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Soluplus®: A novel polymeric solubilizer for optimization of Carvedilol solid dispersions: Formulation design and effect of method of preparation

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ABSTRACT

The aim of this work was to investigate the applicability of different industrially scalable techniques in the preparation of solid dispersions using a novel polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (Soluplus®) for preparing immediate-release formulations of a poorly water-soluble BCS class II drug. Carvedilol (CAR), a non-selective β-blocker, has been selected as poorly water-soluble model drug. The solid dispersions were prepared by three different techniques; solvent evaporation, freeze drying and spray drying in different CAR:Soluplus® ratios using 3^2 full factorial design. Among the formulations tested, CAR solid dispersion preparation using freeze drying method at ratio of 1:10 (CAR: Soluplus®) showed the highest saturation solubility and was selected for further investigation. Solid state characterization was evaluated by differential scanning calorimetry (DSC) and X-ray diffraction study (XRD), scanning electron microscopy (SEM) and Fourier transformation infrared spectroscopy (FTIR). DSC and XRD analyses indicated the complete transformation of CAR in the solid dispersion from crystalline to amorphous state. Selected CAR solid dispersion was further incorporated into ODTs using three commercially mannitol-based fillers; Pearlitol Flash®, Pharmaburst® and Ludifalsh®. The ODTs were evaluated for hardness, disintegration time and drug dissolution. Pearlitol Flash®, and Pharmaburst® ODTs showed shorter disintegration times (<1 min) and significantly higher dissolution profile (>90% within 30 min) compared to Ludifalsh® ODTs. Thus, the development of CAR solid dispersions using Soluplus® as ODTs could be used as a promising approach for improving the solubility and oral bioavailability of poorly water-soluble drugs.

1. Introduction

Solid dispersion is one of the most effective approaches to improve the solubility and dissolution rate and hence the bioavailability of poorly water-soluble drugs [1,2]. However, a major limitation of solid dispersion is that amorphous drug is thermodynamically unstable and tends to re-crystallize during storage, especially when trace amount of crystalline drug is left in solid dispersion which will act as nucleating agents to accelerate re-crystallization of amorphous drug substance [3,4]. Therefore, complete transformation of crystalline drug to amorphous state is the key point to improve physical stability and dissolution performance of the solid dispersion. Nowadays, the term solid dispersion is mostly linked to glass solutions of poorly soluble compounds, using amorphous carriers with high glass transition temperatures. The primary aim of fast release glass solutions is to molecularly release the drug in the intestinal fluids and to generate a supersaturated solution from which the drug will move to the gut wall, permeate and finally appear in the blood [5].

The majority of published research data or marketed solid dispersions are based on carriers like polyethylene glycol, polyvinylpyrrolidone, polyvinylpyrrolidone-co-vinylacetate 64 or hydroxypropyl methylcellulose (and derivatives) [1,6]. Although combinations of polymers or polymers with surface active compounds have been proposed as a means to obtain new carrier systems with advanced properties [7–9], there is a clear need for new carriers.

Polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (Soluplus®) is a new polymer with amphiphilic properties, designed and developed for solid solutions. Unlike classical solubilizers like Cremophore RH40 and Solutol HS15, Soluplus® with its bifunctional character (as a matrix polymer for solid solutions and an active solubilizer through micelle formation in water) can be considered as a member of the fourth generation of solid dispersions [10]. From a theoretical point of view, it is an interesting polymer to be used as a carrier for the formulation of solid dispersions. As it is hydrophilic and non-ionic, its solubility does not change along with the gastrointestinal tract. It is slightly surface active, a property which can be useful to maintain supersaturation of poorly soluble drugs in the gastrointestinal tract.

Soluplus® shows excellent solubilizing properties for BCS class II drugs and offers the possibility of producing solid solutions of several drugs of poor water solubility using extrusion techniques [11].

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Nagy et al. compared the electrospun and extrusion techniques in the development of Soluplus® solid solutions of the poorly water soluble drug, spironolactone [10]. Unfortunately, extrusion technique suffers some disadvantages comprising the high processing temperature and the shear stress, which might influence the polymer and drug stability during production and storage. Another important disadvantage is the limited number of available polymers; thus requires pharmaceutical grade polymers that can be processed at relatively low temperatures limiting the variety of possible formulations [12].

To our knowledge, literature lacks any data about the development of Soluplus® solid solutions using other industrial techniques. Thus, the aim of this work was to investigate the applicability of three industrially scalable technologies: solvent evaporation, spray-drying and freeze-drying for preparing immediate-release formulations of a poorly water-soluble BCS class II drug. Carvedilol (CAR), a non-selective β-blocker, has been selected as poorly water-soluble model drug. Solid-state characterization based on FT-IR spectroscopy, DSC, and powder X-ray diffraction was accomplished to examine the interaction of CAR with Soluplus® in both solution and solid state, in order to investigate the mechanisms of carrier dissolution enhancement. A factorial design was employed to optimize the prepared solid dispersion aiming to develop a soluble form of the drug as a primary step in the development of CAR orodispersable tablet (ODT) formulation.

2. Materials and methods

2.1. Materials

Soluplus® and Ludiflash® were provided by BASF SE (Ludwigshafen, Germany). CAR was provided by Hetero drugs company, India. Pearlitol® Flash was kindly supplied by Roquette, Lestrem, France. Pharmaburst® 500 was obtained from SPI Pharma, New Castle, USA. All other chemicals used in the study were of analytical grade, obtained from El-Nasr Company for Pharmaceutical Chemicals, Cairo, Egypt.

2.2. Phase-solubility studies

Solubility measurements were performed in triplicate using the method reported by Higuchi and Connors [13]. An excess amount of CAR was added to the aqueous solutions of Soluplus® in water containing increasing concentrations of Soluplus® (0–20% w/v). The vials were sealed and shaken at 37 ± 0.5 °C for 48 h in a thermostatically controlled water bath (Memmert Gmgh, Germany) and the samples were filtered through a 0.45 μm membrane filter. The filtrate was suitably diluted and the concentration in the solution was determined spectrophotometrically at λ_{max} 282 nm (Shimadzu UV spectrophotometer, 2401/PC, Japan).

2.3. Preparation of CAR — Soluplus® solid dispersions

Solid dispersion was prepared by three methods: solvent evaporation, freeze drying and spray drying using different CAR: Soluplus® ratios.

2.3.1. Solvent evaporation method

Calculated amount of CAR was dissolved in 2.5 times amount of ethanol, and then the solution was poured onto the polymer, triturated with a pestle, and then kept over anhydrous calcium chloride in desiccators in order to dry [14].

2.3.2. Spray drying method

The spray-drying process was performed using a Büchi mini spray-dryer B-191 (Büchi, Flawil, Switzerland). All spray-dried powders were obtained from solutions of CAR/Soluplus® in 25 ml of distilled H_2O. The spray-dryer inlet temperature was set at 90 °C; the pump rate was 20%, the aspirator was set at 100% and the air flow at 600 L/h. All spray-dried samples were further dried in a vacuum oven at 25 °C until constant mass and then analyzed.

2.3.3. Freeze-drying method

Appropriate quantity of Soluplus® was dissolved in distilled water and then an accurately weighed amount of CAR powder was dispersed in the prepared aqueous solution using a magnetic stirrer. The solution was frozen at −20 °C, and subsequently freeze-dried for 24 h at −45 °C and a pressure of 7×10^{-2} mbar for 24 h using a freeze-dryer (Novalyphe-NL 500; Savant Instruments Corp., USA).

2.4. Determination of saturated solubility of solid dispersions

An excess amount of CAR–Soluplus® solid dispersions was added to 5 mL distilled water, and shaken at 37 ± 0.5 °C for 48 h in a thermostatically controlled water bath. The samples were then filtered through a 0.45 μm membrane filter, suitably diluted and the concentration in the solution was determined spectrophotometrically at λ_{max} 282 nm.

2.5. Optimization of CAR–Soluplus® solid dispersions using a 3^2 full factorial experimental design

CAR–Soluplus® solid dispersions were prepared using a 3^2 full factorial experimental design in order to investigate the joint influence of formulation, and process variables using Design — Expert® (version 8) software. In this design, 2 factors are evaluated, each at 3 levels, and experimental trials are performed at all 9 possible combinations. The independent variables were the method of preparation (X_1) and the ratio of CAR:Soluplus® (X_2) (Table 1). The saturated solubility (Y_1) was selected as the dependent variable.

2.6. Characterization of optimized solid dispersion

2.6.1. Differential scanning calorimetry (DSC) studies

Thermograms for CAR plain powder, Soluplus® plain powder, and the selected solid dispersion formulation were obtained. The samples were sealed in aluminum pans and analyzed using a Shimadzu DSC-60 (Kyoto, Japan). The samples were heated in an atmosphere of nitrogen and thermograms were obtained by heating at a constant heating rate of 10 °C/min in the range of 20–350 °C.

2.6.2. Powder X-ray diffraction (XRD)

Diffraction patterns of CAR plain powder, Soluplus® plain powder, and the selected solid dispersion formulation were determined in a Scintag X-ray diffractometer (USA) using Cu K α radiation with a nickel filter, a voltage of 45 kV, and a current of 40 mA.

2.6.3. Scanning electron microscopy (SEM) analysis

The surface morphology of CAR plain powder and the selected solid dispersion formulation were obtained by means of scanning electron microscope (Jeol-JSM-5300 scanning microscope, Tokyo, Japan) operating at 25 kV. The samples were mounted on a glass stub with double-sided adhesive tape and coated under vacuum with gold in an argon atmosphere prior to observation. Micrographs with different magnifications were recorded to study the morphological and surface characteristics of the solid dispersions.

Table 1
Design parameters and experimental conditions for 3^2 full factorial design.

Independent variable	Levels		
	−1	0	1
Method of preparation	SE	SD	FD
CAR:Soluplus® ratio	1:3	1:5	1:10

SE: solvent evaporation method; SD: spray drying method; FD: freeze drying method.

2.6.4. Fourier transform infrared (FT-IR) spectroscopy

Fourier transform infrared (FT-IR) spectra were obtained using a Perkin Elmer Spectrum RX1 FTIR spectrometer (Genesis II, Mattson, USA) which was employed to characterize the possible interactions between the drug and the carrier in the solid state. Samples of about 2 mg were lightly ground and mixed with IR grade dry potassium bromide and then compressed at 10 tonnes in a hydraulic press for 5 min to form discs. The spectra of CAR plain powder, Soluplus® plain powder, and the selected solid dispersion formulation were scanned over a frequency range 4000–500 cm^{-1} with a resolution of 4 cm^{-1}.

2.7. Powder mixing

Selected CAR solid dispersion system was mixed with readily made filler using mortar and pestle for 5 min. Three different readily made fillers were tested, namely Ludiflash®, Pearlitol® Flash, and Pharmaburst® 500.

2.8. Flow properties of CAR powder and of the powder blends

Useful excipients for direct compression should possess good flow and compression properties. Therefore, two methods were used for powder flowability measurement. At first, bulk density ρ_b (g/cm^3) and tapped density ρ_p (g/cm^3) of the powder blends were determined according to Ph. Eur. 2.9.36 in order to calculate Hausner's ratio and Carr's index [15]. Additionally, it was performed for CAR solid dispersion without the excipients.

Carr's Index was computed from the following equation:

$$\text{Carr's Index} = \rho_p - \rho_b/\rho_p \times 100.$$

Similarly, Hausner's ratio was calculated according to the following equation:

Hausner's Ratio = volume before tapping/volume after tapping. The lower the Hausner's ratio and the Carr's index, the better is the powder flowability.

The second method for flowability characterisation was the angle of repose. This is the maximum angle possible between the surface of a powder pile and the horizontal plane. The angle of repose was measured according to the fixed funnel and free standing cone method. Briefly, the powder was carefully poured through a funnel with its tip positioned at a fixed height (H) on a horizontal surface until the apex of the conical pile formed just reaches the tip of the funnel. If more material is added to the pile, it slides down the sides until the mutual friction of the particles, producing a surface at an angle θ, is in equilibrium with the gravitational force. The angle of repose (θ) was calculated from the equation:

$$\tan\theta = 2h/D$$

D Average diameter of the formed cone.
h Pile height.

2.9. Compression of the optimized solid dispersion into ODTs

Three ODT formulations containing the selected solid dispersion system were prepared by direct compression. Powder mixture (200 mg containing solid dispersion equivalent to 6.25 mg CAR) was manually filled into the die and compressed using single punch tablet press equipped with concave faced 10 mm punches, at a suitable compression force to obtain tablet hardness of about 4 ± 0.5 kg.

2.10. Evaluation of the optimized CAR orodispersible tablets (CAR-ODTs)

2.10.1. Physical characterization

CAR-ODTs were evaluated by carrying out tests for hardness, and disintegration. All the tests were carried out according to the European pharmacopeia [15]. The in vitro disintegration test was carried out on six tablets in distilled water at 37 ± 2 °C using the USP disintegration apparatus (Logan instruments incorporation, USA).

2.10.2. In vitro dissolution studies

Dissolution studies were carried out following the USP XXII paddle method at 37 °C and 100 rpm using a dissolution tester (Pharma Test Dissolution Tester, Germany). The dissolution medium was 500 mL distilled water. Dissolution profiles of CAR-ODTs were compared with the plain drug. At specified time intervals, an aliquot of 5 mL was withdrawn and replaced immediately with equal volume of dissolution medium to maintain total volume constant. The withdrawn samples were filtered through 0.45 μm millipore filter and then assayed for drug content spectrophotometrically at λ_{max} 282 nm after appropriate dilution. Cumulative amount of drug dissolved in the preparations was calculated using calibration equation. Dissolution tests were performed in three vessels per formulation (n = 3).

3. Results and discussion

3.1. Feasibility assessment of Soluplus® as solid dispersion carrier

Proper polymer carrier selection is an important aspect in the formulation of solid dispersions containing high melting point drug [16]. Soluplus® is a polyvinyl caprolactam–polyvinyl acetate– polyethylene glycol graft copolymer (13% PEG 6000/57% vinyl caprolactam/30% vinyl acetate) [17]. Soluplus® is classified as a member of the fourth generation of solid dispersions carriers intended to achieve the highest degree of dissolution enhancement of poorly water soluble drugs and to stabilize the solid dispersion [1]. Soluplus® was reported to effectively enhance the absorption of different BCS class II drugs if applied as a drug carrier [18]. Solid dispersions of Soluplus® have also been prepared to increase the aqueous solubility of the anti-tumor, camptothecin [19]. Considerable dissolution improvement of BCS class II model drug, spironolactone, was achieved by electrospun and extrusion technology using Soluplus® as drug carrier has also been reported [10].

3.2. Phase solubility study

CAR aqueous solubility was observed to be 0.028 mg/mL; therefore, CAR can be defined as practically insoluble drug according to USP. Solubility of CAR alone and in the presence of serial dilutions of Soluplus® is graphically represented in Fig. 1. The solubility of CAR increased as a function of Soluplus® concentrations due to micellar

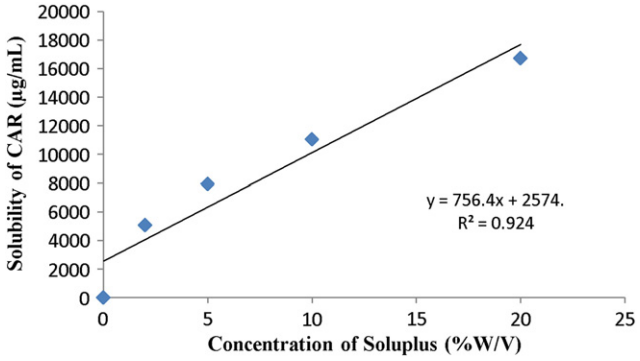

Fig. 1. Phase solubility diagram of CAR in aqueous solution of Soluplus®.

Table 2
Experimental runs, independent variables, and measured response of the 3^2 full factorial experimental design.

	X_1	X_2	Y_1
Formula	Method of preparation	Drug:carrier ratio	Saturated solubility
F1	SE	1:3	249.75
F2	SE	1:5	730.01
F3	SE	1:10	1255.04
F4	FD	1:3	4557
F5	FD	1:5	4926
F6	FD	1:10	5732.04
F7	SD	1:3	2858.62
F8	SD	1:5	3569.63
F9	SD	1:10	5831.44

solubilization. Solubility of CAR in presence of 20% w/v Soluplus® was increased up to 18.71 mg/mL corresponding to 600 fold increase, indicating excellent affinity between CAR and Soluplus® to form a molecular dispersion. Soluplus® is a polymeric solubilizer with an amphiphilic chemical structure, having large number of hydroxyl groups which make it a good solubilizer for poorly soluble drugs in aqueous media. Phase solubility showed an increase in drug solubility with increasing polymer concentration, with r^2 value equal to 0.924. The phase solubility diagram followed an A_N-type system [13].

3.3. Analysis of factorial design

The factorial design, a commonly used statistical approach for planning and optimization of experimental series, was used. The used design comprises a full 3^2 factorial design. The importance and worth of experimental designs have been reported frequently in the literature [20,21].

The experimental runs, with independent variables and the measured response are shown in Table 2. The independent and response variables were related using polynomial equation with statistical analysis through Design — Expert® Software. ANOVA test was performed to evaluate the level of significance of the tested factors on the saturated solubility of the drug in the solid dispersion formulation (Y_1) as well as the interactions between these factors.

3.3.1. Influence of the method of preparation on the solubility of CAR

ANOVA results show that the method of preparation of the solid dispersion had a significant effect on the saturated solubility of the drug in the solid dispersion formulation ($p<0.05$). Fig. 2 shows that the freeze drying technique resulted in significantly higher solubility of the drug in the solid dispersion formulation followed by the spray drying technique and finally the solvent wetting technique. Similar results were obtained by Badr-Eldin et al. where the freeze-drying technique exhibited the most significant effect on the dissolution enhancement of tadalafil compared to the kneading and physical mixture techniques [22]. According to Biradar et al., the freeze-drying technique resulted in greater saturation solubility of the poorly water soluble drug, roxithromycin, compared to the spray-drying and the homogenization technique [23]. Lyophilization resulted in the formation of the amorphous and highly porous product owing to the removal of water by sublimation. They observed that the apparent density of the freeze-dried granules is much lower than that of spray-dried powders (2–3 times) which confirms the large porosity retained in the freeze-dried granules.

3.3.2. Influence of different drug:carrier ratios on the solubility of CAR

As observed in Fig. 3, there was a significant difference in saturation solubility between the formulated solid dispersions using different drug:carrier ratios. Increasing the concentration of Soluplus® relative to the drug significantly increased the drug solubility ($p<0.05$). This solubility enhancement can be attributed to the micellar solubilization properties of Soluplus®. The critical micelle concentration (CMC) of Soluplus® was determined to be 0.0007% (w/v) at 37 °C [17]. Hence, the amounts of Soluplus® in all the studied solid dispersions were above the critical micelle concentration. Consequently, in solid dispersion formulations, micelle concentration increased with respect to the increase in the Soluplus® concentration resulting in enhancement of CAR solubility.

3.4. Physicochemical characterization of the solid dispersion formulation

The solid dispersion formulation prepared using the freeze-drying technique in drug: carrier ratio 1:10 showed the highest drug solubility; therefore it was selected for further physicochemical characterization,

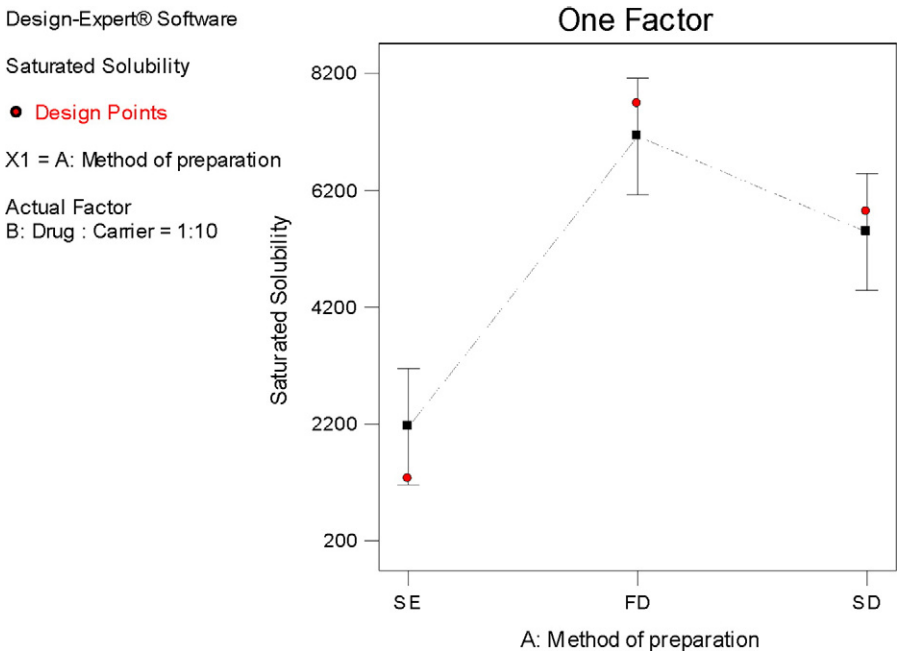

Fig. 2. Main effect plot of the method of preparation on the solubility of CAR.

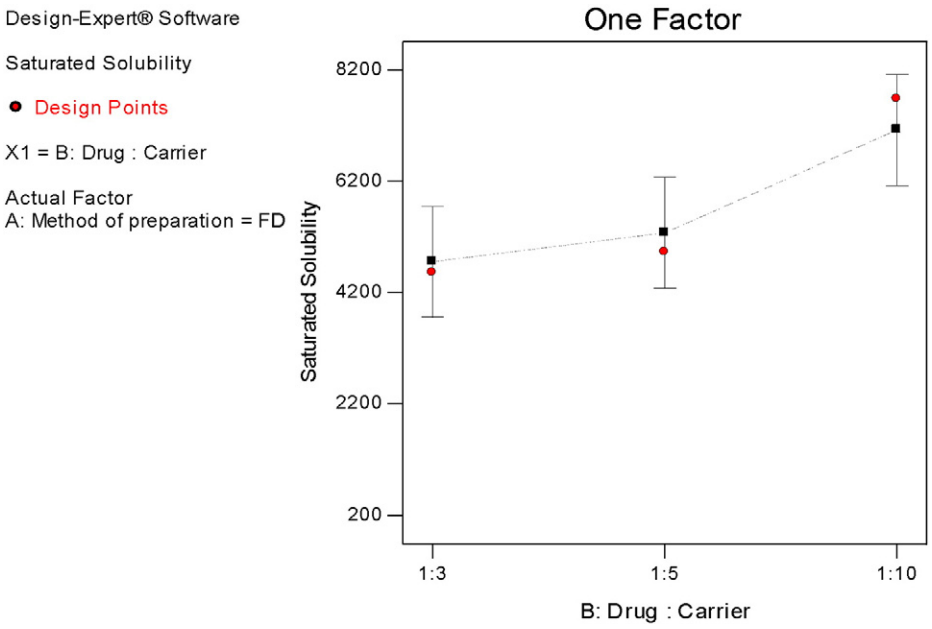

Fig. 3. Main effect plot of the drug:polymer ratio on the solubility of CAR.

and tabletting. In order to elucidate the mechanisms through which solid dispersions prepared with Soluplus® improved CAR solubility, solid state characterization were carried out.

3.4.1. Differential scanning calorimetrical studies (DSC)

DSC was employed to evaluate the phase of transformation of CAR during the formation of solid dispersions. As illustrated in Fig. 4, the free drug was characterized by a single, sharp melting endothermic peak of 116.14 °C corresponding to the melting point of CAR confirming its crystallinity. Soluplus® showed two broad endothermic peaks; at 73.22 °C, and 314.10 °C. The optimized solid dispersion formulation did not show the melting endothermic peak of CAR suggesting a complete conversion of crystalline drug into its amorphous form. Analogous phenomena have been previously reported [24].

3.4.2. Powder X-ray diffraction

In order to further examine the physical form of the drug in the solid dispersion, pure CAR, Soluplus®, and the optimized solid dispersion formulation were investigated using powder X-ray diffraction Fig. 5. The diffractogram of CAR revealed its crystalline nature as indicated

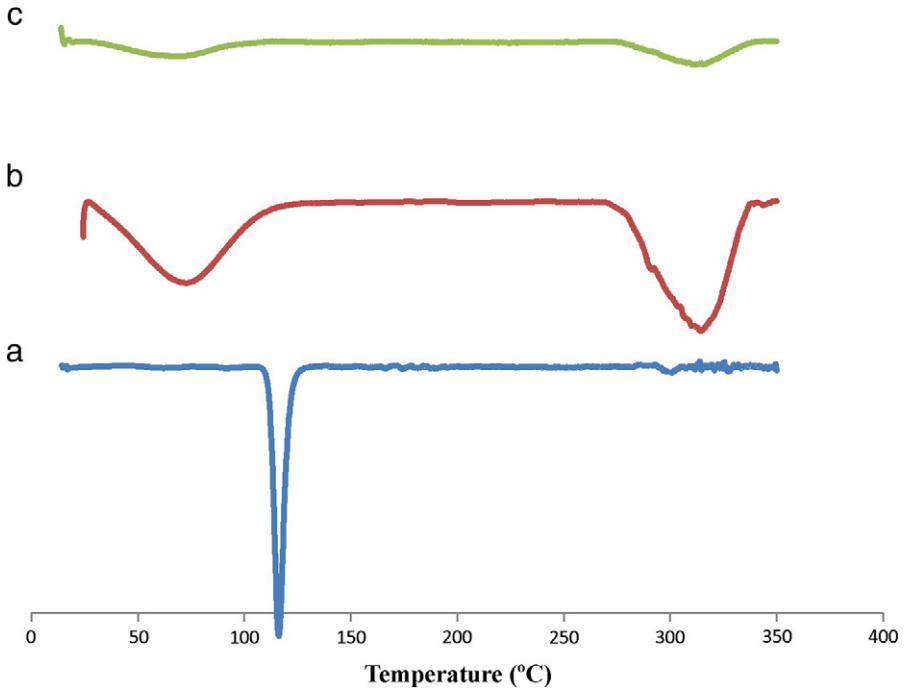

Fig. 4. DSC thermograms of CAR plain powder (a), Soluplus® (b) and CAR in the selected freeze-dried solid dispersion formulation (c).

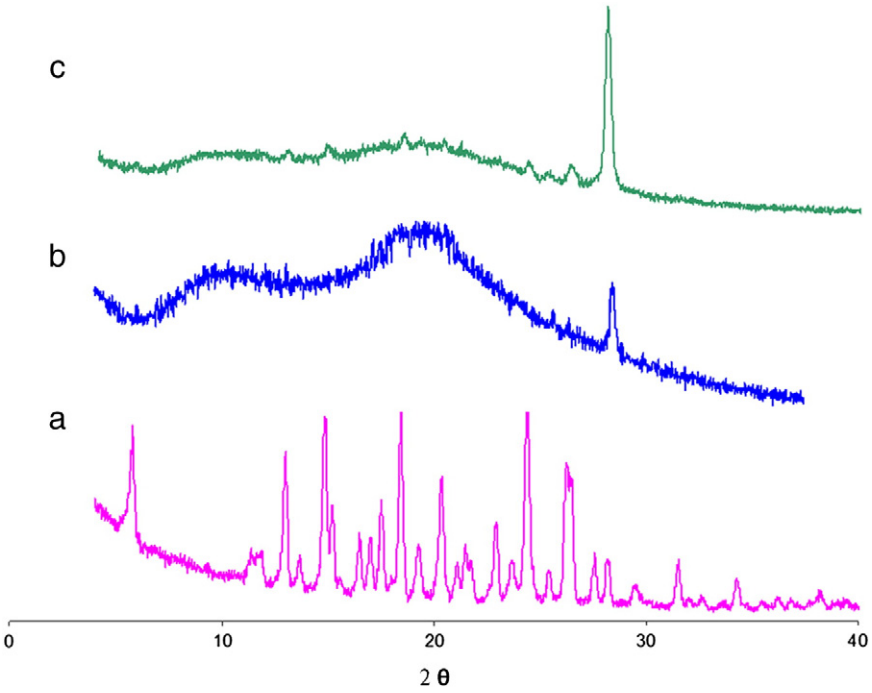

Fig. 5. X-ray diffractograms of CAR plain powder (a), Soluplus® (b) and CAR in the selected freeze-dried solid dispersion formulation (c).

by three prominent diffraction peaks with the highest intensity at 2θ of 14.886° (5.960A˚), 18.45° (4.806 Å), and 24.40° (3.649 Å). On the other hand, the diffractogram of the solid dispersion showed a typical diffuse pattern with complete absence of the numerous distinctive peaks of CAR indicating the entirely amorphous nature of CAR in the solid dispersion.

CAR has a high melting point (116.14 °C), which is indicative of strong crystal lattice energy. This high melting point is one of the factors responsible for poor aqueous solubility [25]. Therefore, any approach which disrupts the crystalline nature and/or results in lower crystal lattice energy would improve the aqueous solubility of the drug. The crystalline nature of the drug can be disrupted by solid-state dispersion of the drug into water soluble carrier molecules which replace the drug molecule in the crystal lattice. This results in a partial or total loss of crystallinity, resulting in a significant increase in solubility. As a water-soluble polymer, Soluplus® has been demonstrated to retard and inhibit the crystallization of drugs, giving amorphous solid dispersions with increased drug dissolution rate and solubility [5,18,19].

3.4.3. Fourier transform infrared spectroscopy (FTIR)

To study the possibility of the interaction between CAR and Soluplus® in the solid state, FTIR analysis was carried out. FTIR spectrum of pure CAR (Fig. 6) showed an intense, well defined characteristic infrared absorption band at 3344.5 cm^{-1} corresponding to the NH stretching vibration of the secondary amine. Three intense absorption bands 2993.87 cm^{-1}, and 2924.5 cm^{-1} corresponding to C–H aliphatic stretching, and 1099 cm^{-1} corresponding to C–O stretching. In addition, other sharp bands appeared at 1500–1400 cm^{-1} (C–C aromatic stretching) and 1253 cm^{-1} (C–N stretching).

Soluplus® showed peaks at 3448.72 cm^{-1} (O–H stretching), 2927.98 cm^{-1} (aromatic C–H stretching), 1735.93 cm^{-1}, 1635.23 cm^{-1}(C═O stretching), and 1477.21 cm^{-1} (C–O–C stretching). The IR spectrum of the solid dispersion shows absence of a characteristic peak of CAR at 3344.5 cm^{-1} corresponding to the NH stretching. This may be attributed to possible interaction between the N–H group of CAR and the C═O group of the Soluplus® leading to formation of amide group.

3.4.4. Scanning electron microscope analysis (SEM)

SEM photomicrographs of free CAR and its selected solid dispersion formulation were utilized to study their surface morphological characteristics. Fig. 7a reveals that pure CAR exists in a smooth-surfaced spherical particles. On the other hand, the prepared solid dispersion appeared as uniform and homogenous mixed mass in which the individual surface properties of the drug were lost during freeze-drying (Fig. 7b). Similar observations were noted with tadalafil solid dispersion [24].

From SEM photomicrographs, it can be speculated that CAR existed in very fine amorphous form with reduced particle size, increased surface area and closer contact between the hydrophilic polymer and the drug which may be influential in enhancing drug solubility and dissolution rate [26].

3.5. Preparation of the powder blends for orodispersable tablet (ODTs)

Excipients for ODTs should be selected based on material characteristics like better compactability and fast disintegration. Mannitol is one of the most commonly used excipients in the preparation of tablets intended to be chewed or dissolved in the mouth. It has a negative heat of solution and imparts a uniquely cooling sensation and pleasant taste. However, when used as untreated powder, the poor flowability, and insufficient binding properties are limiting factors [27]. Hence, co-processed excipients with mannitol are an option. Co-processing means the interacting of two or more excipients at the sub-particle level, which lead to an improved functionality [28,29]. Co-processed mannitol could be a useful tabletting excipient for ODTs. Its low hygroscopicity enables stability comparable with conventional tablets without the need of highly sophisticated primary packaging. Furthermore, the disintegration properties of the obtained tablets are better compared to other polyols like isomalt [30]. Therefore, three commercially available excipients with mannitol as the main component namely Pearlitol Flash®, Pharmaburst® and Ludifalsh®, intended to be used for direct compression of the selected solid dispersion formulation into ODTs, were investigated.

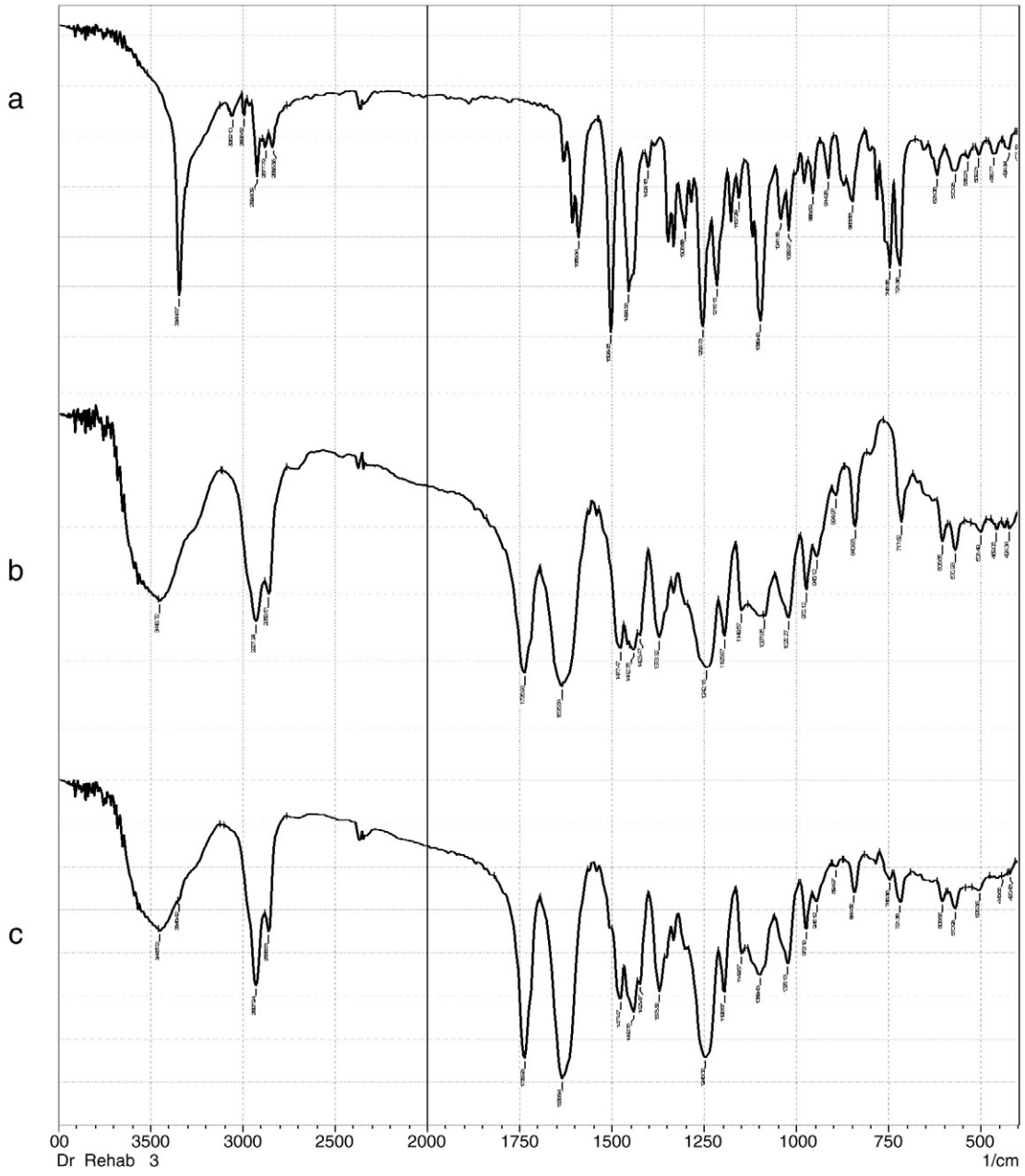

Fig. 6. FT-IR spectra of CAR plain powder (a), Soluplus® (b) and CAR in the selected freeze-dried solid dispersion formulation (c).

3.6. Flow properties of CAR powder and of the powder blends

Powder flow properties are crucial in handling and processing operations such as flow from hoppers, mixing and compression. A uniform flow from the hoppers into the die cavity ensures uniform tablet weight and drug content. Poor flowing powders present many difficulties to the pharmaceutical industry [31]. The effect of three readily made fillers on the flow and dissolution properties of the optimized CAR solid dispersion system was studied. The flowability of the powder blends was determined using Hausner's ratio, Carr's index and angle of repose. Hausner's ratio (HR) was related to the inter particle friction; powders with a low interparticle friction had a ratio of approximately 1.25 indicating a good flow. Generally, powders with Carr's index (CI) below 25% have very good flow properties [31]. Powders with angle of repose above 50° have unsatisfactory difficult flow properties, while those of 25° – 40° represent reasonable flow potential, whereas minimum angles close to 25° correspond to very good flow properties [32]. From the results presented in Table 3, powder blends containing Pearlitol® Flash and Pharmaburst ® 500 showed acceptable Hausner's ratio while that containing Ludiflash® showed a slightly higher Hausner's ratio of 1.27 [33]. Results of Carr's index revealed that Pharmaburst ® 500 followed by Pearlitol® Flash showed acceptable value of Carr's index. The three powder blends showed acceptable values for angle of repose (Table 3). Pearlitol® Flash and Pharmaburst® 500 showed reasonable flowability which could be due to their narrow particle size distribution [27]. Additionally, Pharmaburst ® 500 contains precipitated silicon dioxide for flowability improvement [27]. The powder blends could be ranked, as follows, Pharmaburst ® 500 > Pearlitol® Flash > Ludiflash®. However, the three readily made fillers examined succeeded to improve the very poor flowability of CAR confirmed with the very high values of the three measured parameters (Table 3).

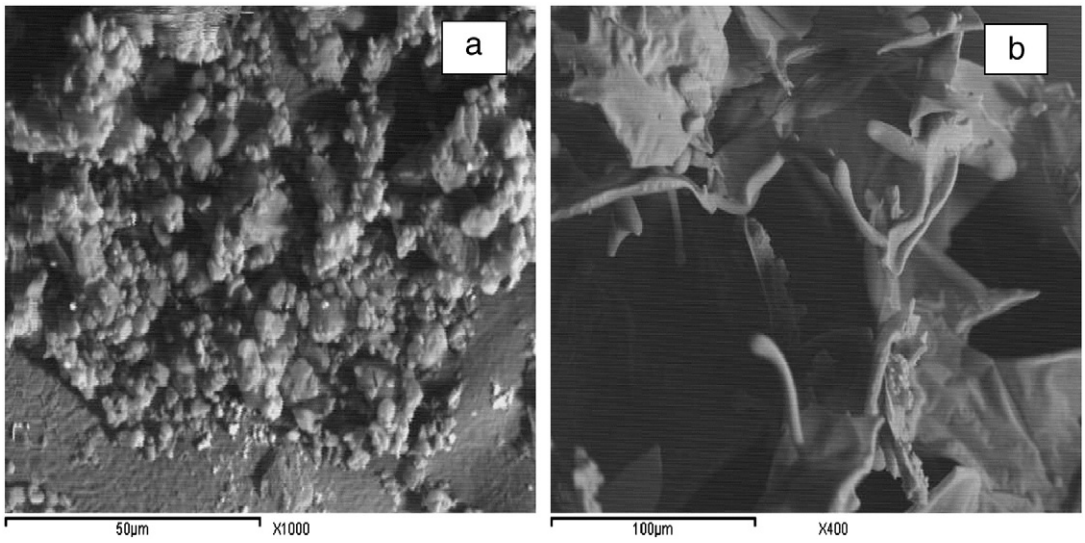

Fig. 7. Scanning electron micrographs of CAR plain powder (a), and the selected freeze-dried solid dispersion formulation (c).

Table 3
Characterization of the prepared CAR — solid dispersion ODT formulations.

Formulation	HR	CI		Q_5 (%)	Q_{30} (%)	In vitro disintegartion time (s)
CAR	1.91	48.5%	54.2	3.70 ± 0.10	11.11 ± 0.23	–
Pearlitol Flash® tablet	1.25	27.1%	22.2	59.06 ± 12.08	94.46 ± 1.76	36.50 ± 2.12
Pharmaburst® tablet	1.19	22.5%	24.9	44.19 ± 1.94	94.21 ± 7.27	47.00 ± 2.83
Ludiflash® tablet	1.27	30.6%	19.3	7.20 ± 3.61	30.75 ± 1.63	> 180

3.7. Evaluation of ODTs

Results of the in vitro disintegration time, and the percent drug dissolved after 5, and 30 min are shown in Table 3. As shown in Table 3, in vitro disintegration studies showed that ODTs containing Pearlitol Flash®, and Pharmaburst® 500 as a filler showed shorter disintegration times (<1 min) compared to that containing Ludifalsh® (>3 min).

3.8. Dissolution studies

The dissolution of a poorly water-soluble drug is crucial where it is the rate-limiting step in the oral absorption process from a solid dosage form and is an important parameter related to bioavailability. The dissolution profiles of pure CAR and different ODT formulations containing the selected solid dispersion prepared with Soluplus® using the freeze-drying technique in the ratio 1:10 are illustrated in Fig. 8. Q_5, and Q_{30} (percent drug dissolved within 5, and 30 min, respectively) were calculated and shown in Table 3.

It was evident that no dissolution was achieved for pure CAR, with only 17.7% dissolved after 60 min, under the specified dissolution conditions. The hydrophobic property of the drug prevented its contact with the dissolution medium causing it to float on the surface, and consequently hindering its dissolution. Results (Table 3) showed that the dissolution of pure CAR was the slowest as compared to different ODT formulations which showed significant enhancement in CAR dissolution. The rapid dissolution of CAR from ODTs may be attributed to its molecular and colloidal dispersion in the hydrophilic carrier matrix. As the soluble carrier dissolves, the insoluble drug gets exposed to dissolution medium in the form of very fine particles which dissolves quickly. In the solid dispersion system, drug undergoes particle size reduction and the consequent increase in the surface area results in the improved dissolution [34]. Moreover, drug solubility and wettability may be increased by surrounding hydrophilic carriers [34]. ODTs containing Ludifalsh® as filler showed considerably slower dissolution of the drug when compared to ODTs containing Pearlitol Flash®, and Pharmaburst®. This may be attributed to the slower disintegration of these tablets.

4. Conclusion

Soluplus®, a novel polymeric carrier was investigated for the solubility enhancement of a poorly water soluble drug CAR using solid dispersion technique. Three industrially scalable methods were employed namely: solvent evaporation, spray drying, and freeze-drying. The saturated solubility of CAR was markedly enhanced in all the prepared systems. The freeze-dried system of CAR with Soluplus® prepared at a ratio of 1:10 was chosen as a suitable delivery system for the formulation of CAR orodispersable tablets, using different co-processed fillers; Pearlitol Flash®, Pharmaburst® and Ludifalsh®. The

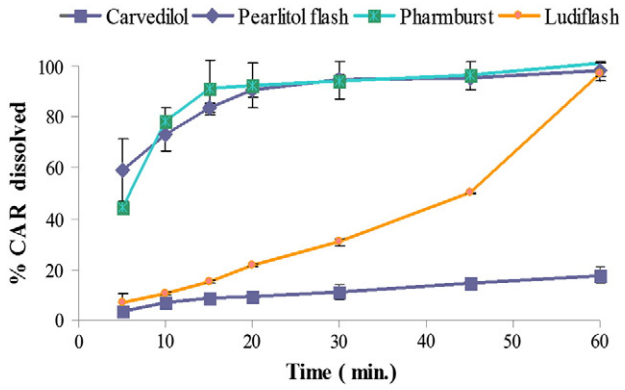

Fig. 8. In vitro dissolution profiles of CAR plain powder, and different ODTs prepared in distilled water.

prepared orodispersable tablets showed fast disintegration and dissolution of the drug when compared to plain CAR. Thus, using Soluplus® as a polymeric carrier together with a convenient method of preparation represent a promising approach playing an important role in enhancing the solubility of poorly water soluble drugs, thus improving their biopharmaceutical performance.

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