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Research article

Impact of drying on dissolution behavior of carvedilol-loaded sustained release solid dispersion: development and characterization

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ABSTRACT

Purpose: The present study aimed to develop carvedilol (CAR)-loaded (25% w/w) sustained release solid dispersion (SRSD), for enhanced dissolution and to explore the applicability of different industrially accessible drying techniques.

Methods: SRSD-CAR containing different ratios of polymers were prepared and physicochemically characterized. Dissolution study was carried out in both sink and supersaturated conditions to identify the possible enhancement in dissolution behavior.

Results: Based on the solubility study, Kolliphor® P188 and Eudragit® RSPO (50:25, % w/w) ratio exhibited the highest solubility among the samples and was chosen as the optimal composition of SRSD-CAR for further characterization. The crystallinity assessments of the optimized formulation indicated amorphization of CAR in the formulation, bring about improved solubility of CAR. The infrared spectroscopic study revealed minor transitions; demonstrating the absence of significant interactions between drug and carrier. Furthermore, the SRSD-CAR exhibited immediate formation of nano particles when dispersed in water. Dissolution study revealed significant improvement in dissolution behavior, with a release of CAR in a gradual manner compared to crystalline CAR. From the dissolution kinetics analysis, the Korsmeyer Peppas model fit the best and diffusion was predominant in release of CAR. The drug release pattern showed insignificant differences between the SRSD-CAR formulations prepared by rotary vacuum drying and freeze drying.

Conclusion: From these experimental findings, SRSD approach might be a favorable dosage option for CAR, offering improved biopharmaceutical properties.

1. Introduction

One of the major challenges in pharmaceutical research is to successfully develop solid oral dosage forms of drugs having poor aqueous solubility [1]. Such poorly soluble drugs are usually classified as the biopharmaceutical classification system (BCS) Class-II drugs with high permeability [2]. Over 70% of newly developed active pharmaceutical ingredients (APIs) and 40% of the existing marketed drugs belongs to BCS class-II compounds and might provide challenges as well as opportunities for scientists to battle these solubility/permeability issues for safe and efficacious treatment of these drugs [3]. It has been reported that the solubility of drug molecules below 100 μg/mL exhibit dissolution limited absorption at sites and might require dose escalation to maintain the effective therapeutic concentration [4]. Although considerable progress in terms of solubility enhancement by different strategies has been made in delivery of BCS class-II drugs, it's still challenging to maintain optimal correlation between drug absorption and corresponding clinical response [5].

Carvedilol (CAR) is a nonselective, α1 and β1, β2 adrenergic receptor antagonist that has emerged as a promising drug moiety for cardiovascular disease, showing a significant improvement in patients suffering from chronic cardiac insufficiency [2, 6]. It is a weakly basic drug with a pKa value 6.8 and practically insoluble in water (4.4 μg/mL) [7]. The absorption of CAR after oral administration is rapid with an elimination half-life of 6–10 h and low absolute bioavailability (BA) (25% or less) [8, 9]. Therefore, poor solubility and short biological half-life limit its clinical application as multiple dosing required to maintain optimum plasma concentration. Considering these drawbacks, different strategies have been implemented to enhance the dissolution characteristics of CAR [2, 6, 10, 11, 12, 13, 14, 15, 16].

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Due to its simple preparation method, solid dispersion (SD) is one of the effective techniques in pharmaceutical formulations to improve the biopharmaceutical characteristics of poorly water soluble drugs. In brief, SD is defined as the dispersion of drug in a matrix at solid state that has been used to improve the solubility of drugs [17]. The enhancement in solubility can be endorsed to better wettability, reduction in particle size, decrease in agglomeration, modification in the physical state of the drug from crystalline to amorphous and even in dispersion of the drug on a molecular level [18, 19]. In addition, sustained release formulations are designed to reduce the dosing frequency and have shown to improve patient compliance and suitability compared with traditional multiple daily dosing regimens [20, 21]. Therefore, SD's with sustained release (SR) effect could be advantageous, as it would provide patients with a reduced total dose and maintain a uniform and prolonged therapeutic effect in the systemic circulation, with minimum side effects [22]. Thus, to overcome the problems associated with CAR, SD with the blend of biocompatible polymers having sustained release characteristics would be a key consideration. In the SRSD, the drug molecule is homogeneously dispensed throughout the polymer matrix and drug release rate is controlled by water-swellable or erodible matrices consisting of several hydrophilic or hydrophobic polymeric excipients [8, 21]. The concept of using of polymer blends to produce synergistic effect has drawn interests of many pharmaceutical scientists because it combines two polymer properties in a single system without any chemical synthesis [23]. Based on the physicochemical and biopharmaceutical behaviors of CAR, especially poor solubility and short half-life, we consider CAR as a promising candidate in this study. While numerous studies on SDs of CAR are reported, far less is known demonstrating the use of amphiphilic and sustained release polymer blends in preparing SRSD containing CAR for improved and sustained release behavior as well as to compare the applicability of different drying approaches.

An amphiphilic polymer comprises of a hydrophilic unit and a hydrophobic unit that enables self-micelleization upon the encapsulation of a lipophilic drug [24]. Amid amphiphilic polymers, poloxamers are nonionic polyoxyethylene-polypropylene block copolymer consisting of hydrophilic core (ethylene oxide) and hydrophobic core (polypropylene oxide) have been widely used to improve the solubility of poorly soluble drugs [12, 25]. Generally the mechanism of improvement of solubility is observed due to its wetting and surface adsorbing properties as well as low melting point [26]. On the other hand, Eudragit® polymers are poly (methacrylic acid-co-methyl methacrylate) derivatives, well known for their solubilizing and sustained delivery properties and hence could be a potential carrier for SRSDs [21, 27]. The increased ionization of carboxylic acids (solubilization) of EUD at the intestinal pH condition induces co-solubilization of water-insoluble drug. Among the Eudragit® polymers; Eudragit® RSPO, due to the presence of low-level quaternary ammonium groups, is insoluble at physiological pH but capable of swelling [28]. Therefore, Kolliphor® P188 and Eudragit® RSPO were chosen to form the polymeric matrix of SRSD formulations in this study for improved biopharmaceutical properties.

This study aimed to develop a SRSD formulation of CAR based on two biocompatible polymers with improved biopharmaceutical behaviors. Furthermore, this study also investigated the applicability of different drying methods in evaporating the solvents used for the preparation of SRSD-CAR. The SRSD-CAR with a drug loading of 25% w/w, was prepared using solvent evaporation process and its physicochemical behaviors were evaluated in terms of crystallinity, morphology, drug-polymer interaction, and particle size. The dissolution behavior of CAR samples were carried out in phosphate buffer (0.05 M, pH6.8) under sink and supersaturated conditions.

2. Materials and methods

2.1. Materials

Reference CAR was purchased from Tokyo chemical industries, Japan and working samples of CAR were kindly provided by Beximco Pharmaceuticals Ltd., Dhaka, Bangladesh. Kolliphor® P188 and Eudragit® RSPO were generous gifts from BASF Bangladesh and Evonik Bangladesh Ltd., respectively. All other chemicals were procured from commercial sources and the solvents were of analytical grade.

2.2. Preparation of SRSD-CAR

A solvent evaporation method was applied for the preparation of SRSD-CAR. Crystalline CAR (25% w/w) and different ratios of Kolliphor® P188 and Eudragit® RSPO (Table 1) were dissolved in methanol and the solution was then dried using rotary vacuum-dryer (RVD) (Heidolph Rota-Vap, Germany) in the selection stage of the polymer ratio. In addition, to compare the effect of drying on the physicochemical behavior of SRSD-CAR, the freeze-drying (FD) process was also applied in the preparation of SRSD-CAR. Crystalline CAR (25% w/w), as well as optimized ratios of the polymers were weighed accurately and dissolved in 1,4-dioxane and subsequently frozen at –80 °C. The frozen formulations were then lyophilized below a pressure of 15 Pa for 24 h with the use of a Eyela FD-1000 freeze dryer (Tokyo Rikakikai, Tokyo, Japan). The temperature of the solvent trapper was kept at –50 °C.

2.3. Preparation of standard curve and determination of CAR content

A stock solution of CAR was prepared by dissolving 100 mg of CAR in sufficient quantity of methanol in a volumetric flask to make the final volume 100 mL, thus the concentration of stock solution was 1 mg/mL. The stock solution was then further diluted to prepare working solutions of varying concentrations in the range of 0.25–5 μg/mL. The absorbance of the prepared solutions was measured using a UV Spectrophotometer (UV-1800, Shimadzu Corporation, Japan) at an absorbance wavelength of 240 nm [11]. The mean regression equations were Y = 0.1267X - 0.01371 (R^2 = 0.9885; $P < 0.0001$) and Y = 0.1264X - 0.01076 (R^2 = 0.9902; $P < 0.0001$), respectively for water and phosphate buffer. The 95% CI predicted for the value of the intercept was -0.05124 to 0.02382 and -0.04533 to 0.02381, respectively. The amount of CAR was determined using the equation derived from the standard curve.

2.4. Equilibrium solubility studies

The equilibrium solubility of CAR samples containing different ratios of Kolliphor® P188 and Eudragit® RSPO was analyzed. Approximately excess amount (10 mg of CAR) of CAR sample based on the theoretical solubility of CAR was added to a closed test tube containing 10 mL of distilled water and kept in an automatic shaker at 37 °C. After 24 h, aliquots of test solutions were picked, centrifuged at 10,000×g for 5 min and diluted with 50% methanol. The CAR content was analyzed following the method as described in the above section.

2.5. Surface morphology

The surface morphology of crystalline CAR and SRSD-CAR was viewed using scanning electron microscopy (SEM) techniques, Miniscope® TM3030 (Hitachi, Tokyo, Japan). The samples were set on an aluminum sample holder by means of double sided carbon tape, followed by coating with platinum using a magnetron sputtering device (MSP-1S, Vacuum Device, Ibaraki, Japan).

2.6. Polarized light microscopy (PLM)

Crystallinity of CAR samples was evaluated using a CX41 microscope (Olympus Co. Ltd., Tokyo, Japan). Each sample was placed on slide glass and a drop of silicone oil was added on it. A cover glass was placed on top and the samples were observed under various conditions including slightly uncrossed polars, differential interface contrast and using a red wave compensator.

Table 1. Preparation of the formulations with different polymer ratio and their equilibrium solubility.

Sample	Ratio (%) of Eudragit® RSPO:Kolliphor® P188:CAR	Equilibrium solubility (μg/mL)
Crystalline CAR		1.93 ± 0.03
F1	37.5 : 37.5 : 25	13.76 ± 0.51
F2	18.75 : 56.25 : 25	34.29 ± 0.25
F3	56.25 : 18.75:25	57.99 ± 2.87
F4	25:50:25	83.29 ± 0.31
F5	50:25:25	73.08 ± 1.23

CAR, carvedilol. Data represent the mean ± SD of 3 experiments.

2.7. X-ray powder diffraction (XRPD)

X-ray diffraction patterns of CAR samples were determined the Mini Flex II (Rigaku, Tokyo, Japan) using Cu Kα radiation at a scanning rate of 4°/min over the 2θ range of 10°–35°.

2.8. Differential scanning calorimetry (DSC)

Thermal analysis of CAR samples was conducted using DSC Q1000 (TA Instruments New Castle, DE, USA) at a heating rate of 5 °C/min. Samples of 3 mg were measured and placed in closed aluminum pans. The sample cells were purged with nitrogen gas (50 mL/min). Indium was used as a reference standard (8–10 mg, 99.999% pure, onset at 156.6 °C) to calibrate the DSC.

2.9. Dynamic light scattering (DLS)

The particle size of water suspended SRSD-CAR samples were measured by a dynamic light scattering method with the use of a Zetasizer Ultra (MALVERN, Worcestershire, UK). The mean diameter was calculated using photon correlation from light scattering and all measurements were performed at 25 °C at a measurement angle of 90°. The determination was repeated three times per sample.

2.10. Fourier transform infrared spectroscopy (FT-IR)

To evaluate the probable hydrophobic interaction between drug and polymers, FT-IR spectroscopy of SRSD samples was performed using IR Prestige-21 with IR solution software (Shimadzu, Kyoto, Japan). 2–3 mg samples of CAR were ground and mixed with dry potassium bromide (300 mg) and then compressed to form KBr discs. A 9-point smoothing function was applied to smooth the obtained spectra.

2.11. Storage stability study

Stability studies of the prepared samples were conducted according to the International Conference of Harmonization (ICH) guidelines (40 °C or 40°C/75 ± 0.5% relative humidity (RH)) for 4 weeks, and 60 °C for 2 weeks respectively in a stability chamber (SRH–15VEVJ2, Nagano Science Co. Ltd., Osaka, Japan). After a month the samples are withdrawn and re-assessed for drug content.

2.12. Dissolution studies

The *in vitro* dissolution test of CAR samples were performed under both sink and supersaturated conditions to clarify the possible enhanced and sustained release of CAR over time. The dissolution study was carried out at 37 ± 0.5 °C using the USP type II paddle method (Universal Dissolution Tester, Logan- UDT 804), where 900 mL of phosphate buffer (pH 6.8) was poured in each vessel rotating at 75 rpm. The SRSD-CAR, with the most satisfactory results in equilibrium solubility study, was selected for *in vitro* dissolution study. Samples (1 mL) were drawn at predetermined time intervals and then centrifuged at 10,000×g for 5 min, and filtered through a 0.45 μm membrane filter and the supernatant was diluted with methanol. The concentration of CAR in the medium was determined spectrophotometrically at 240 nm. The analysis was performed in triplicates.

2.13. Dissolution kinetics

2.13.1. Model independent fit factors

As for example of model independent factor, mean dissolution time (MDT) is calculated from the cumulative curves of dissolved CAR as a function of time [29].

$$MDT = \frac{\sum[t_i.\Delta Q_i]}{Q_\infty} \quad (1)$$

Where t_i is an intermediate time of the interim of sampling time, ΔQ_i is the amount of CAR dissolved in each interval of t and Q_∞ is the maximum of CAR dissolved.

In addition, dissolution efficiency (DE) is the area under the dissolution curve inside a time range, and it was determined by using the following equation [30]:

$$DE\ (\%) = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100\% \quad (2)$$

where y is the percent drug dissolved in time t.

2.13.2. Model dependent dissolution kinetics

To investigate the *in vitro* release kinetics, numerous model-dependent mathematical models for example; zero-order, first-order, Higuchi, Hixson–Crowell, Korsmeyer-Peppas, and Weibull were used. The equations that describe the model dependent mathematical kinetics are as follows:

Zero Order kinetics:

$$Q_t = Q_0 + K_0 t \quad (3)$$

First Order kinetics:

$$lnQ_t = lnQ_0 + K_1 t \quad (4)$$

Higuchi kinetics:

$$Q_t = K_h\, t^{1/2} \quad (5)$$

Hixson–Crowell kinetics:

$$Q_0^{1/3} + Q_t^{1/3} = K_d\, t \quad (6)$$

Korsmeyer-Peppas kinetics:

$$\frac{Q_t}{Q_\infty} = K_{kp} t^n \quad (7)$$

Weibull kinetics:

$$\log\ [-\ln(1-m)] = \beta \log(t - T_i) - \log \alpha \quad (8)$$

where, Q_t is the drug dissolved amount in time t, Q_0 is the initial quantity of drug in the solution, k_0 is the zero-order release constant, k_1 is the first-order release constant, K_h is the Higuchi rate constant, K_d is the dissolution constant of Hixson–Crowell kinetics, Q_t/Q_∞ is a proportion of drug released at time t, K_{kp} is the Korsmeyer release rate constant, m is the accumulated fraction of the drug, β is the shape parameter, T_i is the location parameter, α is the scale parameter.

2.14. Statistical analysis

All data are characterized as mean ± standard deviation (SD). The graphs were charted using Graphpad, Prism 6.0 (GraphPad Software, LaJolla, CA). The mathematical parameters were calculated using DDSolver [31] program. One-way ANOVA with pairwise evaluation by Fisher's least significant difference method was used for statistical analyses. A p-value of less than 0.05 was treated significant in all analyses.

3. Results and discussion

In the emerging field of formulation development and drug delivery, poor solubility of drugs still remains a challenge for formulation scientists. Fortunately, SD has evolved as a promising approach to overcome the limitations of poorly water-soluble drugs [32]. SDs usually contain two components, carrier and API, so the selection of an appropriate carrier is the determinant to achieve optimum drug release for ideal therapeutic outcomes [33]. The use of a blend of carriers could maximize the dissolution rate of the drug, avoid recrystallization, and stabilize the SD [32]. Among different SDs, SRSDs have numerous advantages over the conventional ones, this includes frequent dose reduction, achieving a constant and prolonged therapeutic effect, less side effects and using a lower dose while enhancing the therapeutic effectiveness of the drug [33]. This study employs a blend of polymers to prepare a SRSD of CAR. To examine polymer miscibility, DSC, XRPD, and FT-IR were employed.

3.1. Selection of suitable ratio of the polymers

SRSD-CAR formulations were prepared with different ratios of Kolliphor® P188 and Eudragit® RSPO, and their physicochemical characteristics including equilibrium solubility was evaluated to select the optimum ratio of Kolliphor® P188 and Eudragit® RSPO for further evaluation. Considering the poor aqueous solubility of crystalline CAR, all formulations (F1–F5) exhibited improved solubility of CAR. Among them, F4 and F5 exhibited significantly improved solubility among all formulations. Equilibrium solubility of the prepared SRSD-CAR formulations has been shown in Table 1. Solubility of crystalline CAR was observed to be 1.93 ± 0.03 μg/mL that shows that CAR is practically insoluble in water. With increasing amounts of Kolliphor® P188, solubility of CAR was enhanced significantly 83.29 ± 0.31 μg/mL, which corresponds to a 43-fold increase. In addition, the solubility of CAR with a higher ratio of Eudragit® RSPO in Formulation F5 also displayed a significant increase in solubility to about 73.08 ± 1.23 μg/mL, in comparison to crystalline CAR; exhibiting an increase of 37-fold. This suggests that the blend of two biocompatible polymers, Kolliphor® P188 and Eudragit® RSPO, has improved the solubility characteristics. Kolliphor® P188 is a multifunctional excipient that can act as a stabilizer, solubilizer, plasticizing agent, wetting agent and emulsifier in solid dispersions. The sustained release characteristic of the formulation can be attributed to the polymer, Eudragit® RSPO. It has some exclusive properties such as pH independent swelling, no toxicity, good stability that makes it good candidate for drug loading and drug dispersion [34]. Several investigations [27] suggested that in ternary system, the synergistic effect of polymers might result in both head-head and electrostatic interactions. This is attributed to the hydrophilic groups attached to the surface by cohesive forces, reduced the surface tension thereby forming an inner hydrophobic core and improved the solubility [35, 36, 37]. On the basis of the above results, F4 might be an appropriate candidate for further characterization.

3.2. Physicochemical characterization of optimized CAR formulation

SEM and PLM were used to define the morphology of the samples (Figure 1). From the SEM images, crystalline CAR was present as irregular shaped coarse particles (Figure 1A–I). On the contrary, SRSD-CAR/RVD appeared to be regular and homogenous in structure (Figure 1A–II), suggesting that CAR was significantly incorporated into the polymer. In addition, the SRSD-CAR/FD formulation was similar to a typical flaky freeze-dried material, in appearance (Figure 1A–III). Thus, SEM micrographs clearly indicate that after freeze drying process there was a marked increase in the surface area of drug substances in comparison to crystalline CAR. According to PLM images, a rough block-like structure was observed in crystalline CAR (Figure 1B–I), whereas, small birefringence was observed in SRSD-CAR/RVD (Figure 1B–II); and loss of polarization was observed in SRSD-CAR/FD that might be indicative of inner CAR in the form of amorphous state as evidenced by negligible birefringence (Figure 1B–III). DLS analysis on water-dispersed SRSD-CAR samples (Figure 2) demonstrated the formation of uniformly nano-sized particles with a mean particle size of 180 nm for SRSD-CAR/FD with a poly-dispersity index (PDI) of 0.35; and 197 nm with a PDI of 0.38 for SRSD-CAR/RVD, respectively. Thus, the SEM images and DLS data confirmed the absence of large crystalline CAR during the SRSD-CAR preparation process.

Although the amorphous state of drugs have high energy state compared with the crystalline one, and this would be attributed to improve the solubility of drugs. XRPD and DSC analysis were performed to clarify the possible transition of crystalline state to amorphous state of CAR in formulations (Figure 3). From the results of XRPD analysis, multiple intense peaks were detected for crystalline CAR that indicates stable anhydrous form, whereas the SRSD-CAR/RVD and SRSD-CAR/FD exhibited halo diffraction pattern suggesting amorphization of CAR in the process of preparing the formulation. According to DSC thermograms (Figure 3B), a melting endotherm was observed at ca. 119 °C for crystalline CAR (Figure 3B–I), corresponding to the melting point of CAR [6]. In contrast, there was a decrease of the endothermic peak in SRSD-CAR/RVD and SRSD-CAR/FD at the melting point of crystalline CAR (Figure 3B). The reduction of the endothermic peak indicated that CAR exists in an amorphous state. PLM, XRPD and DSC studies strongly indicated the amorphization of CAR during the preparation process leading to better dissolution behavior.

From previous reports, Onoue and colleagues stated that is a higher possibility of degradation of an amorphous drug in solid dispersion formulation than in a crystalline state [38, 39]. For preferred understanding on the physicochemical stability of CAR, storage stability test on SRSD-CAR samples were carried out under accelerated conditions at 40 °C or 40°C/75% RH for 4 weeks, and 60 °C for 2 weeks, respectively; and the possible changes in physicochemical properties were evaluated. After the storage at 40 °C for 4 weeks, and 60 °C for 2 weeks; respectively, SRSD-CAR/RVD and SRSD-CAR/FD were found to be stable and there was negligible change in visual transitions on surface color of the samples. On the other hand, the appearance was significantly changed with the formation of large aggregates due to highly deliquescence of the samples of SRSD samples stored at 40°C/75% RH for 4 weeks. Both SEM and PLM images indicated negligible transitions during storage at 40 °C for 4 weeks, and 60 °C for 2 weeks, respectively (data not shown). On the basis of XRPD and DSC analysis (data not shown), recrystallization of CAR was negligible during storage under accelerated conditions and suggested that particles were still in a high energy amorphous state. Our results suggested that SRSD approach would provide stable amorphization by retarding nucleation and crystal growth [40]

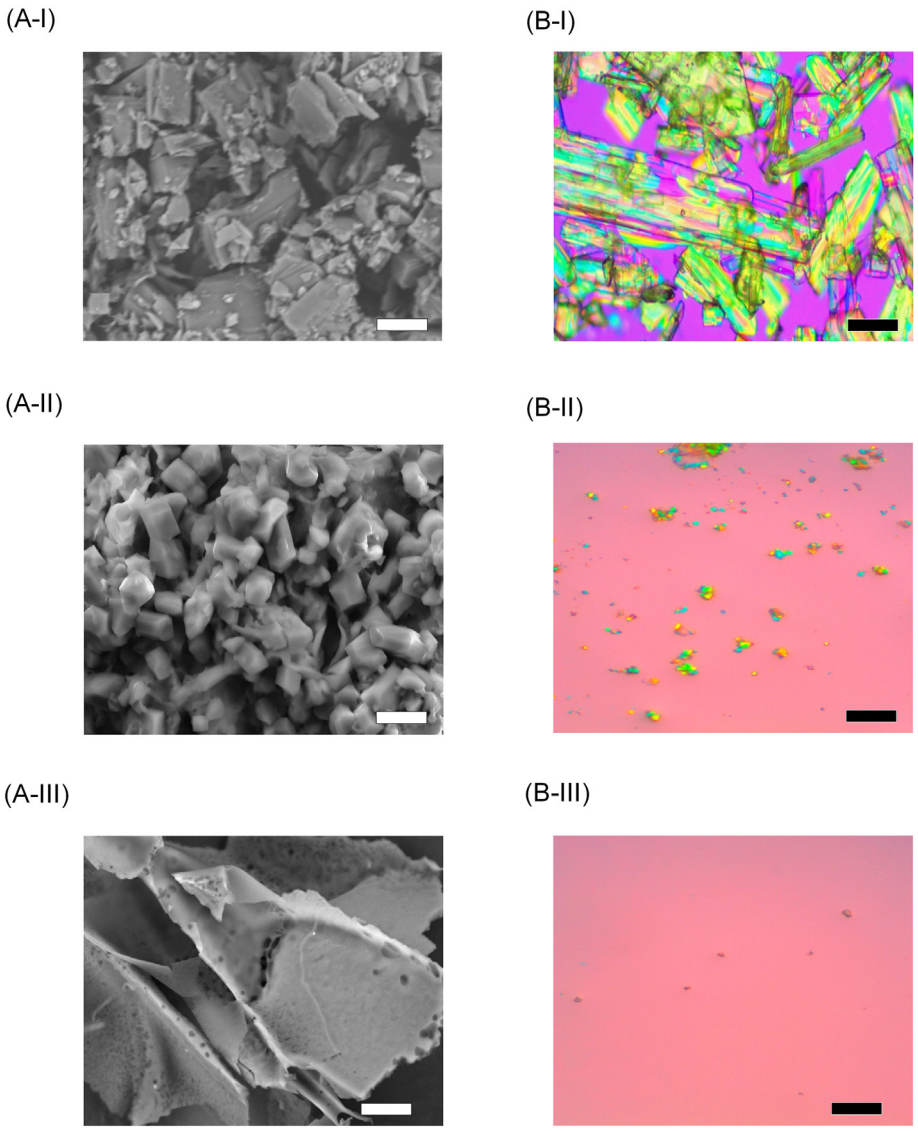

Figure 1. Microscopic images viewed by scanning electron microscope (A) and polarized light microscope (B). (I) Crystalline CAR, (II) SRSD-CAR/RVD, and (III) SRSD-CAR/FD. Each black and white bar represents 50 μm and 100 μm, respectively.

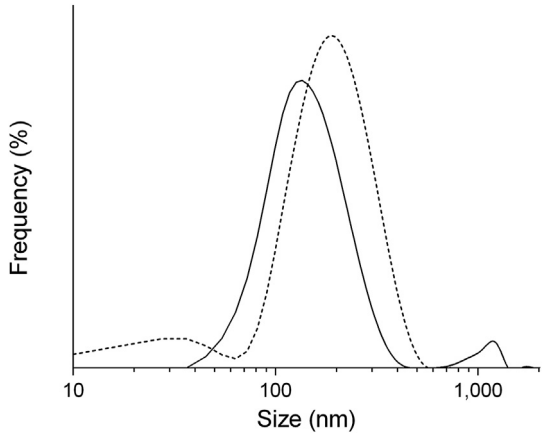

Figure 2. Particle size distribution of CAR samples dispersed in water. The solid line represents the particle size distribution of SRSD-CAR/FD; and the dotted line represents the particle size distribution of SRSD-CAR/RVD.

resulting in improved dissolution behavior and greater oral absorption characteristics.

3.3. Drug-polymer interaction

FT-IR analysis was performed to evaluate the molecular status of crystalline CAR and processed SRSD-CAR. The corresponding FT-IR spectra are presented in Figure 4. In this study, there were no significant differences observed in the IR spectral patterns among crystalline CAR, Kolliphor® P188, Eudragit RSPO®, SRSD-CAR/RVD, and SRSD-CAR/FD. FT-IR spectrum of crystalline CAR (Figure 4–I) showed an intense, well defined characteristic infrared absorption band at 3,344.5 cm^{-1} corresponding to the N–H stretching vibration of the secondary amine. Additional intense absorption bands at 2,993.8 cm^{-1}, and 2,924.5 cm^{-1} corresponding to C–H aliphatic stretching were observed. Kolliphor® P188 showed peaks at 2,800 cm^{-1} (O–H stretch), 1,450cm^{-1} O–H bend), 950 cm^{-1} (O–H bend) and 1,200 cm^{-1} (C–O stretch). The FT-IR spectrum of Eudragit® RSPO clearly exhibited the bands at around 1,650 cm^{-1}, 1,300 cm^{-1} and 1,200–1,000 cm^{-1}, owing to C=O stretching, C–O stretching and C–N stretching of tertiary amine, respectively. In contrast the IR spectrum of the SRSD-CAR/RVD and SRSD-CAR/FD exhibited absence of characteristic peak of CAR at 3,344.5

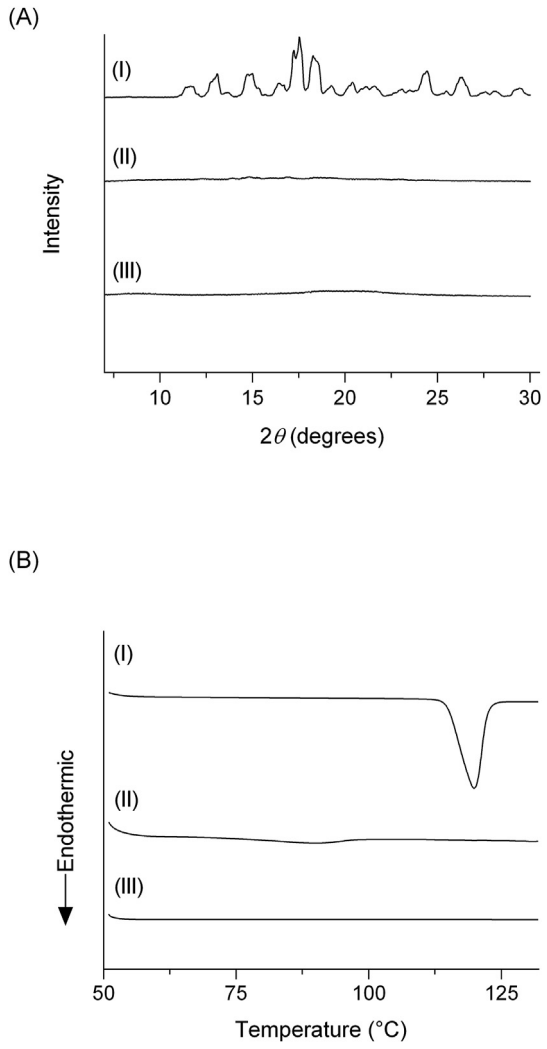

Figure 3. Crystallinity assessment of CAR samples using (A) XRPD and (B) DSC. (I) Crystalline CAR, (II) SRSD-CAR/RVD, and (III) SRSD-CAR/FD.

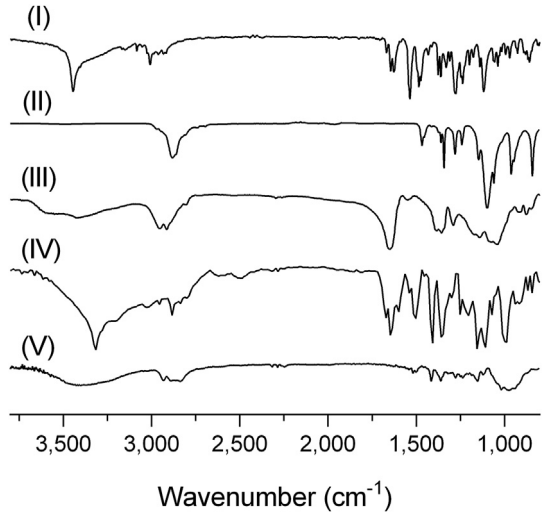

Figure 4. Drug-polymer interaction studies of CAR samples using FT-IR. Baseline-corrected and normalized IR data of CAR samples (800–3,800 cm^{-1}). (I) Crystalline CAR, (II) Kolliphor® P188, (III) Eudragit® RSPO, (IV) SRSD-CAR/RVD, and (V) SRSD-CAR/FD.

cm^{-1} corresponding to the N–H stretching, indicative of possible electrostatic interaction. Therefore, the possible interaction among CAR, Kolliphor® P188, and Eudragit® RSPO observed by FT-IR studies corresponds to the presence of negligible hydrophobic interaction. From a theoretical point of view, this result is beneficial since some drug-polymer interactions might even decrease the dissolution rate, and the thermodynamic driving force for dissolution will be higher in case of very weak or no drug polymer interactions [41, 42].

3.4. Dissolution behavior

To distinguish the possible enhancement in the dissolution behavior of SRSD-CAR with different drying techniques, dissolution tests in phosphate buffer (pH 6.8) media were conducted (Figure 5). Generally weak bases show better dissolution in stomach and tend to precipitate in small intestine [43]. The crystalline CAR, due to its hydrophobic and crystalline nature, fails to show complete dissolution under both supersaturated and sink conditions. However, both formulations achieved 60–70% of drug dissolution within the first hour that indicates initial burst release (Y.S. Lee et al., 2017) and by the end of 12 h about 80–90% of the entrapped CAR was released from the formulations. The dissolution efficiency of SRSD-CAR was significantly higher than that of pure

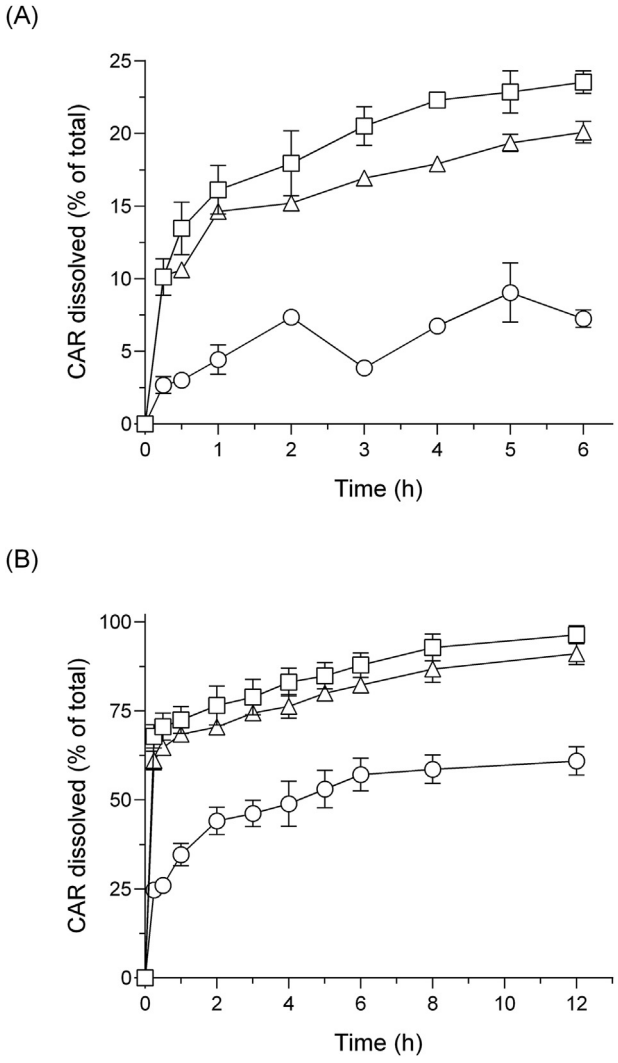

Figure 5. Dissolution tests of CAR samples in phosphate buffer media (0.05 M, pH 6.8). (A) Under supersaturated state and (B) Under sink condition. ○, crystalline CAR; △, SRSD-CAR/RVD; and □, SRSD-CAR/FD. Data represent the mean ± SD of 3 experiments.

Table 2. Various dissolution related model independent fit factors of CAR samples.

	Sample	MDT (h)	T_{50} (h)	T_{80} (h)	Dissolution efficiency (%)	Dissolution rate (hr^{-1})
Sink condition	CAR	1.9	6.6	10.5	51.5 ± 6.9	3.9
	SRSD-CAR/RVD	1.5	4.3	6.9	79.8 ± 1.8	4.3
	SRSD-CAR/FD	1.4	4.0	6.5	85.3 ± 3.0	4.4
Supersaturated condition	CAR	1.1	30.7	49.2	6.0 ± 0.5	1.1
	SRSD-CAR/RVD	1.2	11.6	18.6	16.2 ± 0.2	2.3
	SRSD-CAR/FD	1.1	9.8	15.6	19.2 ± 0.9	2.9

MDT, mean dissolution time; T_{50}, time to dissolve 50% of CAR; T_{80}, time to dissolve 80% of CAR; and DE, dissolution efficiency.

CAR (as shown in Table 2). The drug release (at 6 h) in supersaturated condition was 7.5, 19, and 23% for crystalline CAR, SRSD-CAR/RVD, and SRSD-CAR/FD, respectively. However, the drug release under sink condition was higher (60, 87, and 90% for crystalline CAR, SRSD-CAR/RVD and SRSD-CAR/FD, respectively) and demonstrated a two-fold increase in the dissolution rate when compared to that of crystalline CAR. Amongst the two drying approaches, SRSD-CAR/FD certainly showed better drug dissolution and this could be a result of the complete and stable transition of crystalline state to metastable amorphous form using freeze-drying method. The high dissolution rates might be a combined effect of both Eudragit® RSPO and Kolliphor® P188 in improving the wettability and physical modification of crystalline CAR, which was confirmed by DSC and XRPD analysis. Moreover, Kolliphor® P188, a class of synthetic block copolymers, is composed of one hydrophobic and two hydrophilic domains arranged in a way that enables to form micelles when in contact with aqueous solution.

Dissolution tests performed in phosphate buffer media (pH 6.8) intended to investigate degree of supersaturation of CAR-loaded SRSDs. As seen in Figure 5 (A), SRSD-CAR/RVD exhibited a maximum solubility of 19% after 6 h. The maximum dissolution of SRSD-CAR/FD was higher than that of SRSD-CAR/RVD at all-time points, however there was insignificant difference was observed between these two drying approaches ($p = 0.61$). Compared to the RVD solid dispersion, FD ones' demonstrated higher degree of supersaturation, which suggests that it might inhibit drug precipitation in supersaturated state. Both the solid dispersions showed an initial burst release of the drug, CAR. In Figure 5 (B), SRSD-CAR/FD revealed higher dissolution rate (2.9 h^{-1}) with nearly complete drug dissolution at the end of 12 h. The concentration was maintained at 90% from 8 h onwards, which could suggest slight precipitation of CAR under these conditions. SRSD-CAR/RVD exhibited a slower release rate (2.3 h^{-1}), with a maximum dissolution of 87.5% at 12 h. Both FD and RVD solid dispersions have proven to have the potential to enhance the dissolution rate and simultaneously maintain the supersaturated state for CAR with no significant differences ($p = 0.39$ and $p = 0.61$, respectively for both supersaturated and sink conditions). The two polymers, Eudragit® RSPO and Kolliphor® P188, have the ability to prevent the crystallization tendency of amorphous CAR, which was further confirmed by DSC. Various hydrophilic polymers are known to successfully enhance the oral BA of a drug either by increasing the dissolution rate or the drug concentration in the media [44].

3.5. Dissolution kinetics

In order to understand the release behavior of CAR from SRSD-CAR, the dissolution profiles were analyzed using various model-dependent and model-independent mathematical models that include Higuchi, Zero order, First order, Korsmeyer-Peppas, Hixson-Crowell and Weibull model. The regression parameters of both the formulations, e.g. correlation coefficients and rate constants were determined and compared as shown in Table 3. In case of SRSD-CAR/FD, the goodness of fit was ranked in order of Weibull > Higuchi > Korsmeyer–Peppas > Zero order > Hixson–Crowell > First order. On the other hand, for SRSD-CAR/RVD

Table 3. Determination of dissolution kinetics of different model dependent release kinetic models.

Model	*Parameters*	Sink condition			Supersaturated condition		
		CAR	SRSD-CAR/RVD	SRSD-CAR/FD	CAR	SRSD-CAR/RVD	SRSD-CAR/FD
Zero Order	R^2	0.7777	0.9293	0.937	0.6305	0.9031	0.8815
	Adjusted R^2	0.7499	0.9204	0.9292	0.5689	0.887	0.8618
	K_0	7.63	11.58	12.35	1.63	4.30	5.12
First-order	R^2	0.9651	0.8056	0.7253	0.6655	0.9595	0.99
	Adjusted R^2	0.9608	0.7813	0.691	0.6097	0.9528	0.9883
	K_1	0.15	1.95	2.85	0.02	0.05	0.06
Higuchi	R^2	0.9299	0.9915	0.9916	0.6697	0.9615	0.9632
	Adjusted R^2	0.9211	0.9904	0.9905	0.6146	0.9551	0.957
	K_h	22.54	35.13	37.56	3.52	9.49	11.26
Hixon-Crowell	R^2	0.7205	0.9091	0.922	0.6413	0.8651	0.8311
	Adjusted R^2	0.6855	0.8978	0.9123	0.5815	0.8426	0.803
	K_d	0.04	0.12	0.13	0.01	0.02	0.02
Korsmeyer-Peppas	R^2	0.9762	0.9582	0.9403	0.7394	0.9645	0.9832
	Adjusted R^2	0.9732	0.953	0.9328	0.6959	0.9586	0.9804
	K_{kp}	34.95	68.15	73.88	4.31	13.43	15.47
	n	0.25	0.10	0.10	0.34	0.22	0.25
Weibull	R^2	0.9813	0.8996	0.8416	0.7393	0.9637	0.9843
	Adjusted R^2	0.9790	0.8870	0.8218	0.6959	0.9576	0.9817
	β	0.33	0.77	1.91	0.32	0.25	0.23

R^2, correlation coefficient; adjusted R^2, adjusted correlation coefficient using nonlinear regression; k_0, zero-order release constant; k_1, first-order release constant; K_h, Higuchi rate constant; K_d, Hixson–Crowell kinetics constant; K_{kp}, Korsmeyer release rate constant; n, diffusion coefficient; β, shape parameter.

the goodness of fit was in the order of Higuchi > Weibull > Korsmeyer–Peppas > Zero order > Hixson–Crowell > First order. Accordingly, the drug release data of SRSD-CAR/RVD was best fitted to Higuchi model with an R^2 value of 0.9915, which suggests that the drug release from the formulation may be governed by diffusion. Both formulations showed good correlation to the Korsmeyer–Peppas equation. As shown in Table 3, the diffusion coefficient (n) was found to be 0.10 and it indicates diffusion-controlled release or Fickian diffusion, whereas when $0.5 < n < 1$ is termed non-Fickian or anomalous transport [45]. Release profile for SRSD-CAR/RVD is best described by the Higuchi model and Korsmeyer-Peppas equation. The diffusion coefficient n indicates Fickian diffusion at a value of 0.10 and 0.22 (in sink and supersaturated condition, respectively). For SRSD-CAR/FD, the n values were found to be 0.10 and 0.25, respectively.

From the results of the above experiments with SRSD-CAR, this study is not limited to CAR. Drugs having similar physicochemical behavior (poor solubility, weakly basic in nature) and biopharmaceutical characteristics (poor BA, short elimination half-life), e.g. Disulfiram, Nilvadipine, Ibuprofen, Indomethacin, Diclofenac Sodium, Nifedipine, Ketoprofen, Flurbiprofen etc. can also be considered to do further research by using the SRSD approach [46, 47]. Beside this, in preparing the SRSD with combination use of amphiphilic and sustained release polymers in this study, we used Eudragit® RSPO and Kolliphor® P188; and there might be still a great opportunity for researchers to identify any possible substitute of excipients that can bring similar results with a lower cost. In that case, the possible alternatives would be Methocel® derivatives, Kollidon® SR and some other sustained release polymers; and for amphiphilic polymers Soluplus®, Pluronic® would be another choice; which are also proprietary excipients. However, further study may require to confirm the suitability of the selection and optimization of polymer in case of SRSD formulations.

4. Conclusion

Low oral BA, extensive first pass metabolism, short half-life are major obstacles that are encountered when treating hypertension with CAR. In this study CAR was formulated as SRSD, containing a blended mixture of Eudragit® RSPO and Kolliphor® P188, using two industrially scalable methods namely: solvent evaporation by RVD and freeze-drying. The solubility and dissolution behavior of CAR was markedly enhanced in all the prepared systems. The *in vitro* results suggest that the developed formulation exhibited the dissolution profiles suitable for sustained release and well fitted to Higuchi model, which indicates diffusion controlled drug release. This could be attributed to the amorphization of CAR and homogenous distribution of the drug into the polymeric matrix. Thus, the use of polymer blends as a carrier with a convenient method of preparation represent a promising approach in enhancing biopharmaceutical performance of CAR.

Declarations

Author contribution statement

S. Halder: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

M.A.K. Azad and E.R. Kabir: Conceived and designed the experiments; Wrote the paper.

F. Ahmed: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

M.L. Shuma: Performed the experiments; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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