Enhancement of Solubility of Poorly Soluble Drug Using Drug Solution Dropping Technique

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Abstract- The objective of the present study is to improve dissolution rate of poorly soluble drug from tablet by drug-solution-dropping-technique. Carvedilol was used as a model drug. Carvedilol is a nonselective beta-adrenergic blocking agent with alpha1-blocking activity and is indicated for the treatment of hypertension and mild or moderate heart failure of ischemic or cardiomyopathic origin. Dichloromethane was use to prepare carvedilol drug solution. The drug solution was dropped on tablet by using microsyringe. Blank tablets were prepared by direct compression (DC) method by using dicalciumphosphatedihydrate as diluents. Different types and concentration of superdisintegrants were used. The different superdisintegrants used were sodium starch glycolate, croscarmaellose sodium and crospovidone. The tablets were subjected to thickness, weight variation test, drug content, hardness, friability and invitro release studies. The results were found within the limits. The USP paddle method was selected to perform the dissolution profiles carried out by USP apparatus 2 (paddle) at 50 rpm in 900 ml of 0.1 N HCL. Dissolution profiles of the prepared tablet from the blank tablets were compared to carvedilol tablet prepared by the conventional direct compression method. The surfaces of carvedilol drug-solution-dropping-tablets were characterized by scanning electron microscope. Their morphologies revealed the smoother but not being clear to point out carvedilol particles on the surface of the tablet. FTIR studies showed that there was no interaction between drug and excipients. Hence it can be concluded that drug solution dropping technique can be regarded as a novel technique to improve dissolution properties of potent drugs belonging to BCS class II.

Index Terms- Carvedilol, Drug-Solution-Dropped-Tablets, Enhancing solubility, super Disintegrants.

I. INTRODUCTION

Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous system. Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous system. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration (Kumar SK et.al, Int J of Pharma and Bio Scie.2010; 1: 83-89). Low aqueous solubility is the major problem encountered with formulation development of new chemical entities. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. The absorption rate of poorly water-soluble drug, formulated as an orally administered solid dosage form, is controlled by its dissolution rate in fluid at the absorption site. The dissolution rate is often the rate-determining step in drug absorption. Therefore, the solubility and dissolution behavior of a drug are the key determinants of the oral bioavailability. These two aspects form the basis of the biopharmaceutical classification system (BCS) (Dahan A et.al. The AAPS Journal, 2009; 11: 66-68). Carvedilol is a member of the class-carbazoles (BCS class II drug), is both a beta blocker (β1, β2) and alpha blocker (α1) and is indicated for the treatment of hypertension and mild or moderate (NYHA class II or III) heart failure of ischemic or cardiomyopathic origin. (Bristow MR, American J of Cardiology.2007; 81: 26L- 40L). Over the last few years, various approaches aimed to enhance Carvedilol include dissolution properties using complexation, solid dispersions, particle size reduction, co-solvency etc (Himami bajaj et.al, int J of Pharma and Bio Sciences. 2011; 2: 204-210).

II. MATERIALS AND METHODOLOGY

Materials: Dicalcium Phosphate, Croscarmellose Sodium, Sodium Starch Glycolate, Crospovidone, Carvedilol, Magnesium Stearate (Bright labs).

Equipment: Tablet compression machine Mini press I (Karnavathi, Rimek), Hardness Tester OSSCO (Monsanto Hardness Tester), Friability Test Apparatus INCO (Instrument & chemicals. Pvt. Ltd, India), Tablet Dissolution Test Apparatus TDT 08L (Electro lab USP), UV Visible Spectrophotometer SL 164 (ELICO, Double beam UV, Visible Spectrophotometer), Balance AUX 220 (Shimadzu Digital balance), Hot air oven.

Preformulation studies: Preformulation involves the application of biopharmaceutical principles to the physiochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system.

Drug Excipients compatibility studies were carried out by mixing the drug with various excipients in different proportions (in 1:1 ratio were prepared to have maximum likelihood interaction between them) was placed in a vial and closed with rubber stopper and sealed properly. Studies were carried out in glass vials at Accelerated conditions, 40°C ± 2°C / 75% RH ± 5% RH and a storage period of 12 weeks. After storage, the sample was compared with control at 2-8°C and observed physically for liquefaction, caking, and discoloration.

Analytical method development for Carvedilol

a) Determination of absorption maxima

A spectrum of the working standards was obtained by scanning from 200-400nm against the reagent blank to fix absorption maxima. The wavelength was found to be 240nm. Hence all the further investigations were carried out at same wavelength.

b) Preparation of standard graph in 0.1 N HCL

10 mg of Carvedilol was dissolved in methanol 10 ml, volumetric flask make up to 1000 ml of 0.1 N hydrochloric acid, from this primary stock 1 ml was transferred to another volumetric flask made up to 10 ml with 0.1 N hydrochloric acid to produce 1, 2, 4, 6, 8 µg/ml respectively. The absorbance was measured at 240 nm by using a UV spectrophotometer.

Preparation of drug solution dropping tablets

a) Preparation of drug solution: For the preparation of drug solution dropped tablets a volatile solvent is chosen in which the drug shows the maximum solubility. Carvedilol shows maximum solubility in di chloromethane, about 50 mg of drug was soluble in 1 ml of the solution.

b) Preparation of blank tablet

1) By direct compression method: For the preparation of blank tablets dicalcium phosphate was used as a filler and magnesium stearate was used as a lubricant. The super disintegrant used was croscarmellose sodium in the concentration of 5% and 7.5%. Initially the required amount of dicalcium phosphate was weighed and was blended with magnesium stearate of calculated quantities. To the homogenous powder super disintegrant i.e. croscarmellose sodium was added. The mixed powder was then compressed on instrumented single stroke tabletting machine. The obtained blank tablets had a flat surface with 650mg weight. In the similar manner various concentrations of other super disintegrants like sodium starch glycolate and crospovidone were used. In all the formulations there had been the usage of varied concentrations of super disintegrants.

2) Drug-Solution-Dropping-Tablets (DSDT): The prepared drug solution was taken in to a micro syringe and was dropped on the surface of direct compressed blank tablets. All of the treated tablets were prepared in an oven at 50°C in hot-air oven for half an hour. After the drying of the tablets the tablets are again compressed to get smooth surfaced tablets.[13, 14]

Preparation of conventional tablets: In the preparation of conventional tablets firstly dicalcium phosphate is weighed and magnesium stearate is added to it. This is triturated to make fine powder and to this super disintegrant is added. This is mixed well and finally the drug is added. This is mixed well and finally the drug is added. The powder is punched in a tablet compressing machine to get a flat surface tablets.[37]

Formulation (mg)	DF1	DF2	DF3	DF4	DF5	DF6
Dicalcium phosphate	602.5	602.5	602.5	586.25	586.25	586.25
Magnesium stearate	15	15	15	15	15	15
Drug (Carvedilol)	50	50	50	50	50	50
Croscarmellose sodium	5%	-	-	7.5%	-	-
Sodium starch glycolate	-	5%	-	-	7.5%	-
Crospovidone	-	-	5%	-	-	7.5%

Table 1: Composition of Drug-Solution-Dropped-Tablets

Evaluation of drug-solution-dropping-tablets

Pre compression parameters: Measurement of micromeritic properties of powders are studied by following methods: Angle of repose, Bulk density, Tapped density Compressibility Index, Hausner's ratio.

Post compression parameters:

Thickness -The thickness of drug solution dropping tablets was determined by using Digital micrometer. Ten individual tablets from each batch were used and the results averaged.

Hardness- The hardness of prepared tablets was determined by using Monsanto hardness tester and measures in terms of kg/cm[2.]

Friability The friability values of the tablets were determined using a Roche-type friabilator. Accurately weighed six tablets were placed in Roche friabilator and rotated at 25 rpm for 4 min.

Weight Variation- Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation three batches were calculated. It passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown. It was calculated on an electronic weighing balance.

Assay -The content of drug in five randomly selected drug solution dropped tablets of each formulation. The five tablets were grinded in mortar to get powder; this powder was dissolved in 0.1 N HCL by sonication for 30 min and filtered through filter paper. The drug content was analyzed spectrophotometrically at

240 nm using spectrophotometer. Each measurement was carried out in triplicate and the average drug content was calculated.

Disintegration test -Six tablets are taken randomly from each batch and placed in USP disintegration apparatus baskets. Apparatus was run for 10 minutes and the basket was lift from the fluid, observe whether all of the tablets have disintegrated.

Dissolution test of Carvedilol drug solution dropping tablets- Drug release from carvedilol drug solution dropped tablets was determined by using dissolution test United States Pharmacopoeia (USP) 24 type II (paddle). The parameters used for performing the dissolution were 0.1 N HCL as the dissolution medium of quantity 900 ml. the whole study is being carried out at a temperature of 37°C and at a speed of 50 rpm. 5 ml aliquots of dissolution media were withdrawn each time at suitable time intervals (10, 15, 30, 45, 60 minutes.) and replaced with fresh medium. After withdrawing, samples were filtered and analyzed

after appropriate dilution by UV spectrophotometer. The concentration was calculated using standard calibration curve.

FTIR: FTIR analysis was done on the optimized formula. Five mg of substance was taken on Agate Pestle. It was thoroughly titrated with 100mg of Potassium Bromide. A pellet was made out of the mixture and introduced in the instrument. Resolution of 4cm-1, scanning was done in the range of 400-4000 cm-1.[15]

SEM: Particle morphology from tablet was revealed by SEM (scanning electron microscope). The accelerating voltage was set at 10 kV and magnification at 100x - 1500x. The samples were in the aluminum stub with two-faced glue paper and coated with gold before SEM analysis.

III. RESULTS & DISCUSSION

Formulation code	Angle of Repose (θ)	Loose Bulk Density(g/ml)	Tapped Bulk Density(g/ml)	Carr's Index (%)	Hausner's Ratio
DF1	23.14±0.03	0.480±0.03	0.564±0.02	13.30±0.03	1.15±0.02
DF2	23.90±0.02	0.439±0.04	0.514±0.02	12.83±0.03	1.13±0.02
DF3	21.20±0.03	0.449±0.02	0.521±0.01	13.82±0.02	1.16±0.02
DF4	24.86±0.04	0.431±0.03	0.504±0.02	14.48±0.02	1.17±0.01
DF5	22.10±0.03	0.462±0.02	0.524±0.03	11.83±0.03	1.13±0.02
DF6	22.90± 0.02	0.459± 0.04	0.534± 0.02	14.04±0.03	1.16±0.02

Table 2: Precompression parameters of tablets

Post compression parameters of all tablets

Evaluation Parameters	DF1	DF2	DF3	DF4	DF5	DF6
Hardness (kg/cm^2)	4.3± 0.3	4.6± 0.4	4.5± 0.2	4.4± 0.4	4.9± 0.3	4.9± 0.2
Disintegrationtime (sec)	140± 5	170± 5	160± 4	120± 4	150± 4	130± 3
Thickness (mm)	2.6± 0.03	2.7± 0.02	2.9± 0.02	2.5± 0.04	2.8± 0.01	3.0± 0.01
Weight variation (mg)	698.8± 0.5	699.8± 1.3	702.1± 3.3	700.3± 0.3	703.5± 1.7	704.7± 2.8
Friability (%)	0.54	0.45	0.34	0.26	0.34	0.25
Content uniformity (%)	98.0± 0.2	98.0± 0.8	99.0± 0.2	99.8± 0.5	99.5± 0.6	98.2± 0.5
Drug release (30 min)	85.03	70.02	65.01	99.08	80.02	75.01

Table 3: Evaluation parameters of drug solution dropped tablets

Evaluation Parameters	CF1	CF2	CF3	CF4	CF5	CF6
Hardness(kg/cm^2)	4.5± 0.2	4.8± 0.3	4.7± 0.4	4.9± 0.2	4.9± 0.3	4.8± 0.2
Disintegration time (sec)	260± 3	270± 4	280± 3	240± 9	260± 3	270± 4
Thickness(mm)	2.8± 0.03	2.9± 0.02	3.2± 0.01	3.0± 0.04	2.9± 0.01	3.1± 0.01
Weight variation (mg)	699.1± 0.5	700.8± 1.4	705.1± 0.8	702.4± 1.7	705.5± 0.4	705.7± 1.3
Friability (%)	0.31	0.25	0.63	0.32	0.47	0.72
Content of uniformity (%)	99.0± 0.6	98.9± 0.9	98.6± 1.2	99.8± 0.2	98.8± 0.8	97.5± 0.6
Drug release (30 min)	65.09	46.04	41.04	67.11	49.15	40.06

Table 4: Evaluation parameters of conventional tablets
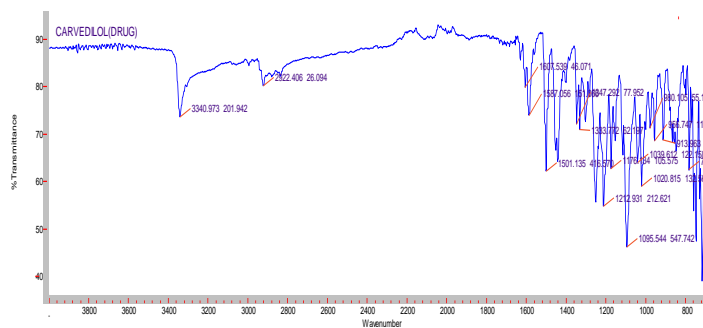
Drug compatibility studies

Fig 1: FTIR of Pure drug

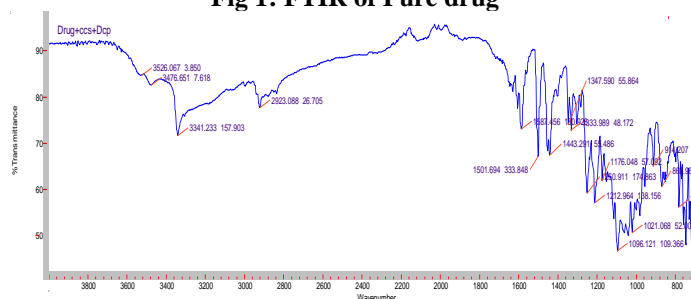**Fig 2: FTIR of Drug+excipients (Optimized formula DF4)**

Drug/ Polymer	N-H, O-H Stretching	C-O Stretching	C=C Stretching	=C-H Bending
Carvedilol	3340.97	1095.54	1501.13	783.57
Optimized Formulation (DF4)	3341.23	1096.12	1501.69	783.54

Table 5: FTIR Absorption bands

Inference It is inferred that FTIR results of drug and drug+excipients showed that there was no incompatability between drug and excipients.

SEM analysis The SEM morphology of the surface of carvedilol-solution-dropping-tablets of optimized formulation were tested are shown in figure. It shows the particles adhered close together. The DSDT surface looked smoother, the surface of DSDT looked like the multiple layer of sheet and carvedilol particles had not been seen. The S.E.M method could not clearly point out the carvedilol particle on the tablet surface and under tablet surface of DSDT from other excipients. It may be possible that the carvedilol solution dropped penetrated into the pores of the tablet. It proves the uniform distribution of drug into the blank tablet.

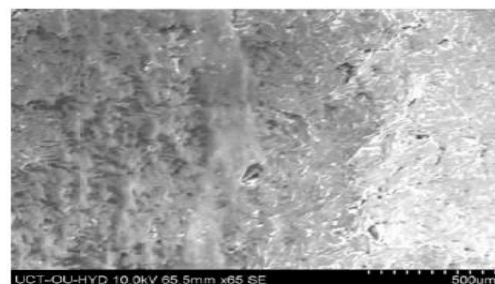DSDT-Drug-Solution-Dropped-Tablets

Fig 3: SEM analysis of formulation DF4

Inference SEM results have shown that there is no drug on the surface it proves the uniform distribution of drug into the tablet.

DISCUSSION
Preformulation studies
Drug-Excipient compatibility study at 40°C/75% RH After 4 weeks of study physical appearance of these compositions were made and compared with the initial observations. After the storage, the samples were observed physically for liquefaction, caking, and discoloration. Physical mixture of drug and other tablet excipients after storage period of 4 weeks at 40°C/75% RH shows no physical changes. Hence the selected excipients are likely to be suitable for the preparation of drug solution dropped tablets (Table 2).

Standard graph of Carvedilol Different standard concentrations and their absorbance values were determined. At all concentration levels the standard deviation value was, supported by high regression value (0.9992).

Formulation studies
Powder flow is a complicated matter and is influenced by so many interrelated factors; the factors' list is long and includes physical, mechanical as well as environmental factors. Therefore, in our study, because of the subjective nature of the individual types of measurements as indicators of powder flow, three flow measurement types were employed; the angle of repose, Carr's index (compressibility index), and Hausner's ratio.

As the angle of repose (θ) is a characteristic of the internal friction or cohesion of the particles, the values of the angle of repose will be high if the powder is cohesive and low if the powder is non cohesive, those having higher angles of repose were considered as non-acceptable.

Powders showing Carr's index (%) up to 21 are considered of acceptable flow properties. In addition to Carr's index, Hausner found that the ratio were related to the inter particle friction so, he showed that powders with low inter particle friction, had ratios of approximately 1.25 indicating good flow. The values are shown in table 2.

Post compression parameters of all tablets
DF4 formulation showed higher dissolution profiles when compared to the rest of the formulations in less time. This may be due to the amount of super disintegrant and increase in the surface area which aid in absorbing excessive amount of liquid in physical mixture.

Drug solution dropped formulations (DF4) containing dicalcium phosphate and crospovidone showed lowest drug release profiles when compared to other formulations. But these formulations are showing excellent flow properties.

In all the formulations it is observed that among various concentrations (i.e., 5%, 7.5%) the formulations with 7.5% of super disintegrant which showed best dissolution in croscarmellose sodium.

DF4 formulations prepared with croscarmaellose sodium at optimized formula, this formulation showed the more dissolution in less time compared with sodium starch glycolate and crospovidone.

From the above results DF4 formulation is the best formulation hence further stability studies were done and the release were compared with marketed formulation. All the drug solution dropped tablets were showing acceptable content uniformity and dissolution profiles.

The most important observation in the drug solution dropped formulations had higher drug dissolution rate than the conventional formulations.

In addition, the study on drug solution dropped tablets verified that drug solution dropped tablets due to their increased wetting properties and surface of drug available for dissolution demonstrated significantly higher drug release rates than those of conventionally made, directly compressed tablets containing micronized drug particles.

Moreover, it was previously established that the higher dissolution rates displayed by drug solution dropped tablets, in comparison with conventional tablets, may also imply enhanced oral bioavailability due to increased wetting properties and surface of drug available for alternative for the formulation of water-insoluble drugs into rapid release tablets dissolution. The values are shown in table 3.

Therefore, they proved that drug solution dropped technique can be a promising technology.

Drug compatibility studies
FTIR The characteristic absorption bands of carvedilol are shown. It is clear from the results; there is no appreciable change in the positions of characteristic bands of the drug when mixed with other excipients. Hence, it can be concluded that the drug maintains its identity without going any chemical interaction with the polymers used. The values are shown in table 5, and figures 1, 2.

SEM The SEM morphology of the surface of carvedilol-solution-dropping-tablets of optimized formulation were tested, shown in figure. It shows the particles adhered close together. The SEM method could not clearly point out the carvedilol particle on the tablet surface and under tablet surface of DF from other excipients. It may be possible that the carvedilol solution dropped penetrated into the pores of the tablet. It proves the uniform distribution of the drug into the blank tablet. The values are shown in figure 3.

IV. CONCLUSION
Of all the drug solution dropped formulations prepared DF4 was found to be optimized formulation as it showing desired release along with acceptable physical properties.

DF4 was showing 99.5% release where as conventional formulation was showing 75.4% release in 30 mins. So optimized formulation is showing better release which is due to the enhanced dissolution behavior which is useful for hypertension and congestive heart failure patients for immediate action. FTIR studies showed that there is no significant interaction between drug and excipients. The SEM method could not clearly point out the carvedilol particle on the tablet surface. It may be possible that the Carvedilol solution dropped penetrated into the pores of the tablet. It proves the uniform distribution of drug into the blank tablet.

From the above discussions it can be concluded that DF4 formulation having 7.5% super disintegrant i.e. croscarmellose

sodium is the best formulation among others. Hence it can be appealed for further research.

Hence it can be concluded that, Drug solution dropped tablets act as a new technique to solve the problem of solubility and dissolution faced by many drugs belonging to BCS class II.

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