

# Development, Characterization and *In vitro* Evaluation of Solid Dispersion Formulations of Low Aqueous Soluble BCS Class II Drug Pitavastatin with Poloxamer 407 and HPMC

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**ABSTRACT:** This study was aimed to boost up the dissolution rate of a sparingly aqueous soluble BCS Class II drug pitavastatin (PTV) by solid dispersion (SD) techniques using two hydrophilic polymers poloxamer 407 and hydroxypropylmethylcellulose (HPMC). Low aqueous solubility of PTV is associated with less oral bioavailability, and a real challenge in preparing appropriate dosage form. To enhance the aqueous solubility, physical mixing and SD formulations of PTV were developed by fusion and solvent evaporation methods using two hydrophilic polymers, poloxamer 407 and HPMC. Scanning electron microscopy (SEM) investigation indicated that PTV molecules were homogeneously dispersed in carrier prepared by different formulation methods at 1:2 and 1:3 ratios of PTV: polymer assuming amorphous SD state. The thermogravimetric profiles demonstrated that PTV was stable up to 198°C and began to decompose rapidly with significant weight loss as the temperature was raised over 190°C. Formulations prepared by SD techniques were stable at high temperature. *In vitro* studies illustrated that cumulative drug release of PTV: HPMC/poloxamer 407 formulations prepared by physical mixing, fusion and solvent evaporation techniques were better compared to pure PTV powder (61.42±0.91%). Among all the approaches, formulations prepared by solvent evaporation and fusion methods displayed higher cumulative releases of PTV than physical mixing formulations. The results of current study clearly indicated that PTV: HPMC/poloxamer 407 (1:2) formulations (S3, S1) developed by solvent evaporation method possess enhanced dissolution profile (96.06%; 95.62%) than the fusion SD formulations (F3; 94.62%, F1; 87.05%). Whereas PTV physical mixing formulations (P2; 82.32%, P4; 80.28%) containing high amount of carrier polymers (ratio 1:3) exhibited superior *in vitro* dissolution rates than formulations (P3; 68.70%, P1; 71.52%) having less quantity (ratio 1:2) of HPMC/poloxamer 407. It is apparent from the findings of this study that SD formulations (S3, S1, F3, F1) of PTV with HPMC/poloxamer 407 is a very promising approach for improving the *in vitro* dissolution profile of the sparingly aqueous soluble PTV. Moreover, 1:2 ratio formulations prepared by fusion and solvent evaporation SD approaches were found more effective to upgrade the release rate of PTV than the 1:3 formulations.

**Key words:** Pitavastatin, aqueous solubility, solid dispersion, dissolution, Poloxamer 407

## INTRODUCTION

Solubility is the phenomenon of dissolving solute into a liquid or gaseous solvent, so as to produce a homogeneous solution.<sup>1</sup> It shouldn't be bemused with the liquefaction of a substance by chemical interaction. The solubility of a substance is

primarily determined by the characteristic of the solvent as well as by the pressure and temperature of the process.<sup>2</sup> It is an important parameter in order to attain an intended drug concentration in the systemic blood circulation.<sup>3</sup> Drugs with poor water solubility may lead to waned drug absorption, insufficient and alterable drug bioavailability as well as gastrointestinal mucosal toxicity.<sup>4</sup> The U.S. Food and Drug Administration provides a Biopharmaceutical Classification System which acts as a guide to foretell the intestinal drug absorption by assessing the

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parameters of drug solubility and intestinal permeability.<sup>5</sup> As per the classification, solubility is the most critical rate limiting step for BCS class II (high permeability and low solubility) molecules in order to attain the desired plasma drug concentration.<sup>6</sup> Therefore, the bioavailability of these drugs can be augmented if we can ameliorate the dissolution rate and solubility of these drugs.<sup>7</sup> To promote the solubility of these hydrophobic drugs, physical or chemical modifications or other solubility enhancement methods have been applied.<sup>8</sup> Physical modifications such as micronation, nanosuspension, solid dispersion, cryogenic, co-crystallization etc. techniques have been applied frequently to promote the solubility of BCS class II molecules.<sup>9,10</sup> On the other hand, chemical modification can be done through the use of buffer, change of pH, complexation, and salt formation etc.<sup>11</sup> Among the approaches of increasing solubility by physical modifications, solid dispersion (SD) method is one of the simplest and most effective methods.<sup>12</sup> It entangles the dispersion of a poor water soluble drug in one or more hydrophilic carrier.<sup>13</sup> It enhances the drug's surface area as well as its solubility, and therefore, the bioavailability of the drug.<sup>13</sup> A number of synthetic and natural polymers are used as hydrophilic carriers in solid dispersion approaches.<sup>12</sup> Povidone, polyethylene glycol (PEG), polymethacrylates etc. are some of the synthetic polymers while hydroxypropylmethylcellulose (HPMC), ethyl cellulose, starch derivatives such as cyclodextrins are some of the examples of natural polymers which are being used frequently in this solubility improvement technique.<sup>14,15</sup> Solid dispersion can be attained by various methods, for examples, melting method or fusion method, melting solvent method, hot melt extrusion process, solvent evaporation method, spray-drying technology, kneading method, supercritical fluid technology, coprecipitation, electrospinning method, lyophilization techniques etc.<sup>16</sup>

Pitavastatin, a BCS class II drug with little water solubility but decent permeability, is a member of statins and used for its blood cholesterol lowering effects by inhibiting the enzyme HMG-CoA

reductase.<sup>17,18</sup> It is encountered with similar or even superior lipid lowering effects than that of atorvastatin when given at a dose of 1 to 4mg per day.<sup>19</sup> Since PTV is a BCS class II molecule, its bioavailability (51%) can be enhanced by boosting the solubility of this active pharmaceutical ingredient.<sup>20</sup> Various tactics have been applied to boost the solubility of PTV such as liquid-solid technique, design of novel lipid based carrier system, solid dispersion and formulation of nanosuspension etc.<sup>21-24</sup> Only few studies regarding improvement of *in vitro* dissolution release rates of PTV using solid dispersions technique have been reported.<sup>23, 24</sup> Mannitol and PEG 6000 were used to formulate SD formulations of PTV to increase the *in vitro* dissolution rate by using melting SD method.<sup>23,24</sup>

The goal of the present study was to augment the *in vitro* dissolution rate of PTV using SD technique. Prepared SD formulations were evaluated and compared with pure drug powder. With an aim to improve the dissolution rate of PTV, SD formulations were developed by fusion and solvent evaporation methods using two hydrophilic polymers poloxamer 407 and HPMC. Fourier Transform Infrared Spectroscopy (FT-IR), SEM and Thermo-gravimetric analysis (TGA) analyses of prepared SD formulations were carried out to assess the physical characteristics and stability of the formulations.

## MATERIALS AND METHODS

**Materials.** PTV calcium, Poloxamer 407, HPMC, PEG 6000 were purchased from Sigma Aldrich and local supplier. Other reagents like methanol, sodium hydroxide, sodium dihydrogen phosphate and sodium phosphate dibasic dihydrate were procured from local vendor.

### Methods

**Physical mixture of PTV and polymers.** PTV calcium and the polymers, Poloxamer 407 and HPMC, were measured accurately in a ratio of 1:2 and 1:3, and the two mixtures were kept separately. Then, using mortars and pestles, the drug-polymer mixtures were compounded perfectly for around 10

minutes. After that, the drug-polymer mixtures were coded as P1 (1:2; Poloxamer 407), P2 (1:3; Poloxamer 407), P3 (1:2; HPMC) and P4 (1:3;

HPMC) (Table 1) and kept in a desiccator at room temperature (30° C) for later use.

**Table 1. Formulations prepared by physical mixture and solid dispersion techniques.**

Name of the Ingredients	Formulations											
	P1	P2	P3	P4	F1	F2	F3	F4	S1	S2	S3	S4
PTV (mg)	4	4	4	4	4	4	4	4	4	4	4	4
Poloxamer 407 (mg)	8	12	-	-	8	12	-	-	8	12	-	-
HPMC (mg)	-	-	8	12	-	-	8	12	-	-	8	12
PEG-6000 (mg)	-	-	-	-	25	25	25	25	-	-	-	-

**Preparation of solid dispersion by fusion method.** Polyethylene glycol 6000 (PEG 6000) were accurately weighed in a ratio of 1:6.25 (Drug: PEG 6000) and kept in separate beakers. PEG 6000 is then heated at a mild temperature of around 55-60°C in a hot plate. When the PEG 6000 was melted, the drug-polymer mixtures of 1:2 and 1:3 ratios were added separately with a nonstop stirring into the two beakers containing melted PEG 6000 to ensure a homogeneous mixing. Then the mixture was cooled at ambient temperature and allowed to get dry for having the dry solid mass of mixture. The mixture was then grinded and to obtain a uniform sized SD powder, it was sieved through a 30-mesh sieve.<sup>25</sup> Then the uniformly sorted solid dispersion powders were kept in a desiccator at ambient temperature and were labeled as F1 (1:6.25:2; Poloxamer 407), F2 (1:6.25:3; Poloxamer 407), F3 (1:6.25:2; HPMC) and F4 (1:6.25:3; HPMC) (Table 1).

**Preparation of solid dispersion (SD) by solvent evaporation method.** PTV and the polymers, Poloxamer 407 and HPMC, were weighed precisely in the proportion of 1:2 and 1:3 and kept in to separate beaker. Methanol (15 ml) was then added sufficiently so that the drug-polymer mixture was completely dissolved and a homogeneous mixture was produced. These mixtures were then heated around 50°C with continuous stirring until a uniform solid mass is produced. The solid mixture was then pulverized using mortar and pestle and kept in a desiccator under a vacuum for 24 hours.<sup>25</sup> The mixtures were encoded as S1 (1:2; Poloxamer 407),

S2 (1:3; Poloxamer 407), S3 (1:2; HPMC) and S4 (1:3; HPMC) (Table 1).

**Wavelength ( $\lambda_{max}$ ) determination.** At the beginning, 100 ml methanol solvent was used to dissolve 10 mg of pure PTV. The concentration of the preparation became 100 µg/ml. This preparation was then diluted to 10 µg/ml by adding distilled water. The absorbance of the solution with a concentration of 10 µg/ml was checked at 200-400 nm range by UV Visible Spectrophotometer (Shimadzu-1700, UV Visible Spectrophotometer, Shimadzu Corp., Kyoto, Japan). As reference solution 0.1N Hydrochloride acid was used.<sup>24</sup> The  $\lambda_{max}$  was established at 245nm.<sup>23</sup>

**Construction of calibration curve of PTV in distilled water.** To construct a standard calibration curve of PTV, 10 mg of pure active pharmaceutical ingredient (API) was dissolved in methanol to make a 100 ml solution which was additional diluted by adding 900 ml of methanol solvent. This preparation was used as stock solution and different concentrations of that pure drug in distilled water such as 0, 5, 10, 15 and 20 µg/ml were formulated from this stock preparation. Absorbance of these preparations were taken spectrophotometrically at 245 nm (Shimadzu-1700, UV Visible Spectrophotometer, Shimadzu Corp., Kyoto, Japan) and a calibration curve was created ( $y = 0.0803x - 0.0754$ ;  $R^2 = 0.9856$ ) via MS excel.

**Preparation of calibration curve of PTV in phosphate buffer.** At first, 100 ml of methanol was used to dissolve 10 mg of the pure API and then the

solution was diluted by adding 900 ml of phosphate buffer. This stock solution was then used to prepare different concentrations of PTV in phosphate buffer (0, 2, 4, 8, 12, 16, 20 µg/ml). The absorbance of these prepared solutions were taken via UV Visible Spectrophotometer at 245 nm (Shimadzu-1700, UV Visible Spectrophotometer, Shimadzu Corp., Kyoto, Japan) and a standard calibration curve was created ( $y = 0.0421x - 0.0169$ ;  $R^2 = 0.9948$ ) by MS excel.<sup>26</sup>

**In vitro dissolution study.** In an 8-station USP type-II apparatus (Erweka, Germany), the dissolution rate of pure PTV, binary physical mixings and ternary SD powders equivalent to 4 mg of PTV was measured in a buffer solution (pH 6.8) at  $37^\circ\text{C} \pm 0.5^\circ\text{C}$  temperature. The paddle of the apparatus was rotating at 50 rpm. At a previously determined time interval, 5 ml of the solution from dissolution medium was substituted with 5 ml of buffer solution. A Filter Paper No 41 (Whatman plc, UK) was used to filter the collected samples and the absorbance of that pooled samples were taken spectrophotometrically at 245 nm.<sup>25</sup>

**Drug release kinetics and statistical analysis.** To obtain the expected pharmacological effect, drug release from its pertinent dosage form should be evaluated and maintained properly. In order to estimate the API release, different pharmacokinetic models like zero order and first order model, Higuchi and Hixson-Crowell models were used. One-way analysis of variance (ANOVA) was also performed to evaluate the variation in release of drugs from different formulations.<sup>25, 27</sup>

### Physicochemical properties

**Fourier transform infrared spectroscopy.** Shimadzu IR Prestige 21 (Kyoto, Japan) was used for conducting the Infrared Spectroscopy. The sample was mixed with accurate amount of KBr in the ratio of 0.1:100 by crushing in an agate mortar. Then pellets were made in a way so that each of them contains 100 mg of mixture. FT-IR Spectra were filed in the  $4000\text{-}400\text{ cm}^{-1}$  range with FT-IR 8400S Shimadzu IR Prestige 21 Spectrophotometer (Kyoto,

Japan). Resolution was  $4\text{ cm}^{-1}$  and the number of scans was 30 times.<sup>28</sup>

**Scanning electron microscopy (SEM).** Scanning electron microscope (SEM-8100FM; Shimadzu, Japan) was applied to carry out the Scanning Electron Microscopic study. Using a double-sided adhesive tape, the pure PTV, physical mixture formulations and SD samples were ascended on to the stubs. After that, gold-palladium alloy (150-200A) was used to coat the samples as a very thin layer. The Scanning Electron Microscope was run at a stimulated voltage of about 20 KV and a working distance of about 12-14 mm. The Scanning Electron Microscopy was magnified by 2000 times and was utilized to evaluate the particle shape of pure PTV.<sup>25</sup>

**Thermo-gravimetric analysis.** Thermal gravimetric analysis was performed to evaluate the thermal stability of the components. TGA-50 Shimadzu Thermo gravimetric Analyzer was used for this purpose. The samples were heated in an open aluminum pans and nitrogen gas was passed with a flow rate of 10 ml/min. Around  $600^\circ\text{C}$  temperature was maintained during the process.<sup>29</sup>

## RESULTS AND DISCUSSION

**Scanning electron microscopy.** SEM analysis of the pure PTV powder indicated that the particle shape of the API is crystal-like (Figure 1). As dissolution rate of SD formulations were better than the physical mixtures (discussed later in this Article), SD formulations prepared by fusion and solvent evaporation methods at 1:3 ratio were analyzed in SEM. It was observed that the drug particles remained dispersed and physically adsorbed on the carrier particles' surface. The formulations of PTV, poloxamer 407, and HPMC and PEG 6000 displayed a homogenous dispersion which suggested that the API molecules were homogeneously dispersed in carrier prepared by fusion method, solvent evaporation method at 1:3 ratio which is an indication of reduction of PTV crystallinity or conversion to amorphous state (Figure 1).

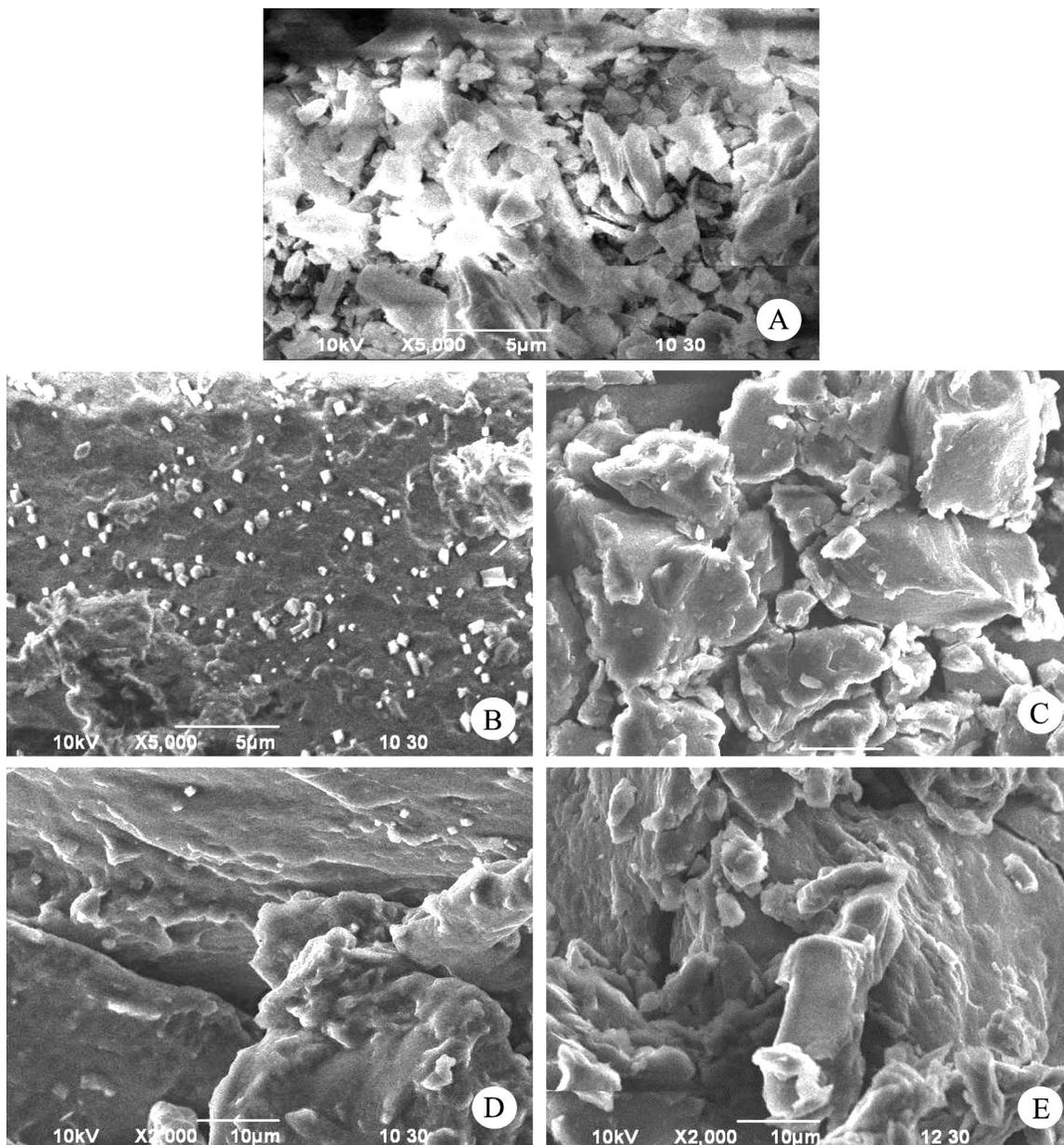


Figure 1. Scanning electron microscopic analysis of pure PTV (A), PTV with HPMC prepared by Solvent Evaporation Method (S4; B), PTV with HPMC prepared by Fusion Method (F4; C), PTV with Poloxamer 407 prepared by Solvent Evaporation Method (S2; D), PTV with Poloxamer 407 prepared by Fusion Method (F2; E).

**Thermogravimetric analysis.** The thermogravimetric analysis demonstrated that PTV was stable up to 198°C (Figure 2). The weight reduction was 7.02 % when the temperature was raised to the melting temperature of PTV form ( $T_m = 190\text{-}192^\circ\text{C}$ ) (Figure 2). PTV began to decompose rapidly and significant weight loss was found as the temperature was lifted over 190°C (Figure 2). PTV

with poloxamer by solvent evaporation was stable up to 218°C, PTV with poloxamer by fusion method was stable up to 202°C, PTV with HPMC by solvent evaporation was stable up to 190°C (Figure 2). Thus, from the analysis it can be stated that physical mixings and SDs formulations of PTV were stable at high temperatures.

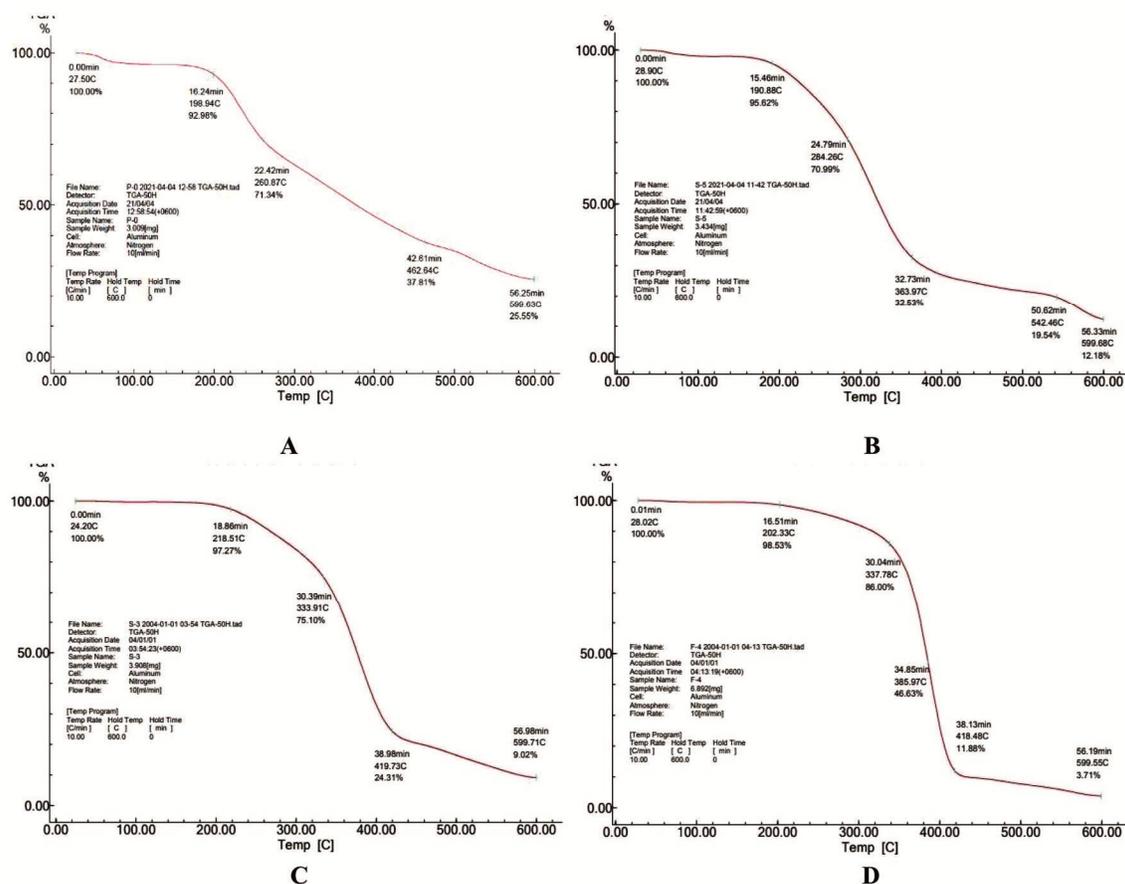


Figure 2. Thermogravimetric analysis of pure PTV (A), PTV with HPMC prepared by Solvent Evaporation Method (B), PTV with poloxamer 407 prepared by Solvent Evaporation Method (C), PTV with poloxamer 407 prepared by Fusion Method (D).

**Fourier transform infrared (FTIR) spectroscopy.** FTIR spectroscopy analysis was performed to detect any physicochemical interactions between PTV and polymers, Poloxamer 407 and HPMC, in solid dispersion formulations (Figure 3). No noteworthy change in peaks was observed in the FTIR analysis of SD formulations compared to pure drug analysis (Figure 3). These indicated that there were no interactions among the API and polymers during or after the formulation.

### ***In vitro* Drug Release Studies**

**Drug release study of PTV from binary solid dispersion formulation prepared by physical mixing.** The release rate of pure PTV was found to be 61.42% in 60 minutes (Figure 4). All the

formulations yielded through physical mixing exhibited a higher release rate than that of pure PTV. The release rate of P1, P2, P3 and P4 were found to be 71.52% (Std. dev.=4.60), 82.32% (Std. dev.=3.71), 68.78% (Std. dev.= 8.49) and 80.28% (Std. dev.=1.34) respectively in 60 minutes (Figure 4). P2 and P4 formulations containing high amount of polymer (1:3 ratios) exhibited greater cumulative % release of PTV than the P1 and P3 formulations (1:2 ratios). Again, higher release rate of P2 than P4 illustrated that Poloxamer 407 is a better option than HPMC in designing binary SD formulations.

One-way ANOVA confirmed that cumulative release (%) of PTV from binary solid dispersion formulations prepared by physical mixing differed significantly ( $P < 0.05$ ) for both the polymers at different concentrations (Table 2).

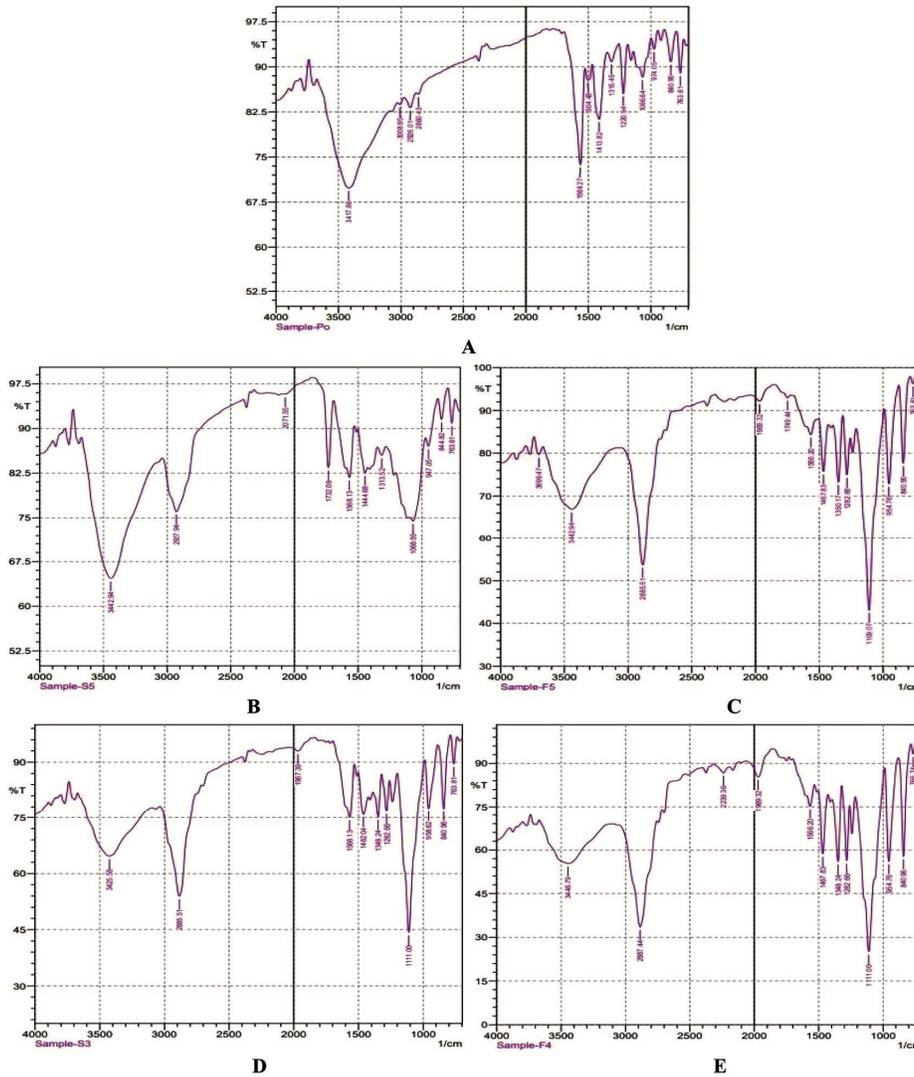


Figure 3. FTIR analysis of pure PTV (A), PTV with HPMC with Solvent Evaporation Method (B), PTV with HPMC with Fusion Method (C), PTV with poloxamer 407 with Solvent Evaporation Method (D), PTV with poloxamer 407 with Fusion Method (E).

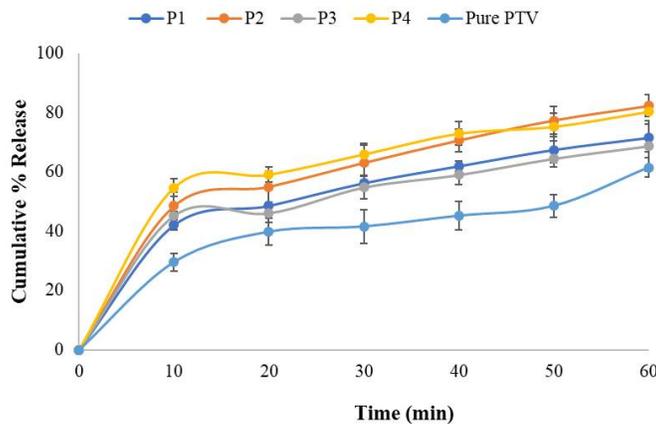


Figure 4. Cumulative % release (Zero order) of pure PTV and P1, P2, P3, P4 formulations prepared by physical mixing technique.

**Table 2. ANOVA (Analysis of Variance) of the optimized physical mixings (PMs) of PTV.<sup>25</sup>**

Physical mixing	Ratio drug: polymer	Source of variation	SS	df	Ms	F	P- value	F <sub>crit</sub>
Poloxamer 407	1:2	Between group	1355.007	1	1355.007	2.575	0.1345	4.73
		Within groups	6313.136	12	526.0946			
	1:3	Between group	2499.255	1	2499.255	4.049	0.0671	4.73
		Within groups	7406.585	12	617.215			
HPMC	1:2	Between group	1179.963	1	1179.963	2.365	0.150	4.73
		Within groups	5986.895	12	498.9079			
	1:3	Between group	2802.247	1	2802.247	4.6357	0.0523	4.73
		Within groups	7253.863	12	604.4886			

**Table 3. Different kinetic parameters of PTV release for physical mixing (binary) formulations.**

Physical mixing	Ratio of drug: polymer	Zero order		First order		Higuchi model		Hixson- Crowell Model	
		R <sup>2</sup>	K <sub>0</sub>	R <sup>2</sup>	K <sub>1</sub>	R <sup>2</sup>	K <sub>h</sub>	R <sup>2</sup>	K <sub>Hc</sub>
Poloxamer 407	1:2	0.7898	0.9955	0.9223	-0.008	0.9652	8.9442	0.8834	-0.023
	1:3	0.796	1.1443	0.9551	-0.011	0.9658	10.245	0.915	-0.029
HPMC	1:2	0.7445	0.9205	0.8768	-0.007	0.9351	8.3846	0.8359	-0.020
	1:3	0.7017	1.0565	0.8862	-0.010	0.9174	9.818	0.8291	-0.027
Pure PTV	-	0.78	0.84	0.9	-0.006	0.95	7.5	0.83	-0.018

Further inspection of the release curve of PTV was done to ensure if it fits the various model. The best-fitted model of the dissolution release study data of PTV for binary physical mixing formulations was the Higuchi model. The order of the fitted model for the binary physical mixing of PTV and polymers were: Higuchi model (1<sup>st</sup>), First order (2<sup>nd</sup>), Hixson Crowell (3<sup>rd</sup>) and Zero order (4<sup>th</sup>) (Table 3).

**In vitro dissolution study of PTV from solid dispersion formulations prepared by fusion method.** The dissolution release rates for physical mixing formulations were promising with ratios of 1:2 and 1:3 (drug: polymer). So, ratio 1:2 and 1:3 were also considered for preparing ternary SD formulation. Formulations of PTV with polymer Poloxamer 407/HPMC in PEG 6000 carrier were prepared in a ratio (1:6.25:2) and (1:6.25:3) using the fusion method and their cumulative release percentages were measured. F1, F2, F3 and F4 formulations prepared by SD fusion method presented improved release rate of 87.05% (Std. dev.= 4.83), 93.48% (Std. dev.= 3.25), 94.62% (Std.

dev.= 2.12) and 89.38% (Std. dev.= 3.73) respectively in 60 minutes which were much higher than the cumulative percent release of pure PTV (Figure 5). Fusion method was experimentally more effective than physical mixing to improve the release rate of PTV as cumulative percent release of F1, F2, F3 and F4 were better than that of P1, P2, P3 and P4. The F3 formulation exhibited higher cumulative percent release than all the physical mixings and other fusion method formulations. This indicates that 1:2 ratio formulation with HPMC more effectively improved the release rate of PTV in fusion method-based preparation whereas 1:3 ratios of HPMC displayed slightly lower release rate (89.38%) than anticipation.

One-way ANOVA confirmed that cumulative release (%) of PTV from ternary solid SD formulation prepared by fusion method differed significantly ( $P < 0.05$ ) for both the polymers for all their different concentrations (Table 4).

As for physical mixing formulations, the best-fitted kinetic model of the dissolution study data of

PTV from fusion SD formulations was the Higuchi model. The order of the fitted model for the fusion SDs of PTV and polymers were: Higuchi model (1<sup>st</sup>),

Hixson Crowell (2<sup>nd</sup>), First order (3<sup>rd</sup>), Zero order (4<sup>th</sup>) (Table 5).

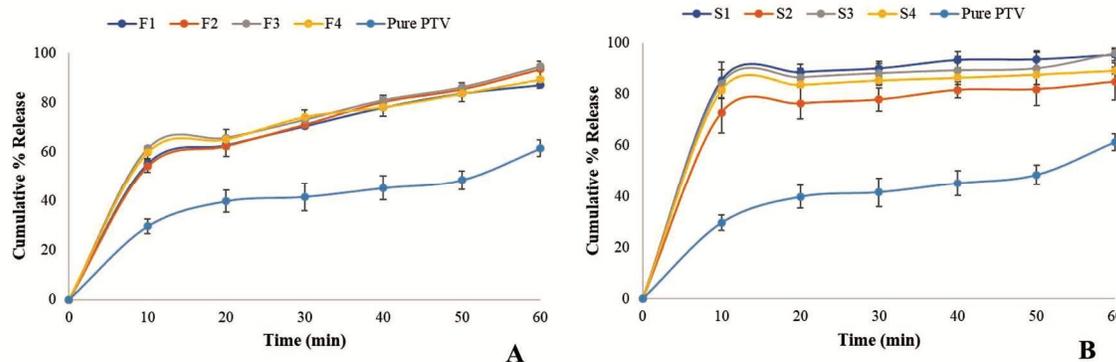


Figure 5. (A) Cumulative % release (Zero order) of pure PTV and F1, F2, F3, F4 formulations prepared by fusion SD technique. (B) Cumulative % release (Zero order) of pure PTV and S1, S2, S3, S4 formulations prepared by solvent evaporation SD technique.

Table 4. ANOVA analysis of the optimized SDs of PTV by fusion method.<sup>25</sup>

Fusion method	Ratio of drug: polymer	Source of variation	SS	df	Ms	F	P-value	F crit
Poloxamer 407	1:2	Between groups	3692.359	1	3692.359	5.4568	0.0376	4.73
		Within group	8117.027	12	676.4189			
	1:3	Between groups	3995.836	1	3995.836	5.5537	0.0362	4.73
		Within group	8633.869	12	719.489			
HPMC	1:2	Between groups	4544.536	1	4544.536	6.2816	0.0275	4.73
		Within group	8681.515	12	723.4596			
	1:3	Between groups	4130.59	1	4130.59	6.0076	0.0305	4.73
		Within group	8250.707	12	687.558			

Table 5. Kinetic parameters of PTV release from ternary solid dispersion (1:2 and 1:3 ratios) formulations by fusion method.

Fusion method	Ratio drug: polymer	Zero order		First order		Higuchi model		Hixson- Crowell Model	
		R <sup>2</sup>	K <sub>0</sub>	R <sup>2</sup>	K <sub>1</sub>	R <sup>2</sup>	K <sub>h</sub>	R <sup>2</sup>	K <sub>Hc</sub>
Poloxamer 407	1:2	0.7463	1.1904	0.9504	-0.0135	0.9445	10.885	0.8962	-0.033
	1:3	0.797	1.2886	0.9598	-0.0172	0.9667	11.534	0.9446	-0.040
HPMC	1:2	0.7381	1.2452	0.9311	-0.0177	0.933	11.378	0.9104	-0.04
	1:3	0.7084	1.1743	0.9326	-0.0139	0.9214	10.885	0.8728	-0.034

**In vitro dissolution study of PTV from solid dispersion formulation prepared by solvent evaporation method.** Formulation of PTV with polymer poloxamer 407 /HPMC was prepared in ratios of 1:2 and 1:3 using solvent evaporation method and its cumulative release percentage was compared with pure PTV and other formulations

prepared by physical mixing and fusion process. S1, S2, S3 and S4 formulations presented an improved cumulative % release of 95.62% (Std. dev.= 2.57), 85.04% (Std. dev.= 7.32), 96.06% (Std. dev.= 1.42) and 89.31% (Std. dev.= 1.51) respectively in 60 minutes (Figure 5 (B)). Among the formulations made by solvent evaporation method, S3

demonstrated better drug release in 60 minutes which indicates that HPMC is more favorable to improve PTV release in ternary SD formulation prepared by solvent evaporation method. Again, higher cumulative % release of PTV from S1 and S3 compared to that from S2 and S4 respectively indicates that 1:2 ratio formulations more effectively upgraded the release rate of PTV from the mixtures than the 1:3 formulations. One-way ANOVA confirmed that cumulative percent release of PTV from ternary SD formulation prepared by solvent

evaporation method differed significantly ( $P < 0.05$ ) for both the polymers for all their different concentrations (Table 6).

As like physical mixing formulations, the good-fitted model of the *in vitro* dissolution study data of PTV from formulations by solvent evaporation method was the Higuchi model. The order of the fitted model for the ternary SDs (by solvent evaporation method) of PTV and polymers were: Higuchi model (1<sup>st</sup>), First order (2<sup>nd</sup>), Hixson Crowell (3<sup>rd</sup>), Zero order (4<sup>th</sup>) (Table 7).

**Table 6. ANOVA of the optimized PMs of PTV by solvent evaporation method.**

Solvent evaporation method	Ratio of drug: polymer	Source of variation	SS	df	Ms	F	P-value	F <sub>crit</sub>
Poloxamer 407	1:2	Between groups	8137.022	1	8137.022	9.7565	0.0075	4.73
		Within group	10008.04	12	834.0034			
	1:3	Between groups	5065.652	1	5065.652	7.3252	0.0190	4.73
		Within group	8298.353	12	691.529			
HPMC	1:2	Between groups	7535.091	1	7535.091	9.33123	0.0099	4.73
		Within group	9690.151	12	807.5126			
	1:3	Between groups	6622.884	1	6622.884	8.69487	0.01217	4.73
		Within group	9140.457	12	761.7048			

**Table 7. Kinetic parameters of PTV release from ternary solid dispersion (1:2 & 1:3 ratios) formulations by solvent evaporation method.**

Solvent evaporation method	Ratio of drug: Polymer	Zero order		First order		Higuchi model		Hixson- Crowell model	
		R <sup>2</sup>	K <sub>0</sub>	R <sup>2</sup>	K <sub>1</sub>	R <sup>2</sup>	K <sub>h</sub>	R <sup>2</sup>	KHC
Poloxamer 407	1:2	0.4704	1.1004	0.7542	-0.018	0.7482	11.28	0.6347	-0.037
	1:3	0.5043	0.9951	0.6722	-0.010	0.7765	10.036	0.6102	-0.026
HPMC	1:2	0.4757	1.0819	0.7392	-0.016	0.7491	11.035	0.6371	-0.036
	1:3	0.4603	1.0101	0.606	-0.011	0.7299	10.449	0.5407	-0.029

There are many hydrophilic polymers and, poloxamer 407 and HPMC belong to that class. In the past, poloxamer 407 has been used in several SD formulations to enhance the dissolution rate and it successfully demonstrated a rise in dissolution of desloratadine, ibuprofen and also to improve the dissolution rate of Coenzyme Q10 by solvent evaporation method due to wetting capability.<sup>30,31,32</sup> HPMC upgrades the dissolution rate of different hydrophobic drugs formulated applying solid

dispersion methods such as control release of carvedilol by solid dispersion technique using HPMC, enhancing the release rate of extended release tablet by lipid based solid dispersion using HPMC, establishing the new preparation technique of tacrolimus and in preparation and characterization of curcumin.<sup>33,34,35</sup> PTV calcium drug particle has crystalline characteristic (Figure 1). Hence variety of reasons can be responsible for a higher release rate of PTV in SD formulations preparing with polymer

poloxamer 407 and HPMC. One reason could be the reduction of crystallinity of PTV or its physical transformation into an amorphous shape which is confirmed by SEM analysis (Figure 1). This could have also been due to a decrease in particle size and for an increase in the surface area thus ensuing in an improved dissolution rate.<sup>25,36,37</sup>

## CONCLUSION

It can be concluded that polymers like poloxamer 407 and HPMC could be used in the SD method for poorly aqueous soluble drug molecules like PTV. From the obtained result it can be interoperated that 1:2 ratio of PTV-polymer displayed a better dissolution rate particularly in case of solvent evaporation approach. On the other hand, high amount of polymer in physical mixing formulations enhanced the dissolution rate of PTV better. TGA, FT-IR, SEM analysis of SD formulations revealed that SD formulations are stable at high temperature, little or no interactions were observed between drug and polymers and conversion of crystal-like PTV to amorphous state. From the outcomes it can be concluded that these polymers could be used to improve the solubility of this API and other BCS class II drugs because of their availability, feasibility, and affordability. However, *in vivo* studies will need to be carried out in future to confirm the findings of improved *in vitro* dissolution rate of PTV as well as the oral bioavailability of PTV solid dispersion formulations.

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