

AN IMPROVEMENT IN PHYSICOCHEMICAL PROPERTIES OF CARVEDILOL THROUGH SPHERICALLY AGGLOMERATED SOLID DISPERSIONS WITH PVP K30

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Abstract: Spherically agglomerated solid dispersions of carvedilol (CAR) were prepared with polyvinylpyrrolidone (PVP) using acetone, water and dichloromethane as solvent, non-solvent and bridging liquid, respectively. The prepared agglomerates were evaluated for its percentage yield, drug content, morphology, thermal behavior, micromeritic properties, aqueous solubility and *in vitro* drug release. Differential scanning calorimetric and powder X-ray diffraction studies confirm that formulation process altered the crystalline nature of carvedilol. The recrystallized agglomerates exhibited significant increase ($p < 0.05$) in micromeritic properties than untreated carvedilol. Solubility and *in vitro* drug release studies indicated that the spherical agglomerates showed significant increase ($p < 0.05$) in solubility and dissolution rate than pure carvedilol alone.

Keywords: carvedilol, spherically agglomerated solid dispersion, solubility, micromeritic properties, dissolution rate

Carvedilol (CAR), an antihypertensive agent, is used in the treatment of hypertension, congestive heart failure, cardiac arrhythmias and angina pectoris (1). It is a nonselective β -adrenergic blocker with selective α -adrenergic blocking (2). However, drug bioavailability is very limited (25–30%), since it is practically insoluble in water and its dissolution is rate limiting for its absorption from gastro-intestinal tract. Also CAR is poorly flowable and compressible drug (3, 4). One of the approaches to enhance the dissolution rate is the use of solid dispersions. At present, the solvent method and melting method are widely used in the preparation of solid dispersions (5, 6). In general, subsequent grinding, sieving, mixing and granulation are necessary to produce different desired formulations. The spherical agglomeration technique has been used as an efficient particle preparation technique (7, 8). Initially, spherical agglomeration technique was used to improve powder flowability and compressibility (9, 10). Then, polymers were introduced in this system to modify their release (11–13). Currently, this technique is used more frequently for the solid dispersion preparation of

water-insoluble drugs in order to improve their solubility, dissolution rate and simplify the manufacturing process. Spherical agglomeration is carried out by following methods: 1) Solvent change system, 2) Quasi-emulsion solvent diffusion system (QESD), 3) Ammonia diffusion system, 4) Neutralization technique. Out of these techniques, the QESD is most commonly used. This method employs three solvents: 1) Good solvent – solvent that dissolves API, 2) Poor solvent – solvent in which API is insoluble, 3) Bridging liquid – solvent that dissolves API and is immiscible with poor solvent while miscible with good solvent. When bridging liquid plus good solvent containing API are poured into the poor solvent under agitation, quasi-emulsion droplets of bridging liquid or good solvent form in the poor solvent and induce crystallization of the drug followed by agglomeration.

In the present study, to overcome the problems related to solubility, dissolution rate, flowability and compressibility, the spherically agglomerated solid dispersions of CAR were prepared by QESD by using a hydrophilic polymer polyvinylpyrrolidone K30 (PVP K30).

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and HR were calculated from the loose and tapped densities. Tapped density was determined by tapping the samples into a 10 mL measuring cylinder. The CI and HR was calculated according to the following equation:

$$CI = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

$$HR = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Solubility studies

A quantity of crystals (about 100 mg) was shaken with 10 mL of distilled water in stoppered conical flask in incubator shaker for 24 h at room temperature. The solution was then passed through a Whatman filter paper (no. 42) and amount of drug dissolved was analyzed spectrophotometrically.

Dissolution rate studies

The dissolution rate studies of carvedilol alone and its spherical agglomerates were performed in triplicate in a dissolution apparatus (Electrolab, India) using the paddle method (USP Type II). Dissolution studies were carried out using 900 mL of 0.1 M HCl (pH 1.2) at $37 \pm 0.5^\circ\text{C}$ at 50 rpm according to US FDA guidelines (16, 17). Carvedilol (12.5 mg) or its equivalent amount of spherical agglomerates were added to 900 mL of 0.1 M HCl (pH 1.2). Samples (5 mL) were withdrawn at time intervals of 10, 20, 30, and 60 min. The volume of dissolution medium was adjusted to 900 mL by replacing each 5 mL aliquot withdrawn with 5 mL of fresh 0.1 M HCl (pH 1.2). The solution was immediately filtered, suitably diluted and the concentrations of carvedilol in the samples were determined spectrophotometrically at 286 nm. The results obtained from the dissolution studies were statistically validated using ANOVA.

Dissolution efficiency studies

The dissolution efficiency (DE) of the batches was calculated by the method mentioned by Khan (18). It is defined as the area under the dissolution curve between time points t_1 and t_2 expressed as a percentage of the curve at maximum dissolution, y_{100} , over the same time period or the area under the dissolution curve up to a certain time, t , (measured using trapezoidal rule) expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. DE_{60} values were calculated from dissolution data and used to evaluate the dissolution rate (19).

Stability studies

The agglomerates were charged for the accelerated stability studies in accordance with ICH guidelines ($40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ RH for a period of six months). The initial drug content of optimized agglomerates was determined. Then, they were placed in USP type I flint glass vials, closed with bromobutyl rubber bung and sealed with aluminium caps. The vials were placed in stability chamber (Thermolab, Mumbai, India) and samples were withdrawn at predetermined time intervals (15, 30, 60, 90 and 180 days) and evaluated for drug content.

Formulation studies

The optimized agglomerates based on their *in vitro* dissolution profile were selected to formulate into tablet dosage form. Formulation excipients were selected on the basis of preliminary test which demonstrated no interference of these excipients with λ_{max} of CAR. Tablets containing 12.5 mg of CAR were made by direct compression using different formulation excipients like microcrystalline cellulose (Avicel PH 102), sodium starch glycolate and magnesium stearate. Tablets containing agglomerates equivalent to 12.5 mg of CAR were made similarly. For third assay, tablets were crushed and a blend equivalent to 12.5 mg of CAR was weighed and dissolved in dissolution medium. The tablets were studied in triplicates for release profile of drug using the same methodology as described in *in vitro* dissolution studies.

Statistical analysis

Statistical data analysis was performed using the Student's *t*-test or analysis of variance with $p < 0.05$ as the minimal level of significance using Graph Pad InStat software (GPIS; version 5.0) and Microsoft Excel 2007. The dissolution efficiency (DE) was calculated using the Origin software (Origin pro; version: 8.1).

RESULTS AND DISCUSSION

Formulation and development

Spherically agglomerated solid dispersion of CAR were prepared by quasi emulsion solvent diffusion method (QESD) using a three solvent system. It involves good solvent, poor solvent and a bridging liquid. The selection of these solvents depends on the miscibility of the solvents and the solubility of drug in individual solvent. Accordingly, acetone, dichloromethane and water were selected as a good solvent, bridging liquid, and poor solvent, respectively. CAR is soluble in acetone, but poorly soluble

in water. It is also soluble in dichloromethane which is immiscible in water. Hence, this solvent system was used in the present study. In QESD method, when good solvent solution of drug plus bridging liquid were poured in the poor solvent under agitation, quasi emulsion droplets of bridging liquid and good solvent were produced. Then the good solvent diffuses gradually out of the emulsion droplet into the outer poor solvent phase. The counter-diffusion of the poor solvent into the droplets induces the crystallization of the drug within the droplet due to the decrease in solubility of the drug in the droplet containing the poor solvent. The bridging liquid wets the crystal surface to cause binding and promotes the formation of liquid bridges between the drug crystals to form spherical agglomerates. The spherically agglomerated crystals are formed by coalescence of these dispersed crystals. The PVP K30 was incorporated into the agglomeration process to increase the aqueous solubility along with other physicochemical properties. The polymer PVP K30 produced a high viscosity during the formation of coacervation droplets, and often caused the droplets to agglomerate into masses of irregular shapes and adhere to the propeller or the vessel wall. To overcome this, Aerosil 200 Pharma, as a dispersion agent was introduced into the formulation to avoid the coalescence of the droplets.

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectra of CAR as well as its spherical agglomerates are presented in Figure 1. FTIR of CAR showed characteristic peaks at 3343.96 (N-H str. aromatic amine), 3062.41 (C-H str. aromatic hydrocarbon), 2923.56 (C-H str. in $-\text{CH}_3/-\text{CH}_2$), 1592.91 (C=C str. aromatic) and 1253.5, 1214.93, 1099.23 (C-O str. in Ar C=C-O-C) cm^{-1} . There was no considerable change in the IR peaks of the spherical agglomerates when compared with pure CAR. Major IR peaks of CAR and its spherical agglomerates are shown in Table 2.

Differential scanning calorimetry (DSC)

CAR exists in different polymorphic forms (20). It also exists as hydrates and various solvates (21). The DSC thermogram of untreated CAR and its agglomerates are shown in Figure 2. DSC thermogram of CAR showed endothermic peak at 120.47°C, which represented melting of carvedilol form II. Thermal behavior of CAR obtained from DSC data confirmed that CAR used in present study exists in form II. The DSC thermogram of CP-1 exhibited endothermic peak onset at 97.71°C and of CP-6 exhibited endothermic peak onset at 96.33°C for both agglomerates. DSC thermograms of CAR agglomerates represented form III and confirmed the phase transition (form II to III) of CAR during

Table 2. Major IR peaks of CAR and its spherical agglomerates.

Sample	Major peaks (wave numbers, cm^{-1})	Chemical moiety
CAR	3343.96	N-H str. aromatic amine
	3062.41	C-H str. aromatic hydrocarbon
	2923.56	C-H str. in $-\text{CH}_3/-\text{CH}_2$
	1592.91	C=C str. aromatic
	1253.5, 1214.93, 1099.23	C-O str. in Ar C=C-O-C (ether)
CP-1	3401.82	N-H str. aromatic amine
	3058.55	C-H str. aromatic hydrocarbon
	2938.98	C-H str. in $-\text{CH}_3/-\text{CH}_2$
	1592.91	C=C str. aromatic
	1257.36, 1222.65, 1103.08	C-O str. in Ar C=C-O-C (ether)
CP-6	3401.82	N-H str. aromatic amine
	3058.55	C-H str. aromatic hydrocarbon
	2938.98	C-H str. in $-\text{CH}_3/-\text{CH}_2$
	1589.06	C=C str. aromatic
	1257.36, 1222.65, 1099.	C-O str. in Ar C=C-O-C (ether)

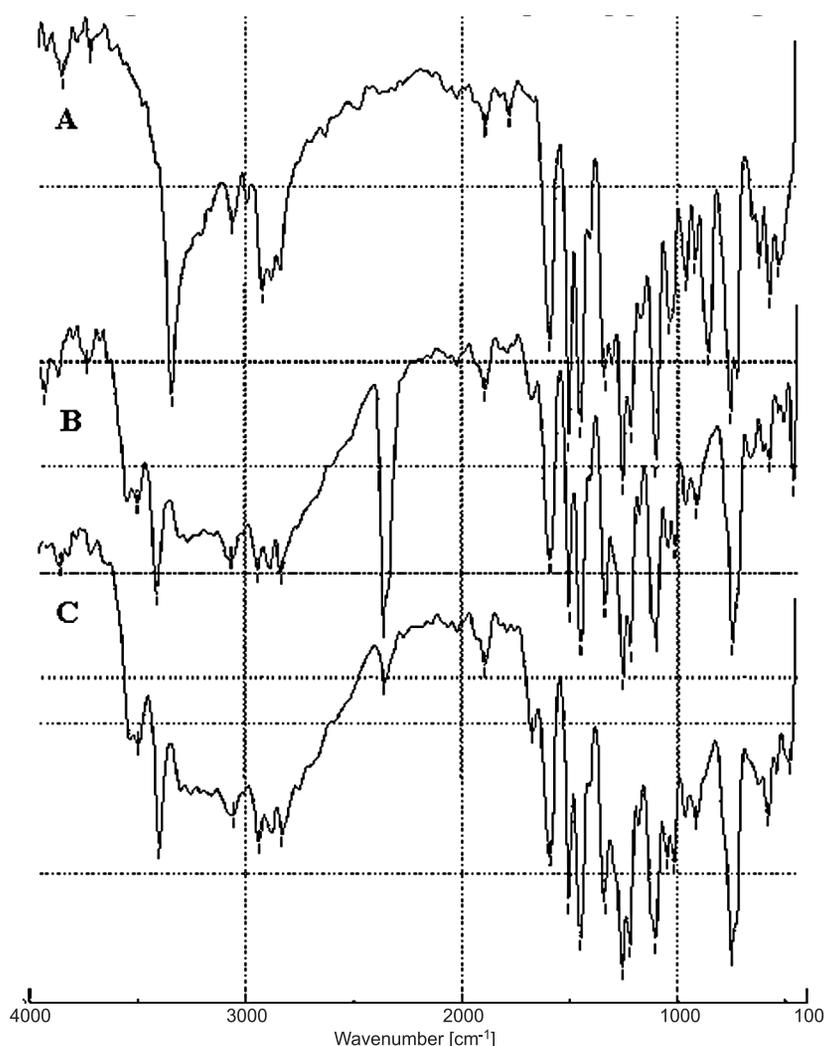


Figure 1. FTIR spectra of A: CAR, B: CP-1, C: CP-6

formulation and development. Moreover, literature revealed that the carvedilol form III is also biologically active.

Powder X-ray diffraction studies (PXRD)

PXRD patterns of CAR and its agglomerates are illustrated in Figure 3. The intense peaks at 2θ of 26.16° , 27.48° , 36.47° and 39.34° with peak intensities (counts) 310, 256, 228 and 135, respectively, obtained from CAR confirmed the form II crystals of CAR. PXRD patterns of agglomerates CP-1 exhibited intense peaks at 2θ of 25.05° , 30.10° , 32.22° and 38.94° with peak intensities (counts) 77, 88, 142, and 81, while those of CP-6 exhibited intense peaks at 2θ of 25.01° , 30.09° , 31.89° and 38.88° with peak intensities (counts) 77, 72, 121 and 98, which confirmed the phase transi-

tion of form II to form III during formulation development. Also a decrease in intensities of peaks in CP-6 revealed little amorphous nature of drug. The results obtained from PXRD studies were further confirmed by DSC thermogram. During scanning of PVP K30, a broad endotherm ranging from 58.89 to 121.92°C was observed indicating the loss of water due to extremely hygroscopic nature of PVP polymers.

Scanning electron microscopy (SEM)

The results of surface morphology studies are shown in Figure 4. The SEM results revealed the spherical structure of agglomerates. The surface morphology studies also revealed that the agglomerates were formed by very small crystals, which were closely compacted into spherical form. These pho-

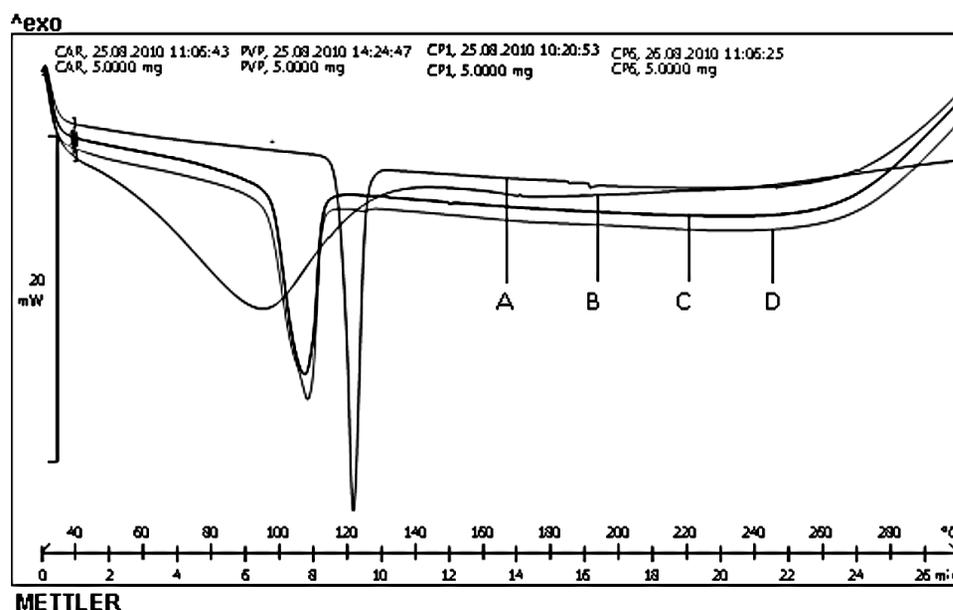


Figure 2. DSC patterns of A: CAR, B: PVP K30, C: CP-1, D: CP-6

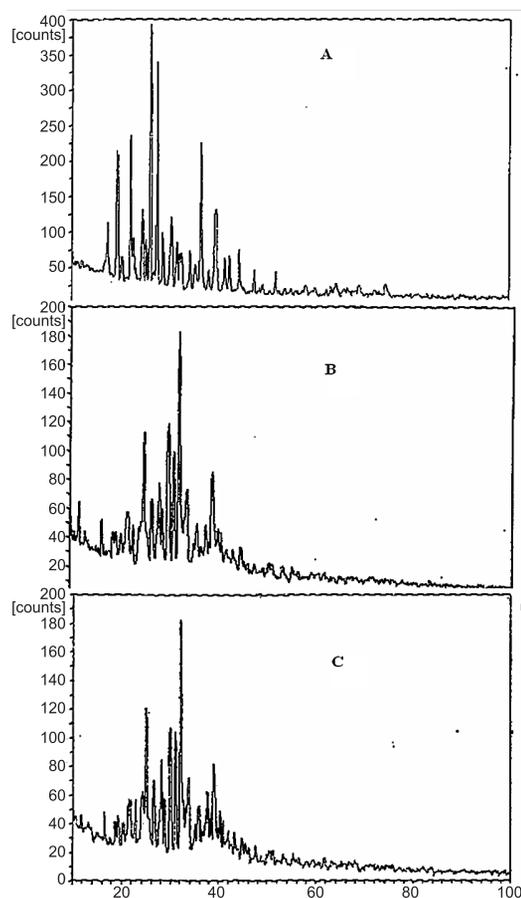


Figure 3. PXRD patterns of A: CAR, B: CP-1, C: CP-6

tomicrographs show that the prepared agglomerates were spherical in shape, which enabled them to flow very easily.

Drug content and percentage yield

Percentage yield of spherical agglomerates was found to be in the range of 93.8 ± 4.9 to $98.7 \pm 3.1\%$ and percentage drug content was found to be in the range of 92.9 ± 1.22 to $98.4 \pm 1.15\%$ (Table 3).

Micromeritics and morphology studies

Flowability of CAR and its agglomerates with PVP K30 was assessed by determination of Carr's index (CI), Hausner's ratio (HR) and angle of repose. Micromeritic behaviors of the untreated carvedilol powder and all engineered carvedilol spherical agglomerates are listed in Table 3. Table 3 shows that the flowability represented in terms of Carr's index, Hausner's ratio and angle of repose was much improved compared to those of original powders (untreated carvedilol). In case of pure CAR, powder could not pass through the funnel during the angle of repose experiment. The poor flow of carvedilol could be due to the irregular shape and high fineness of the powder, which posed hurdles in the uniform flow from the funnel. These results are significantly different from those of untreated carvedilol ($p < 0.05$). It is obvious from Carr's index values that the flow of untreated carvedilol is extremely poor due to a high cohesivity and adhe-

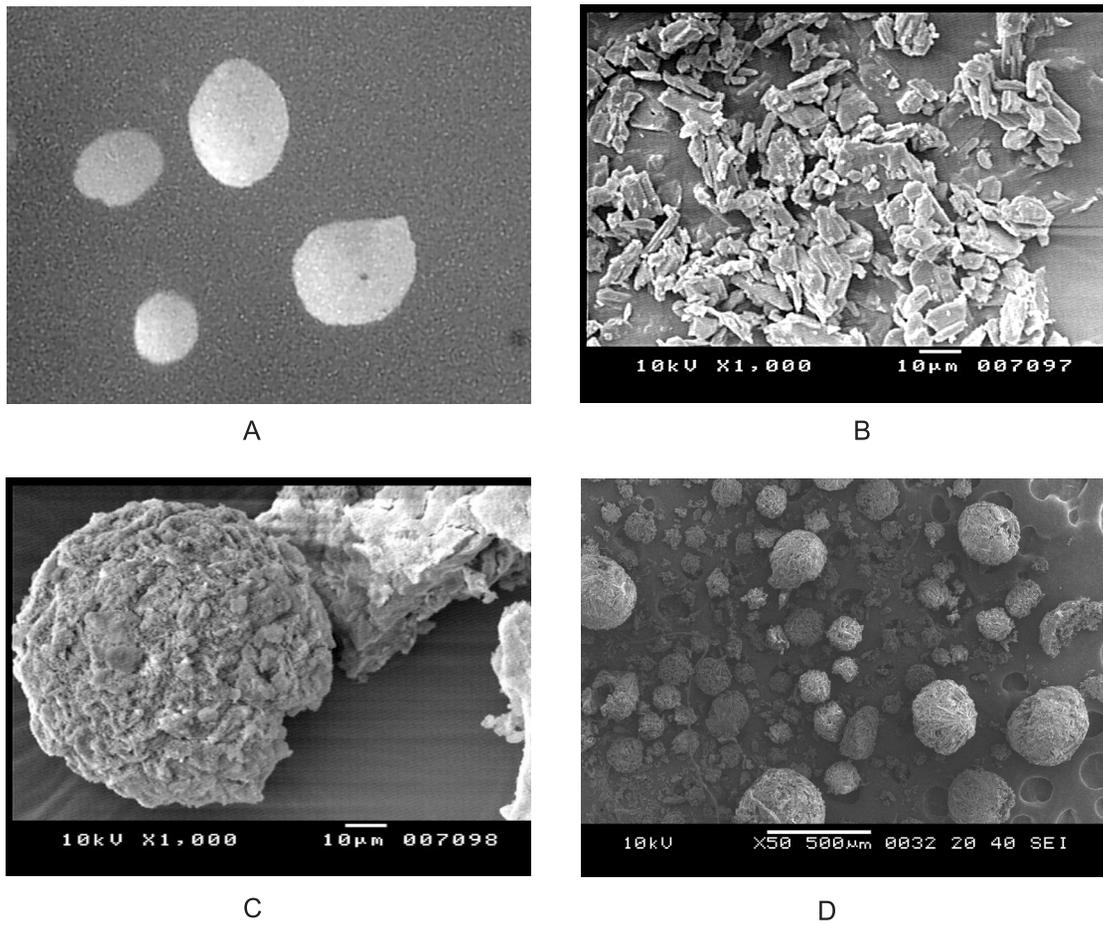


Figure 4. A: Optical micrograph of CP-6; SEM images of B: CAR, C: CP-1, D: CP-6

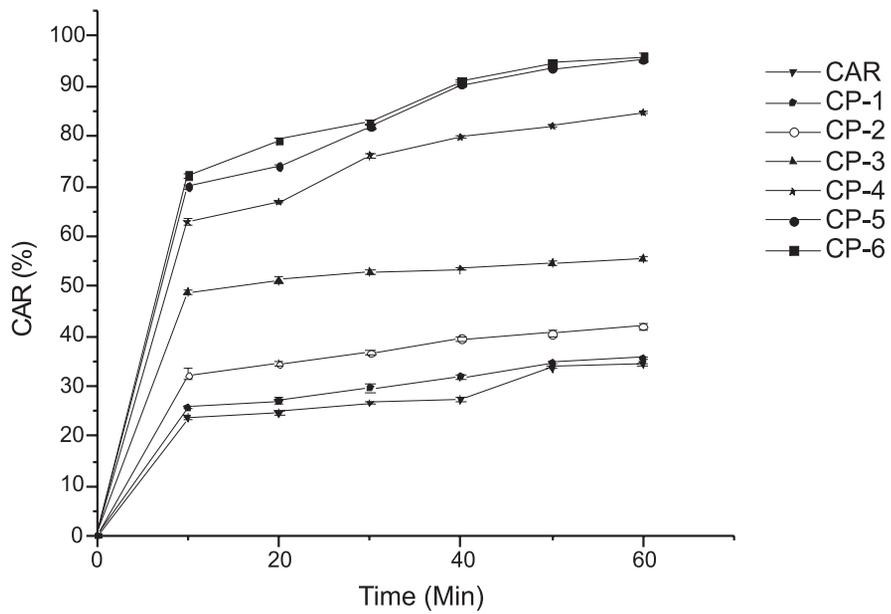


Figure 5. Dissolution profile of CAR and its agglomerates. The mean \pm SD, n = 3

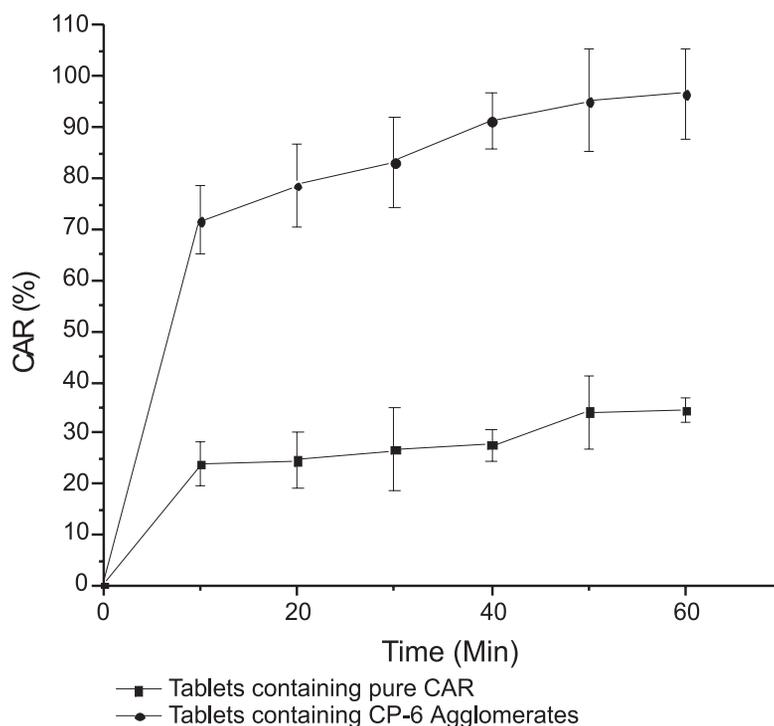


Figure 6. Release profile of CAR from tablets containing pure CAR and CP-6 agglomerates. The mean \pm SD, $n = 3$

sivity. Because of poor flowability and compactibility of the untreated carvedilol powder, in most cases the drug has to be granulated before tableting. The micromeritic properties of carvedilol can be improved forming spherical agglomerates. Table 3 shows that all carvedilol spherical agglomerated solid dispersions showed lower Carr's index than the untreated carvedilol powder, which is an indication of an improvement in flow behavior of carvedilol powder. The increase in powder flow of engineered particles could be partly due to an increase in true density of carvedilol powders. The differences in the bulk density of various carvedilol samples may be related to their markedly different crystal habits, leading to different contact points and frictional and cohesive forces between the crystals. These factors in turns affect the sliding of the particles against each other, leading to different packing geometry and hence different bulk densities. These data are in good agreement with morphology of carvedilol spherical agglomerates since the untreated carvedilol shows needle-like crystals hence low bulk density and low flowability. The study also showed that the presence of additive in the crystallization medium can improve flow of carvedilol powders. The mean particle diameter of agglomerates is shown in Table 3. The pure carvedilol exhibited very small particle size ($71.55 \pm 5.37 \mu\text{m}$, $n = 3$)

whereas the size of prepared agglomerates was found between 373.5 ± 15.68 and $578.14 \pm 21.89 \mu\text{m}$, $n = 3$, which is significantly different from that of pure drug ($p < 0.05$).

Solubility studies

The results of solubility studies indicate that CAR possesses a very low solubility in water ($21.0 \pm 1.51 \mu\text{g/mL}$, $n = 3$); the drug solubility from agglomerates increased significantly ($p < 0.05$), demonstrating that the incorporation of hydrophilic polymers enhances the drug solubility. Also, as the concentration of hydrophilic polymer increased, the drug solubility also increased. Amongst the prepared agglomerates CP-6 agglomerates show maximum solubility ($183.0 \pm 4.38 \mu\text{g/mL}$, $n = 3$). The aqueous solubility data are given in Table 3.

Dissolution rate studies

The dissolution curves of untreated carvedilol and its spherical agglomerates in 0.1 M HCl (pH 1.2) are shown in Figure 5. The release rate profiles were expressed as the percentage drug released vs. time. Table 4 shows percentage of drug dissolved in 60 min (DP_{60}) and dissolution efficiency values at 30 min (DE_{30}) for carvedilol and its spherical agglomerates. These values are tested statistically through one way ANOVA fol-

Table 3. Percentage yield, drug content, micromeritic properties and dissolution data of CAR and its spherical agglomerates^a.

Sample	Percentage yield	Drug content [%]	Carr's index	Hausner ratio	Angle of repose [°]	Particle size [µm] (µg/mL)	Aqueous solubility
CAR	–	100.0 ± 0.0	34.37 ± 1.79	1.52 ± 1.26	–	71.55 ± 5.37	21.0 ± 1.51
CP-1	98.7 ± 3.1	98.4 ± 1.15	13.33 ± 1.56 ^b	1.15 ± 1.22 ^b	32.11 ± 1.23	373.5 ± 15.68 ^b	34.2 ± 1.38
CP-2	97.1 ± 4.6	96.4 ± 1.57	11.66 ± 1.24 ^b	1.13 ± 1.56 ^b	29.55 ± 1.90	412.16 ± 19.34 ^b	52.6 ± 1.22 ^b
CP-3	95.8 ± 3.8	95.5 ± 2.25	10.71 ± 2.24 ^b	1.12 ± 1.77 ^b	26.01 ± 1.91	421.22 ± 21.30 ^b	77.0 ± 1.12 ^b
CP-4	94.5 ± 1.4	94.8 ± 0.40	10.34 ± 3.12 ^b	1.11 ± 0.92 ^b	24.45 ± 1.35	525.44 ± 22.81 ^b	91.7 ± 1.39 ^b
CP-5	94.1 ± 4.2	93.9 ± 1.67	08.77 ± 2.81 ^b	1.09 ± 1.02 ^b	23.12 ± 1.45	564.63 ± 19.08 ^b	128.4 ± 2.43 ^b
CP-6	93.8 ± 4.9	92.9 ± 1.22	09.67 ± 1.21 ^b	1.10 ± 1.08 ^b	21.37 ± 1.16	578.14 ± 21.89 ^b	183.0 ± 4.38 ^b

^a The mean ± SD, n = 3. ^bSignificantly different compared to pure carvedilol (p < 0.05).

lowed by Dunnett's multiple comparison test and are found significantly different (p < 0.05) from untreated carvedilol powder. As indicated, carvedilol was dissolved more than 90% from agglomerates after 60 min while the untreated powder was just dissolved 34.37% at comparable time. The results revealed that the spherical agglomerates with 9% w/v PVP K30 (CP-6) caused significant increase (p < 0.01) in drug release compared to the pure drug. Enhancement in dissolution rate of spherical agglomerates as compared to pure drug may be due the presence of polymer, PVP K30.

Stability study

The values of drug content for spherical agglomerates were at day 0: 92.90 ± 1.22%; and after 15 days: 92.72 ± 1.93%, n = 3; 30 days: 92.04 ± 2.14%, n = 3; 60 days: 91.77 ± 1.04%, n = 3; 90 days: 91.43 ± 1.38%, n = 3; 180 days: 91.09 ± 1.73%, n = 3. On storage, the CP-6 agglomerates did not show considerable change in drug content for the period of six months at accelerated condition when compared with initial value, which indicates good stability of agglomerates.

Formulation studies

In the present study the optimized agglomerates selected were CP-6 depending on their micromeritics and drug release profile. In general, compressibility index values up to 15% and angle of repose between 25 and 30° results in good to excellent flow properties. The values, as shown in Table 2, indicate good compressibility and flowability for CP-6 making it suitable for tableting. The release profile of CAR from conventional tablet containing CAR and tablets containing CAR agglomerates (CP-6) is shown in Figure 6. During the *in vitro* dissolution studies, CP-6 agglomerates exhibited more than 80% drug release within 30 min as compared to tablets containing pure CAR.

CONCLUSION

The spherical agglomerates of carvedilol were successfully prepared by quasi emulsion solvent diffusion technique. The micromeritic properties of agglomerates such as flowability, packability and compactibility were dramatically improved. The main factor in improvement of flowability and packability was significant reduction in interparticle friction, due to their spherical shapes and smooth surfaces. DSC studies demonstrated the phase transition (form II to III) of CAR during agglomerates

Table 4. Drug release and dissolution efficiency^a.

Sample	Carvedilol release after 1 h [%]	Dissolution efficiency at 30 min [%]
CAR	34.37 ± 0.19	20.56 ± 0.09
CP-1 3	5.70 ± 0.31	22.48 ± 0.29 ^b
CP-2	42.03 ± 0.62	28.35 ± 0.47 ^b
CP-3	55.58 ± 0.50	42.13 ± 0.33 ^b
CP-4	84.61 ± 0.24 ^b	55.89 ± 0.19 ^b
CP-5	95.13 ± 0.43 ^c	61.56 ± 0.20 ^b
CP-6	95.84 ± 0.80 ^c	64.25 ± 0.31 ^b

^aThe mean ± SD, n = 3. ^bSignificantly different compared to carvedilol (p < 0.05). ^cSignificantly different compared to carvedilol (p < 0.01).

formation. In the present investigation, PVP K30 has significantly improved dissolution rate of carvedilol. The prepared agglomerates also show good stability. However *in vivo* bioavailability studies are required to ensure whether, the results obtain in this investigation can be extrapolated to the *in vivo* conditions.

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