INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

FORMULATION AND EVALUATION OF SOLID DISPERSIONS OF CARVEDILOL, A POORLY WATER SOLUBLE DRUG BY USING DIFFERENT POLYMERS

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ABSTRACT

The objective of the study was to formulate and evaluate as well as to improve the aqueous solubility and dissolution of carvedilol, a poorly water soluble antihypertensive drug by solid dispersion technique. Polyethylene glycol (PEG 6000), poloxamer 407, hydrory propyl methyl cellulose (HPMC) 6cps and Na-starch Glycolate (SSG) were used as carrier polymers. Solid dispersion of carvedilol was prepared by both fusion and solvent evaporation method. Drug release was studied by the USP basket method at 75 rpm and 37±0.5°C by using 0.1 N HCl solution as dissolution medium. percent drug release was measured from the UV absorbance at 284 nm. The study shows that all the polymers enhanced the release profile of carvedilol. The drug release data were fitted to different kinetic models and formulations followed the Higuchi model. FT-IR spectra of carvedilol and solid dispersion indicated no interaction between carvedilol and polymers. Solid dispersion technique may be used to enhance the dissolution as well as absorption of poorly water soluble drug carvedilol.

Keywords: Solid dispersion, carvedilol, dissolution, bioavailability.

INTRODUCTION

Carvedilol is a novel, multiple-action cardiovascular drug that is currently approved in many countries for the treatment of hypertension. The reduction in blood pressure, produced by carvedilol, results primarily from beta-adrenoceptor blockade and vasodilation, the latter resulting from alpha 1-adrenoceptor blockade.[1-3]

Much of the research that has been reported on solid dispersion technologies involves drugs that are poorly water-soluble and highly permeable to biological membranes as with these drugs dissolution is the rate limiting step for absorption. Hence, the rate of absorption will be concurrently accelerated with an increase in the rate of drug dissolution. In the Biopharmaceutical Classification System (BCS) drugs with low aqueous solubility and high membrane permeability are categorized as Class II drugs. Therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs. [4]

Solid dispersion, which was introduced in the early 1970s,[5] is essentially a multi-component system, having drug dispersed in hydrophilic carrier(s). Solid dispersion technique has been used for a wide variety of poorly aqueous soluble drugs such as nimesulide, ketoprofen, tenoxicam, nifedipine, nimodipine, ursodeoxycholic acid and albendazole. Various hydrophilic carriers, such as polyethylene glycols, polyvinylpyrrolidone, hydroxypropylmethylcellulose, gums, sugar, mannitol and urea have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous-soluble drugs. Solid dispersion can be prepared by various methods such as solvent evaporation and melting method. Solid dispersion technique has been extensively used to increase the

solubility of a poorly water-soluble drug. In this technique, a drug is thoroughly dispersed in a water-soluble carrier by different methods. In Solid dispersion the particle size of drug is reduced to submicron size or to molecular size.[9] The particle size reduction generally increases the rate of dissolution; secondly, the drug is changed from crystalline to amorphous form, the high energetic state which is highly soluble; finally, the wettability of the drug particle is improved by the dissolved carrier.[6-7] In the present investigation, solvent evaporation and melting methods were employed for the preparation of carvedilol solid dispersions. The carriers used were polyvinyl pyrrolidone (PVP) K-30, polyethylene glycol (PEG) 4000 and PEG 6000. The samples were prepared at various drug-to-carrier weight ratios.[8]

MATERIALS AND METHODS

Materials

Carvedilol (Xamim, China), Poloxamer 407 (MERCK, Germany), HPMC 6cps (Samsung, Korea), HPMC 15 cps (MERCK, Germany), Sodium Starch Glycolate (Samsung, Korea), PEG 6000 (MERCK, Germany), paraffin liquid (MERCK, India) etc.

Methods

Preparation of solid dispersion by solvent evaporation method

Carvedilol and polymer were weighed accurately according to Table 1 and taken into dry and clean glass vials. 1 ml methanol was added on each vial. Then drug and polymer were dissolved in the solvent using a vortex mixer. Solvent was then evaporated by using hot air dryer until dry powder was formed. The formulations were withdrawn from vials, crushed and passed through 40 mesh sieves. Then the resulted samples were weighed and vials with proper labeling and its double amount of lactose was added on each vials and mixed well. Formulations were packed in vials with proper labeling and stored in desiccators until further study.

Preparation of solid dispersion by fusion method

Accurately weighed carvedilol and polymer taken in glass vial according to Table 1. Vials were heated at 120°C to melt the ingredients. Then drug and polymer combination was cooled with constant stirring to disperse the drug throughout the mixture homogeneously. Finally the formulations were withdrawn from vials, crushed in mortar and pestle, passed through 40 mesh sieves. The resulted samples were weighed and transferred to fresh vials with proper labeling and were kept in desiccators until further study.

Preparation of solid dispersion by physical mixing method

Accurately weighed carvedilol and polymer taken in glass vial according to Table 1. The physical mixing was carried out by means of shaking the vials slowly and then the mixture was poured in the wax paper and mixed by the help of a spatula. Finally, the mixture was passed through 40 mesh sieve. After mixing well, the formulations were kept in desiccators until further study.

In vitro dissolution study of carvedilol from solid dispersion

In vitro dissolution study was performed in a paddle type dissolution apparatus (USP apparatus II). Accurately weighted solid dispersion containing 20 mg carvedilol from each batch were used for dissolution study. 0.1 N hydrochloric acid solution was used as dissolution medium at a temperature of 37 ± 0.5°C and a paddle speed was 75 rpm. Dissolution study was carried out for 60 min and 10 ml sample was withdrawn at predetermined intervals of 5, 10, 15, 20, 30, 40, 50 & 60 min. The sink condition was maintained by adding 10 ml fresh medium every time. Dissolution samples were filtered with syringe filter (0.45 µm) and analyzed by UV-VIS spectrophotometer (UV-mini-1240, SHIMADZU, Kyoto, Japan) at 284 nm.

Fourier Transform Infrared (FTIR) Spectroscopy studies

To study the interaction between drug and polymers used in the preparation of formulation FT IR spectroscopy was carried out for the test samples. FT IR spectrum of pure carvedilol , solid dispersions and physical mixtures were recorded by using FT-IR 8400S (SHIMADZU, Kyoto, Japan).

Differential scanning calorimetry (DSC) thermograms analysis

The differential scanning calorimetry (DSC) thermograms were recorded for carvedilol, different polymers and solid dispersion using a differential scanning calorimeter (Perkin-Elmer). Approximately 2-5 mg of each sample was heated in an open aluminum pan from 0-400°C at a scanning rate of 10°C/min under stream of nitrogen.

RESULTS AND DISCUSSION

Solid dispersion of carvedilol prepared by both fusion and solvent evaporation method were found stable during preparation. No discoloration was found during heating or storage condition.

In vitro release study of carvedilol from solid dispersion and physical mixture

It was found that the dissolution rate of carvedilol increased with the increasing amount of hydrophilic carriers or polymers in different formulations. This was due to the increase in solubility of drug by the presence of hydrophilic carrier surrounding the drug particle. This may be attributed to the improved wetting of carvedilol in the presence of inter-molecular hydrogen bonding and the hydrogen atom in the hydroxyl group of carvedilol. Percent drug release from physical mixture and solid dispersion has been shown in figure 1 to 4.

From the figure 1, it is clear that as the poloxamer 407 content was increased from 0.02 gm to 0.08 gm, percent of drug release of the formulations were also found to be increased from 5.86% to 34.74%; 9.12% to 42.34% and 10.32% to 49.12% at 60 minutes for physical mixing, fusion and solvent evaporation method respectively whereas drug release was only 4.68% from pure drug at 60 minutes time point.

From the figure 2, it is clear that as the HPMC 6 cps content was increased from 0.02 gm to 0.08 gm, percent of drug release of the formulations were also found to be increased from 11.15% to 28.41%; 50.40% to 60.02% and 58.12% to 65.11% at 60 minutes for physical mixing, fusion and solvent evaporation method respectively.

From the figure 3 and 4, it is clear that as the PEG-6000 and SSG content was increased from 0.02 gm to 0.08 gm, percent of drug release of the formulations were also found to be increased from 13.13% to 41.34% and 22.14% to 39.44%;18.19% to 42.86% and 26.17% to 55.21% and 35.46% to 48.11% and 27.32% to 58.34% at 60 minutes for physical mixing, fusion and solvent evaporation method respectively. The possible reason of increased dissolution rate of carvedilol was the use of hydrophilic polymers for which the wettability and spreadability of the precipitated drug occur by reducing aggregations in the readily soluble state.

The correlation coefficients values of different mathematical model for physical mixing, fusion and solvent evaporation method are presented in the table 2, 3 and 4 respectively. The data showed that formulation of Physical Mixing (F1 to F12), Fusion (F1 to F12) and Solvent evaporation (F1 to F12) method were best fitted in Higuchi release model.

Effect of different excipients on Percent Release of Carvedilol after Five Minutes of Dissolution

Figure 5 to 8 show that only 1.167% carvedilol was released for the first five minutes from pure drug. However the percent release was remarkably increased when different polymers like Poloxomer 407, PEG 6000, HPMC 6 cps and SSG were used in solid dispersion or physical mixture. The percent release for the first five minutes of the formulations F3 were 13.12%, 16.02% and 20.72% for Poloxomer 407; formulations F6 were 8.31%, 31.05% and 42.34% for HPMC 6 cps, formulations F9 were 24.11%, 27.12% and 32.35% for SSG and formulations F12 were 9.11%, 31.22% and 42.67% for PEG-6000 respectively using physical mixing, fusion and solvent evaporation method. As the different polymers content in the formula increased, release rate from the solid dispersion was also increased.

Drug-polymer compatibility study by Fourier Transform Infrared (FTIR) Spectroscopy

FT-IR spectra of carvedilol alone and its combination with polymers are shown in figure 9. An FT-IR spectrum of pure carvedilol showed the peaks 3343.34 cm–1 (N-H, stretching), 2923.68 cm–1 (C-H, stretching), 2842.60 cm–1 (C-H, stretching) and 1097.31cm–1 (C-O, stretching). These peaks can be considered as characteristic peaks of carvedilol and were not affected and prominently observed in IR spectra of carvedilol along with polymers as shown in the figure 9, indicated no interaction between carvedilol and polymers. As various polymers were used in those formulations in different amounts, the IR spectra's were different from the active one.

Differential scanning calorimetry (DSC) thermograms analysis

The thermograms of the carvedilol, solid dispersion and physical mixture were shown in figure 10. The thermograms of the pure drug and polymer or carrier showed respective endothermic peaks corresponding to their melting points around 119.5°C and 54.5°C. From the thermograms of solid dispersion and physical mixture it was observed that there was no peak corresponding to melting point of drug, suggesting amorphous form of carvedilol in solid dispersion as well as physical mixture.

CONCLUSION

This study shows that the dissolution rate of carvedilol can be enhanced considerably by formulating solid dispersion from hydrophilic polymers using fusion and solvent evaporation method. This study indicated that Poloxomer 407, PEG 6000, HPMC and SSG increased dissolution by inhibiting the crystallization of drug or by reducing the size of the particle size or by enhancing wettability of drug molecule. The dissolution rate of carvedilol from solid dispersion was depended on the concentration of the polymers. Dissolution of drug increased with an increase in polymer content. A high proportion of polymers in the solid dispersion significantly increased the dissolution rate compared to pure drug.

On the other hand, the present study has shown that dissolution rate of the solid dispersion by solvent evaporation method was highest whereas dissolution of drug by fusion method was higher than by physical mixing method.

In conclusion it can be mentioned that PEG 6000, Poloxamer 407 and HPMC can be used to improve the dissolution of carvedilol in which the vehicles may act here as dispersing agents for the liberated drug, thus preventing the formation of any water-insoluble surface layers.

ACKNOWLEDGEMENT

The authors would like to acknowledge the support received from the Pharmaceutics Research Laboratory of the Department of Pharmacy, University of Asia Pacific. Authors also acknowledge Mohammad Aziz ullah, Sanofi-Aventis Ltd. for gift sample of Carvedilol.

Table 1: Formulation of Solid Dispersion using different polymers by Solvent Evaporation (SE), Fusion Method (FM) and Physical mixing (PM) method

Ingredients	CV-SE-FM-PM-F1	CV-SE-FM-PM-F2	CV-SE-FM-PM-F3	CV-SE-FM-PM-F4	CV-SE-FM-PM-F5	CV-SE-FM-PM-F6	CV-SE-FM-PM-F7	CV-SE-FM-PM-F8	CV-SE-FM-PM-F9	CV-SE-FM-PM-F10	CV-SE-FM-PM-F11	CV-SE-FM-PM-F12
Carvedilol (gm)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Poloxamer 407 (gm)	0.2	0.4	0.8	-	-	-	-	-	-	-	-	-
HPMC 6 cps (gm)	-	-	-	0.2	0.4	0.8	-	-	-	-	-	-
Sodium Starch Glycolate (gm)	-	-	-	-	-	-	0.2	0.4	0.8	-	-	-
PEG 6000 (gm)	-	-	-	-	-	-	-	-	-	0.2	0.4	0.8
Methanol (ml)	1	1	1	1	1	1	1	1	1	1	1	1

Table 2: Correlation coefficient (R^2) Values for the formulation of Physical mixing method

Product	Correlation coefficient (R^2) value			
Formulation	Zero order	First order Plot	Hixon Crowel Plot	Higuchi Plot
F1	0.967	0.942	0.747	0.984
F2	0.984	0.931	0.740	0.988
F3	0.977	0.954	0.693	0.980
F4	0.960	0.969	0.670	0.986
F5	0.973	0.952	0.727	0.995
F6	0.963	0.944	0.737	0.995
F7	0.970	0.959	0.713	0.995
F8	0.915	0.962	0.650	0.985
F9	0.901	0.642	0.953	0.980
F10	0.942	0.922	0.672	0.976
F11	0.935	0.933	0.657	0.980
F12	0.940	0.939	0.722	0.985

Table 3: Correlation coefficient (R^2) Values for the formulation of Fusion method

Product	Correlation coefficient (R^2) value			
Formulation	Zero order	First order Plot	Hixon Crowel Plot	Higuchi Plot
F1	0.950	0.995	0.680	0.998
F2	0.973	0.952	0.727	0.995
F3	0.963	0.944	0.737	0.995
F4	0.970	0.959	0.713	0.995
F5	0.915	0.962	0.650	0.985
F6	0.901	0.642	0.953	0.980
F7	0.942	0.962	0.672	0.976
F8	0.935	0963	0.657	0.980
F9	0.980	0.930	0.762	0.988
F10	0.924	0.912	0.659	0.991
F11	0.945	0.921	0.669	0.993
F12	0.987	0.931	0.692	0.996

Table 4: Correlation coefficient (R^2) Values for the formulation of Solvent evaporation method

Product	Correlation coefficient (R^2) value			
Formulation	Zero order	First order Plot	Hixon Crowel Plot	Higuchi Plot
F1	0.924	0.920	0.630	0.963
F2	0.913	0.868	0.621	0.961
F3	0.953	0.979	0.605	0.988
F4	0.966	0.961	0.674	0.967
F5	0.928	0.895	0.621	0963
F6	0.918	0.990	0.658	0.959
F7	0.950	0.988	0.680	0.956
F8	0.907	0.806	0.622	0.96
F9	0953	0.979	0.605	0.988
F10	0.910	0.959	0.713	0.981
F11	0.915	0.962	0.650	0.985
F12	0.951	0.642	0.953	0.989

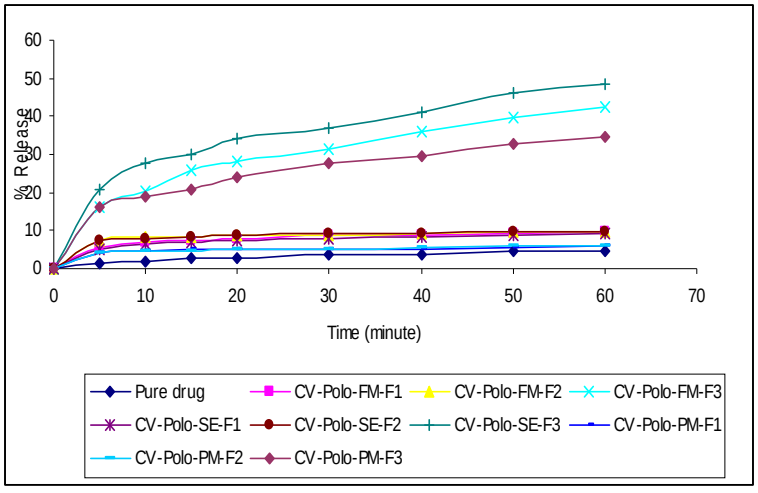

Fig. 1: Percent release curve of Carvedilol with Poloxomer 407 for the formulations F1 to F3 prepared by solvent evaporation, fusion and physical mixing method

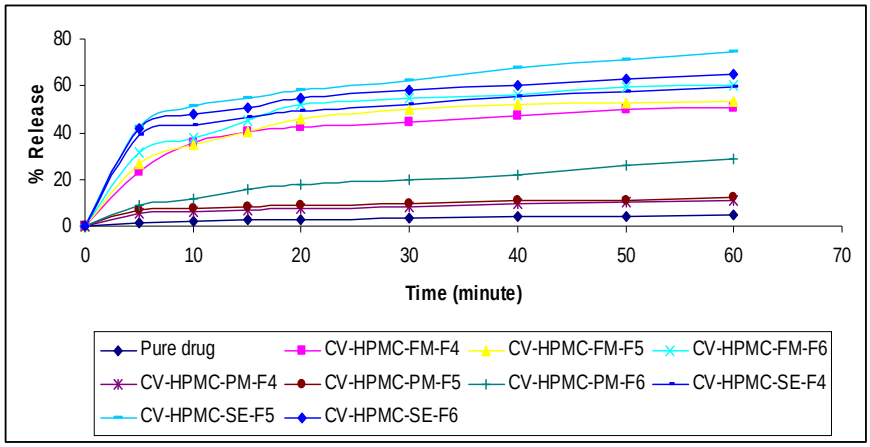

Fig. 2: Percent release curve of Carvedilol with Hydroxy propyl methyl cellulose (HPMC) for the formulations F4 to F6 prepared by solvent evaporation, fusion and physical mixing method

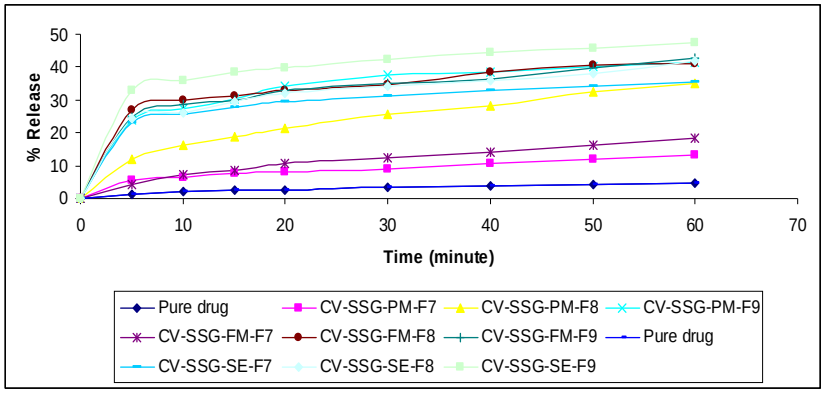

Fig. 3: Percent release curve of Carvedilol with Sodium Starch glycolate (SSG) for the formulations F7 to F9 prepared by solvent evaporation, fusion and physical mixing method

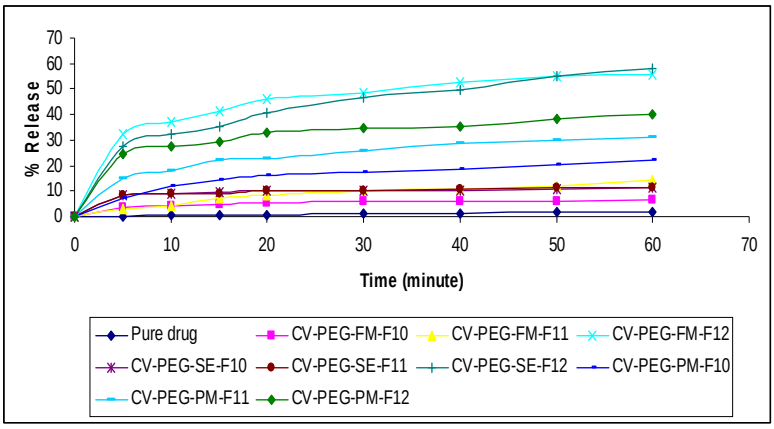

Fig. 4: Percent release curve of Carvedilol with PEG-6000 for the formulations F10 to F12 prepared by solvent evaporation, fusion and physical mixing method

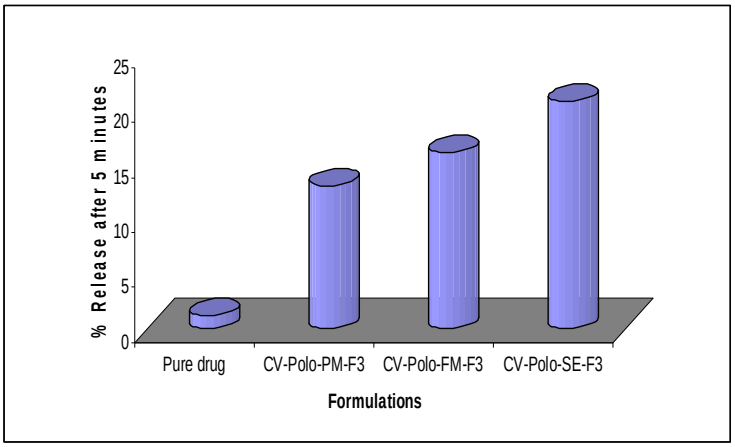

Fig. 5: Effect of poloxomer 407 on Percent Release of Carvedilol after Five Minutes of Dissolution using physical mixing, fusion and solvent evaporation method

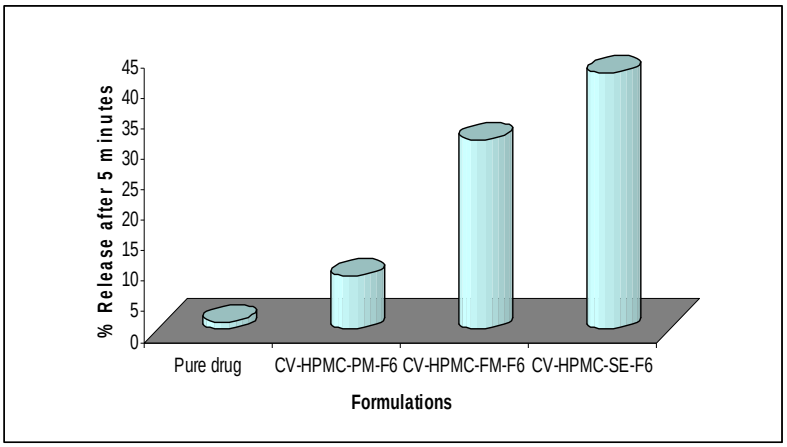

Fig. 6: Effect of HPMC 6 cps on Percent Release of Carvedilol after Five Minutes of Dissolution using physical mixing, fusion and solvent evaporation method

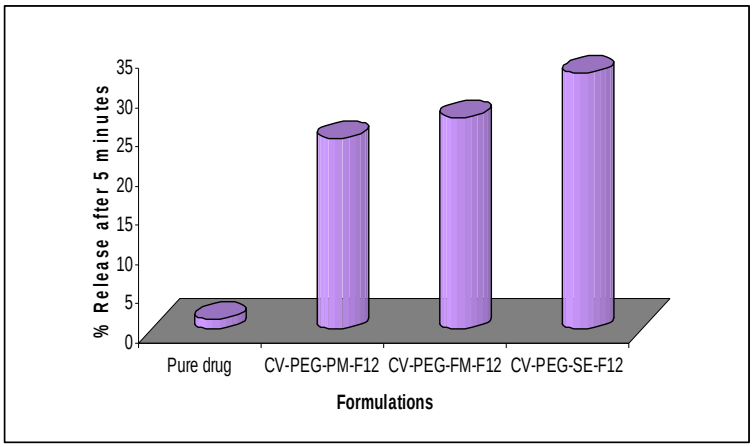

Fig. 7: Effect of PEG 6000 on Percent Release of Carvedilol after Five Minutes of Dissolution using physical mixing, fusion and solvent evaporation method

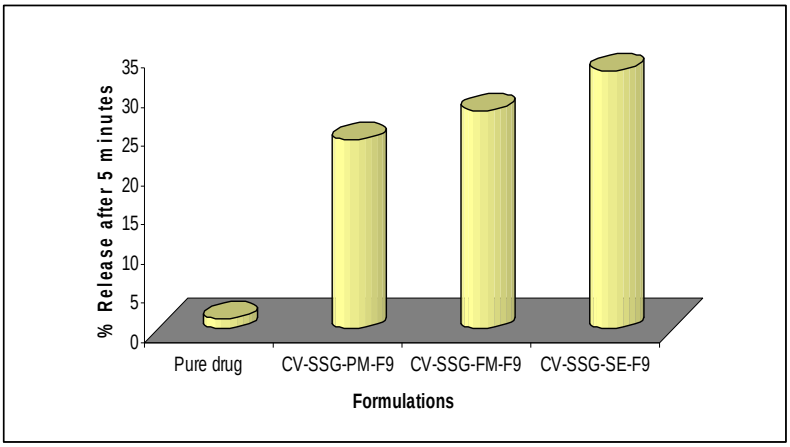

Fig. 8: Effect of SSG on Percent Release of Carvedilol after Five Minutes of Dissolution using physical mixing, fusion and solvent evaporation method

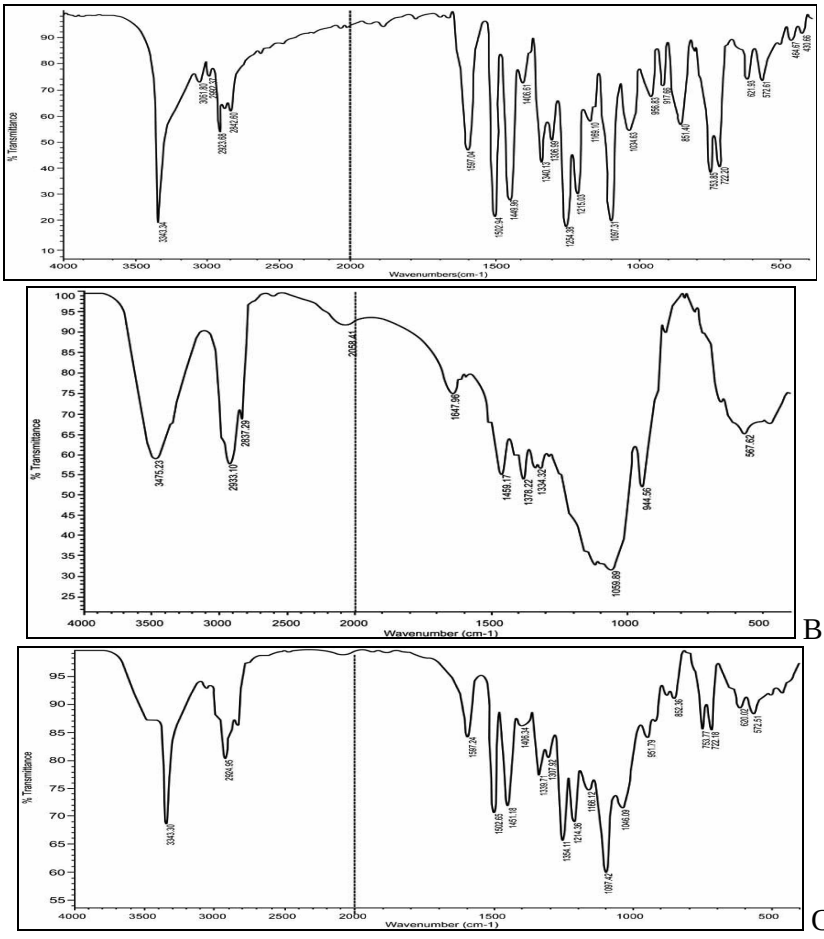

Fig. 9: Fourier Transform Infrared (FTIR) Spectroscopy spectra of different samples: A. Carvedilol (pure drug), B. Carvedilol: HPMC 6cps (Solvent Evaporation); C. Carvedilol: PEG 6000 (Fusion Method)

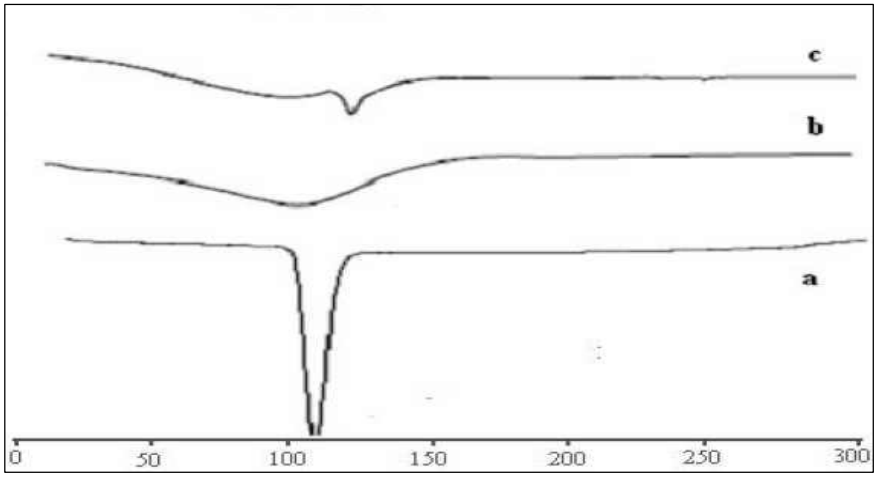

Fig. 10: DSC thermograms of a) Carvedilol b) solid dispersion c) physical mixture

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