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ENHANCEMENT OF SOLUBILITY AND DISSOLUTION OF CARVEDILOL BY SOLID DISPERSION TECHNIQUE

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Abstract:

Despite significant advancements in the science of drug delivery, solubilization of poorly aqueous soluble drugs still remains a challenging task for formulation. The purpose of the study was to improve the physicochemical properties of poorly aqueous soluble drug Carvedilol like solubility, dissolution properties and stability of poorly soluble drug by forming dispersion with skimmed milk powder as carrier. Carvedilol was formulated by solid dispersions using rota-evaporation method and lyophilization method in different ratios 1:1 to 1:12 of drug and carrier (skimmed milk powder). The formulations were evaluated for various in vitro parameters (Drug content, Drug release, phase solubility studies, dissolution efficiency, FTIR) as well as changes in the physical state during storage under different humidity conditions. In vitro dissolution showed that increment of dissolution rate in case of SD than pure drug. Carevdilol phosphate with skimmed milk (1:6) showed the better results, maximum amount of drug released within 7 hours. It observed that no change in structure but change in physical state of the drug from crystalline to amorphous. The IR spectra of the drug, skimmed milk and the solid dispersion were performed to detect the possible molecular interaction between drug and carrier. The all above characteristics peaks of drug appear in the spectra of all ternary system at same wave number no modification or no interaction of the drug and carrier.

Keywords: *Carvedilol, Solid dispersions, Skimmed milk, Carrier, FTIR, in-vitro release.*

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INTRODUCTION:

Several techniques are commonly used to improve dissolution and bioavailability of poorly water-soluble drugs, such as size reduction, the use of surfactants and the formation of solid dispersions [1]. The latter are defined as dispersions of one or more active ingredients in an inert carrier in the solid state. Mechanisms involved include increased wettability, solubilization of the drug by the carrier at the diffusion layer and reduction or absence of aggregation and agglomeration [2]. Moreover, transformation of the crystalline drug to the amorphous state upon solid dispersion formulation increases the dissolution rate since no lattice structure has to be broken down for dissolution to take place. Carvedilol (CAR), an antihypertensive agent, is used in the treatment of hypertension, congestive heart failure, cardiac arrhythmias and angina pectoris. It is a nonselective β-adrenergic blocker with selective α-adrenergic blocking [3]. 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 [4].

Carvedilol is practically insoluble in water and exhibits pH-dependant solubility. Its solubility is less in water. However, up to fourfold improvement of carvedilol bioavailability could be achieved by increasing the carvedilol solubility [5]. The solubility of carvedilol in aqueous solutions with pH ranging from 1 to 4 is limited due to its protonation, resulting in "in situ" hydrochloride salt formation, which exhibits lower solubility in media containing chlorine ions due to the common-ion effect. It's extremely low solubility at alkaline pH levels may prevent the drug from being available for absorption in the small intestine and colon, thus making it a poor candidate for an extended-release dosage form [6]. Carvedilol undergoes significant stereoselective first-pass metabolism, resulting in low absolute bioavailability (30% or less). However, some sources suggest that this low bioavailability is the result of poor aqueous solubility.4 The objective of the present study was enhancement of solubility of poorly soluble carvedilol with Skimmed milk powder by solid dispersion [7].

The solid binary systems were prepared by maintaining constant drug concentration and increasing carrier concentrations using physical mixing and solvent evaporation techniques [8]. The skimmed milk is a colloidal suspension of casein micelles, globular proteins and lipoprotein particles. The objective of the present study was enhancement of solubility of poorly soluble carvedilol with skimmed milk powder by solid dispersion.

MATERIALS AND METHODS:

Materials:

Carvedilol phosphate was obtained from Dr. Reddy's laboratories Ltd. Dimethyl Sulphoxide was obtained from Merck specialties Pvt ltd., Mumbai, India. Skimmed milk was purchased from Departmental Store, Hyderabad, India.

Methods:

Skimmed milk powder Preparation

Skimmed milk (200ml) was subjected to vacuum evaporation using rotary vacuum evaporator at 100rpm, 35°C under vacuum for about 120 min. The resultant viscous mass was then dried in a desiccator containing calcium chloride at room temperature for 48 hr, triturated, sieved through sieve no. 60 and then stored in an air tight container until further use [9]. The yield of skimmed milk powder obtained was approximately 1g/10ml of milk.

Preparation of solid dispersions by solvent evaporation method

About 20 mg of drug was mixed with appropriate quantity of skimmed milk (20, 40, 60, 80, 100, 120,140,160,180,200,220 and 240 ml) to obtain different ratios of drug: carrier using a magnetic stirrer at 50°C for about 30 min. The resultant suspension was then dried in a rotary vacuum evaporator at 100 rpm, 35°C under vacuum for about 45 min [10]. The mass obtained was then dried over a calcium chloride containing desiccators at room temperature for 24 hr, triturated, sieved through sieve no.60 and stored in closed container until further use.

Table 1: Formulation chart of solid dispersion powder (SD)

S.No.	Formulation code	Quantity of drug (mg)	Quantity of milk (ml)
1	SD 1 (1:1)	20	20
2	SD 2 (1:2)	20	40
3	SD 3 (1:3)	20	60
4	SD 4 (1:4)	20	80
5	SD 5 (1:5)	20	100
6	SD 6 (1:6)	20	120
7	SD 7 (1:7)	20	140
8	SD 8 (1:8)	20	160
9	SD 9 (1:9)	20	180
10	SD 10 (1:10)	20	200
11	SD 11 (1:11)	20	220
12	SD 12 (1:12)	20	240

Preparation of physical mixtures

About 20mg of drug was mixed with 20, 40, 60, 80, 100, 120, 140, 160, 180, 200, 220 and 240mg of skimmed milk powder using a motor and pestle [11]. The mixture was dried over a calcium chloride containing desiccators at room temperature for 24 hr, triturated, sieved through sieve no.60 and stored in an air tight container until further use.

Table 2: Formulation chart of physical mixtures (PM)

S.NO	Formulation Name	Quantity of drug (mg)	Quantity of skimmed milk powder (mg)
1	PM 1 (1:1)	20	20
2	PM 2 (1:2)	20	40
3	PM 3 (1:3)	20	60
4	PM 4 (1:4)	20	80
5	PM 5 (1:5)	20	100
6	PM 6 (1:6)	20	120
7	PM 7 (1:7)	20	140
8	PM 8 (1:8)	20	160
9	PM 9 (1:9)	20	180
10	PM 10 (1:10)	20	200
11	PM 11 (1:11)	20	220
12	PM 12 (1:12)	20	240

Solubility Studies of Solid Dispersions and Physical Mixtures:

Excess amount of carvedilol phosphate, its solid dispersions and physical mixtures with skimmed milk powder were added in 2 ml clicklock micro centrifuges containing 1 ml of pH 6.8 buffers. These centrifuges were shaken in an orbital shaker for 48 hrs at 25°C maintained at 100 rpm and then subjected to centrifugation at 1000 rpm for 10 min [12]. 1 ml of supernatant was carefully withdrawn, appropriately diluted and amount of drug dissolved was measured spectrophotometrically at 285 nm.

Micromeritic properties:

Angle of repose:

The powder sample for analysis is slowly poured down the funnel until the apex of the conical pile that is generated just touches the funnel tip (H). The average powder cone diameter (d) and the tangent to the angle of repose are calculated [13].

$$\tan\theta = \frac{h}{r}$$

Bulk Density:

The bulk density of a powder is primarily influenced by the distribution of particle size, shape, and cohesion [14]. A dry 5 ml cylinder was filled with a 1 g powder mixture without being compacted. The unsettled apparent volume, Vo, was measured after

the powder was thoroughly levelled without compacting. The bulk density was calculated using the following formula.

$$\text{Bulk density } (\sigma b) = \frac{Mass}{Poured\ volume}$$

Tapped Density:
The cylinder containing the sample was tapped using an appropriate mechanical tapped density tester at a nominal rate of 300 drops per minute after following the process described in the measurement of bulk density. The cylinder was first tapped 500 times, then 750 times, until the difference between subsequent measurements was less than 2%, and finally, the tapped volume, Vf, was measured to the nearest graded unit. The tapped density was calculated, in gm per ml, using the following formula [15].

$$Tapped\ density\ (\sigma t) = \frac{Mass}{Tapped\ volume}$$

Carr's index:
A measurement of a powder's susceptibility to be compressed is the compressibility index, often known as the Carr's index. From the bulk and tapped densities, it is calculated [16]. These differences are reflected in the Carr's index which is calculated using the following formula.

$$\text{Carr's index} = \frac{(\sigma t - \sigma b)}{\sigma t} \times 100$$

Where, σt = bulk density,
σb = tapped density.

Hausner's Ratio:
It represents the proportion of tapped density to bulk density. According to general consensus, a value of less than 1.25, or 20% of Carr's index, denotes favourable flow qualities [17].

$$\text{Hausner's ratio} = \frac{\rho t}{\rho b} \times 100$$

Where, ρt = bulk density,
ρb = tapped density.

Drug content of solid dispersions and physical mixtures:
In 100 ml of pH 6.8 phosphate buffer, the physical mixture and solid dispersions equivalent to 10 mg of medication were taken and dissolved separately [18]. Filtered and further diluted, the solution now falls within the standard curve's range of absorbance. Solutions' absorbances at 285 nm were measured. From the absorbance total drug content in the batches was calculated.

***In vitro* dissolution study:**
The in vitro dissolution rate of pure drug, physical mixture, solid dispersion and marketed formulation was determined using type II USP dissolution apparatus (DS 800, Labindia, India) in pH 6.8 phosphate buffer at 37°C and 100 rpm [19]. Aliquots of samples were withdrawn at 5, 10, 15, 30, 45, 60, 90 and 120 min, filtered through membrane filter and amount of drug released was determined spectrophotometrically at 285 nm.

Solid state characterization:
FTIR study:
To determine whether the drug and excipients were compatible, a Fourier Transform Infrared Spectrophotometer (FTIR) study was conducted. Using the KBr dispersion method, the spectrum of a dried mixture of the drug and potassium bromide was run, and last, the spectrum of the drug containing excipients in the 4000–400 cm^{-1} wavelength range [20].

RESULTS AND DISCUSSION:

Solubility studies

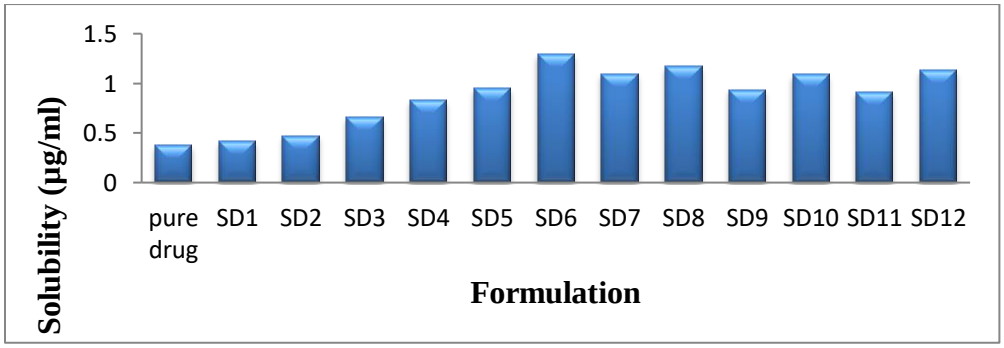

Fig 1: Comparative solubility of pure dug and solid dispersion in pH6.8 Phosphate Buffer

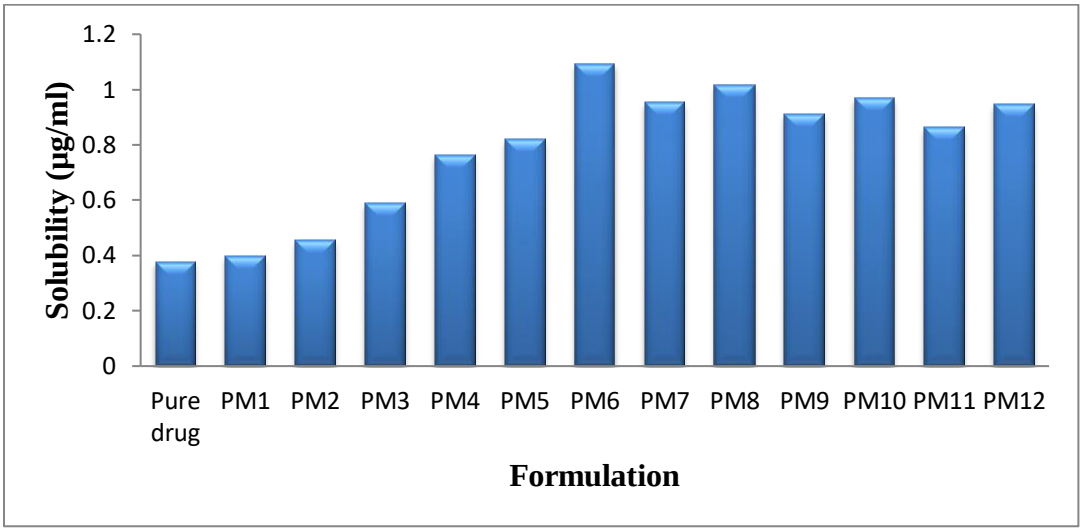

Fig 2: Comparative solubility of pure drug and physical mixture in pH 6.8 Phosphate Buffer

Solubility of drug, its physical mixture with skimmed milk powder and solid dispersion was determined as per K.Venkatesh Kumar *et.al*. The solubility studies (Table 5.3.1, fig 5.3.1 & Table 5.3.2, fig 5.3.2) showed that SD 6 having drug: carrier ratio of 1:6 and physical mixture having dug: carrier ratio of 1:6 is having highest solubility, The order of solubility could give as: pure drug< PM <SD.

Micromeritic properties of solid dispersion and physical mixture:

Table 3: Results of micromeritic properties of solid dispersions

FORMULATION	ANGLE OF REPOSE (θ)	BULK DENSITY (g/cm^3)	TAPPED DENSITY (g/cm^3)	CARR'S INDEX (I)	HAUSNER'S RATIO
SD1	23.17 ± 0.31	0.42 ± 0.28	0.44 ± 0.17	7.97 ± 0.18	0.85 ± 0.21
SD2	25.38 ± 0.59	0.37 ± 0.54	0.41 ± 0.36	9.13 ± 0.41	0.89 ± 0.37
SD3	22.41 ± 0.63	0.46 ± 0.31	0.48 ± 0.28	10.53 ± 0.35	1.18 ± 0.56
SD4	27.63 ± 0.42	0.31 ± 0.64	0.35 ± 0.16	16.36 ± 0.57	0.91 ± 0.42
SD5	25.12 ± 0.35	0.35 ± 0.51	0.39 ± 0.57	8.19 ± 0.33	0.90 ± 0.33
SD6	26.36 ± 0.24	0.48 ± 0.13	0.49 ± 0.63	6.37 ± 0.45	0.94 ± 0.26
SD7	28.13 ± 0.16	0.32 ± 0.37	0.37 ± 0.36	11.75 ± 0.25	0.83 ± 0.37
SD8	24.31 ± 0.51	0.36 ± 0.56	0.42 ± 0.45	16.81 ± 0.18	0.88 ± 0.41
SD9	27.19 ± 0.32	0.45 ± 0.26	0.47 ± 0.25	15.17 ± 0.47	0.86 ± 0.23
SD10	26.23 ± 0.25	0.39 ± 0.84	0.43 ± 0.33	12.25 ± 0.36	0.82 ± 0.59
SD 11	24.81 ± 0.17	0.34 ± 0.49	0.39 ± 0.66	9.16 ± 0.19	0.93 ± 0.11
SD 12	23.55 ± 0.24	0.36 ± 0.15	0.41 ± 0.37	13.65 ± 0.33	0.87 ± 0.45

Table 4: Results of micromeritic properties of physical mixture

FORMULATION	ANGLE OF REPOSE (θ)	BULK DENSITY (g/cm^3)	TAPPED DENSITY (g/cm^3)	CARR'S INDEX (I)	HAUSNER'S RATIO
PM1	25.09 ± 0.25	0.47 ± 0.35	0.53 ± 0.21	10.53 ± 0.56	0.95 ± 0.31
PM2	27.17 ± 0.21	0.45 ± 0.25	0.51 ± 0.33	13.26 ± 0.17	1.21 ± 0.17
PM3	26.51 ± 0.37	0.51 ± 0.32	0.62 ± 0.47	12.45 ± 0.35	0.86 ± 0.25
PM4	27.13 ± 0.76	0.41 ± 0.45	0.54 ± 0.56	11.13 ± 0.51	0.96 ± 0.41
PM5	26.23 ± 0.51	0.48 ± 0.56	0.58 ± 0.41	13.17 ± 0.59	0.95 ± 0.36
PM6	28.57 ± 0.47	0.54 ± 0.26	0.61 ± 0.37	9.26 ± 0.37	0.93 ± 0.54
PM7	29.31 ± 0.53	0.43 ± 0.31	0.57 ± 0.11	14.55 ± 0.64	0.88 ± 0.65
PM8	25.16 ± 0.44	0.45 ± 0.57	0.52 ± 0.51	15.17 ± 0.13	0.85 ± 0.37
PM9	27.59 ± 0.33	0.52 ± 0.63	0.60 ± 0.31	8.62 ± 0.60	0.89 ± 0.27
PM10	28.16 ± 0.46	0.46 ± 0.59	0.55 ± 0.25	15.35 ± 0.17	0.86 ± 0.33
PM 11	26.37 ± 0.53	0.42 ± 0.65	0.57 ± 0.33	12.56 ± 0.36	0.84 ± 0.67
PM 12	25.26 ± 0.55	0.45 ± 0.37	0.53 ± 0.45	10.23 ± 0.57	0.89 ± 0.24

The powder blends of solid dispersions and physical mixtures were evaluated for their flow properties, the results were shown in Table 5.4.1 & 5.4.2. Angle of repose (θ) was in the range from 26.36±0.24 to 28.13±0.16 and 28.57±0.47 to 29.31±0.53 indicating good flow powder for all formulations of SD and PM respectively. The values of bulk density were found to be in the range of 0.35±0.51 to 0.48±0.13 g/cm^3 and 0.48±0.56 to 0.54±0.26 g/cm^3, the tapped density was in the range of 0.39±0.57 to 0.49±0.63 g/cm^3 and 0.58±0.41 to 0.61±0.37 g/cm^3 for SD and PM. The Carr's index (%) was found to be in the range of 35.13±0.21 to 42.5±0.42 and 11.10±0.03 to 16.20±0.02, the Hausner's ratio was found to be in the range of 0.94±0.26 to 1.18±0.56 and 0.93±0.54 to 1.21±0.17 for SD and PM. These numbers show that all of the powder blends' micromeritic characteristics are within acceptable bounds, and they also show good flow characteristics and compressibility.

Drug Content:

The percentage of drug content for SD and PM was found to be in between 89.11±4.38 to 93.67±2.56 and 92.17±2.59 to 92.56±2.13 of carvedilol phosphate respectively, and were found to be in compliance with official specifications (95 to 110%).

Table 5: Drug content

S.NO	FORMULATION	DRUG CONTENT
1	Pure Drug	92.56 ± 2.13
2	SD1	86.35 ± 1.37
3	SD2	91.56 ± 2.16
4	SD3	92.15 ± 3.19
5	SD4	90.09 ± 1.67
6	SD5	89.11 ± 4.38
7	SD6	93.67 ± 2.56
8	SD7	92.54 ± 1.81
9	SD8	88.17 ± 3.16
10	SD9	89.58 ± 2.19
11	SD10	92.12 ± 3.11
12	PM1	92.17 ± 2.59
13	PM2	91.63 ± 3.92
14	PM3	93.51 ± 4.65
15	PM4	93.8 ± 2.63
16	PM5	93.4 ± 1.65
17	PM6	94.13 ± 5.13
18	PM7	93.63 ± 4.17
19	PM8	92.36 ± 2.51
20	PM9	92.55 ± 3.08
21	PM10	93.04 ± 4.61

***In vitro* Release Study:**

The in vitro dissolution profile of pure drug, physical mixture and solid dispersion are presented in Table 5.6.1, fig 5.6.1, 5.6.2 & Table 5.6.2, fig 5.6.3, 5.6.4, from the data, it is clear that percentage cumulative drug release from solid dispersion as well as physical mixture was remarkably higher than pure drug and marketed formulation. From the data, SD6 and PM6 were optimized. At the 420th minute, 76.4 ± 2.8% of drug was released from SD6, 68.21 ± 1.18% from PM6 while from the marketed formulation only 34.6 ± 1.20% was released.

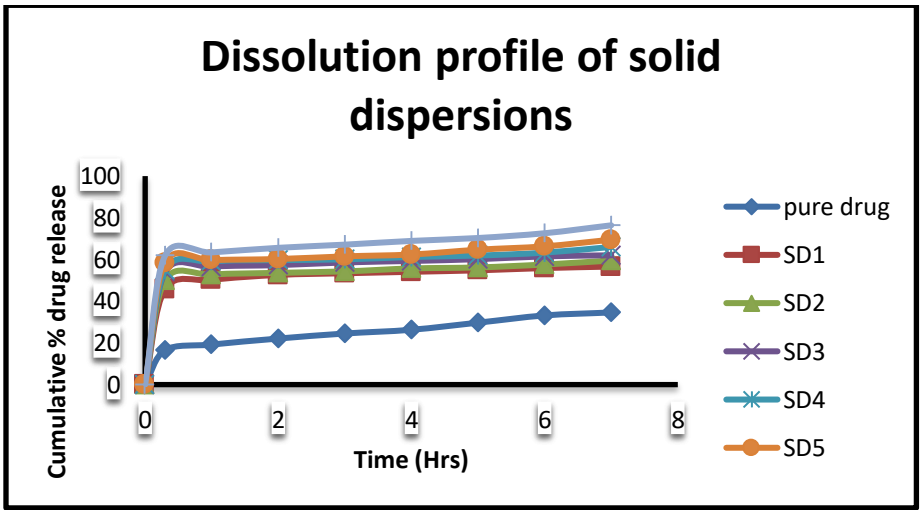

Fig 3: Dissolution graph of pure drug and solid dispersion

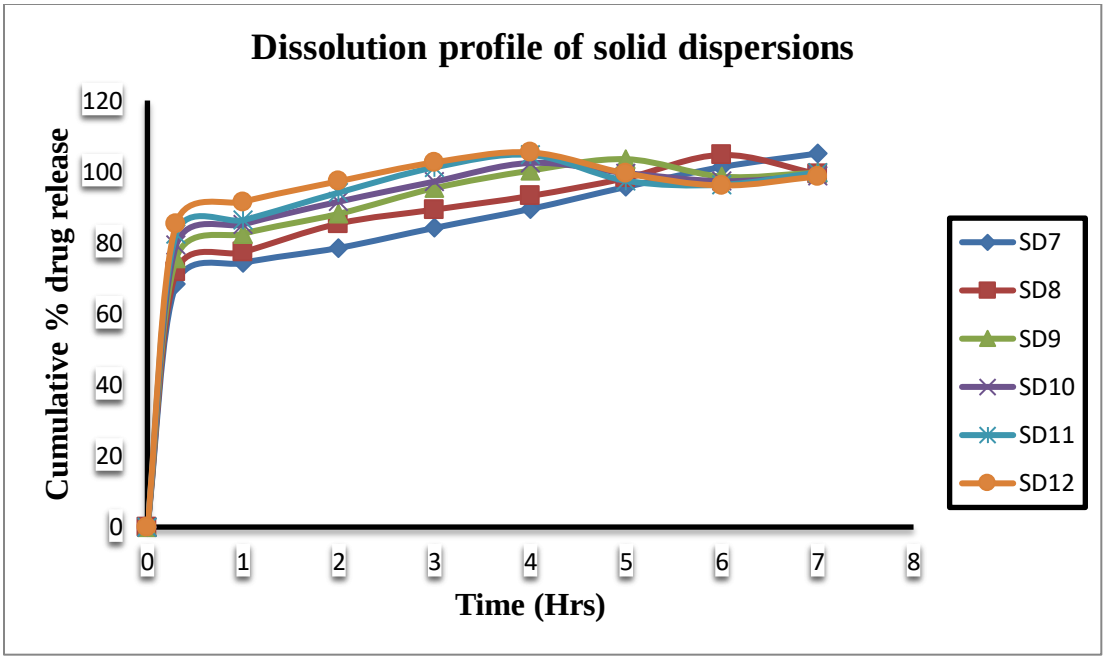

Fig 4: Dissolution graph of solid dispersion

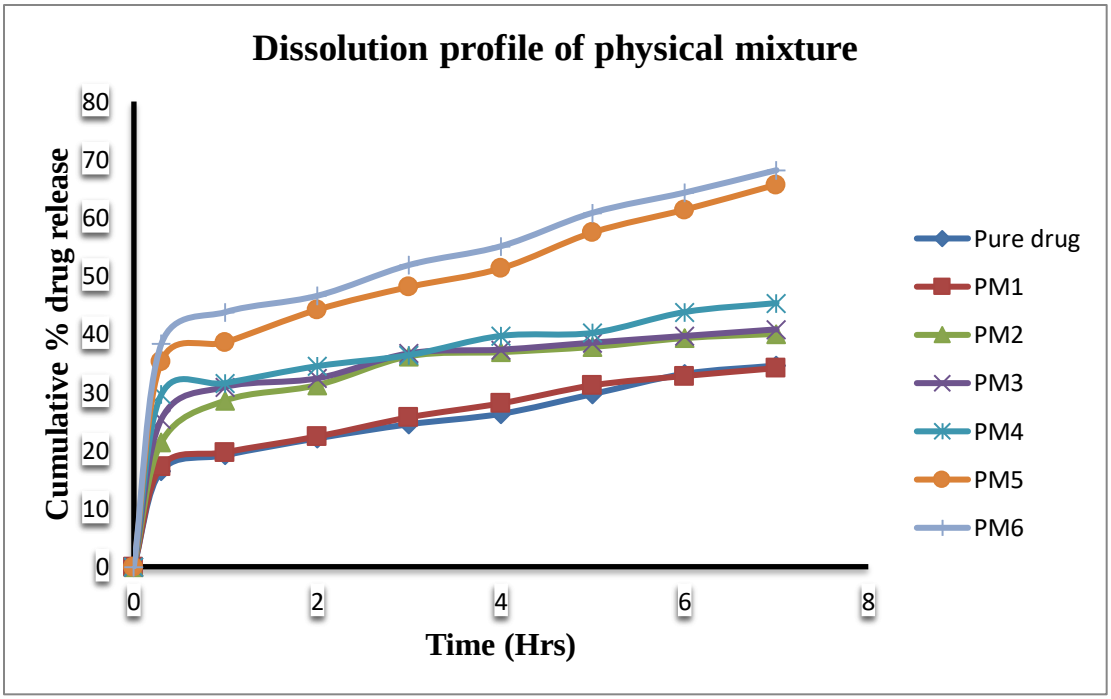

Fig 5: Dissolution graph of pure drug and physical mixture

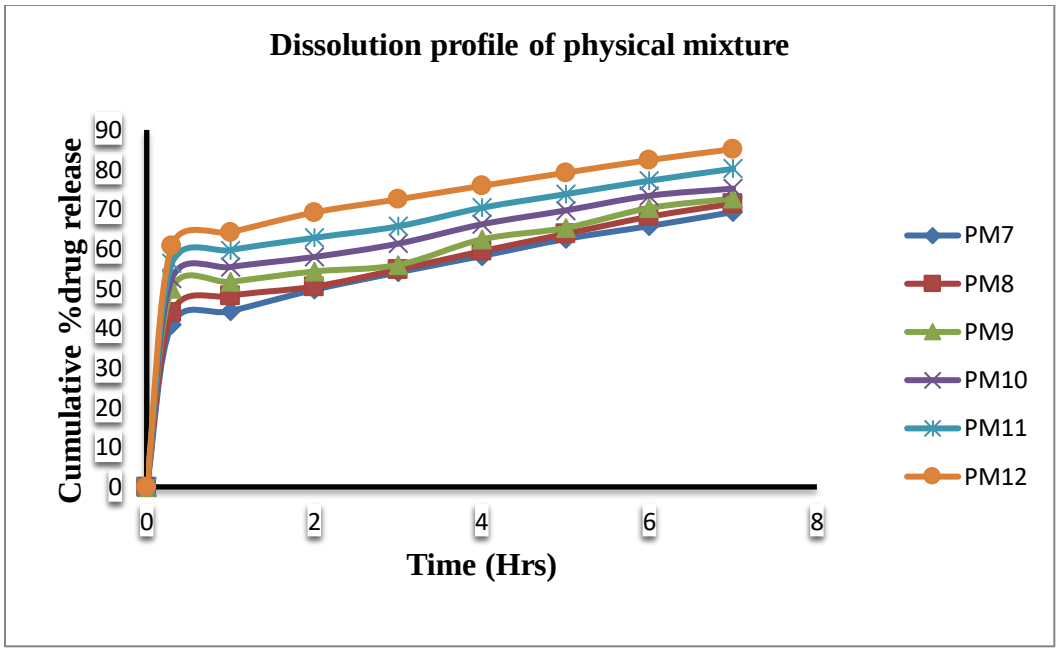

Fig 6: Dissolution graph of physical mixture

Fourier Transform Infrared Spectroscopy:

The pure substance had multiple distinctive, high intensity peaks that demonstrated the drug's crystalline form. The diffused peaks in the SD suggest that the substance has amorphized. In order to distinguish the drug from SD and PM, characteristic peaks attributed to the functional group contained in the drug's structure were allocated. Carvedilol phosphate's FTIR spectra revealed recognizable peak.

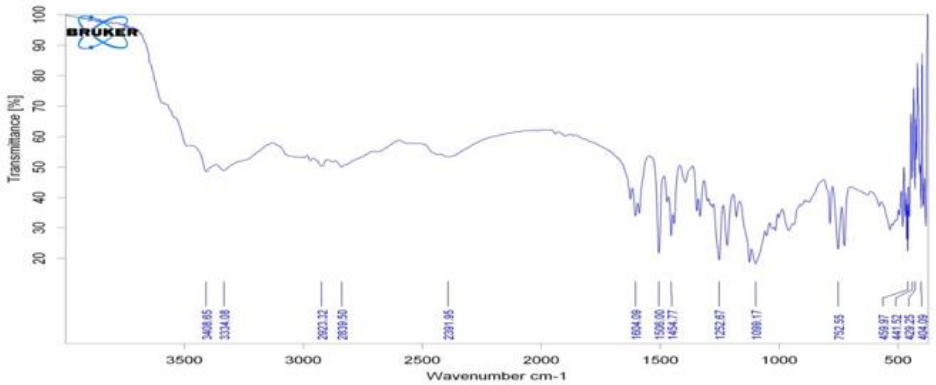

Fig 7: FTIR spectra of Carvedilol phosphate

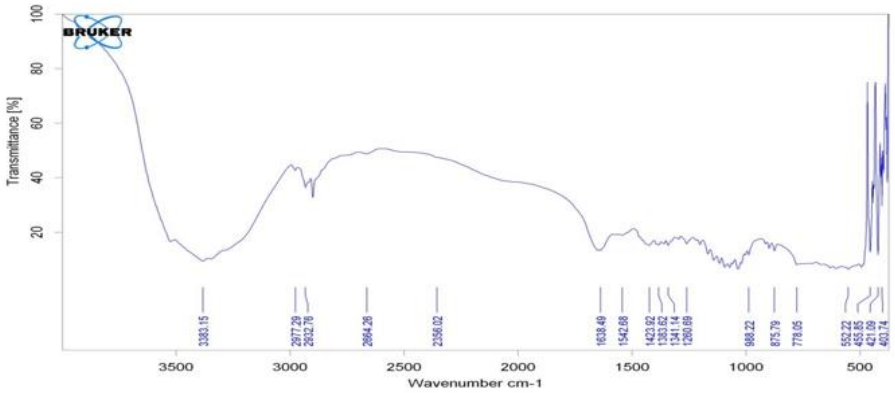

Fig 8: FTIR spectra of Skimmed milk Powder

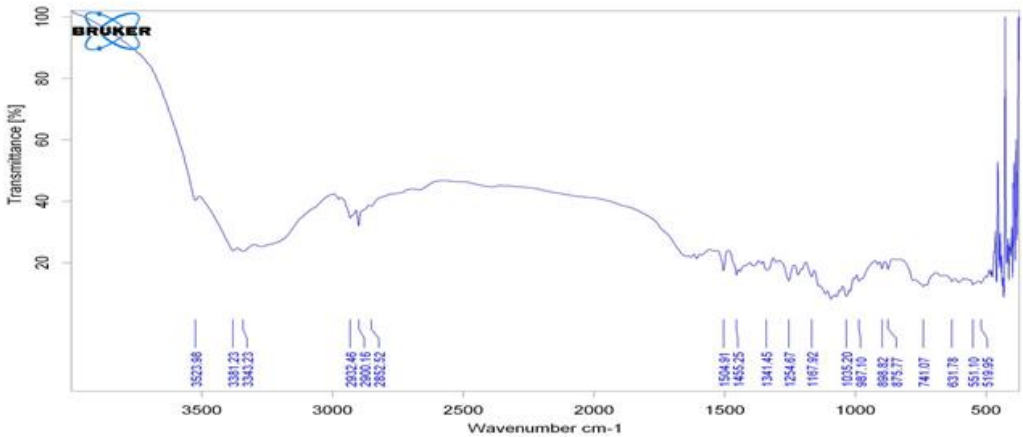

Fig 9: FTIR spectra of Optimized SD formulation

CONCLUSION:

Solid dispersions of carvedilol phosphate prepared using skimmed milk showed considerable increase in solubility and hence dissolution when compared to pure drug. Physical mixtures of drug and skimmed milk powder also improved the solubility. However, the improvement was not comparable to solid dispersions. Moreover, skimmed milk being natural in origin and easily available, it can be a better alternative to synthetic carriers. Also, from the literature it is evident that milk being a source of amino acids. Therefore, preparation of solid dispersions of cavedilol phosphate using skimmed milk is a good technique to improve the solubility

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