

Enhancement of Carvedilol Dissolution; Surface Solid Dispersion Versus Solid Dispersion

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Abstract

The aim of this work was to improve the aqueous solubility of carvedilol (CRV), poorly water soluble drug, using surface solid dispersion (SSD) technique. Drug was deposited over the surface of a hydrophilic, water-insoluble carrier (Avicel pH 101) by solvent evaporation. Pluronic F68 was added as a wetting agent to some formulations. To estimate the effect of SSD technique on drug dissolution, solid dispersions (SDs) of dug and Pluronic F68 were prepared by solvent evaporation. Pluronic F68 was selected due to its inhibiting effect to CYP3A4, an enzyme that contribute to hepatic metabolism of CRV. All formulations were characterized by *in vitro* dissolution studies; X-ray powder diffraction and scanning electron microscopy. SSD enhanced drug dissolution compared to pure drug. The addition of polymer to drug/carrier composite greatly improved drug dissolution compared to that without the polymer. Compared to SD, SSD showed a better drug release rate. X-ray diffraction indicated the complete reduction in drug crystallinity and the formation of the amorphous form in case of SSD, with limited reduction in crystallinity for SD. The obtained dissolution efficiency of SSD was comparable to that obtained from the marketed CRV product. The study thus presented a system capable of increasing the dissolution rate of CRV with a potential for increased oral bioavailability by inhibiting its pre-systemic metabolism as well.

Key words: Carvedilol, enhance dissolution, poor aqueous solubility, solid dispersion, surface solid dispersion

INTRODUCTION

The bioavailability of poorly water soluble drugs is a true challenge that faces the development of many dosage forms, especially oral ones. In consequence of the low water solubility of such drugs, bad dissolution profile and erratic bioavailability are usually accompanying those drugs.^[1]

Recent advances in biotechnology, together with combinatorial chemistry and parallel synthesis are increasing the number of lipophilic molecules which are difficult to deliver due to bioavailability issues.^[2] Carvedilol (CRV) is one such compounds that suffer from poor aqueous solubility. CRV is non-selective beta blocker with alpha-1 receptor blocking action with multiple cardiovascular effects. CRV is currently approved in many countries to treat high blood pressure, ischemic heart diseases, post-myocardial infarction, and mild-to-severe congestive heart failures.^[3,4] CRV is categorized as class II compound as per the

Biopharmaceutical Classification System with poor aqueous solubility and good membrane permeability.^[5] It possess very poor bioavailability (25–35%) and shows significant first pass metabolism.^[6]

Many trials have been conducted to improve the solubility of CRV such as the use of surfactant,^[7] liquisolid compact,^[8] self-emulsifying drug delivery system,^[9] inclusion complex,^[10] spray drying,^[11] and solid dispersion (SD).^[12] To avoid hepatic first-pass metabolism, other researchers investigated enhancement of transdermal delivery of CRV^[13,14] or preparation of bucco-adhesive bilayer tablets.^[15]

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The aim of this work was to enhance CRV dissolution through the use of surface solid dispersion (SSD). SSD is a method utilized to reduce the agglomeration of the drug particles by increasing their surface area which could help increasing the dissolution rate. SSD may be achieved by the incorporation of the drug solution into carrier forming a slurry and subsequent deposition of the drug solution over adsorbent carrier surface.^[16] Variable materials reported to perform as carriers in SSD are non-biodegradable, porous materials and mostly hydrophilic in nature such as microcrystalline cellulose, sodium starch glycolate, and croscarmellose.^[17] SSD has been demonstrated as a successful method to improve the dissolution rate and the solubility of many drugs such as glibenclamide,^[16] glimepiride^[18] and nifedipine.^[19]

Surface solid dispersion of CRV was prepared using microcrystalline cellulose (Avicel pH 101) as carrier. The drug was precipitated over the carrier in the presence and absence of Pluronic F68. The selected polymer is a solid hydrophilic block copolymer that was shown to inhibit CYP3A4 that contribute to CRV metabolism during the first pass effect.^[20] The same polymer was also used to prepare CRV SD by the traditional solvent evaporation method, and a comparison was made between the two techniques regarding drug dissolution to elucidate the implication of SSD technique.

MATERIALS AND METHODS

Materials

Carvedilol was a generous gift from Sigma Egypt Co. Ltd., Egypt. Pluronic F68 and Avicel pH 101 were obtained from Memphis Co. (Cairo, Egypt). Other chemicals and reagents were of analytical grade.

Methods

Construction of the calibration curve

Standard stock solutions were prepared by dissolving 100 mg of standard drug sample in 100 mL volumetric flask, and the volume was made up with methanol to get a concentration of 1 mg/mL. From this, suitable dilutions were made in methanol to get the working standard solutions of 5–30 µg/mL of CRV. The absorbance of the spectra was measured spectrophotometrically (Shimadzu UV-160A Spectrophotometer, Shimadzu, Japan) at 284 nm for CRV. Five replicates analyses were carried out. Absorbance versus concentrations were plotted to obtain the calibration graph. The drug obeyed Beer's law with 'r' value of 0.998.

Preparation of surface solid dispersion

The SSDs of CRV and the water insoluble, but hydrophilic, carrier (Avicel pH 101) were prepared at drug/carrier weight ratios of 1:19 and 1:9, according to the previously published

ratio after the necessary modification.^[16] SSD formulations were prepared using solvent deposition technique.^[18] Table 1 shows the composition of all tested formulations.

The calculated amount of drug (100 mg), with or without wetting agent, was dissolved in methanol (5 mL). This solution was added to the carrier with continuous mixing until a homogenous mixture was attained. The obtained slurry was stirred using a magnetic stirrer at room temperature till the complete evaporation of the organic solvent. Residual solvent was removed by keeping the resulted mass under reduced pressure at ambient temperature overnight. The resulting mass was lightly grinded by glass rode, passing through a 355 µm sieve and transferred to a desiccator containing CaCl₂ and stored until used.

Preparation of solid dispersion

Solid dispersion was prepared by solvent evaporation method at 1:1 CRV: Pluronic F68 weight ratio. Drug and polymer were dissolved in methanol. The organic solvent was removed at ambient temperature, under reduced pressure. The pulverized powder was passed through a 355 µm sieve and stored in the desiccators till used.

Preparation of physical mixture

Physical mixture (PM) was prepared by simple mixing of the same ingredients as that of F3 by geometric dry blending of the drug and polymer with the aid of mortar and a pestle. The PM was also passed through a 355 µm sieve before packing in a tightly closed bottle.

Content uniformity

Drug contents were calculated by dissolving an exact amount of each formula in 10 mL of methanol and analyzed spectrophotometrically at 284 nm for drug.

In vitro dissolution studies

In vitro dissolution, studies were carried out using USP dissolution tester (Pharma Test, Germany), Apparatus II

Table 1: Key formulation characteristics of the prepared SSD, SD and PM

Formula code	Technique	Drug:Carrier ratio w/w	Drug:Wetting agent ratio*
F1	SSD	1:19	-
F2	SSD	1:9	-
F3	SSD	1:9	1:1
F4	SSD	1:9	1:3
F5	SSD	1:9	1:5
F6	SD	-	1:1
PM	PM	1:9	1:1

*Wetting agent is Pluronic F68. SSD: Surface solid dispersion, SD: Solid dispersion, PM: Physical mixture

Paddle method. Accurately weighed samples equivalent to 12.5 mg of CRV were packed in hard gelatine capsules. Each capsule was placed in a dissolution vessel containing 900 mL of 0.1 N HCL as dissolution medium, kept at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ and rotated at 100 rpm. Aliquots were withdrawn at predetermined time interval and filtered through 0.45 mm membrane filter. To maintain sink conditions, an equal volume of fresh dissolution medium was immediately replaced. The concentration of CRV at each sampling time was analyzed spectrophotometrically at 284 nm. The results were compared to the dissolution data of the marketed formulation (Riacavilol, Riyadh Pharma, Saudi Arabia), where the dissolution data of the product were obtained after adding the tablet to the dissolution vessels while stirring as before.

Solid state characterization

X-ray powder diffraction

X-ray powder diffraction (XRPD) pattern were recorded using (Unisantis XMD-300, powder diffractometer. Powder X-ray diffraction pattern were traced for CRV, Avicel, SSD (F3) and SD (F6). Samples were slightly ground and packed into the aluminum sample containers. The scanning rate employed was $8^{\circ}/\text{min}$ over a 2θ range of 0–30.

Scanning electron microscopy

Surface morphology of CRV, Avicel pH 101, SSD formula F3 was examined using a scanning electron microscope (JSM-5350A, JOEL, Tokyo, Japan). Samples were mounted on an aluminum stub using a double sided adhesive tape and then making it electrically conductive by coating with a thin layer of gold (approximately 24 nm) in a vacuum.

Statistical analysis

All experiments were conducted in triplicates, and Student's *t*-test was used to analyze all the data. Results were quoted as significant where $P < 0.05$.

RESULTS AND DISCUSSION

Content uniformity

Monitoring drug content uniformity in the early stages of the formulation is an important matter in the pharmaceutical field as it is required for the control of drug quality and durability of the process. All tested formulations showed reasonable drug content uniformity (ranging from 97% to 101%), indicating a homogeneous distribution of prepared formulations.

Solid state characterization

X-ray powder diffraction

X-ray powder diffraction was used to trace any change in the crystalline state of the drug that may affect its solubility, by determining the atomic and molecular structure of a crystal. XRPD was used for solid state characterization for SSD F3 formula and SD F6, pure drug and Pluronic F68. The X-ray diffractograms are shown in Figure 1. Numerous diffraction peaks of CRV were observed at 2θ of 12.8° , 15.62° , 17.46° , 18.56° , 20.1° , 24.3° and 26.2° indicating the presence of the crystalline nature of CRV.^[21] In SSD formula F3, there was a complete disappearance of these peaks, with the presence of the peak corresponding to the carrier (Avicel pH 101) at the diffraction angle of 2θ at 22.0° .^[16] This indicates the full disappearance of the crystalline structure of the drug and confirms the presence of the drug at the amorphous state. For SD F6, the reduced intensity of peaks indicates the reduction of drug crystallinity, but not complete amorphousness. We should take into consideration that all these findings need further confirmation by thermal analysis.

Scanning electron microscopy

The different particle shape of pure CRV, Avicel pH 101 and SSD formula F3 are shown in Figure 2. CRV showed typical

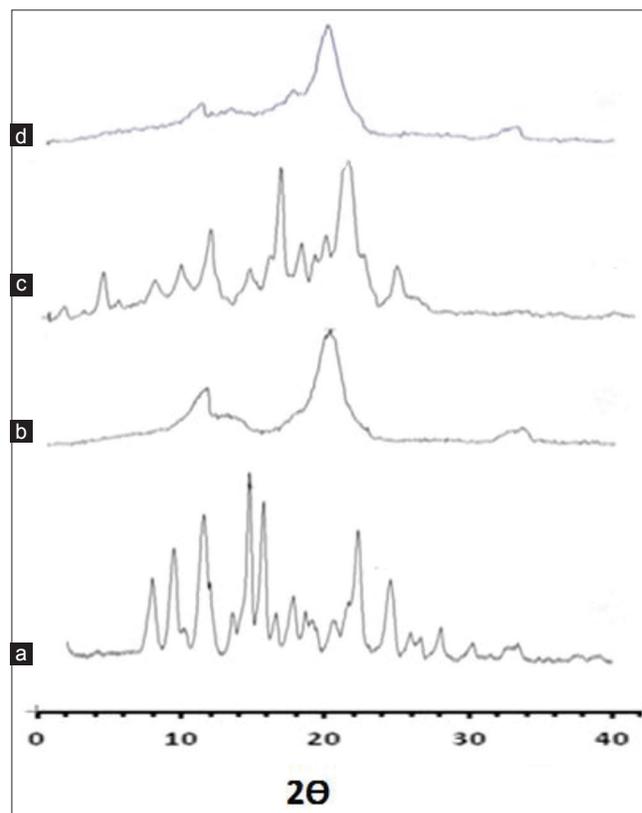


Figure 1: X-ray powder diffractograms of carvedilol (a), Avicel pH 101 (b), solid dispersion (SD) formula F6 (c) and surface SD F3 (d)

crystalline structure. Avicel pH 101 showed irregular crystals in agreement with published data.^[22] For SSD F3, there was a complete disappearance of the characteristic CRV crystals, only the irregular particles of the carrier with irregular porous surface of uniform mass with some surface crusts. The porous surface may have resulted from the evaporation of the solvent during processing. The surface crust may be formed as a result of the superior movement of the surfactant to the liquid/gas interface during evaporation due to surfactant amphiphilic nature.

Dissolution studies

Dissolution profiles of all formulations are presented in Figure 3 as cumulative drug released versus time plots. Dissolution parameters represented as the percentage drug released after 10 min (Q_{10}), and the time required for the release of 50% of the drug (t_{50}) were calculated [Table 2]. In addition, percentage dissolution efficiency (%DE) after 30 and 90 min (%DE₃₀ and %DE₉₀, respectively) was calculated from the area under each dissolution curve at certain time (t), and measured using the trapezoidal rule and expressed as a percentage of the area of the rectangle described by 100% dissolution at the same time.^[23]

First we will discuss the drug release from SSD prepared by precipitating the drug onto carrier at the two ratios 1:19 and 1:9 w/w, respectively, using crude drug as control [Figure 3a]. Pure CRV showed poor dissolution, where the Q_{10} was only about 17%. The overall amount of drug released was 48% at the end of the 90 min, with %DE₃₀ and %DE₉₀ of 6.42 and 35.1, respectively. Such reasonable dissolution behavior is due to the use of acidic dissolution media for the basic CRV. Preparing the SSD (F1 and F2) enhanced drug

Table 2: Dissolution parameters of carvedilol from different formulations and pure drug; where Q_{10} is the percentage drug released after 10 min, t_{50} is the time required for the release of 50% of the dose and %DE₃₀ and %DE₉₀ are the %DE after 30 and 90 min, respectively

Formula code	Q10	%DE ₃₀	%DE ₉₀	t_{50} (min)
Pure drug	17.7±1.3	6.42±0.92	35.1±1.6	>90
F1	58.0±2.5	19.5±1.3	76.5±3.1	<10
F2	66.2±2.9	22.5±2.3	80.3±2.2	<10
F3	84.4±6.6	26.0±2.6	95.5±2.5	<10
F4	91.3±4.5	26.3±6.1	92.2±6.3	<10
F5	93.2±3.4	28.2±3.1	88.7±4.2	<10
F6	63.1±3.2	17.9±2.4	79.1±1.9	10
PM	31.0±2.1	10.5±0.89	49.5±2.1	40
Commercial drug	89.6±3.5	28.3±1.3	95±3.2	<10

%DE: Percentage dissolution efficiency, PM: Physical mixture

dissolution compared to pure drug ($P < 0.05$). There was a rapid release of the drug with Q_{10} of 66% and 58% for F1 and F2, respectively. This enhancement may be due to the disposition of the drug over the carrier surface in an extremely fine state of subdivision. The assumed reduction in particle size with the concomitant increase in the surface area resulted in increased dissolution rate compared to control. This would indicate that SSD using Avicel pH 101 is a suitable technique to enhance drug dissolution, and consequently bioavailability.

There was no difference ($P > 0.05$) between the two carrier ratios regarding the dissolution parameters [Table 2]. This would signify the use of the smaller ratio (1:9) with less amount of carrier to obtain a reasonable weight and reduce

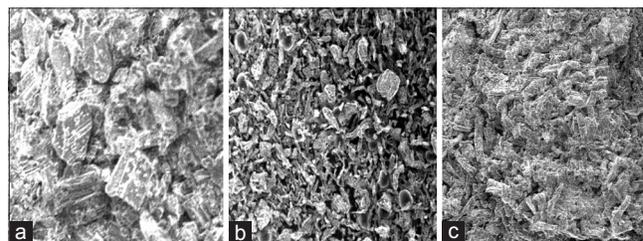


Figure 2: Scanning electron microscopy of: Carvedilol (a), Avicel pH 101 (b) and surface solid dispersion formula F3 (c)

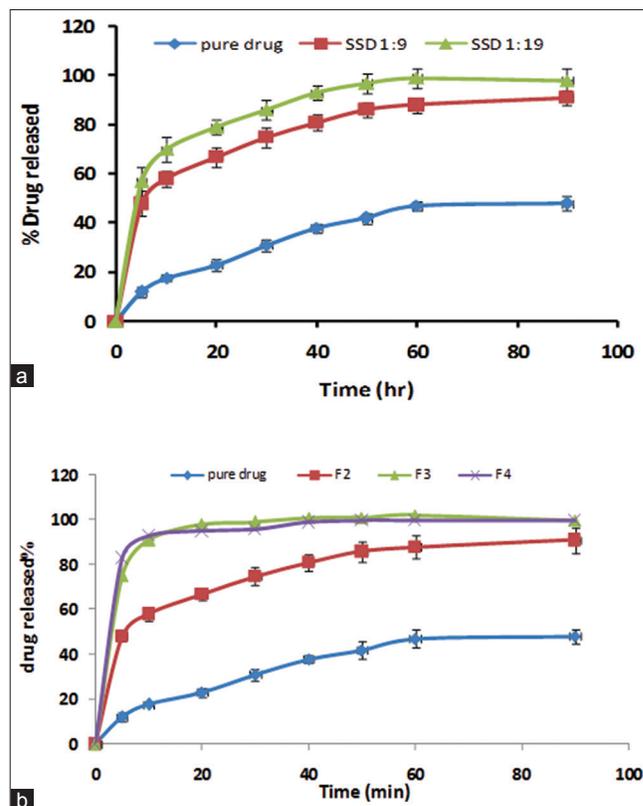


Figure 3: Dissolution profiles of (a) pure carvedilol (CRV), surface solid dispersion (SSD) at 1:19 and 1:9 drug:carrier ratio; (b) pure CRV, SSD with (F3 and F4) and without (F1) wetting agent ($n = 3 \pm SD$). For details of formulations refer to Table 1

workable amount in pharmaceutical formulations. This will be more suitable from the financial and administration point of view.

Traditionally, the utilization of surfactants for the purpose of enhancing the solubility of drugs is widely and acceptably established. Being adsorption enhancers, surfactants enhance both dissolution rate as well as permeability, promote wetting of the solid particles. Therefore, the effect of the polymeric wetting agent (Pluronic F68) in the solubility of the drug from the water-insoluble carrier was investigated. Pluronic F68 was used at a drug: polymer ratio of 1:1, 1:3 and 1:5 (F3, F4, and F5, respectively) to formula F2. Pluronics are group of triblock copolymers namely polyethylene oxide (PEO)-polypropylene oxide - PEO. They are non-ionic surfactants that have been widely used as wetting and solubilizing agent due to their ability to alter physical properties such as hydrophobicity and wetting properties.^[24] The selection of Pluronic F68 was also based on the reported data of being a potent *in vitro* inhibitor for CYP3A4, an enzyme that contributes to metabolism of CRV during hepatic first pass effect. This would suggest a potential for modifying the pharmacokinetics of orally administered CRV.^[20]

The dissolution profiles are shown in Figure 3b. Dissolution parameters are presented in Table 2. Both formulations enhanced drug dissolution with a Q_{10} of 75%, 79%, and 83% for F3, F4, and F5, compared to only 17%, and 58% for pure drug and F2, respectively. Both formulations showed a similar increase in the %DE₃₀ with about 4-folds enhancement compared to drug alone, with the overall increase in DE₉₀ by about 3-folds. Enhanced dissolution may be attributed to the de-aggregation and increased wetting of drug due to the presence of the polymeric wetting matrix. Drug and polymer co-precipitated forming SD at the carrier surface. In SD, drug was molecularly embedded in the hydrophilic polymer; the latter could be now considered as a matrix for the drug. The hydrophilic polymer undergoes rapid dissolution upon exposure to the dissolution medium and reaches high concentration in the diffusion layer creating high concentration gradient which is the driving force for drug dissolution and increased dissolution rate of CRV.^[25] The enhancement of drug release was achieved as the drug could be present at its amorphous state, as shown by X-ray data and the formation of solid solution at the surface of the carrier. Drug in the amorphous state tends to have higher solubility as no energy is required to break up the crystal lattice during the dissolution process.

It is worth noting that increasing Pluronic F68 concentration did not significantly increased drug dissolution over that of F3 [Table 2]. To explain this, the thermoreversible gel formation behavior of the polymer could be considered, which a known phenomenon of Pluronic family. The gel formation capability of Pluronic based on both its critical micelle temperature (CMT) and concentration. CMT is the temperature at which micelles are formed and is reported to

be about 24°C.^[26] Above the critical micelle concentration, the liquid-phase micelles formed by Pluronic F68 copolymers undergo transition into liquid crystal gel phases as a result of increased temperature, that is, above CMT.^[27] It was reported that Pluronic F68 forms gel above a certain concentration of about 15% w/v.^[28] In this study, the concentration of the polymer was below that required to form a gel structure. However, deep at the microenvironment level around the polymer, particularly in the diffusion layer, the concentration is at the saturation level. This may result in the formation of a gel microenvironment that would slow down drug movement through it by increasing the viscosity. This could explain why higher Pluronic F68 concentration showed less drug dissolution efficiency.

It was necessary to ensure that the improved drug dissolution is due to the technique of SSD, so we compared drug release from F3 (best formula) to that of the PM. The dissolution parameters were then compared to that of pure drug and F3 [Figure 4 and Table 2]. There was no significant t ($P > 0.05$) increase in drug dissolution from PM compared to the control drug suggesting that the net effect of formula F3 is not just a solubilizing effect of the polymer and the mixture has to be formulated into SSD.

It was suggested that the improved drug dissolution from SSD, when Pluronic F68 was added to CRV/carrier composite, was due to the formation of solid solution deposit on the surface of the carrier. This section will discuss the drug release from SD, and dissolution parameters will be compared to those of pure drug and F3 to estimate the SSD as a technique in drug release. Formula F6 (SD) was prepared as 1:1 drug:polymer ratio. The dissolution profiles [Figure 4] showed improved CRV dissolution from compared to pure drug ($P < 0.05$). About 50% of the dose dissolved after 10 min with about 3- and 2-folds enhancement in %DE₃₀ and %DE₉₀, respectively [Table 2]. A strong contribution to the enhancement of drug solubility in SD is related to the drug wettability. It has been suggested that the presentation

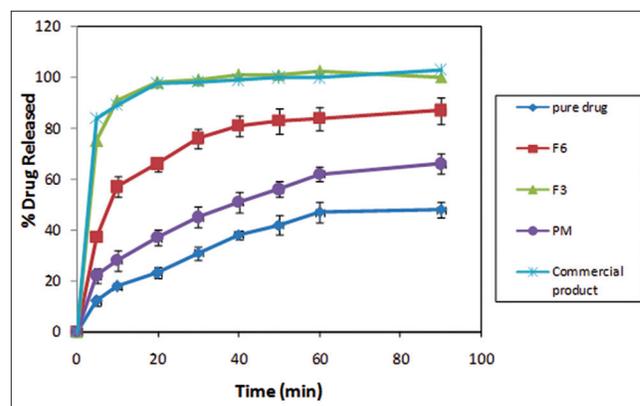


Figure 4: Dissolution profiles of carvedilol from pure drug, surface solid dispersion (SD) F3, physical mixture, SD F6, and commercial drug [error bars were sometimes omitted for clarity, formulation details are presented in Table 1]

of particles to the dissolution medium as physically separate entities may reduce aggregation. In addition, the wetting properties of Pluronic F68 may lead to reduced agglomeration and increased surface area. Moreover, the reduced drug crystallinity (as revealed by X-ray data) could be an added factor.

Compared to SSD, F3 is superior regarding drug dissolution compared to F6. Therefore, the possible formation of solid solution film over each carrier particle during solvent evaporation creates a large surface area of the drug-exposed to the dissolution media. The dual effect of increased surface area augmented by solid solution formation would signify the better enhancement in dissolution from SSD technique.

Therefore, we can suggest that SSD technique can provide a useful alternative strategy to prepare SD with improved dissolution and stability. The technique will alleviate the need for grinding of the solid mass obtained in SD technique. This grinding would result in changes in the drug crystallinity and may affect drug stability.

Compared to commercial CRV tablets (Riacavilol, Riyadh Pharma), there were a comparable dissolution behavior between F3 and commercial product with similar ($P > 0.05$) dissolution parameters [Figure 4 and Table 2]. The study thus presented a system capable of introducing a formulation of CRV with a potential for increased drug bioavailability similar to marketed drug products.

CONCLUSION

Surface solid dispersion technique was a successful tool in enhancing the dissolution rate of CRV, poorly water soluble drug. Water insoluble, hydrophilic carrier accompanied by Pluronic F68, as a wetting agent, largely improved drug dissolution that was comparable to the marketed product of CRV. Solid state characterization revealed that the enhanced drug dissolution was due to the presence of the drug at its amorphous state. SD improved drug solubility but to a lesser extent compared to SSD. The study thus presented a system capable of increasing the dissolution rate of CRV with a potential for increased oral bioavailability by reducing its pre-systemic metabolism due to the presence of Pluronic F68.

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