Employment of Spray Drying As An Impending Particle Engineering Tool For Development of Solid Dispersion of Carvedilol

Sharwaree R. Hardikar[1*], **Sunil K. Jena**[2] , **Ashok V. Bhosale**[3]
[1]HOD and Associate Professor, P. G. Scholar[2] , Professor and HOD[3], Department of Pharmaceutics
PDEA'S Seth Govind Raghunath Sable College of Pharmacy, Saswad, Pune - 412301, Maharashtra, India.

Corresponding Author:
Dr. Sharwaree R. Hardikar
E-mail: sharwareehardikar@gmail.com

Submission: 23.12.2018 Acceptance: 05.01.2019 Publication:15.02.2019

https://www.doi.org/10.63778/PDEASIJRAAS-ARJCPL/2019_2153

Abstract:

Carvedilol (CAR) belongs to Biopharmaceutics Classification System (BCS) class II and hence there is strong need of improvement in its dissolution characteristics. The widely accepted approach to achieve this is the preparation of solid dispersion (SD) of CAR. The objective of the present investigation was to improve the dissolution rate of CAR, through thermodynamically stable solid dispersion. Since instability of physical form of SD is major hurdle in its commercial application: spray drying method was used to prepare SD of CAR. The SDs prepared in various compositions was found to be stable when exposed to 40ºC and 75% relative humidity for 3 months. Physicochemical characterization and dissolution study of SD at the end of stability studies clearly indicated that stability of SD was due to hydrogen bonding between drug and poloxamer 188 and HPMC E-5. This bonding remained unaffected even under stressful conditions of high temperature and humidity. These facts were further supported by significant improvement in dissolution efficiency of SD at t15min as compared to pure drug even at the end of stability studies.

Key Words: Carvedilol, Solid dispersion, Hydroxypropylmethylcellulose E-5, Poloxamer 188, Stability.

Introduction:

Amorphous drugs are advantageous over their crystalline counterparts with higher solubility, faster dissolution rate and hence better bioperformance(1) but are relatively less stable or unstable than crystalline forms.(2) Drug-polymer solid dispersion has been demonstrated as a feasible approach to formulate poorly water soluble drugs in the amorphous form.(3) Manufacturing technique adopted in the preparation of solid dispersion has great influence on physicochemical properties of the product. Spray drying is one of the most commonly used procedures in the production of solid dispersions to obtain directly compressible material with highest degree particle size control.(4) However application of spray drying technique to low Tg drugs is limited because of possibility of formation of cohesive supercooled liquid and hence poor dissolution at 37 ºC.(5) Pokharkar et al suggested ternary solid dispersion system of low Tg drug, if spray drying has to be adopted as manufacturing process. Here ternary system comprises of low Tg drug, suitable polymer with high Tg and an adsorbant.

Carvedilol (CAR) is a nonselective β-adrenergic blocking agent with α1-blocking activity. It is widely used to treat hypertension and congestive heart failure. It is a white, non-hygroscopic, crystalline powder that is practically insoluble in water. (6) Such drugs after oral administration often show dissolution as the rate limiting step for their in vivo absorption and the appearance of the pharmacological effect.

In the present study, along with carvedilol (a low Tg drug) hydroxypropylmethylcellulose E-5 (HPMC E-5) was selected as a carrier (for elevation of Tg of ternary solid dispersion. Such carrier is also reported to reduce the chances of recrystallinity of a drug due to drug entrapment in carrier matrix and hence decreased drug mobility as the solvent is removed during spray drying. (5) Poloxamer 188 was selected not only as surfactant but also as a third generation carrier. Third generation carriers are known to stabilize solid dispersion avoiding recrystallization. Other expected advantages of inclusion of poloxamer 188 as one the component of ternary system was to obtain free flowing drug particles with improved wettability. It was confirmed from the results of differential scanning calorimetry (DSC), Fourier - transform infrared spectroscopy (FT-IR), X-ray powder diffraction (XRPD), dissolution studies and stability studies as per ICH guidelines that stable spray dried solid dispersion of carvedilol was obtained partially due to formation of hydrogen bonds between drug and both the polymers i.e. HPMC E-5 and poloxamer 188 and possibility due to low molecular mobility of amorphous carvedilol in carrier matrix.

2. Material And Methods:

2.1 Materials:

Carvedilol was received as a gift sample from Cipla, Kurkumbh, India. Hydroxypropyl- methylcellulose (HPMC E-5) and Poloxamer 188 were kindly provided by Colorcon, Goa, India and BASF Corporation, New jersey, USA respectively. All other chemicals and solvents were of reagent grade and used without further purification.

2.2 Methods:

2.2.1 Preparation of spray dried solid dis persion of Carvedilol

Spray dried solid dispersions of Carvedilol, HPMC E5 and poloxamer 188 were prepared in various ratios as given in Table 1 by using ethanol: water (8:2 v/v) as a solvent system. To prepare solid dispersions by spray drying method, carvedilol was dissolved in ethanol and HPMC E5 and poloxamer 188 were dissolved in water, the final homogenous solution was prepared by mixing the two solutions. Spray drying was carried out using laboratory scale spray dryer (Labultima LU 222 advanced) under following set of conditions: Inlet temperature: 115°C; outlet temperature: 54-56°C; feed rate: 10 mL/min; atomization air pressure: 35psi and aspiration: 40mmWC. All spray dried solid dispersions were dried in desiccators with blue silica gel before their physicochemical properties were tested as mentioned below.

Table 1
Composition of the solid dispersions of carvedilol

Formulation code	Drug (Carvedilol)	Poloxamer 188	HPMC E-5
S1	1	1	2
S2	1	1.5	2
S3	1	2	2
S4	1	1	3
S5	1	1.5	3
S6	1	2	3
S7	1	1	4
S8	1	1.5	4
S9	1	2	4

2.2.2 preparation of physical mixtures (PMs)

Physical mixtures in the same ratios were prepared by physically mixing drug and excipients thoroughly for 10 min in a mortar until a homogenous mixture was obtained. All the samples were passed through fine mesh (120µm) and stored in desiccated environment until further study.

2.2.3 Determination of percent yields:

The percent yield of each spray dried solid dis- persion was determined according to the total recoverable final weight of micro particles and the total original weights of carvedilol, polox- amer 188 and HPMC E-5.

2.2.4 Drug content:

Solid dispersions equivalent to 10mg of carvedilol were weighed accurately and dissolved in 10mL of methanol to extract the drug. From the above solution aliquot of 0.1mL was withdrawn and transferred to 10mL volumetric flask and the volume was adjusted upto the mark with methanol. After filtration through Whatman filter paper no.41, concentra- tion of carvedilol was determined at 240.6 nm by UV-spectrophotometer (V-630, JASCO, Japan) against the blank solution of methanol.

2.2.5 Dissolution study:

The dissolution studies were performed using USP 24 type II dissolution test apparatus (ElectrolabTDT-08L, India). The samples equivalent to 12mg carvedilol were placed in dissolution vessel containing 900mL phosphate buffer (pH 6.8) maintained at 37 ± 0.5°C and stirred at 50rpm. Aliquots of sample were collected periodically and replaced with a fresh dissolution medium. After filtration through Whatman filter paper no.41, concentration of carvedilol was determined spectropho-tometrically at 240.6 nm. The samples of spray dried solid dispersions of composition specified in Table 1 and physical mixtures of drug and polymers used in solid dispersion in the same proportion as reported in Table 1 were compared for dissolution behavior.

2.2.6 Fourier - transform Infrared spectroscopy (FT-IR):

Fourier-transform infrared (FT-IR) spectra of carvedilol and solid dispersion of carvedilol with poloxamer 188 and HPMC E-5 (spray dried) were obtained using IR spectrophotome- ter (Shimadzu, FTIR-8400S, Japan). The samples were scanned over the wave number range from 4000 to 400 cm–1.

2.2.7 Scanning electron microscopy (SEM):

Microscopic observations of carvedilol and solid dispersion (S9) were performed using a scanning electron microscope (SEM, JEOL JSM-6360A, Tokyo, Japan) at an acceleration voltage of 10kV. Samples were sputtered (JEOL JFC-1600 Auto fine coater, Tokyo, Japan) with gold-palladium and then observed at different magnifications.

2.2.8 Differential scanning calorimetry (DSC):

The DSC patterns were recorded on a METTLER TOLEDO (Stare SW 920). Each sample (2-4mg) of solid dispersion (S9) was heated in crimped aluminum pans with a pierced lid at a scanning rate of 5ºC/min in an atmosphere of nitrogen gas purge (40mL/min) using the range of 40-200ºC. The DSC was calibrated for baseline using empty pans, and for temperature and enthalpy using indium.

2.2.9 X-ray powder diffraction (XRPD):

The XRPD patterns of samples were recorded on X-ray diffractometer (PW 1729, Philips, Netherlands). The source was a Cu Kα 1 tube (wavelength 1.5406 Å) at 40 kV and 40 mA. The samples were scanned from 2° to 40° 2θ at a scan rate of 0.1° 2θ per min. The time per step was 1 min and the step size was 0.1° 2θ.

2.2.10 Stability study of solid dispersion (S9) as per ICH guidelines:

The accelerated stability of SD 1:2:4 (Carvedilol : Poloxamer188:HPMC E-5) was checked as per ICH guidelines at 40°C/75% RH upto 3 months. Samples were characterized by using XRPD and DSC techniques for the degree of crystallinity and FT- IR to study the effect of moisture on H-bonding after a period of 15 days, 1 month, 2 months and 3 months. The dissolution study was also performed after a period of 3 months.

3. Results And Discussion:

3.1 Characterization of solid dispersions for various physicochemical properties

The percentage yields of the spray dried solid dispersions of carvedilol were found to be in between 55% to 60 %. Such small yield for the solid dispersion was considered to be acceptable for small scale spray drier as a result of inability of the cyclone separator to trap particles smaller than 2μm and adherence of these particles to the inner wall of the spray drier.(7,8) The drug content of each batch of spray dried solid dispersions (S1 to S9) of carvedilol was found to be above 99%. It is reported in Table 2. Moreover it was found that as the concentration of poloxamer 188 increased the percentage drug content was increased possibly due to the inhibition of the formation of super cooled rubbery state avoiding sticking of the product to the inner walls of spray dryer. Earlier it was reported that in case of low Tg drug, it is very difficult to obtain stable amorphous product in the form of a free flowing powder by spray drying. As the outlet temperature rises above the Tg, there is always a possibility that the final product is present in the supercooled rubbery state. Also such product is often sticky or tacky, which causes decrease in product recovery and hampers handling in subsequent processes.(9) The results of dissolution studies of plain drug, spray dried solid dispersions of drug and physical mixtures of drug and polymers used in preparation of spray dried solid dispersions are reported in Table 3.

Table 2
Percentage Yield and drug content of individual spray dried solid dispersion

Sr. No.	Formulation codes	% Yield	% Drug Content*
1	S1	56.72	99.39 ± 1.09
2	S2	58.24	99.54 ± 1.21
3	S3	57.28	101.01 ± 0.19
4	S4	55.73	99.72 ± 1.19
5	S5	58.56	99.84 ± 1.12
6	S6	57.67	100.1 ± 0.17
7	S7	58.57	99.87 ± 1.21
8	S8	57.48	99.58 ± 1.10
9	S9	59.58	99.97 ±1.08

***All values are expressed as Mean ± SD, (n - 3)**

Table 3
Results of dissolution studies of crystalline drugs, physical mixtures of crystalline drug and polymers used in preparation of solid dispersions and solid dispersions

Formulation codes	Ratio of Drug Poloxamer 188 : HPMC E-5	Form	Q10 (n = 3)	Q60 (n = 3)	Dissolution rate increase	
					Q10	Q60
-	-	Crystalline Carvedilol	15.0 ± 3.8	32 ± 4.2	-	-
S1	1 : 1 : 2	Physical mixture	24.8 ± 2.9	32.9 ± 3.8	1.65	1.02
		Solid dispersion	64.2 ± 1.5	86.0 ± 1.9	4.28	2.68
S2	1 : 1. 5 : 2	Physical mixture	41.5 ± 3.2	47.9 ± 2.7	2.77	1.5
		Solid dispersion	86.2 ± 2.9	99.6 ± 1.3	5.74	3.11
S3	1 : 2 : 2	Physical mixture	45.3 ± 3.5	48.1 ± 3.4	3.02	1.5
		Solid dispersion	85.02 ± 2.3	99.7 ± 1.1	5.68	3.11
S4	1 : 1 : 3	Physical mixture	46.2 ± 2.1	50.3 ± 1.9	3.08	1.57
		Solid dispersion	85.6 ± 3.8	99.7 ± 1.2	5.7	3.11
S5	1 : 1 : 5 : 3	Physical mixture	40.0 ± 2.9	46.4 ± 1.8	2.67	1.45
		Solid dispersion	64.9 ± 2.8	87.8 ± 1.6	4.32	2.74
S6	1 : 2 : 3	Physical mixture	43.4 ± 3.3	48.9 ± 2.5	2.89	1.52
		Solid dispersion	72.1 ± 3.1	89.4 ± 2.1	4.8	2.79
S7	1 : 1 : 4	Physical mixture	50.1 ± 2.7	53.9 ± 2.6	3.34	1.68
		Solid dispersion	93.5 ± 1.3	100.8 ± 0.5	6.23	3.15
S8	1 : 1 : 5 : 4	Physical mixture	48.8 ± 3.9	51.1 ± 4.3	3.25	1.59
		Solid dispersion	90.5 ± 2.1	99.9 ± 1.1	6.03	3.12
S9	1 : 2 : 4	Physical mixture	54.2 ± 1.2	55.7 ± 2.2	3.61	1.74
		Solid dispersion	99.3 ± 2.9	100.6 ± 0.9	6.62	3.15

Dissolution profiles of all solid dispersions showed considerable increase in dissolution rate compared with the physical mixture and crystalline drug. Solid dispersion of drug: poloxamer 188: HPMC E5 in a ratio of 1:2:4 showed a 6.6 fold increase in drug release (99.3%) at 10 min as compared to drug alone (15%). Solid dispersions S7 (1:1:4), S8 (1:1.5:4) and S9 (1:2:4) showed maximum dissolution as 93.5%, 90.5% and 99.3% respectively at 10 min as compared to other solid dispersions. The possible reason for this including the presence of an amorphous drug, might be decreased drug particle size up to the molecular level and relatively strong hydrogen bonding between the drug and poloxamer 188 and drug and HPMC E5. The increase in hydrogen bonding may limit the rapid loss of HPMC E5 from the spray dried particles due to the hydrophobization of hydrophilic polymer which was described by Van Drooge.(10) Van Drooge explained the concept of hydrophobiza- tion in which due to the formation of hydrogen bonding between the drug and PVP; there was negligible loss of PVP from the spray dried particles and decreased water vapor uptake by the glass solution compared to physical mixture. It was worthy to note that a slight increase in poloxamer concentration did not revealed a significant change in dissolution rate of drug from the spray dried solid dispersion of carvedilol. The FT-IR spectrum of carvedilol along with FT-IR spectrum of solid dispersion of carvedilol prepared by kneading with poloxamer 188; solid dispersion of carvedilol prepared by kneading with HPMC

E5 and spray dried solid dispersion (S9) are shown in Fig. 1, Fig. 2 and Fig. 3 respectively. The FT-IR spectra of crystalline carvedilol showed a characteristic peak at 3346.61cm-1 (N-H stretching). In comparison, the spectra of solid dispersion of drug with poloxamer 188 (Fig. 1), solid dispersion of drug with HPMC E5 (Fig. 2) and spray dried solid dispersion of drug with HPMC E5 and poloxamer 188 (Fig. 3) exhibited a significant change at 3346.61 cm-1, related to weakening or removal of the N-H stretching. The disappearance of N-H stretching in all the specified figures of solid dispersions of Carvedilol was a strong evidence of H-bonding between the drug and both the polymers via the secondary amine group of carvedilol. The presence of H-bonding has been also linked to the physical stability of amorphous dispersions.(11)

Figures and Tablels

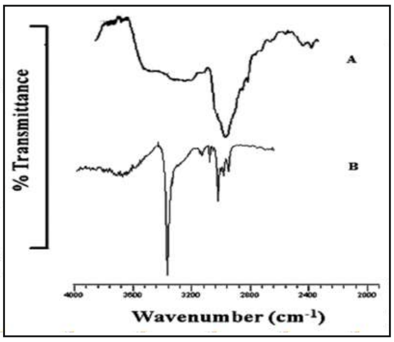

Fig. 1. FT-IR spectrum of A) solid dispersion of carvedilol prepared by kneading with poloxamer 188; B) Crystalline carvedilol

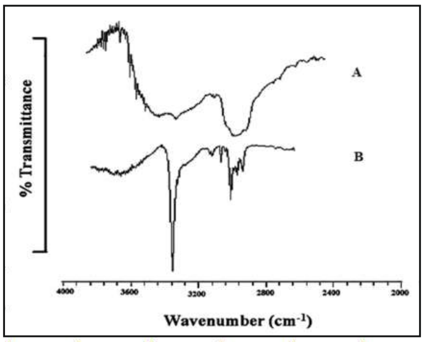

Fig. 2. FT-IR spectrum of A) solid dispersion of carvedilol prepared by kneading with HPMC E5; B) Crystalline carvedilol

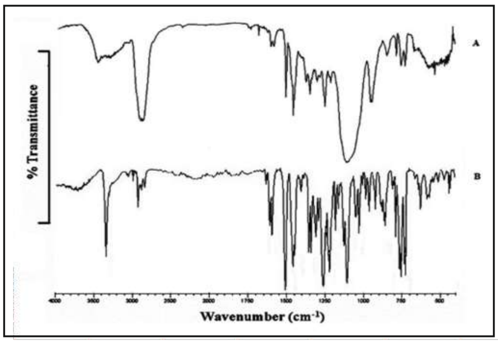

Fig. 3. FT-IR spectrum of A) Spray dried solid dispersion of carvedilol with HPMC E5 and poloxamer 188 (S9);B) Crystalline carvedilol

Taylor and Zografi have reported that hydrogen bond interactions can occur in mixtures of amorphous oligosaccharides and PVP between the sugar hydroxyl groups and the polymer carbonyl group.(12) Since HPMC E5 is a partially substituted polysaccharide and given the presence of unsubstituted hydroxyl groups on the cellulose chain as well on the hydroxypropyl substituent groups(13), it seems to be reasonable to conclude that HPMC E5 may interact with carvedilol to form H-bond. Ether oxygen of polyethylene oxide (PEO) block of poloxamer 188 forms H-bond with water molecules which are responsible for its water solubility.(14) Hence, it seems to be rea- sonable to conclude that poloxamer 188 may interact with carvedilol to form H-bond.

Scanning electron microscopy (SEM) of the pure drug carvedilol and spray dried solid dispersion were carried out to study the surface morphology. SEM of pure carvedilol appears as crystalline structure, almost rectangular in shape (Fig. 4 A) with particle size in a range of 5-10µm whereas the SEM of solid dispersion (Fig. 4 B) showed significant

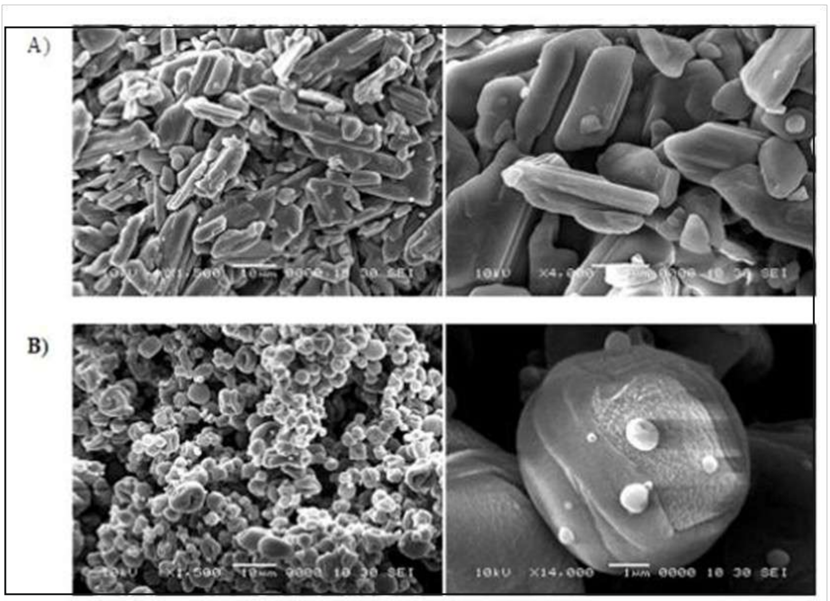

Fig. 4. Scanning Electron Microscopy images of A) crystalline Carvedilol; B) Spray dried solid dispersion (S9)

changes in particle shape and surface topography. Particles appeared as almost spherical shaped with surface smoothness indicating the complete miscibility of drug and polymer with an amorphous nature. Moreover the particle size reduced to 1μm resulted in increased surface area which might be responsible for the enhanced dissolution rate of the drug from the solid dispersion. DSC thermogram of crystalline carvedilol (Fig. 5) exhibited a melting endotherm at 119°C, with an enthalpy of fusion of 58.05 J/g. The spray dried solid dispersion exhibited a broad weak endotherm at 49-52°C corresponding to melting transition of poloxamer 188 and at 50-100°C due to water dehydration with no evidence of a drug melt (Fig. 5). This clearly indicated the existence of amorphous state of the drug after spray drying, which was also confirmed by XRPD. XRPD was used to determine the crystallinity of the solid dispersions. The X-ray diffractograms of the solid dispersion was compared with those of crystalline drug and physical mixture of drug with HPMC E5 and poloxamer 188. Carvedilol had characteristic peaks occurring at 2θ angles of 14.8°, 24.3°, 24.4°, and 26.2°. From Fig. 6, it was observed that the peaks were apparent in XRPD of both the physical mixtures and pure drug substances, but absent in the diffractograms of the solid dispersion. Poloxamer 188 had two distinct bands occurring at 19.3° and 23.6°.(15) From Fig. 6, it was observed that the intensity of these two distinct bands were decreased which revealed a partial amorphisation of the polymer also. This confirmed that the drug was present in the solid dispersion in its amorphous state.

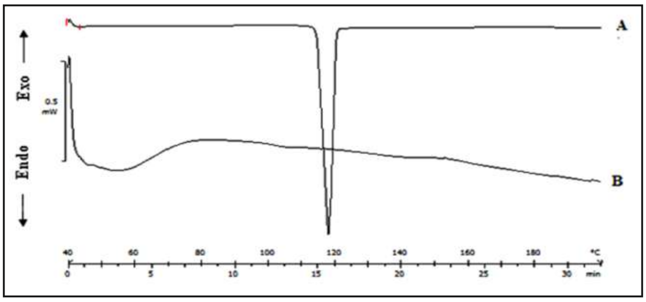

Fig. 5. DSC thermogram of A) crystalline Carvedilol; B) initially prepared spray dried solid dispersion (S9).

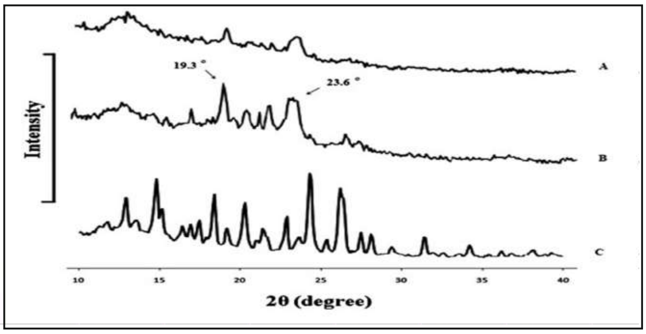

Fig. 6. Powder X-ray diffraction patterns of A) Spray dried solid dispersion (S9); B) physical mixture of drug with HPMC E5 and poloxamer 188; C) crystalline carvedilol.

3.2 Physical stability of solid dispersion (S9):

Recrystallization is the major disadvantage of solid dispersions. As amorphous systems, they are thermodynamically unstable and have the tendency to change to a more stable state after recrystallization. Hence in the present study, accelerated stability studies were performed at 40ºC/75% RH as per the ICH guidelines to confirm the stability of amorphous form of solid dispersion. Solid dispersion in a ratio of 1:2:4 (Drug: Poloxamer 188: HPMC E-5) was selected based on the dissolution study data to study the physical stability of the spray dried solid dispersion of carvedilol.

There was insignificant decrease in in vitro drug release (Fig. 7) after a period of 3 months (from about 100.9% to around 98.83% drug dissolution at the end of 60 min). The possible reason might be the stability of intermolecular hydrogen bonding between the drug and polymers (HPMC E5 and Poloxamer 188).

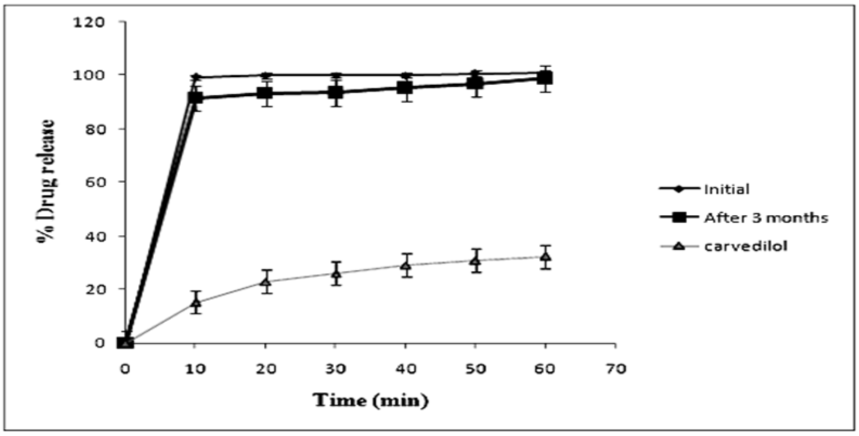

Fig. 7. Dissolution profiles of crystalline carvedilol and spray dried solid dispersion (S9) (initial and after 3 months)

From Fig. 8 it was clear that disappearance of characteristic peak at 3346.61cm-1 (N-H stretching) in all the FT-IR spectra of solid dispersion (S9) recorded at various time intervals during stability study; hydrogen bonding between drug and polymers was intact.

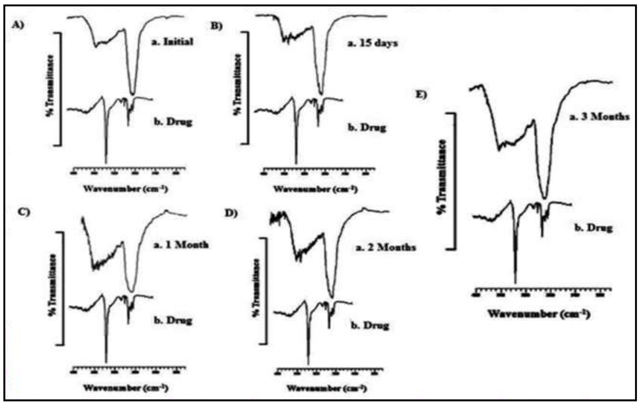

Fig. 8. FTIR spectra of different samples of carvedilol taken at different time intervals
A) a. Spray dried solid dispersion (S9) initial:
b. crystalline carvedilol;
B) a. Spray dried solid dispersion (S9) after 15 days:
b. crystalline carvedilol;
C) a. Spray dried solid dispersion (S9) after 1 month:
b. crystalline carvedilol;
D) Spray dried solid dispersion (S9) after 2 months:
b. crystalline carvedilol;
a. Spray dried solid dispersion (S9) after 3 months:
b. crystalline carvedilol

From the XRPD diffractograms (Fig. 9) it was observed that the characteristic peaks of carvedilol were absent from the diffractograms of the solid dispersion even after a period of 3 months. This revealed that the drug remained in amorphous form in the spray dried solid dispersion of carvedilol which was further supported by DSC studies.

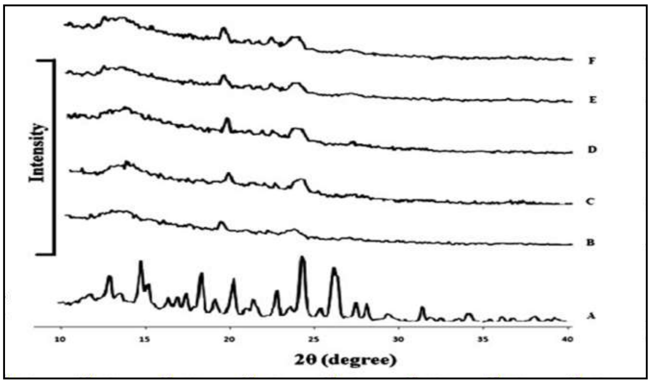

Fig. 9. XRPD patterns of different samples of carvedilol
A) crystalline carvedilol;
B) Spray dried solid dispersion (S9) initial;
C) Spray dried solid dispersion (S9) after 15 days;
D) Spray dried solid dispersion (S9) after 1 month;
E) Spray dried solid dispersion (S9) after 2 months;
Spray dried solid dispersion (S9) after 3 months

Absence of endothermic peak of carvedilol in solid dispersion (S9) initially and even at the end of 3 months stability testing period suggested molecular dispersion of carvedilol in HPMC E5 and poloxamer 188 throughout the testing period. This fact proved that the polymer mixture of HPMC E5 and poloxamer 188 prevented crystallization of carvedilol (Fig. 10).

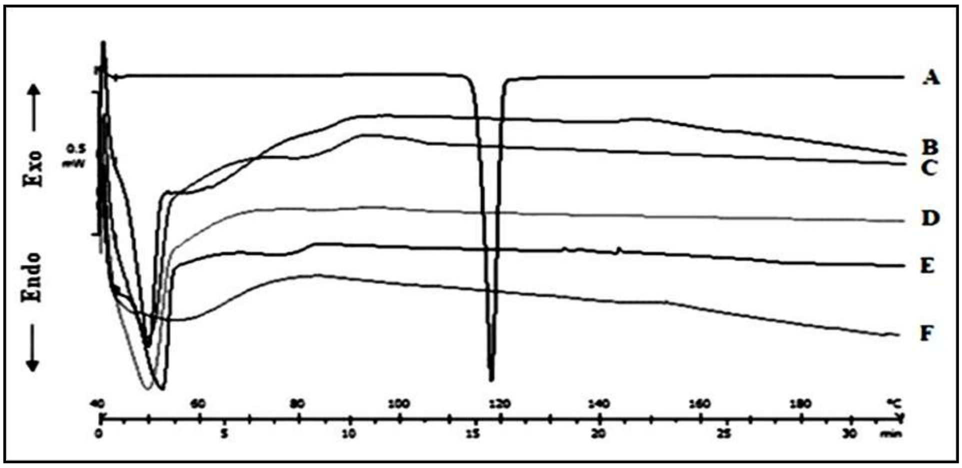

Fig. 10. DSC thermograms of different samples of carvedilol
A) Crystalline carvedilol;
B) Spray dried solid dispersion (S9) after 3 months;
C) Spray dried solid dispersion (S9) after 2 months;
D) Spray dried solid dispersion (S9) after 1 month;
E) Spray dried solid dispersion (S9) after 15 days;
F) Spray dried solid dispersion (S9) initial.

Conclusion:

Spray dried solid dispersion of carvedilol with HPMC E5 and poloxamer 188 showed appreciably good release profile of drug as compared to physical mixture and drug alone. XRD and DSC studies revealed that the drug was stable in its amorphous form in the spray dried solid dispersion. The spray dried particles exhibited excellent micromeritic properties as expected in all the samples. Moreover the surface morphology of the particles showed smooth surface indicating complete or perfect miscibility of drug and polymer to form uniform solid dispersion.Amorphous material tends to change to a more stable polymorph during storage. However, the noted hydrogen bonding between the drug and the excipients had a stabilizing effect on the solid dispersions. This might had hindered the phase transitions to more stable polymorphs. Very slight decrease in dissolution was observed with no evidence of crystallinity during accelerated stability studies of S9. Thus, mouth dissolving or sublingual tablet dosage form prepared by using this solid dispersion may give promising results as the absorption of CAR is well reported through oral and epigastric region.

Acknowledgements:

The authors would like to express their gratitude to Seth Govind Raghunath Sable College of pharmacy, Saswad for providing necessary facilities to carry out this research work.

Source of Support: Nil

Conflict of Interest: Nil

References:

1. Martin A. Physical Pharmacy, Fourth ed., Williams and Wilkins, Baltimore 1993.
2. Serajuddin A. 1999. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs, Journal of Pharmaceutical Sciences. 88 : 1058-1066.
3. Patterson JE, James MB, Forster AH, Lancaster RW, Butler JM, Rades T. 2007. Preparation of glass solutions of three poorly water soluble drugs by spray drying, melt extrusion and ball milling, International Journal of Pharmaceutics. 336: 22-34.
4. Elversson J, Fureby AM.2005. Particle size and density in spray drying-effects of carbohydrate properties, Journal of Pharmaceutical Sciences. 94 : 2049-2060.
5. Pokharkar VB, Mandpe LP, Padamwar MN, Ambike AA, Mahadik KR, Paradkar AR, 2006. Development, characterization and stabilization of amorphous form of a low Tg drug, Powder Technology. 167 : 20–25.
6. Company literature on COREG® (Carvedilol) Tablets. GlaxoSmithKline, NC, USA, pp. 1–2.
7. Maa YF, Nguyen PA, Sit K, Hsu CC. 1998. Spray drying performance of bench-top spray dryer for protein aerosol powder preparation. Biotechnology and Bioengi- neering. 60: 301-309.
8. Maury M, Murphy K, Kumar S, Shi L, Lee G. 2005. Effects of process variables on the powder yield of spray-dried trehalose on a laboratory spray-dryer. European Journal of Pharmaceutics and Biopharmaceutics. 59 : 565-573.
9. Ambike AA, Mahadik KR, Paradkar AR. 2005. Physico-chemical characterization and stability study of amorphous simvastatin. Drug Development and Industrial Pharmacy. 31: 895–899.
10. Drooge DJV, Hinrichs WLJ, Visser MR, Frijlink HW. 2006. Characterization of the molecular distribution of drugs in glassy solid dispersions at the nano-meter scale, using differential scanning calorimetry and gravimetric water vapour sorption techniques. International Journal of Pharmaceutics. 310: 220–229.
11. Taylor LS, Zografi G. 1997. Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersion systems. Pharmaceutical Research. 14 : 1691- 1698.
12. Taylor LS, Zografi G. 1998. Sugar-polymer hydrogen bond interactions in lyophilized amorphous mixtures Journal of Pharmaceutical Sciences. 87 : 1615-1621.

13 Nyamweya N, Hoag SW. 2000. Assessment of polymer-polymer interactions in blends of HPMC and film forming polymers by modulated temperature differential scanning calorimetry. Pharmaceutical Research. 17 (5) : 625-631.

14. Schmolka IR. 1991. Poloxamers in the pharmaceutical industry, In: P.J. Tarch (Eds.), Polymers for controlled drug delivery, Boca Raton, FL, CRC Press. 1991. pp. 189-215.
15. Andrews GP, Zhai H, Tipping S, Jones DS.2009. Characterization of the thermal, spectroscopic and drug dissolution properties of mefenamic acid and polyoxyethylene - polyoxypropylene solid dispersions. Journal of Pharmaceutical Sciences. 98: 4545-4556.