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Short Communication

AN IMPROVEMENT OF MICROMERITIC PROPERTIES AND DISSOLUTION BEHAVIORS OF CARVEDILOL SPHERICAL AGGLOMERATES CRYSTALLIZED IN PRESENCE OF INUTEC SP1

Amit TAPAS[1]*, Pravin KAWTIKWAR[2], Dinesh SAKARKAR[1]

[1]Sudhakarrao Naik Institute of Pharmacy, Department of Pharmaceutical Chemistry, Pusad 445204, Dist: Yavatmal, Maharashtra, INDIA

[2]Shri Sureshdada Jain Institute of Pharmaceutical Education and Research, Jamner 424206, Dist: Jalgaon, Maharashtra, INDIA

Abstract

The objective of the present work was to improve micromeritic properties and dissolution rate of a poorly water soluble drug, carvedilol, by spherical agglomeration in presence of Inutec SP1. In the present work acetone, water and dichloromethane were used as good solvent, poor solvent and bridging liquid respectively for the agglomeration process. The prepared spherical agglomerates were evaluated for its percentage yield, drug content, morphology, thermal behavior, micromeritic properties and in vitro drug release. The percent drug content of spherical agglomerates was found to be in the range of 93.21±2.01 to 100.0±0.0. 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. In vitro drug release studies indicated that the spherical agglomerates CI-1 showed significant increase ($P<0.05$) in dissolution rate than pure carvedilol alone.

Key words: *Carvedilol, Spherical Agglomeration, Inutec SP1, Micromeritic properties, Dissolution rate.*

Inutec SP1 ile Kristalize Edilen Karvedilol Küresel Aglomeratlarının Toz Özellikleri ve Çözünme Davranışlarının İyileştirilmesi

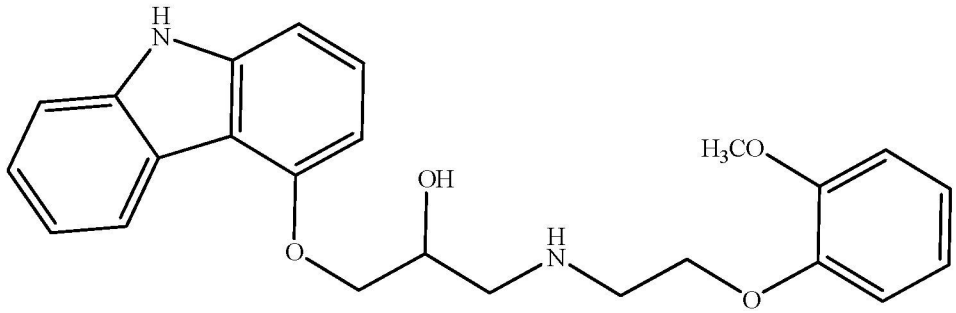
Bu çalışmanın amacı, suda az çözünen bir ilaç olan karvediolol'ün "Inutec SP1" kullanılarak küresel aglomerasyon yardımı ile toz özelliklerinin ve çözünme hızının iyileştirilmesidir. Bu çalışmada, aglomerasyon işlemi için aseton, su ve diklorometan sırası ile iyi çözücü, zayıf çözücü ve bağlayıcı sıvı olarak kullanılmıştır. Hazırlanan küresel aglomeratlar, verim ilaç içeriği, morfoloji, termal davranış, toz özellikleri ve in vitro ilaç salınımı incelenerek değerlendirilmiştir. Küresel aglomeratların ilaç içeriği %93.21 ± 2.01 - % 100.0 ± 0.0 arasında bulunmuştur. Diferansiyel taramalı kalorimetri X-ışını kırınımı çalışmalarıyla yönteminin karvediololun kristal yapısını değiştirdiğini doğrulamıştır. Yeniden kristalizasyon ile elde edilen aglomeratlar, işlem görmemiş karvedilol e göre toz özeliklerinde anlamlı ($p<0.05$) düzelme göstermiştir. In vitro salım çalışmaları ile küresel CI-1 aglomeratlarının dilisyon hızının, tek başına saf karvediolole göre anlamlı ($p<0.05$) oranda yüksek olduğu gösterilmiştir.

Anahtar kelimeler: *Karvedilol, Küresel aglomerasyon, Inutec SP1, Toz özellikleri, Çözünme hızı.*

Correspondence: E-mail- amit.tapas@gmail.com; Tel/Fax: +91-7233-245308

INTRODUCTION

The quality and efficiency of a solid pharmaceutical preparation is influenced by primary micrometric properties (shape, size of crystals etc) and micrometric properties (bulk density, flowability) of active medical substances and inactive substances especially when the large amounts of non water-soluble drug with poor rheologic properties are formulated. The formulation and manufacturing of tablet, the most convenient and widely used pharmaceutical dosage form should comprise only a few working steps. The material used for the production of tablet should be in physical form that flow smoothly and uniformly, have bindability/ compressibility and physically stable, so as to achieve rapid production capability of tablet formulation. Direct compression is the modern and the most efficient process used in tablet manufacturing. Spherical agglomeration is a novel crystallization technique that can transform directly the fine crystals produced in the crystallization process into a spherical shape (1). The spherical crystallization technique appears to be an efficient alternative for obtaining particle destined for direct tabletting, since crystallization and agglomeration are carried out in a single step (2). Various polymers can be incorporated in the spherical agglomeration system to enhance the dissolution rate of drugs with poor dissolution profile (3). One such polymer is Inutec SP1 (Inulin Lauryl Carbamate) (4-6). Also the crystal habit of a drug is an important variable in pharmaceutical manufacturing. Different crystal forms of a particular drug possess different planes and thus differ not only in their specific surface, but also in their free surface energy. Therefore, they may exhibit different micromeritic properties. It has been shown that properties such as dissolution rate, powder flow, and compressibility, which are of pharmaceutical interest, can differ for different habits of the same drug (7-9).
Carvedilol (CAR), an antihypertensive agent, is used in the treatment of hypertension, congestive heart failure, cardiac arrhythmias and angina pectoris (10). It is a nonselective β-adrenergic blocker with selective α-adrenergic blocking. 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. Therefore the aim of the present investigation was to develop spherical agglomerates of carvedilol in order to improve physicomechanical properties and dissolution performance.



1-(9*H*-carbazol-4-yloxy)-3-(2-(2-methoxyphenoxy)ethylamino)propan-2-ol

Figure 1. Chemical structure of Carvedilol.

EXPERIMENTAL

Materials

Carvedilol was supplied by Dr. Reddy's Laboratory, Hyderabad, India as a gift sample. Inutec SP1 was gift sample from Beneo-orafti, Oreye, Belgium. All the reagents were of analytical grade.

Preparation of spherical agglomerates

Spherical agglomerates of carvedilol were prepared by quasi emulsion solvent diffusion method. CAR (1.0 g) was dissolved in good solvent acetone (12.0 ml). The bridging liquid dichloromethane (DCM) (2.0 ml) was added to it. The resulting solution was then poured dropwise in to the poor solvent (distilled water, 100.0 ml) containing different concentrations of Inutec SP1 and Aerosil 200 pharma (0.1 g) with a stirring rate of 1000 rpm using propeller type agitator (Remi Motors Ltd., Mumbai, India) at room temperature. After agitating the system for 0.5 h, the prepared agglomerates were collected by filtration through whatmann filter paper no. 42, placed in a thin layer in an oven at 60 °C for 1 h. The composition of various spherical agglomerates is given in Table 1.

Table 1 Composition of spherical agglomerates.

Ingredients/ Parameters	**CA-0**	**CI-0.5**	**CI-1**
Carvedilol (g)	1.0	1.0	1.0
Acetone (ml)	12.0	12.0	12.0
DCM (ml)	2.0	2.0	2.0
Water (ml)	100	100	100
Inutec SP1 (%w/v)	0.0	0.5	1.0
Aerosil 200 pharma (g)	0.1	0.1	0.1
Stirring speed (rpm)	1000	1000	1000

Percentage yield and drug content study

The yield of spherical agglomerates was determined by comparing the whole weight of the agglomerates formed against the combined weight of the polymer and drug.

$$\text{Percentage Yield} = \frac{\text{Weight of agglomerates obtained}}{\text{Total weight of drug and polymer used}} \times 100$$

The drug content study of agglomerates was determined by dissolving 100 mg of crystals in 3 ml methanol and diluting further with distilled water (100 ml) followed by measuring the absorbance of appropriately diluted solution spectrophotometrically (PharmaSpec UV-1700, UV-Vis spectrophotometer, Shimadzu) at 286 nm.

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectra of powder CAR, and their agglomerates were recorded on an FTIR spectrophotometer (JASCO, FTIR V-430 Plus).

Differential scanning calorimetry (DSC)

DSC analysis was performed using a DSC 823 calorimeter (Mettler Toledo model) operated by STARe software. Samples of CAR and its agglomerates were sealed in an aluminium crucible and heated at the rate of 10 °C/min up to 300 °C under a nitrogen atmosphere (40 ml/min).

Powder X-ray diffraction studies

Powder X-ray diffraction patterns (XRD) of the CAR and its spherical agglomerates were monitored with an x-ray diffractometer (Philips Analytical XRD) using copper as x-ray target, a voltage of 40 KV, a current of 25 mA and with 2.28970 Å wavelength. The samples were analyzed over 2θ range of 10.01-99.99^0 with scanning step size of 0.02^0 (2θ) and scan step time of 0.8 second.

Scanning electron microscopy

The surface morphology of the agglomerates was accessed by SEM. The crystals were splutter coated with gold before scanning.

Micromeritics properties

The size of agglomerates was determined by microscopic method using stage and eyepiece micrometers. The shape of the agglomerates was observed under an optical microscope (×60 magnification) attached to a computer. Flowability of untreated carvedilol and agglomerates was assessed by determination of angle of repose, Carr's index (CI) and Hausner's ratio (HR) (11). Angle of repose was determined by fixed funnel method (12). The mean of three determinations was reported. The CI and HR was 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

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

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

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 0.1N HCl (pH 1.2) at 37 ± 0.5 ^{0}C at 50 rpm as per US FDA guidelines (13, 14). 12.5 mg of carvedilol or its equivalent amount of spherical agglomerates were added to 900 ml of 0.1N 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 0.1N HCl (pH 1.2). The solution was immediately filtered, suitably diluted and the concentrations of carvedilol in 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 (15). 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, y100, 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 (16).

$$\text{Dissolution efficiency} = \frac{\int_0^t y\,dt}{y100\,(t_2 - t_1)} \times 100\%$$

RESULT AND DISCUSSION

Formation of spherical agglomerates

The spherical agglomerates of carvedilol were prepared by quasi emulsion solvent diffusion method (QESD) using three solvent systems. 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, water were selected as a good solvent, bridging liquid, and poor solvent, respectively. Carvedilol is soluble in acetone, but poorly soluble in water. Also it is 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 (containing different concentrations of Inutec SP1) 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 polymer Inutec SP1 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 were introduced into the formulation to avoid the coalescence of the droplets.

Percentage yield and drug content study

Percentage yield of spherical agglomerates was found to be in the range of 95.25±1.31 to 98.38±1.29 and percentage drug content was found to be in the range of 93.21±2.01 to 100.0±0.0 (Table 2). The improved flowability and compressibility of spherical agglomerates may be due to the sphericity, regular and larger size of the crystals.

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectra of CAR as well as its spherical agglomerates is presented in fig. 1. FTIR of CAR showed a characteristic peaks at 3343.96 (N-H str. Aromatic Amines), 3062.41 (C-H str. Aromatic Hydrocarbon), 2923.56 (C-H str. in $-CH_3$/ $-CH_2$), 1592.91 (C=C str.

Aromatic), 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 compaired with pure CAR. Major IR peaks of CAR and its spherical agglomerates is shown in Table 3.

Table 2. Percentage yield, drug content, micromeritic properties and dissolution data of CAR and its spherical agglomerates[a].

S.No	Samples	Percentage Yield	Drug Content	Carr's Index	Hausner Ratio	Angle of Repose	Particle Size	DP_{60}	DE_{30}
1	CAR	---	100.0±0.0	34.37±1.79	1.52±1.26	---	71.55±5.37	34.37±0.78	20.56±0.09
2	CA-0	98.38±1.29	100.0±0.0	16.14±1.81	1.50±1.37	33.17±1.38	278.0±3.19	35.67±0.59	21.26±0.12
3	CI-0.5	96.57±1.52	94.32±1.83	14.23±1.15	1.14±0.03	31.15±1.64	354.6±4.23	84.62±0.36	55.66±0.18
4	CI-1	95.25±1.31	93.21±2.01	12.63±1.35	1.12±0.02	28.47±1.47	410.4±3.98	95.55±0.41	61.35±0.24

[a]Mean ± SD, n = 3

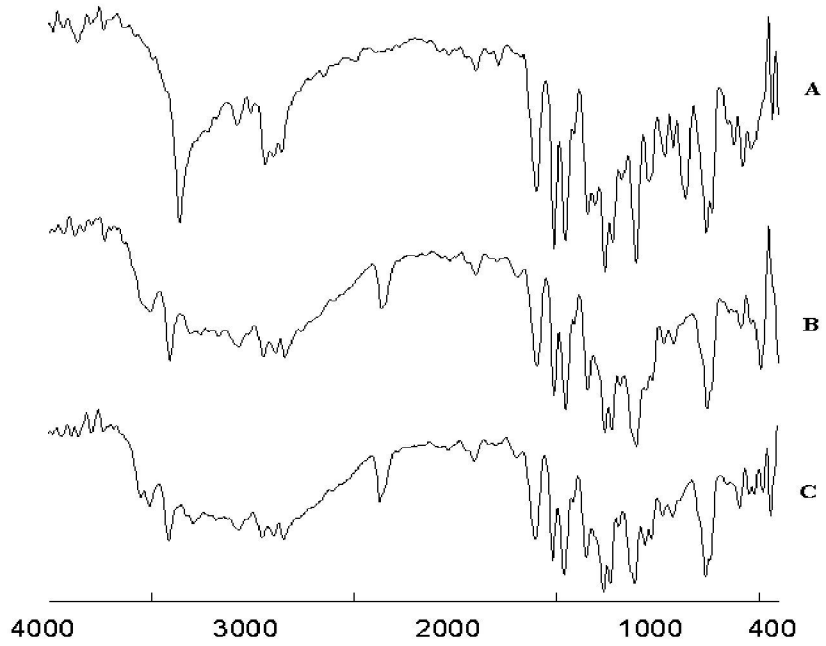


Figure 2. FTIR spectra of A: CAR, B: CA-0, C: CI-1

Table 3. 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 Amines
	3062.41	C-H str. Aromatic Hydrocarbon
	2923.56	C-H str. In $-CH_3$/ $-CH_2$
	1592.91	C=C str. Aromatic
	1253.5, 1214.93, 1099.23	C-O str. in Ar C=C-O-C (ether)
CA-0	3401.82	N-H str. Aromatic Amines
	3062.41	C-H str. Aromatic Hydrocarbon
	2938.98	C-H str. In $-CH_3$/ $-CH_2$
	1589.06	C=C str. Aromatic
	1257.36, 1222.65, 1099.23	C-O str. in Ar C=C-O-C (ether)
CI-1	3401.82	N-H str. Aromatic Amines
	3054.69	C-H str. Aromatic Hydrocarbon
	2928.31	C-H str. In $-CH_3$/ $-CH_2$
	1592.91	C=C str. Aromatic
	1257.36, 1222.65, 1103.08	C-O str. in Ar C=C-O-C (ether)

Differential scanning calorimetry (DSC)

CAR exists in different polymorphic forms (17). It also exists as hydrates and various solvates (18). The DSC thermogram of untreated CAR and its agglomerates are shown in fig. 2. DSC thermogram of CAR showed endothermic peak at 120.47^0C, 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 CA-0 exhibited endothermic peak onset at 100.02^0C and of CI1 exhibited endothermic peak onset at 95.88^0C followed by exothermic recrystallization which subsequently melted at 122.23^0C which represented form III for both agglomerates. DSC thermograms of CAR agglomerates represented the form III and confirmed the phase transition (form II to III) of CAR during formulation and development. Moreover literatures 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 fig.3. The intense peaks at 2θ of 26.16^0, 27.48^0, 36.47^0 and 39.34^0 with peak intensities (counts) 310, 256, 228 and 135 respectively obtained from CAR confirmed that form II crystals of CAR. PXRD patterns of agglomerates CA-0 exhibited intense peaks at 2θ of 24.95^0, 31.94^0, 32.18^0 and 38.88^0 with peak intensities (counts) 96, 125, 121 and 81 while that of CI1 exhibited intense peak at 2θ of 25.03^0, 32.02^0, 32.25^0 and 38.87^0 with peak intensities (counts) 72, 125, 110 and 67 which confirmed that phase transition of form II to form III during formulation development. Also decrease in intensities of peaks in CI1 revealed little amorphous nature of drug. The results obtained from PXRD studies were further confirmed by DSC thermogram.

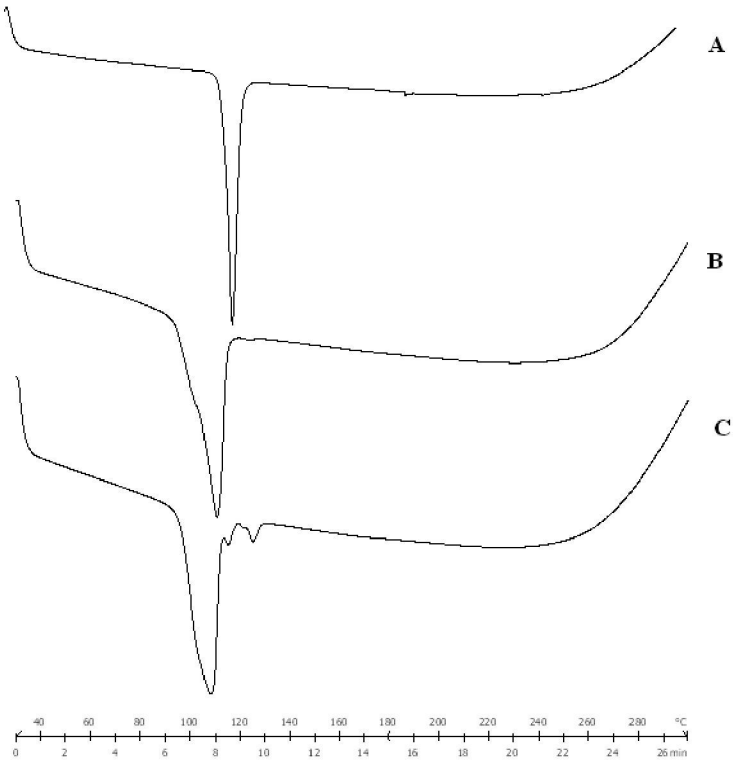


Figure 3. DSC patterns of A: CAR, B: CA-0, C: CI-1

Scanning electron microscopy (SEM)

The results of surface morphology studies are shown in fig. 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 photomicrographs show that the prepared agglomerates were spherical in shape which enabled them to flow very easily.

Micromeritics and morphology studies

Flowability of untreated carvedilol and its engineered agglomerates was assessed by determination of carr's index (CI), hausner's ratio (HR) and angle of repose. Micormeritic behaviours of the untreated carvedilol powder and all engineered carvedilol spherical agglomerates are listed in Table 2. The Table 2 shows that the flowability that represented in the terms of carr's index, hausner's ratio and angle of repose was much improved compared to those of original powders (untreated carvedilol). These results are significantly different from that 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 adhesivity. Because of poor flowability and compactibility of the untreated carvedilol powder, in most cases the drug has to be granulated before tableting. The micrormeritic properties of carvedilol can be improved forming spherical agglomerates. Table 2 shows that all engineered carvedilol spherical agglomerates showed lower Carr's index than the untreated carvedilol powder which is an indication of an improvement in flow behaviour 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 2. The pure carvedilol exhibited very small particle size (71.55±5.37 μm, n=3) whereas the size of prepared agglomerates was found between 278.0±3.19 and 410.4±3.98 μm, n = 3, which is significantly different from that of pure drug ($p < 0.05$).

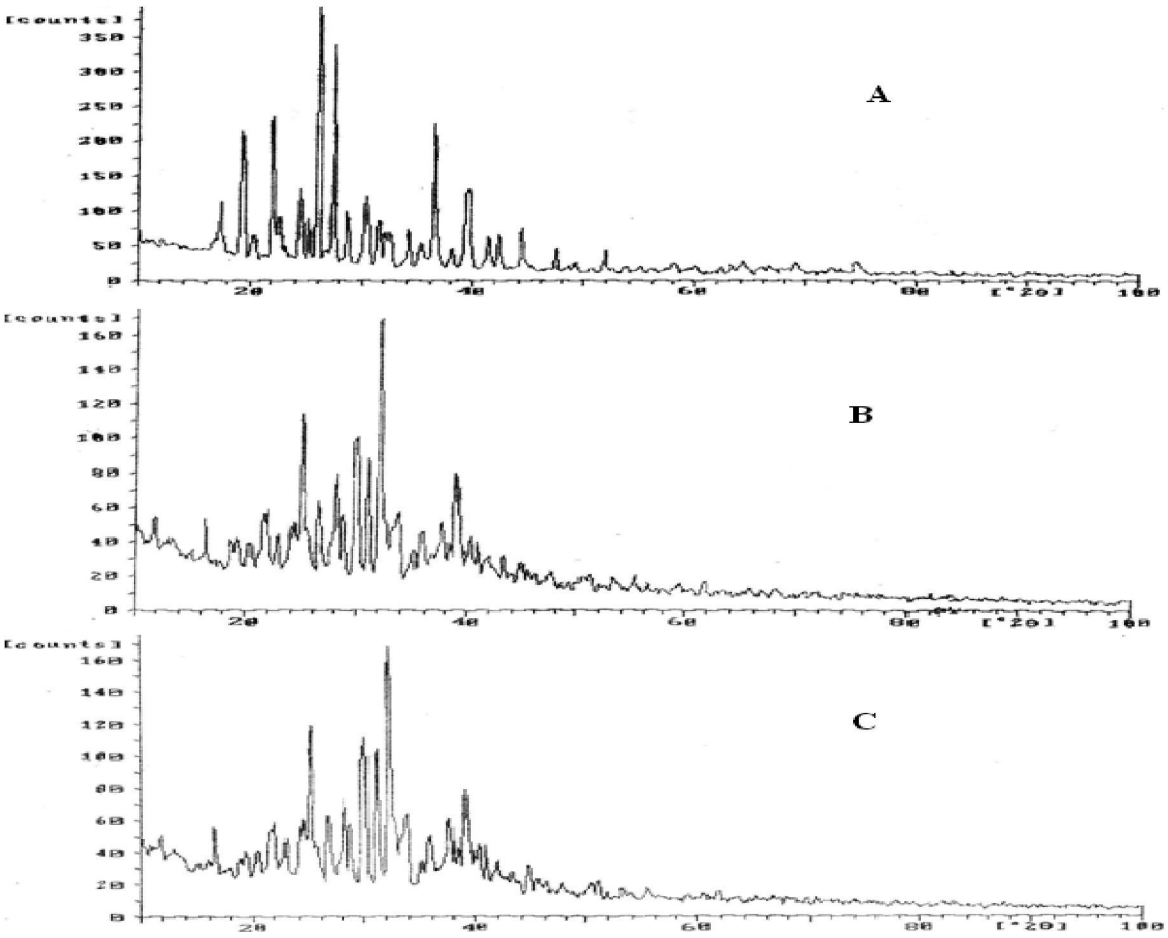


Figure 4 .PXRD patterns of A: CAR, B: CA-0, C: CI-1

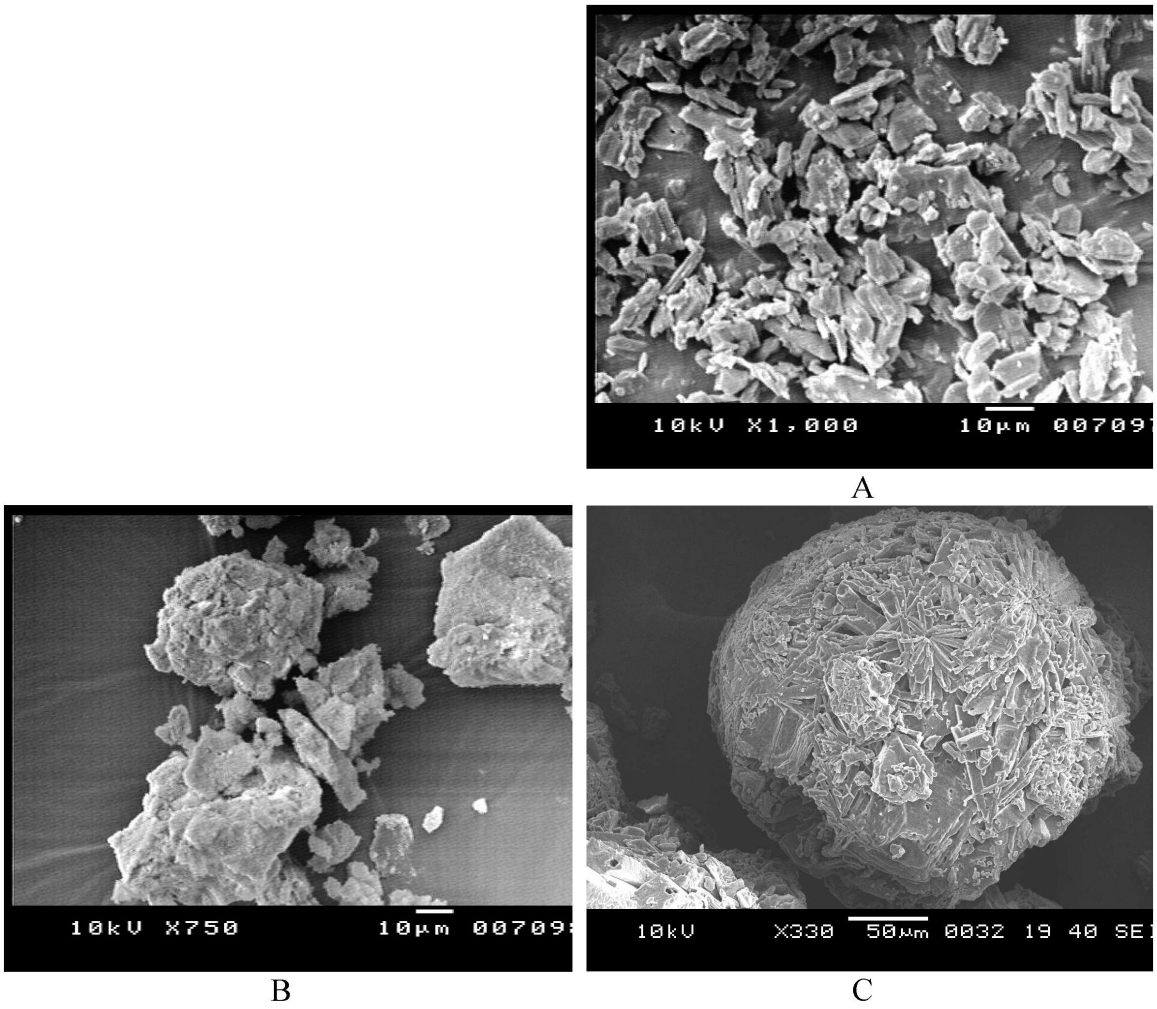


Figure 5. SEM images of A: CAR, B: CA-0, C: CI-1

Dissolution rate studies

The dissolution curves of untreated carvedilol and its spherical agglomerates in 0.1 N HCl (pH 1.2) are shown in fig. 5. The release rate profiles were expressed as the percentage drug released vs. time. Table 2 shows % 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 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 1% w/v Inutec SP1 (CI-1) caused significant increase ($P<0.05$) 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, Inutec SP1, which is a polymeric surfactant with a high HLB value, hence its solubility in a lipophilic or a hydrophobic phase is extremely low. Due to the polymeric character, this type of surfactant tends to form aggregates when dispersed in water, resulting in a slightly turbid solution. However, this means that when an oil or hydrophobic particles are added to an aqueous dispersion of Inutec SP1, the polymeric surfactant will concentrate on the interface between the hydrophobic particles and water, leading to improved wetting and hence dissolution.

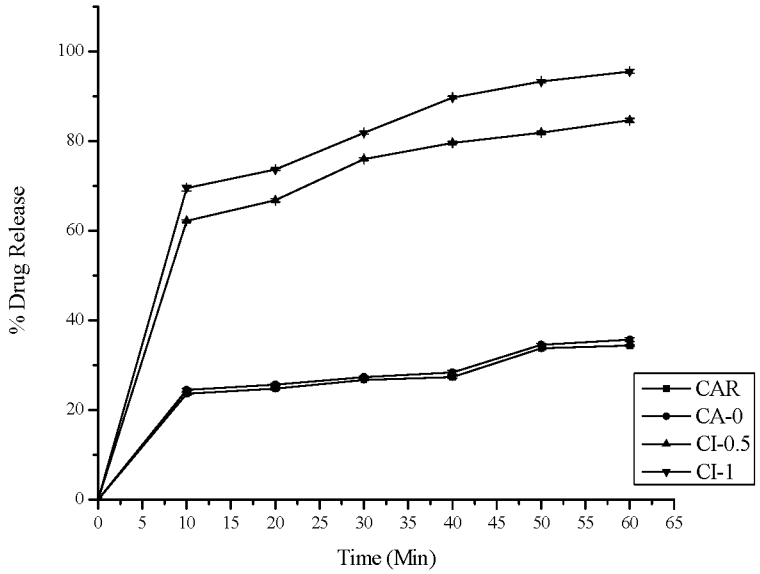


Figure 6. Dissolution curves of carvedilol alone and its spherical agglomerates

CONCLUSIONS

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 formation. In the present investigation Inutec SP1 has significantly improved dissolution rate of carvedilol. Therefore this technique can be exploited to obtain agglomerates for tabletting. 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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