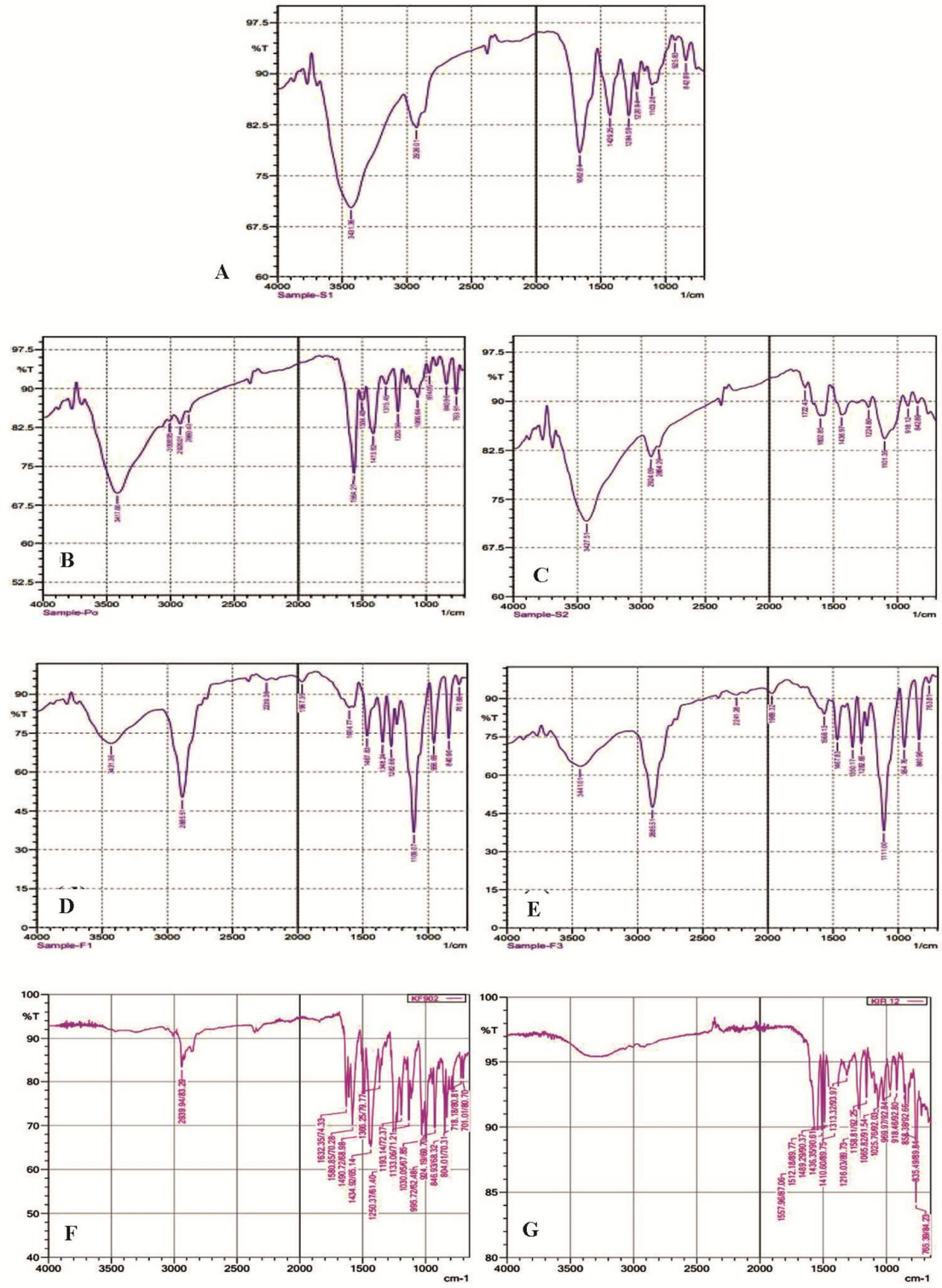

Figure 5. FTIR spectra of (A) PTV, (B) PTV with Kollidon 90F by solvent evaporation (SKN4), (C) PTV with Kollidon 90F by fusion method (FKN4), (D) PTV with Kollicoat IR by solvent evaporation (SKT3), (E) PTV with Kollicoat IR by fusion method (FKT3), (F) PTV with Kollidon 90F by PM method (PKN4), (G) PTV with Kollicoat IR by PM method (PKT3).

Differential scanning calorimetry (DSC): From the DSC analysis, it was observed that the melting point of the pure PTV, Kollicoat IR, and Kollidon 90F was in 90.26°C, 57.25°C and 88.58°C respectively (Figure 6). The shifted endothermic peaks (59.21°C and 57.91°C) in DSC analyses of fusion formulations (FKT3 and FKN4) indicated loss/reduction of drug crystallinity which is in agreement with the enhance dissolution rate of these formulations (Figure 6F-G) (Fouad *et al.*, 2011; Sikdar *et al*., 2021). It is worth to mention that the reduction of drug crystallinity upsurges the dissolution properties. Similar endothermic peak shifts were also detected for formulations SKT3 (disappeared) and SKN4 (75.36°C) in DSC analyses whereas in the PM formulations endothermic peak especially for PKT3 remained same (90.53 °C) as the pure PTV (Figure 6).

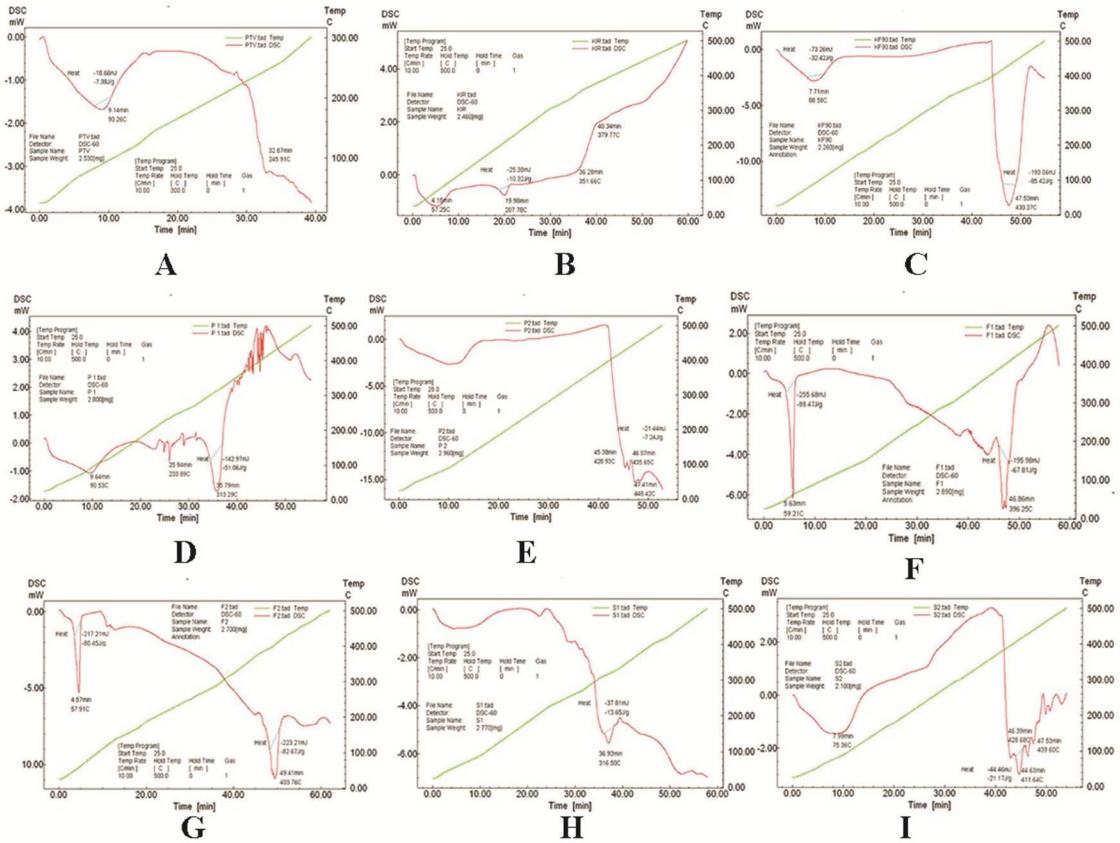

Figure 6. DSC thermographs of (A) PTV, (B) Kollicoat IR, (C) Kollidon 90F, (D) PTV with Kollicoat IR (1:3) by PM method (PKT3), (E) PTV with Kollidon 90F (1:3) by PM method (PKN4), (F) PTV with Kollicoat IR (1:3) by fusion method (FKT3), (G) PTV with Kollidon 90F (1:3) by fusion method (FKN4), (H) PTV with Kollicoat IR (1:3) by solvent evaporation (SKT3), (I) PTV with Kollidon 90F (1:3) by solvent evaporation (SKN4).

Thermogravimetric analysis (TGA): TGA measures the weight change of a sample when it is heated or cooled at a fixed temperature. Moisture content can also be determined using TGA analysis (Mikrani *et al.*, 2022). The thermo-gravimetric profiles demonstrated PTV's stability up to 190 °C. There was a 7.02% weight loss when the temperature reached the PTV form's melting point (Tm = 190–192°C) (Mikrani *et al.*, 2022). Initial very small loss of weight of the PTV due to may be the evaporation of water from the sample. PTV began to clearly degrade as the temperature exceeded 200 °C, and the weight loss sharply increased, as shown in the illustration in Figure 7 (A). Besides, PTV with

Kollidon 90F by solvent evaporation was stable up to 200 °C, PTV with Kollidon 90F by fusion method was stable up to 248 °C, PTV with Kollicoat IR by solvent evaporation was stable up to 220 °C and PTV with Kollicoat IR by fusion method was up to 245 °C (Figure 7). As a result, the data support the claim that PTV formulations made by SDs were stable at elevated temperatures. As little/no chemical alteration or stability issue was not detected in TGA analysis of SD formulations, PM formulations were not assayed in TGA despite PM formulations were found to be improved the dissolution characteristic of PTV.

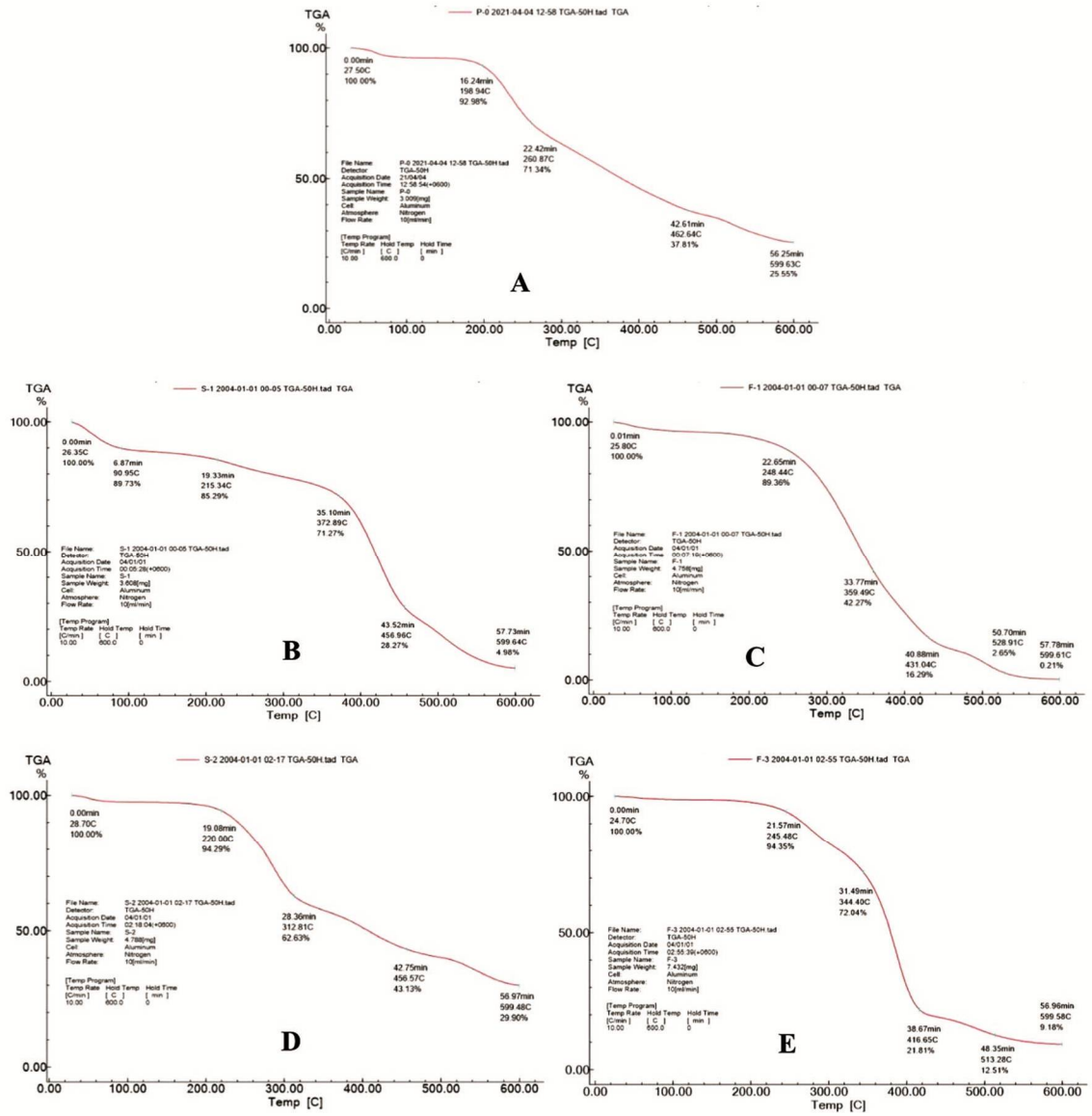

Figure 7. TGA thermograms of (A) PTV, (B) PTV with Kollidon 90F by solvent evaporation (SKN4), (C) PTV with Kollidon 90F by fusion method (FKN4), (D) PTV with Kollicoat IR by solvent evaporation (SKT3), (E) PTV with Kollicoat IR by fusion method (FKT3).

Scanning electron microscopic (SEM) analysis: In SEM analysis the particles of the pure drug PTV were crystal-like in shape (Figure 8A) (Mikrani *et al.*, 2022). SEM analysis was limited to fusion and solvent evaporation SD formulations (1:3 ratios). On the surface of the hydrophilic polymers, it was found that the drug particles remained dispersed and physically adsorbed. The SD formulation of

Pitavastatin, Kollicoat IR, Kollidon 90F and the homogeneity dispersion of PEG 6000 showed that PTV particles were distributed consistently in polymers made using the solvent evaporation method and the fusion technique, assuming that API in both formulations was in an amorphous solid dispersion condition (Figure 8 B-E).

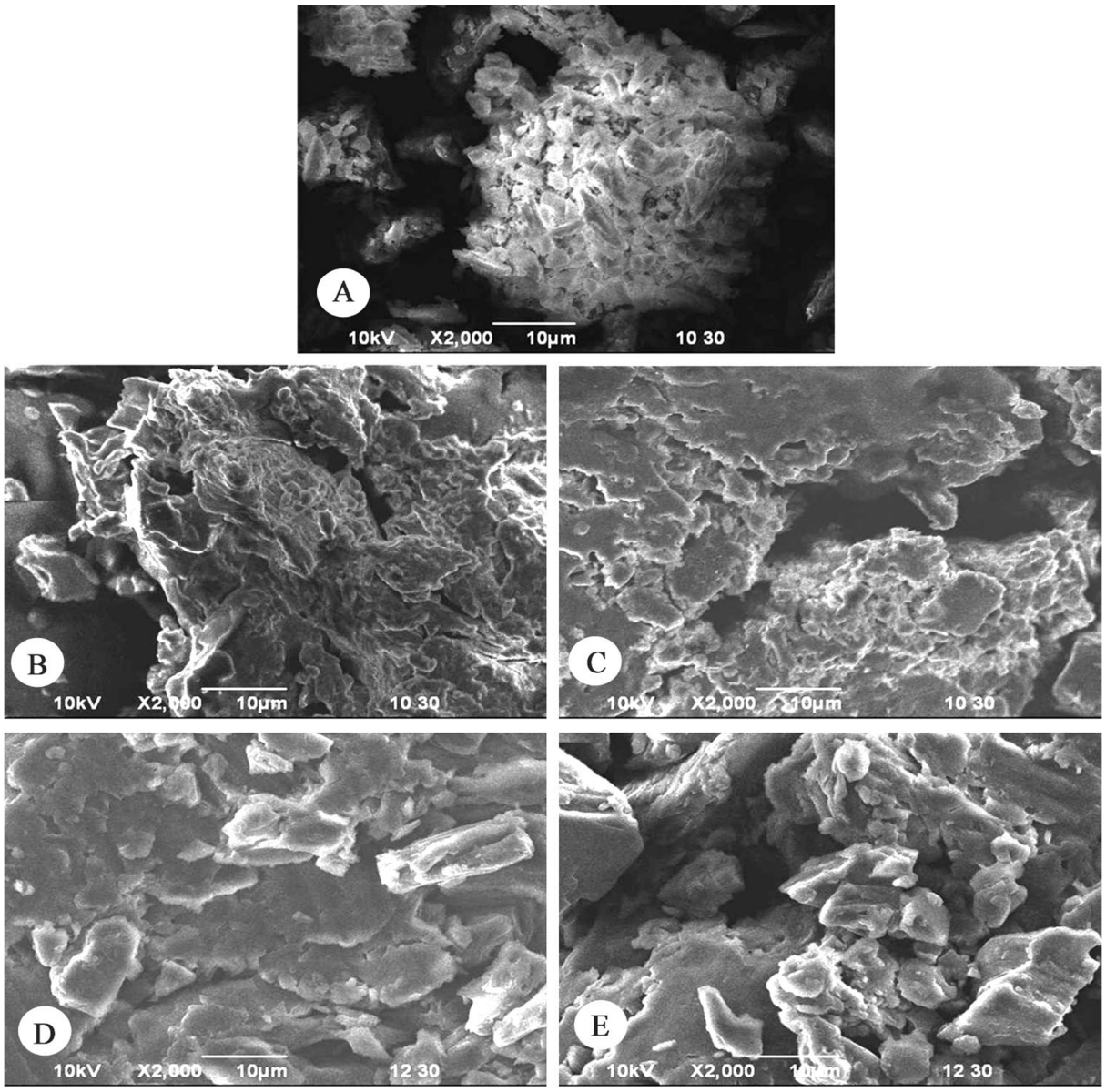

Figure 8. Scanning Electron Microscopic analysis of (A) pure Pitavastatin at X2000 magnification, (B) Pitavastatin with Kollidon 90F prepared by solvent evaporation (SKN4) at X2000 magnification, (C) Pitavastatin with Kollidon 90F prepared by fusion method (FKN4) at X2000 magnification, (D) Pitavastatin with Kollicoat IR prepared by solvent evaporation (SKT3) at X2000 magnification, (E) Pitavastatin with Kollicoat IR prepared by fusion method (FKT3) at X2000 magnification.

Study of drug release kinetics and statistical evaluation: Utilizing various kinetic models, including the Higuchi, Hixson-Crowell, zero-order, and first-order models, the kinetics of drug release were studied (Mikrani *et al.*, 2022; Sikdar *et al.*, 2021). Comparing the Higuchi model with the various kinetics models, PMs' formulations were the most successfully suited. The formulation PKT3 had the

highest R2 value (0.9824), indicating that it suited the data the best among the others (Table 2). The Higuchi model, which was established for the study of low-aqueous soluble and water-soluble drug molecules in semisolid or solid matrices, demonstrated that the formulations had improved in solubility following PM formulations. A similar outcome was also seen for PTV with Poloxamer 407 and HPMC (Mikrani *et al*., 2022).

It was determined that the first-order kinetics was best suited by both SD formulations. FKN2 and SKN2 were the best-fitted formulations with R^2 values 0.9865 and 0.9879, respectively (Table 2).

One-way ANOVA was performed out in order to investigate how polymer concentration (Kollicoat IR and Kollidon 90F) affected the dissolving activity of PTV. The results confirm that the cumulative percent drug release of the developed SD formulations enhanced as a result of the improved polymer concentrations (Table 3).

Table 2. Drug release kinetic of PTV from PM formulations, SD by fusion and solvent evaporation method and pure PTV.

Formula-tion Code	Drug: Polymer	Zero Order		First Order		Higuchi Model		Hixson- Crowell Model	
		R^2	K_0	R^2	K_1	R^2	K_h	R^2	K_{HC}
PKT1	1:2	0.8719	1.0976	0.9509	-0.0095	0.9729	9.4232	0.9368	-0.0264
PKN2	1:3	0.8651	1.139	0.9597	-0.0105	0.9772	9.8391	0.9443	-0.0285
PKT3	1:2	0.8297	1.1463	0.957	-0.0105	0.9824	10.138	0.9243	-0.0287
PKN4	1:3	0.8562	1.2097	0.9611	-0.0125	0.979	10.513	0.949	-0.0325
FKT1	1:2	0.7679	1.1478	0.9132	-0.0125	0.9335	10.286	0.8889	-0.0317
FKN2	1:3	0.7566	1.3586	0.9865	-0.0241	0.9534	12.395	0.9564	-0.0494
FKT3	1:2	0.8242	1.3014	0.9369	-0.0175	0.96	11.415	0.9402	-0.0406
FKN4	1:3	0.7787	1.3219	0.9459	-0.0211	0.9492	11.862	0.9437	-0.0453
SKT1	1:2	0.7959	1.1359	0.9478	-0.0112	0.9592	10.135	0.9115	-0.0297
SKN2	1:3	0.84	1.2995	0.9879	-0.0152	0.987	11.439	0.9623	-0.0376
SKT3	1:2	0.77	1.1801	0.95	-0.013	0.9507	10.646	0.9098	-0.0329
SKN4	1:3	0.81	1.2575	0.9224	-0.0158	0.9595	11.102	0.9264	-0.0377
PTV	-	0.78	0.8386	0.86	-0.0058	0.95	7.526	0.83	-0.0175

(-): no activity.

SEM, DSC analyses indicated that PTV is crystalline (Figure 8A, 6A). Improved release rate of PTV in solid dispersion formulations with the water-soluble polymers Kollicoat IR and Kollidon 90F were observed which might be due to many reasons. One reason could be due to the physical conversion of API to an amorphous shape or the reduction/loss of crystallinity (Figure 8). This may also be a result of a decrease in particle size and an increase in surface area, both of which lead to a greater dissolving profile (Mallick *et al*., 2003; Tous *et al*., 2012). The release rates of PTV from SD formulations were comparable with previous reported release rate of PTV SD formulations with other polymers (Messa and Ampati, 2016; Mikrani *et al*., 2022; Nirmala *et al*., 2016). For instances Nirmala *et al.* enhanced the cumulative release rate of PTV from 43.1% to 99.68% by melting method using 1:4 ratio drug to mannitol (Nirmala *et al*., 2016).

From the cumulative percent drug release pattern, it was obtained that formulation PKN4, FKT3 and SKN4 had given the highest drug release after 60 min compared to pure PTV 61.76% and other formulations (Figure 3). The outcomes demonstrated that increasing Kollidon 90F/Kollicoat IR concentration raises the PTV's in vitro dissolving rate. The release rates from various formulations made by different technique's increasing order would be SDs

prepared with Kollidon®90F/Kollicoat®IR by fusion method >Kollidon®90F/Kollicoat®IR by solvent evaporation> PMs using Kollidon®90F/Kollicoat®IR (Figure 3). From FTIR and TGA thermogram analyses revealed that most of the formulations were stable and the API and polymers did not interact chemically in a significant way (Figure 5).

Table 3. ANOVA analysis of the formulations prepared by PM and SD (fusion and solvent evaporation method) of PTV with polymers.

Formulation Code	Drug: Polymer	Source of variation	SS	Df	Ms	F	P-value	F_{crit}
PKT1	1:2	Between group	1199.35	1	1199.35	2.158	0.1675	4.747
		Within groups	6668.68	12	555.72			
PKN2	1:3	Between group	1590.04	1	1590.04	2.726	0.124	4.747
		Within groups	6999.13	12	583.26			
PKT3	1:2	Between group	2007.36	1	2007.36	3.329	0.0930	4.747
		Within groups	7234.56	12	602.88			
PKN4	1:3	Between group	2248.67	1	2248.67	3.557	0.0837	4.747
		Within groups	7585.46	12	632.12			
FKT1	1:2	Between group	2821.54	1	2821.54	4.452	0.0565	4.747
		Within groups	7603.74	12	633.64			
FKN2	1:3	Between group	5630.92	1	5630.92	7.016	0.0212	4.747
		Within groups	9630.61	12	802.55			
FKT3	1:2	Between group	3514.57	1	3514.57	4.931	0.0463	4.747
		Within groups	8553.58	12	712.80			
FKN4	1:3	Between group	4684.43	1	4684.43	6.188	0.0285	4.747
		Within groups	9083.88	12	756.99			
SKT1	1:2	Between group	2405.68	1	2405.68	3.933	0.0706	4.747
		Within groups	7339.09	12	611.59			
SKN2	1:3	Between group	3251.30	1	3251.30	4.634	0.0523	4.747
		Within groups	8419.26	12	701.61			
SKT3	1:2	Between group	3198.48	1	3198.48	4.887	0.0472	4.747
		Within groups	7853.51	12	654.460			
SKN4	1:3	Between group	3259.84	1	3259.84	4.744	0.0500	4.747
		Within groups	8245.14	12	687.095			

Abbreviations: SS: Sum of square, Df: Degree of freedom, Ms: Mean squares, F: F statistic, P value: Probability of obtaining results, Fcrit: F critical value.

Conclusion

The dissolution property of poorly aqueous soluble drug PTV has increased significantly when the drug was included in SD systems. The present study demonstrates that dispersions of PTV in hydrophilic polymers Kollicoat®IR and Kollidon®90F improves the dissolution of PTV compared to the pure PTV. The results (ANOVA) also confirm that dissolution enhancement of PTV is concentration-dependent of excipients. The SD formulations' TGA study demonstrates that the preparations are stable in high temperatures (≥ 200° C) and the drug and polymers did not interact in any way, according to FTIR measurements. The SEM analysis assumes that the dispersion of PTV in polymers affects the crystallinity of PTV and thereby, represents conversion of the amorphous state for improving drug dissolution. These findings recommend that SD dispersion of PTV is a promising method to enhance the bioavailability of PTV. Future research will be

done in animals to confirm the enhancement in PTV's oral bioavailability.

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