



ENHANCEMENT OF DISSOLUTION RATE OF POORLY SOLUBLE DRUG CARVEDILOL BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

The main objective of present work enhancement of dissolution rate and oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of drug development. In the present investigation studies were carried out on enhancement of dissolution rate of Carvedilol by Solid Dispersion technology (physical mixture, solvent evaporation, Kneading method) employing various water dispersible carriers. γ -CD's, β -CD's were evaluated as carriers for Solid Dispersions and for enhancing the dissolution rate of poorly soluble drug. All the dissolution parameters estimated i.e. R2 and K1 values indicated rapid and higher dissolution of drug (Carvedilol) from Solid Dispersions than that of corresponding pure drug. The order of increase in dissolution rate with different Cyclodextrin's is γ -CD's < β -CD's with Pure Carvedilol in powder form. Over all the carriers gave marked enhancement of solubility of Carvedilol. Among all β -CD's in the ratio 1:1 (KM II) was found to be good carrier for Solid Dispersions for enhancing the dissolution rate of Carvedilol.

KEYWORDS: Carvedilol, γ -CD's, β -CD's, kneading Method.

INTRODUCTION

Solubility of the drug is the main obstacle in the delivery of the NCE's and also existing drugs. The ability of improving the solubility and delivery of poorly soluble drug is very important step in formulation development. Poorly soluble drugs such as Nifedipine and Felodipine have motivated the development of drug delivery technologies to overcome the poor solubility. By many estimates several techniques are developed to deliver the poorly soluble drugs successfully. Solubility property enhanced through either altering the macromolecular characteristics of the drug particles, or chemical or mechanical modification of the environment surrounding the drug molecule. Particle size reduction, addition of surfactant, pH adjustment, self-emulsifying systems and inclusion in cyclodextrin-drug complexes are the best examples for the solubility enhancement techniques. Together with the solubility, permeability also considered in the development of formulation for oral

administration. With the recent advent of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenges to formulation scientist in the pharmaceutical industry. The Noyes-Whitney equation explain how the dissolution of poorly soluble drug takes place and also provides some hints to improve the dissolution

Where dc/dt is the rate of dissolution, A is the surface area available for the dissolution, D is the diffusion coefficient of the compound, C_s is the solubility of the compound in the dissolution medium, C is the concentration of drug in the medium at time t and h is the thickness of the diffusion boundary layer adjacent to the surface area of the dissolving compound.

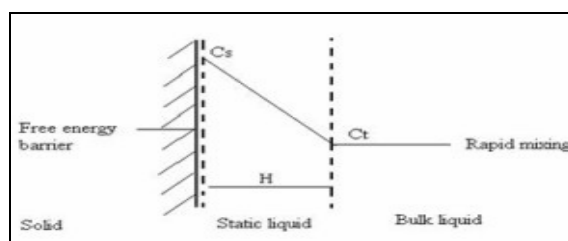


Figure 1: Diagrammatic representation of the free energy barrier to dissolution.

As well as the physical features of the drug, many physiological parameters can also play a role in determining the dissolution rate. The dissolution can be improved by increasing the surface area available for dissolution by decreasing the particle size of the solid compound and/or by optimizing the wetting characteristics of the compound surface, decreasing the boundary layer thickness and by maintaining sink conditions for dissolution. Although some research effort has been directed towards permeability enhancement using appropriate excipients, results to date have not been particularly encouraging. Administration of drug in the fed state may be an option to improve the dissolution rate and also to increase the time available for dissolution, the likely magnitude of the food effect can be forecasted from dissolution tests in bio relevant media.

MATERIALS AND METHODS

Preparation of dispersions:

In the present study three methods were used to enhance the solubility of poorly soluble drug Carvedilol i.e., Physical mixture, Solvent evaporation method and Kneading method.

A. Physical mixtures(PM):

The physical mixtures of EFA and CD's are 1:1M was obtained by mixing individual components that had been previously sieved (#80) together with a spatula.

B. Solvent Evaporation Method (SE):

Solvent evaporation of drug Carvedilol carriers were prepared at mass ratios (1:1) Carvedilol was dissolved in methanol to get clear solution. After that carrier (passed through sieve no. (#80)) was added to clear drug solution and stirring. The solvent, methanol was removed by evaporation technique (or) dried properly using Heating mantle at 45°C for 60min. The mass obtained was further dried at 50°C for 24hrs in an Hot air oven. The product was crushed, pulverized and passed through a sieve number (#80). The prepared/obtained product was then filled in glass bottles, sealed and stored in a desiccator until further use.

C. Kneading method (KM):

In Kneading method the drug (Carvedilol) and surface active carriers γ -CD's, β -CD's in the ratio of i.e. 1:1 were weighed accurately and triturated in a mortar and pestle by adding drop by drop of methanol for size reduction of the particles. This method was continued for nearly 45 min and made into dough like mass. The Kneaded dispersion was dried at 50°C for 24hrs in a Hot air oven. The product was crushed, pulverized and passed through a sieve number (#80). The prepared/obtained product was then filled in glass bottles, sealed and stored in a desiccator until further use.

Evaluation of solid dispersions

Angle of repose:

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a

characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and horizontal plane. The angle of repose was determined by funnel method suggested by Newman. Angle of repose is determined by following formula:

$$\tan \theta = \frac{h}{r}, \theta = \tan^{-1} \frac{h}{r}$$

Where, θ = angle of repose,

h = height of the cone,

A funnel was fixed at a height of approximately of 2-4 cm over the platform. The sample was slowly passed along the wall of funnel, till the cone of the powder formed. Angle of repose was determined by measuring the height of the cone of powder and radius of the heap of the powder.

Bulk density (D_b):

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/mL and is given by

$$D_b = M/V_0$$

Where, M is the mass of powder

V_0 is the Bulk volume of the powder.

Tapped density (D_t):

Tapped density was determined by using graduated cylinder. An accurately weighed sample was carefully added to the graduated cylinder with the aid of funnel. The initial volume was noted and the sample was tapped on a horizontal base. Tapping was continued until no further reduction in sample volume was observed. Volume was noted and tapped density is calculated by using the following formula.

$$D_t = M/V_0$$

Where, M is the mass of powder

V_0 is the Bulk volume of the powder

Carr's Index (I):

It indicates the ease with which a material can be induced to flow and powder compressibility. It is expressed in percentage and is given by

$$I = (D_t - D_b / D_t) \times 100$$

Where, D_t is the tapped density of the powder

D_b is the bulk density of the powder.

Compressibility Index and Hausner's ratio (H):

In recent years the compressibility index and the closely related Hausner's ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. The compressibility index has been proposed as an indirect measure of the bulk density, size, shape, surface area, moisture content and cohesiveness of the materials. Both the compressibility index and the Hausner's ratio were determined by using bulk density and the tapped density of the powder.

Compressibility Index = $(1 - V/V_0) \times 100$

Where,

V = volume of powder blend before tap

V_0 = volume of powder blend after 100 tapping's.

Hausner's ratio (H) is a number that is correlated to the flowability of a powder. The Hausner's ratio is related to the Carr's Index by the formula

$H = 100 / (100 - C)$

Hausner's ratio also expressed as,

$H = D_t / D_b$ (or) Hausner's ratio = tapped density/ bulk density.

In-vitro evaluation studies:

The quantity of Solid Dispersion equivalent to 50mg of carvedilol was placed in dissolution medium. The

dissolution study of dispersion was conducted using dissolution testing apparatus II (paddle method) in 900 ml of 2%W/V SLS solution at $37 \pm 0.5^\circ\text{C}$ and at speed of 50 rpm. Aliquots of 5 ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain volume after each sampling and analyzed Spectrophotometrically at 246 nm against suitable blank using UV-visible Spectrophotometer (Elico SL150). The dissolution experiments were conducted in triplicate. Mean percent $\pm$ SD of Carvedilol at different time intervals are reported.

RESULTS AND DISCUSSION

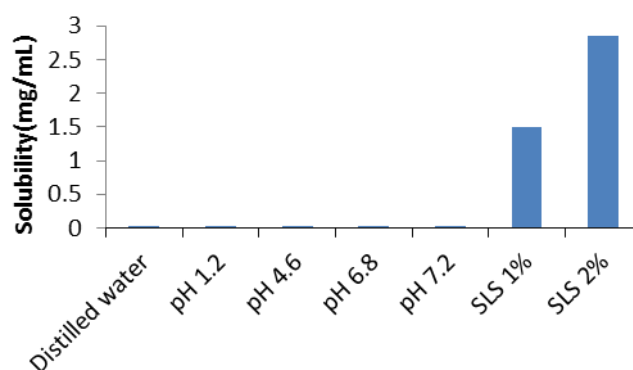


Figure 1: Solubility analysis plot of carvedilol in various solutions.

Table no. 1: Physical evaluation of solid dispersions carvedilol with γ -CD's.

Parameters (γ -CD')	Formulation code		
	Physical mixture (PM I)	Solvent evaporation (SE I)	Kneading method (KM I)
	PM 1:1	SE 1:1	KM 1:1
Angle of repose	19.86 $\pm$ 0.45	20.18 $\pm$ 0.47	24.06 $\pm$ 0.54
Bulk density (g/cc)	0.62 $\pm$ 0.57	0.74 $\pm$ 0.64	0.83 $\pm$ 0.44
Tapped density (g/cc)	0.89 $\pm$ 0.20	0.90 $\pm$ 0.54	0.91 $\pm$ 0.05
Carr's Index (%)	17.64	18.87	19.78
Hausner's ratio	1.038	1.022	1.011
Flow comment	GOOD	GOOD	GOOD
Drug content (%)	93.09 $\pm$ 0.09	96.53 $\pm$ 0.30	98.24 $\pm$ 0.90

Table 3: Physical evaluation of solid dispersions carvedilol with β -CD's.

Parameters (β -cd's)	Formulation code		
	Physical mixture (pm ii)	Solvent evaporation (se ii)	Kneading method (km ii)
	Pm 1:1	Se 1:1	Km 1:1
Angle of repose	20.86 $\pm$ 0.45	22.18 $\pm$ 0.47	26.06 $\pm$ 0.54
Bulk density (g/cc)	0.72 $\pm$ 0.57	0.84 $\pm$ 0.64	0.93 $\pm$ 0.44
Tapped density (g/cc)	0.92 $\pm$ 0.20	0.95 $\pm$ 0.54	1.01 $\pm$ 0.05
Carr's index (%)	18.64	17.87	9.78
Hausner's ratio	1.336	1.021	1.103
Flow comment	Good	Good	Excellent
Drug content (%)	94.09 $\pm$ 0.60	96.72 $\pm$ 0.60	99.95 $\pm$ 0.60

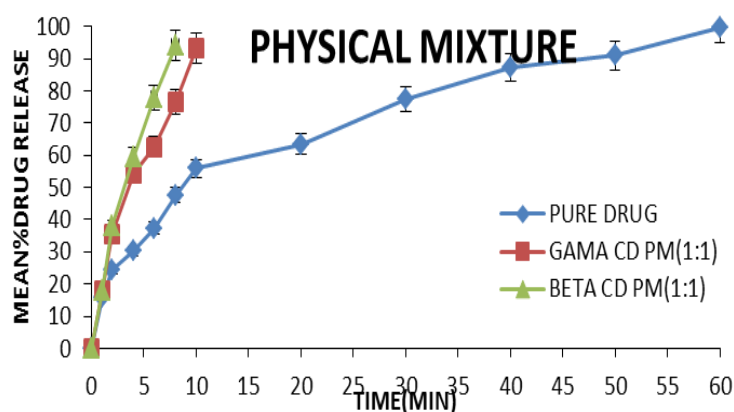


Figure 3 (a): Comparative *in-vitro* dissolution profiles of Carvedilol Solid Dispersions by PHYSICAL MIXING using γ - CD's, β - CD's (PM I, PM II) and Pure Drug (PD) (Mean $\pm$ SD., n=3).

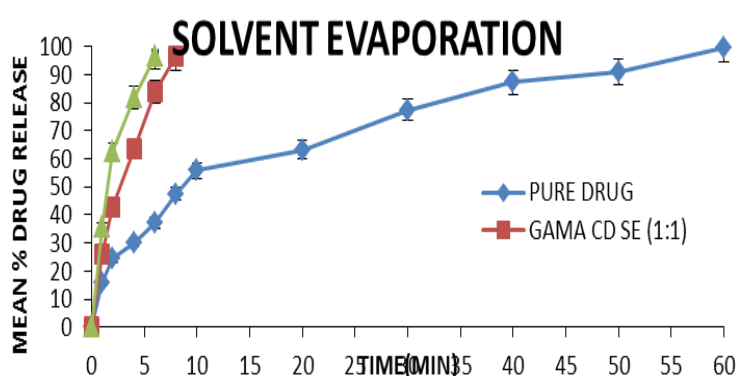


Figure 4 (a): Comparative *in-vitro* dissolution profiles of Carvedilol Solid Dispersions by SOLVENT EVAPORATION method using γ - CD's, β - CD's (SE I, SE II) and Pure Drug (PD) (Mean $\pm$ SD., n=3).

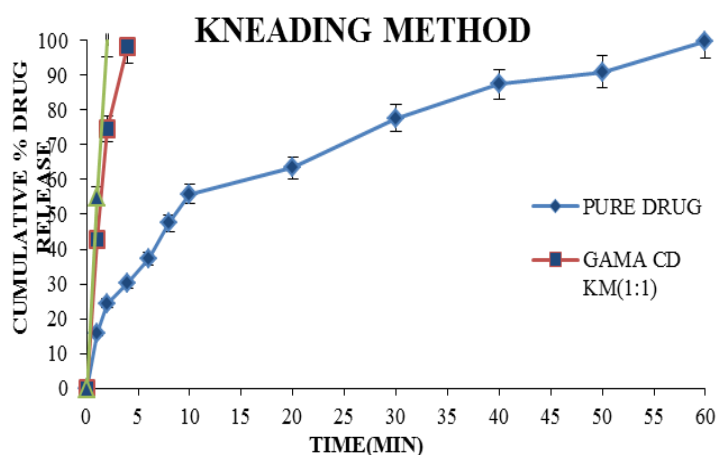


Figure 5 (a): Comparative *in-vitro* dissolution profiles of Carvedilol Solid Dispersion KNEADING METHOD using γ - CD's, β - CD's (KM I, KM II) and Pure Drug (PD) (Mean $\pm$ SD., n=3).

Solubility studies

In the present work the drug is added to Buffers like pH 1.2 HCL Buffer, pH 4.6 Acetate Buffer, pH 6.8 Phosphate buffer, pH 7.2 Phosphate Buffer and also 1%SLS, 2%SLS Solutions as follows: An excess of Carvedilol was added to 5mL of each fluid in a 25 mL stoppered conical flasks and the mixture were shaken for 48 hrs at room temperature ($25 \pm 1^\circ\text{C}$) on a rotary flask shaker. After 48 hrs of shaking 1 mL aliquots were

withdrawn and filtered immediately using a 0.45 μ nylon disc filter. The filtered samples were diluted suitably and assayed for drug measuring absorbance at 246 nm. Shaking was continued until three constructive estimations were same. The solubility experiments were run in triplicate. The results of solubility studies revealed that CARVEDILOL is more soluble in 2%SLS Solution. The order of solubility is 2%SLS > 1%SLS > 1.2 pH > DW > 6.8 pH > 7.2 pH > 4.6 pH.

Drug content estimation

Solid Dispersions of Carvedilol with various Carriers i.e. γ -CD's, β -CD's were prepared by physical mixture, Solvent Evaporation method and Kneading method with mass ratios (1:1). The percentage drug content for all the prepared dispersions were found to be in the range of 93.09 ± 0.09 to 99.05 ± 0.60 indicating uniform drug distribution.

Physical evaluation of solid dispersion

Twelve batches of Solid Dispersions were prepared using Carvedilol as a drug and various carriers like γ -CD's, β -CD's, corresponding to the mass ratios of 1:1. The Solid Dispersions were prepared by three methods such as physical mixture Solvent evaporation and Kneading method. The prepared Solid Dispersions were evaluated for Angle of repose, Tapped density, Bulk density, Carr's Index, Hausner's ratio, Solubility and Drug content as shown in the table.

In-vitro dissolution studies of CARVEDILOL and it's solid dispersions:

When an assumed drug – CD's is dispersed in a dissolution medium, a very rapid dissolution is often observed. Dissolution rate tests are based on this observation in order to characterize the inclusion complexation between drug and cyclodextrins. The most often used dissolution rate tests for monitoring drug products stability and manufacturing process control. Ideally, the dissolution method used for a particular product *in-vitro* relates to the bioavailability of the drug *in-vitro*.

In vitro dissolution studies

In **physical mixture** (PM I) dissolution study of CARVEDILOL with γ -CD's in 1:1 ratio, the data showed that 35.55 ± 0.18 % of drug was released within 2 minutes. The drug release in physical mixture (PM II) Carvedilol with β -CD's in 1:1 ratio was found to be 38.0 ± 0.02 % within 2 min. For initial periods of time for 1min, the drug release in 1:1 with γ -CD's and β -CD's was found to be 17.82 ± 0.03 % and 18.0 ± 0.15 % respectively this indicates that as the carrier is changed the dissolution is increased. The complete dissolution in 1:1 with γ -CD's and β -CD's obtained in 10 and 8 min respectively. In **Solvent Evaporation** (SE I) dissolution study of Carvedilol with γ -CD's in 1:1 ratio, the data showed that 42.78 ± 1.51 % of drug was released within 2 minutes. The drug release in solvent evaporation method (SE II) 1:1 ratio was found to be 62.50 ± 0.91 % within 2 min. For initial periods of time for 1min, the drug release in 1:1 with γ -CD's and β -CD's was found to be 26.03 ± 0.45 % and 35.4 ± 1.97 % respectively this indicates that carrier is changed the dissolution is increased. The complete dissolution in 1:1 with γ -CD's and β -CD's in 8 and 6min respectively. In **kneading method** (KM I) dissolution study of Carvedilol with γ -CD's in 1:1 ratio, the data showed that 74.60 ± 3.95 % of drug was released within 2 minutes. The drug release in kneading method (KM II) 1:1 ratio was found to be 99.05 ± 0.60 % within 2

min. For initial periods of time for 1min, the drug release in 1:1 with γ -CD's and β -CD's was found to be 42.84 ± 6.29 % and 55.0 ± 3.64 % respectively this indicates that carrier is changed, the dissolution is increased.

CONCLUSION

The enhancement of dissolution rate and oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of drug development. Among the various methods of enhancement the dissolution rate and oral bioavailability, solid Dispersion technologies were found to be more successful with a number of drugs. In the present investigation studies were carried out on enhancement of dissolution rate of CARVEDILOL by Solid Dispersion technology (physical mixture, solvent evaporation, Kneading method) employing various water dispersible carriers. γ -CD's, β -CD's were evaluated as carriers for Solid Dispersions and for enhancing the dissolution rate of poorly soluble drugs.

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