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Formulation and Evaluation of Fast Disintegrating Tablet of Solid Dispersion of Carvedilol - A Research

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ABSTRACT

The aim of the present work is Formulation and Evaluation of Fast Disintegrating Tablet of Solid Dispersion of Carvedilol. The solid dispersions of Carvedilol were prepared with PEG6000 and PVP K30 in 1:1, 1:2, 1:3 by using Kneading method. The prepared solid dispersions were analyzed for FTIR. Solid dispersions showed a better dissolution compared to the pure drugs and among all the other formulations. The F3 formulation shows high percentage drug release i.e. 96.61% in 40 min and selected as an optimized formulation for the preparation of fast disintegrating tablets of Carvedilol. Crosscarmellose sodium and Crospovidone used in the preparation of fast disintegrating tablets prepared by direct compression method. The post compression parameters of all the prepared tablets were within the limits. FD6 was selected as optimized formulation based on its highest disintegration time 48 sec and drug release 94.87% in 40 min. Hence it concluded that solid dispersions incorporated fast disintegrating tablets is very useful approach for fast disintegration of Carvedilol to treat high blood pressure.

KEYWORDS: *Solid dispersion, Carvedilol, Kneading method, Bioavailability*

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INTRODUCTION:

Solubility is one of the most important physicochemical properties of any drug because low solubility can affect the bioavailability of orally administered dosage form. Thus, it is very important to enhance the solubility of poorly soluble drug. Carvedilol is a poorly water soluble drug having short half-life of 2-8 hours. The aim of the present study is to enhance the solublity of Carvedilol using different solid dispersion techniques with various carriers, which may results in increase absorption and thereby improved bioavailability. Oral bioavailability of drugs depends on its solubility and/or dissolution rate, therefore major problems associated with these orally administered drugs was its low solubility in biological fluids, which results into poor bioavailability after oral administration. Solid dispersion is defined as a dispersion of one or more active ingredients in an inert carrier or matrix at solid state. Is a well-known approach for improvement of the dissolution rate and bioavailability of drugs that are poorly water soluble. The carriers used have to be physiologically inert compounds that are readily water-soluble or water insoluble for fast or controlled dissolution respectively. To achieve faster dissolution rate of poorly water-soluble drug, the drug is dispersed at molecular level in a rapidly water-soluble inert carrier to form a solid dispersion. Successful dispersion of the drug in the carrier, at molecular level, leads to formation of homogeneous phase of the solid dispersion. When such a product comes in contact with gastric fluid, then the water- soluble carrier rapidly dissolves leading to immediate release of the drug at the desired molecular level to cause dissolution with consequent improvement of bioavailability.

FAST DISINTEGRATING TABLET

The tablet is the most widely used dosage form existing today because of its convenience in term of self-administration, compactness and ease I manufacturing. However Pediatric and geriatric patients find it difficult to swallow solid dosage forms

like tablets. fast disintegrating tablet that dissolve or disintegrate rapidly in oral cavity result in solution, is an ultimate remedy for this problem. In addition they give pleasing mouth feeling. FDT has advantages such as patient compliance, quick onset of action, improved bioavailability, etc. Therefore, fast disintegrating tablets are attractive alternative to liquid and conventional tablet dosage forms. In recent past, several manufacturing technologies such as sublimation technique, spray drying technique... etc. are employed to overcome the limitations of conventional tablet dosage forms. Once the fast disintegrating tablets are prepared they are required to be evaluated for various parameters so as to have long term stability and better therapeutic efficacy.

The Basic approaches to develop dispersible tablet include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water soluble excipients in the formulation, dispersible tablet can be achieved by various direct technical compression.

MATERIALS AND METHODS

Following drug, excipients were used for the formulation and evaluation studies. Carvedilol was gift sample by Lupin Pharma, Sikkim. PEG 6000, PVP K30 were provided by Research-lab fine chem. Industries, Mumbai. Crosspovidone , Croscarmellose sodium, Microcrystalline cellulose, Mannitol, Magnesium Stearate,Talc were provided by Research lab fine chem. Industries, Mumbai.

PREFORMULATION STUDIES OF CARVEDILOL

The various physicochemical properties of drug and excipients were checked.

Identification and Characterization of Carvedilol

1. Organoleptic Evaluation

The drug sample was evaluated for its color, odour and appearance. The results are shown in Table 10.1

2. Melting Point:

Melting point of drug sample was determined by capillary method by using melting point apparatus.

3. Solubility Profile

The solubility of Carvedilol was determined by adding excess amount of drug in the solvent and equilibrium solubility was determined by taking supernatant and analyzed by using spectrophotometer at 242 λmax.

UV SPECTROSCOPIC ANALYSIS OF CARVEDILOL

UV-Spectroscopic Analysis of Drug

A. Determination of Absorption Maxima

UV scanning was done in Shimandzu double beam UV spectrophotometer using 10 µg/ml drug solutions in the wave length range of (200-400 nm). 0.1 N HCl solution used as a blank

B. Preparation of Calibration Curve

1. Preparation of 0.1 N HCl

Dissolve 8.5 ml of concentrated HCl in 1000 ml of distilled water

2. Preparation of standard drug solution Stock solutiom:

10 mg of Carvedilol was dissolved in 10 ml of 0.1 N HCl, to get a solution of 1000 µg/ml concentration.

Standard solution:

1 ml of stock solution was made upto 10 ml with 0.1 N HCl thus giving a concentration of 100 µg/ml. The standard drug solution ranging from 0.2ml, 0.4 ml, 0.6 ml, 0.8ml and 1 ml were transferred into 10 ml volumetric flask and were diluted up to the mark with 0.1 N HCl. Thus the final concentration ranges from 2-10 µg/ml. Absorbance of each solution was measured at 242 nm against 0.1 N HCl as a blank. A plot of concentrations of drug versus absorbance was plotted.

Drug- Excipient Compatibility Studies

1. FT-IR Spectroscopy of Carvedilol

Infrared spectra matching approach was used for the detection of any possible chemical reaction between the drug and the excipients. A drug and polymer was prepared and mixed with suitable quantity of Potassium bromide. About 100 mg of this sample was compressed to form a transparent pellet using a hydraulic press at 10 tons pressure. It was scanned from 4000 to 600 cm^{-1} FTIR Spectrophotometer. The interaction between drug-excipients was observed from IR spectral studies by observing any shift in peaks of drug in the spectrum of physical mixture of drug.

PREPARATION OF SOLID DISPERSION

1. Preparation of Solid Dispersions by Kneading Method

Carvedilol+PEG6000 and Carvedilol+PVP K30 in (1:1,1:2,1:3) ratio were prepared by kneading method. Polymer was mixed in glass mortar along with solvent to obtain homogenous paste. The drug was then slowly added to the paste and the mixture was triturated for 30 min. During this process adjusted to maintain the consistency of paste. The paste dried in oven. Dried powder was passed through sieve.

Table 1.3: Formulation of Drug and Polymer using by Kneading Method

Formulations	Composition	Ratio
F1	Carvedilol + PEG 6000	1:1
F2	Carvedilol + PEG 6000	1:2
F3	Carvedilol + PEG 6000	1:3
F4	Carvedilol + PVP K30	1:1
F5	Carvedilol + PVP K30	1:2
F6	Carvedilol + PVP K30	1:3

EVALUATION OF SOLID DISPERSION

The solid dispersion of Carvedilol were prepared and then subjected to evaluation parameter such as solubility study, percentage yield, drug content, dissolution study.

Physical Appearance

It include the visual inspection of solid dispersion. All the batches of drug and polymer solid dispersions were evaluated for color and appearance.

Solubility Study

Solubility of pure drug and all solid dispersions prepared by Kneading method has been studied. The amount of solid dispersion powder containing 2.5 mg equivalent Carvedilol weighed accurately in volumetric flask and was dissolved by sonication in 5 ml distilled water for 15 min. Filtered through a whatman filter paper no.1. Filtered solution was diluted properly with distilled water. The diluted solution was analysed spetrophotometry at 242 nm. The measurement of solubility shown in Table 2.8

Percentage Yield

Yield was calculated with respect to dry product. Based on the practical yield (P.Y) obtained and the calculated theoretical yield (T.Y), % yield was calculated by using the following formula:

PY(%)=[Practical weight/Theoretical weight (Drug +Carrier)]x100 .....Eq^{n}9.1

Where,

a = Practical weight of solid dispersion preparation.

b = Theoretical weight of solid dispersion obtained.

It was calculated to know about % practical yield or efficiency of any method which will halp in selection of appropriate method. The % practical yield for each formulation is shown in Table 2.9

Drug Content

An accurately weighed 100 mg of formulations was taken into a 50 ml volumetric flask and dissolved in 40 ml of methanol. The solution was made up to the volume with methanol. The solution was then suitably diluted with 0.1N HCl and assayed for drug content using the UV spectrophotometric method at 242 nm. The Actual Drug Content was calculated using the following equation

In-Vitro Drug Release Study Pure Drug and Solid Dispersion Prepared By Kneading Method

All the formulations of solid dispersions of Carvedilol prepared by Kneading Method were subjected to *in vitro* release study. *In vitro* drug release studies were carried out using using the USP Type II Dissolution test apparatus (Electrolab Model TDT-08L) set with a paddle speed of 50 rpm. Dissolution was performed in 900 ml of 0.1N HCl maintained at $37^0 \pm 0.5^0$C. The drug 10mg of Carvedilol was taken in a muslin cloth and tied to the rotating paddle kept in vessel of dissolution apparatus, the paddle was rotated at 50 rpm. The 5 ml sample was withdrawn at predetermined time interval and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. The solution was filtered through Whatman filter paper. The filtrate was analyzed by UV-Visible spectrophotometer. Three trials for each batch were performed and average percentage drug release was determined. The results are shown in Table 3.3 and accordingly the graph was plotted to calculated % drug release of pure drug in 0.1 N HCl and shown in Figure 2.8

FT-IR Study of Solid Dispersion

Procedure of FTIR study mentioned in above experimental work

FORMULATION OF FAST DISINTEGRATING TABLET OF SOLID DISPERSION OF CARVEDILOL

After evaluation of solid dispersion of Carvedilol prepared by Kneading Method. The fast disintegrating tablets were prepared by using solid dispersion of F3 formulation. Formulation of fast disintegrating tablet given in Table 9.2

Table 1.4: Formulation of Fast Disintegrating Tablet of Solid Dispersion of Carvedilol

Formulations	FD1	FD2	FD3	FD4	FD5	FD6
Ingredient	Unit Formula (mg per tablet)					
Solid Dispersion complex (Equivalent to 12.5mg)	50	50	50	50	50	50
Crosscarmellose sodium (Superdisintegrant)	10	15	20	-	-	-
Crospovidone (Superdisintegrant)	-	-	-	10	15	20
Microcrystalline cellulose(Diluent)	136	131	126	136	131	126
Magnesium Stearate(Lubricant)	2	2	2	2	2	2
Talc(Glidant)	2	2	2	2	2	2
Total	200	200	200	200	200	200

EVALUATION OF BLEND OF FAST DISINTEGRATING TABLET OF SOLID DISPERSION OF CARVEDILOL

The powder blend was evaluated for its flow properties; the parameter like angle of repose, bulk density, Tapped density, Compressibility Index and Hausner ratio was calculated and was shown in Table 1.4

Bulk Density

Apparent bulk density (ρ *b*) was determined by pouring blend into a graduated cylinder. The bulk volume (Vb) and weight of the powder (M) was determined. The bulk density was calculated using the formula.

BD = Weight of the powder/Volume of the powder. ……Eq^{n}9.3

Tapped Density

The minimum volume (Vt) occupied in the cylinder and the weight (m) of the blend was measured. The tapped density (ρ t) was calculated using the following formula.

TBD=Weight of the powder/Tapped volume of the powder ……Eq^{n}9.4

Hausner's Ratio

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula;

Hausner's ratio= ρ t/ρ b ……Eq^{n}9.5

Where,
ρ **t** is tapped density
ρ **b** is bulk density

Table 1.6: Standards for Hausner's Ratio

Hausner's ratio	Flow
1.2-1.3	Excellent
1.3-1.4	Good
1.4-1.5	Fair
1.5-1.6	Poor

Compressibility Index

The simplest way for measurement of free flow of powder is compressibility, a indication of the case with which a material can be induced to how is given by compressibility index (I) which is calculated as follows

Carr's compressibility index (%) = [(TBD-BD)/ TBD x100 ……Eq^{n}9.6

Table 1.7: Standards for Compressibility Index

Carr's Index	Properties
5-15	Excellent
12-16	Good
18-21	Fair to Passable
23-35	Poor
35-38	Very Poor
>40	Very Very Poor

Angle of Repose

The flow characteristics are measured by angle repose. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane

Θ=tan^{-1} (h/r) ……..Eq^{n} 9.7

Table 1.8: Standards for Angle of Repose

Angle of Repose	Flowability
25-30	Excellent
30-35	Good
35-40	passable
>40	Very Poor

PREPARATION OF FAST DISINTEGRATING TABLET OF CARVEDILOL CONTAINING SOLID DISPERSION BY DIRECT COMPRESSION METHOD

Accurately weighed 200mg of powder blend was homogeneously mixed and was fed manually and compressed with constant compression force and hardness on 10 stations tablet compression machine with 8 mm, breakthrough, and flat faced punches on RIMEK MINIPRESS-IIMT. Total nine formulations were prepared. The results are shown in Table 1.4

EVALUATION OF FAST DISINTEGRATING TABLET

Appearance

The tablets were visually observed for capping, chipping and lamination.

Thickness

Three tablets were selected randomly from each batch and thickness was measured by using Vernier Caliper.

Hardness

Hardness or tablet crushing strength (F^o) the force required to break a tablet in a diametric compression was measured using Pfizer Hardness Tester. For each formulation, the hardness of 6 tablets was determined using the Pfizer hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm^2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm^2.

Friability

Friability of the tablets was determined using Roche Friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and roping the tablets height of 6 inches in each revolution.

preweighed sample of tablets was placed in the friabilator and were subjected to 25 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed, the friability (F) is given by the formula.

% F = (Initial wt. - Final wt. / Initial wt.) x 100. ……..Eq^{n}9.8

Content Uniformity

The Carvedilol content was estimated as follows.

Method

20 tablets were finely powdered and weight equivalent to 10 mg of Carvedilol was dissolved in 100 ml of 0.1N HCl and assayed for drug content using UV-Visible spectrophotometer at 242 nm

Weight Variation Method

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviate from the average weight.

Table 1.9: Specifications of % weight variation allowed in tablets

Average Weight of Tablet	% Deviation Allowed
80 mg or less	10
More than 80 mg but less that 250 mg	7.5
250 mg or more	5

Disintegration Time

The disintegration time of tablet was determined by using Disintegration test apparatus. Tablets were placed in disintegration test assembly and disc was placed was placed on tablets in each glass tube of assembly. The assembly was dipped in a vessel containing 900ml 0.1N HCl at 37^{0}C.The time for disappearance of tablet residue above mesh was noted as disintegration time.

***In-vitro* Dissolution Studies**

In vitro drug release studies were carried out using the USP Type II Dissolution test apparatus (Electrolab Model TDT-08L) set with a paddle speed of 50 rpm. Dissolution was performed in 900 ml of 0.1N HCl maintained at 37^0± 0.5^{0}C. The tablet of Carvedilol was taken in vessel of dissolution apparatus, the paddle was rotated at 50 rpm. The 5 ml sample was withdrawn at predetermined time interval and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced and the sample was diluted suitably with dissolution medium. The solution was filtered through Whatmann filter paper. The filtrate was analyzed by UV-

Visible spectrophotometer. Three trials for each batch were performed and average percentage drug release was determined and shown in figure 2.1

RESULTS AND DISCUSSION

Preformulation Studies

The results of physiochemical evaluation are as follows.

Identification and Characterization of Carvedilol

1. Organoleptic Properties

The Carvedilol was studied for physicochemical parameters such as colour, taste, odour and appearance. Sample of Carvedilol was found to be similar as in I.P. On the basis of physicochemical evaluation, it is concluded that the sample of Carvedilol complies with I.P.

Table 2.1: Organoleptic Properties of Carvedilol

Test	Specification/ Limit	Observation
Appearance	Fine Powder	Complies as per I.P
Color	White	Complies as per I.P
Odour	Odourless	Complies as per I.P

Organoleptic evaluation reveals that the sample of Carvedilol obtained was complied with I.P standards.

2. Melting point of Drug

Test	Specification/ Limit	Observation
Melting point	114^0c	112 - 115^0c

3. Solubility Study of Drug

Carvedilol was found to be insoluble in water (1.34 µg/ml)

UV Spectroscopic Analysis of Carvedilol

1. Determination of Absorption Maxima

The UV spectrum of Carvedilol was obtained in 0.1N HCl which shows absorbance maximum (λ max) at 242 nm as presented in Figure 10.1

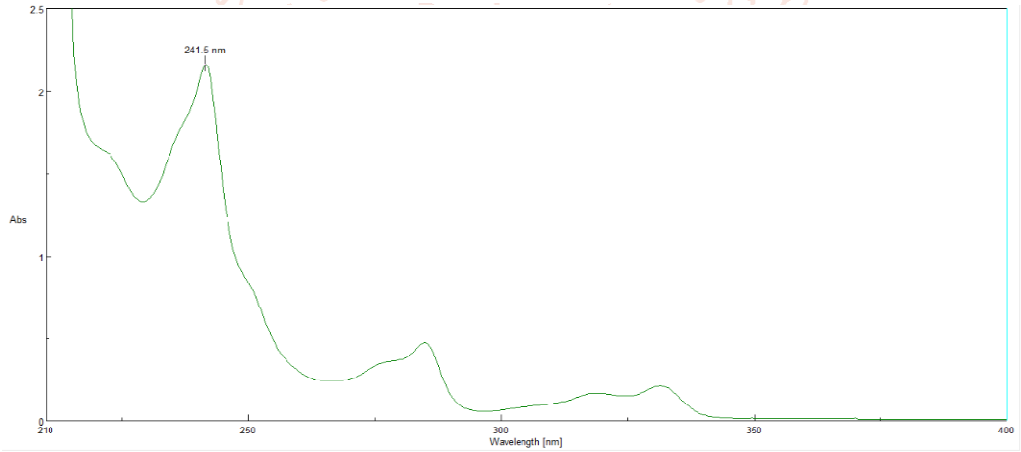

Figure 1.1: UV Spectra of Carvedilol in 0.1N HCl

2. Determination of Standard Calibration Curve of Carvedilol

Standard Calibration Curve of Carvedilol was determined by plotting Absorbance Vs Concentration at 242 nm using 0.1N HCl. It was found that the dilutions of Carvedilol in 0.1N HCl show linearity (R^2 = 0.9964) and obeys Beer-Lambert law.

Table 2.2: Standard Calibration Curve of Carvedilol

Sr.no.	Concentration (µg/ml)	Absorbance
1.	0	0
2.	2	0.247
3.	4	0.448
4.	6	0.603
5.	8	0.827
6.	10	0.982

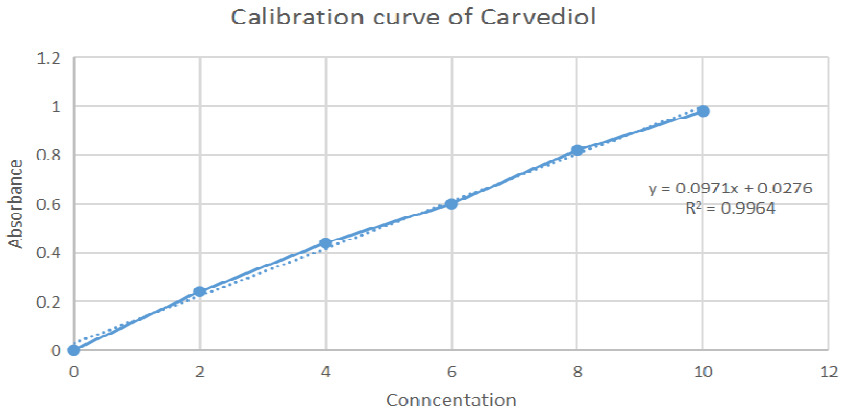

Figure 1.2: Standard Calibration Curve of Carvedilol

FT – IR Spectrum of Drug:

Major functional groups present in Carvedilol show characteristic peaks in IR spectrum. Table shows peaks observed at different wave numbers and the functional group associated with these peaks. The major peaks are identical to functional group of Carvedilol. Hence, the sample was confirmed as Carvedilol.

Carvedilol

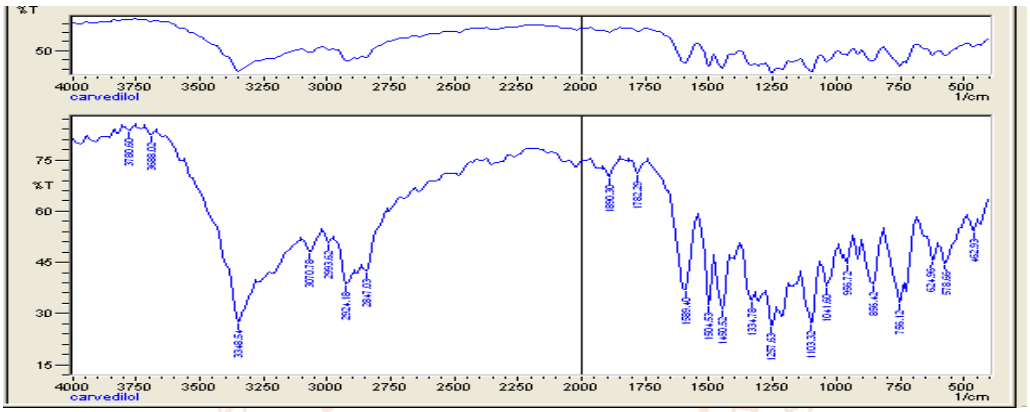

Figure 1.3: FTIR Studies of Carvedilol

Table 2.3: Interpretation of FTIR Spectrum of Carvedilol

Sr.no.	Reference Peak Wavenumber(cm^{-1})	Observed Peak Wavenumber(cm^{-1})	Functional Group
1	3300 – 3350	3345.54	N-H stretching
2	3050 – 3000	3042.06	C-H Stretching
3	3000 – 2500	2924.18	O -H Stretching
4	1600 –1450	1589.40	C=C Stretching
5	1350 –1260	1255	C –O Stretching

The IR spectrum of Carvedilol in figure 2.3 is characterized by Principal absorption peak at 3345.54 cm^{-1} (N-H Stretching), 3042.06 cm^{-1} (C-H Stretching), 2915 cm^{-1} (O-H Stretching), 1589.40 (C=C Stretching) and 1255 (C-O Stretching).

DRUG-EXCIPIENTS COMPATIBILITY STUDIES:

Carvedilol + PEG 6000

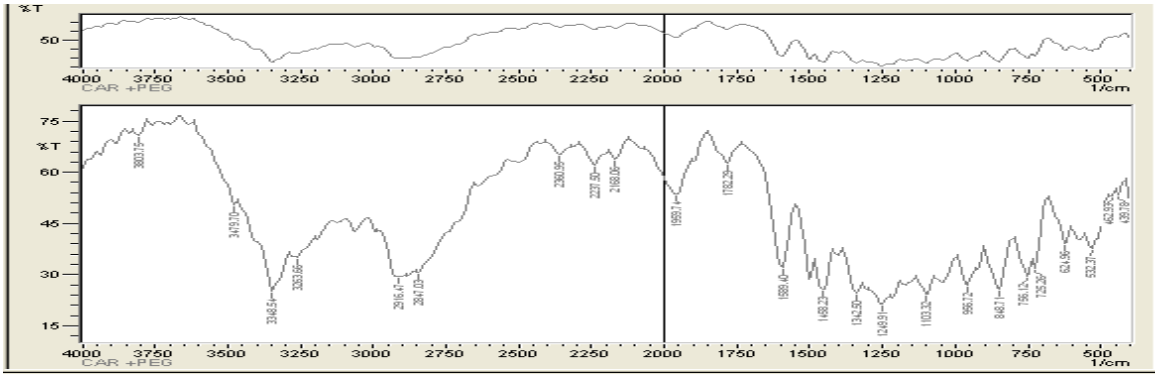

Figure 2.4: FTIR Studies of Carvedilol + PEG 6000

Table 2.4: Interpretation of FTIR Spectrum of Carvedilol + PEG 6000

Sr.no.	Reference Peak Wavenumber(cm^{-1})	Observed Peak Wavenumber(cm^{-1})	Functional Group
1	3300 – 3350	3348.54	N-H Streching
2	3000 – 2500	2847.03	C-H Streching
3	1310 – 1250	1103.32	C-O Stretching
4	1250 -1000	1249.91	O-H Stretching
5	1600 –1450	1589.40	C=C Stretching

Carvedilol + PVP K30

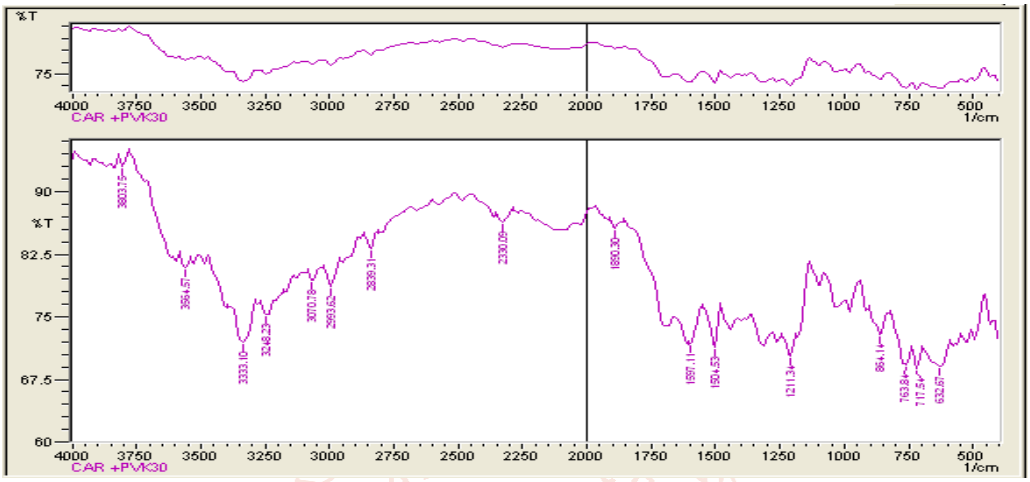

Figure 2.5: FTIR Studies of Carvedilol + PVP K30

Table 2.5: Interpretation of FTIR Spectrum of Carvedilol + PVP K30

Sr.no.	Reference Peak Wavenumber(cm^{-1})	Observed Peak Wavenumber(cm^{-1})	Functional Group
1	3500 -3350	3348.54	N-H Stretching
2	3000 – 2500	3070	C-H Stretching
3	1350 – 1140	1103.33	C-O Stretching
4	1600 – 1450	1504.53	N-H Bending
5	1350 – 1260	1257.63	O-H Stretching

Carvedilol + Crosspovidone

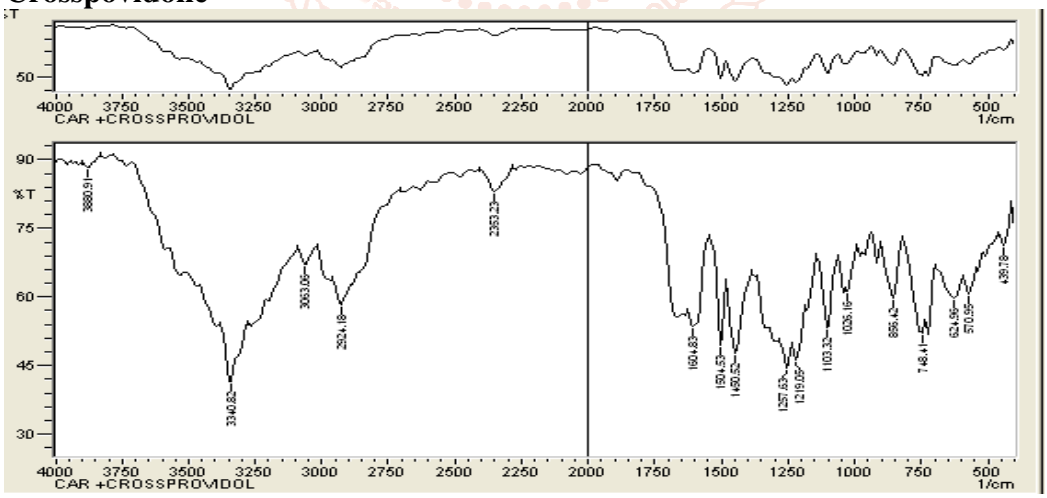

Figure 2.6: FTIR Studies of Carvedilol + Crosspovidone

Table 2.6: Interpretation of FTIR Spectrum of Carvedilol + Crospovidone

Sr.no.	Reference Peak Wavenumber(cm^{-1})	Observed Peak Wavenumber(cm^{-1})	Functional Group
1	3300-3350	3340	N-H stretching
2	3500 – 3000	3063.06	O –H Stretching
3	3000-2500	2924.18	C –H Streching
4	1600 – 1450	1504.53	C -N Stretching
5	1500 -1000	1103.39	C = O Stretching

Carvedilol + Croscarmellose Sodium

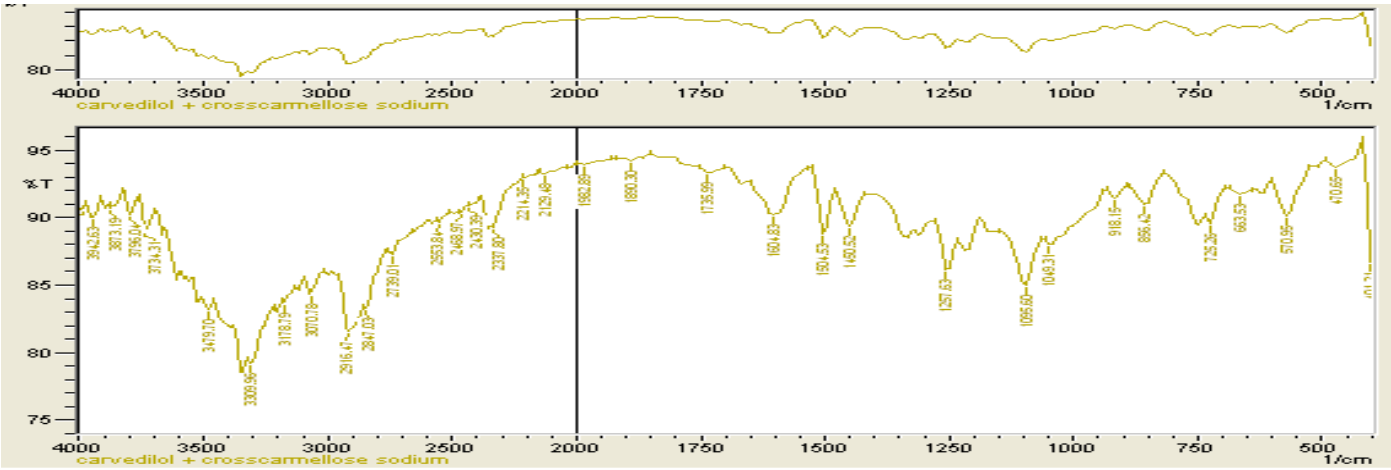

Figure 2.7: FTIR Studies of Carvedilol + Croscarmellose Sodium

Table 2.7: Interpretation of FTIR Spectrum of Carvedilol + Crosscarmellose sodium

Sr.no.	Reference Peak Wavenumber(cm^{-1})	Observed Peak Wavenumber(cm^{-1})	Functional Group
1	3300-3350	3309	N-H stretching
2	3500 – 3000	3070.78	O –H Stretching
3	3000 – 2500	2916.47	C –H Stretching
4	1600 – 1450	1504.53	C = O Stretching
5	1500 -1000	1257.63	C-N stretching of tertiary amine
6	1340 – 1530	1450.52	C=C Stretching

The FTIR spectrum of Drug and Excipients physical mixture showed in figure 2.4 – 2.7. In IR spectra did not show any significant difference from those obtained for their physical mixture. The obtained results indicate that there was no positive evidence for interaction between Carvedilol and Excipients. These results clearly indicate that the above excipients can be used without any interaction for preparation of Solid dispersion and Fast Disintegrating tablet Carvedilol.

PREPARATION SOLID DISPERSION OF CARVEDILOL

The solid dispersion of Carvedilol were prepared by using different polymer ratios. Six formulations of Kneading Method (F1-F6) were prepared and the composition is given in experimental work.

EVALUATION OF SOLID DISPERSION

The solid dispersion of Carvedilol prepared by Kneading Method.These prepared formulations were evaluated for parameters like physical appearance,% practical yield, solubility study, drug content, in-vitro dissolution study, compatibility study.

Physical Appearance

All formulations of Carvedilol solid dispersion were evaluated for color and appearance. The physical appearance of each formulation is shown in Table 2.8

Table 2.8: Physical Appearance of Formulations Drug and Polymer

Formulations	Physical Appearance	
	Color	Appearance
F1	White	Powder
F2	White	Powder
F3	White	Powder
F4	White	Powder
F5	White	Powder
F6	White	Powder

Solubility Study of Solid Dispersion

Solubility study of various formulations of solid dispersion of Carvedilol prepared by Kneading method was performed and shown in table 2.9

Table 2.9: Solubility Study of Solid Dispersion

Formulations	Drug: Carrier	Solubility(µg/ml)
Pure drug	Pure drug	1.34
F1	Carvedilol +PEG 6000(1:1)	11.81
F2	Carvedilol +PEG 6000(1:2)	14.58
F3	Carvedilol+PEG6000 (1:3)	19.87
F4	Carvedilol +PVP K30 (1:1)	9.46
F5	Carvedilol +PVP K30 (1:2)	12.21
F6	Carvedilol +PVP K30 (1:3)	17.39

Solubility study of various solid dispersion trial batches was performed. Solid dispersion prepared showed improved solubility of Carvedilol as compared to pure drug and solid dispersions prepared by Kneading method. The solid dispersion from batch F3 was more soluble than pure drug and other formulation batches.

Percentage Practical Yield Study of Solid Dispersion

Percentage practical yield was calculated to know about % yield or efficiency of any method which will help in selection of appropriate method. The practical yield for each batch is reported in Table 2.10

Table 2.10: Percentage Practical Yield Study of Solid Dispersion

Formulation	Ratio	Theoretical Weight	Practical Weight	% Practical Yield
F1	1:1	0.325	0.273	84.00
F2	1:2	0.458	0.415	88.79
F3	1:3	0.578	0.569	98.26
F4	1:1	0.325	0.269	82.76
F5	1:2	0.318	0.276	86.79
F6	1:3	0.458	0.437	95.41

Different trial batches of solid dispersions showed % practical yield from range 84.00 to 98.26%.The batch F3 Showed 98.26 % practical yield.

Drug Content of Solid Dispersion

The drug content of solid dispersion of Carvedilol of optimized formulation F3 Carvedilol+PEG6000 (1:3) was found to be 98.23%, indicating good content in solid dispersion.

Table 3.1: Drug Content Study of Solid Dispersion

Formulation	Drug Content %
F1	88.39
F2	92.53
F3	98.23
F4	86.78
F5	90.45
F6	94.69

The drug content of solid dispersion of Carvedilol was found to be 86.78 to 98.23%, it indicating good content in Solid Dispersion.

***In vitro* Drug Release Study**

The dissolution study of pure drug and all formulations were carried out to calculate the % drug release.

1. Dissolution Study of Pure Drug

Dissolution study of pure drug in 0.1 N HCl was carried out and absorbance was taken in UV spectrophotometer which is reported Table 3.2

Table 3.2: Dissolution Study of Pure Drug

Time (min.)	Cumulative % drug release
0	0.00
5	10.25±0.64
10	11.12±0.44
15	13.07±0.91
20	15.20±0.75
25	16.59±0.14
30	18.37±0.42
40	21.35±0.34

Results are the mean of three determinations

The % drug release of pure drug after 40 min was 21.35% each reading is taken was triplicate and then mean values were calculated.

2. Dissolution Profile of Solid Dispersions Prepared by Kneading Method

The formulations of solid dispersions prepared by Kneading method(F1-F6) were subjected to dissolution study. The percentage drug release of formulations is showed in Table 10.12 and accordingly the graph was plotted to calculate the percentage drug release of formulations in 0.1N HCl and it is shown in Figure 2.8.

Table 3.3: Dissolution Profile of Solid Dispersions Prepared by Kneading Method

Time(min)	Cumulative % Drug Release					
	F1	F2	F3	F4	F5	F6
0	00	00	00	00	00	00
5	31.54±0.21	33.27±0.25	36.43±0.22	30.31±0.57	32.04±0.35	33.45±0.20
10	44.28±0.25	47.13±0.14	48.53±0.32	43.00±0.42	45.13±0.54	48.32±0.23
15	55.02±0.13	59.04±0.46	61.08±0.71	68.06±.0.35	59.10±0.26	59.25±0.45
20	68.18±0.18	70.76±0.51	72.17±0.64	75.80±0.18	69.76±0.46	71.86±0.64
25	77.96±0.94	80.17±0.15	82.50±0.24	82.50±0.78	76.03±0.37	80.39±0.32
30	85.70±0.34	87.93±0.42	90.36±0.82	85.05±0.46	84.63±0.48	88.24±0.24
40	90.93±0.21	92.92±0.81	96.61±0.37	89.02±0.63	91.85±0.78	94.61±0.37

Results are the mean of three determinations

Out of Six formulations F3 showed maximum drug release i.e. 96.61 %. Solid dispersion (F3) of Carvedilol with PEG 6000 prepared by Kneading method showed significant improvement in solubility and dissolution rate. Increased wetting and solubilizing effect of PEG 6000 as well as the molecular dispersion of drug in solid dispersion and alteration of surface properties of drug particle may be responsible for the enhanced dissolution rate of Carvedilol from solid dispersion compared to pure Carvedilol.

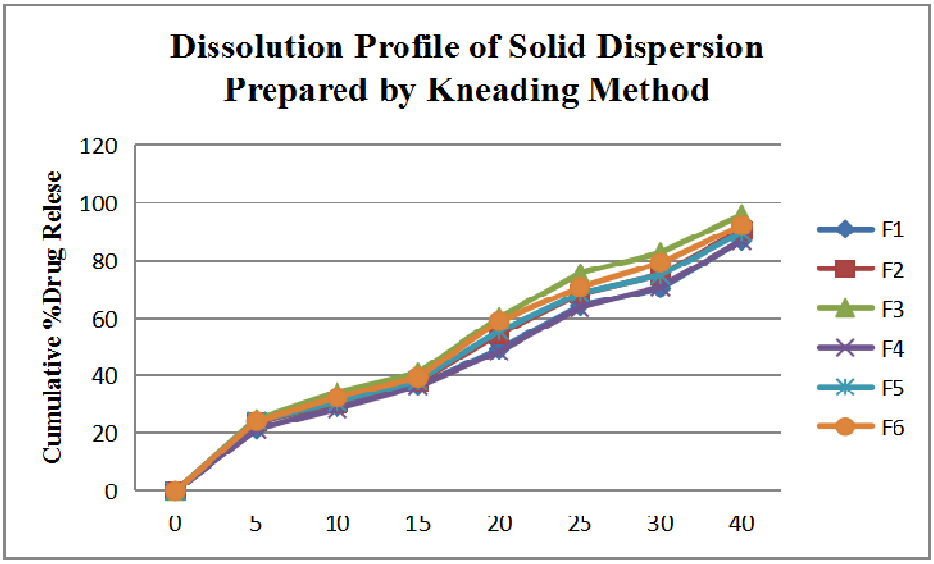

Figure 2.8: Dissolution Profile of Solid Dispersions Prepared by Kneading Method

FT-IR Study of Solid Dispersion

1. **Fourier Transform Infrared Spectroscopy (FTIR) Interpretation Solid Dispersion (F3) Prepared by Kneading method**

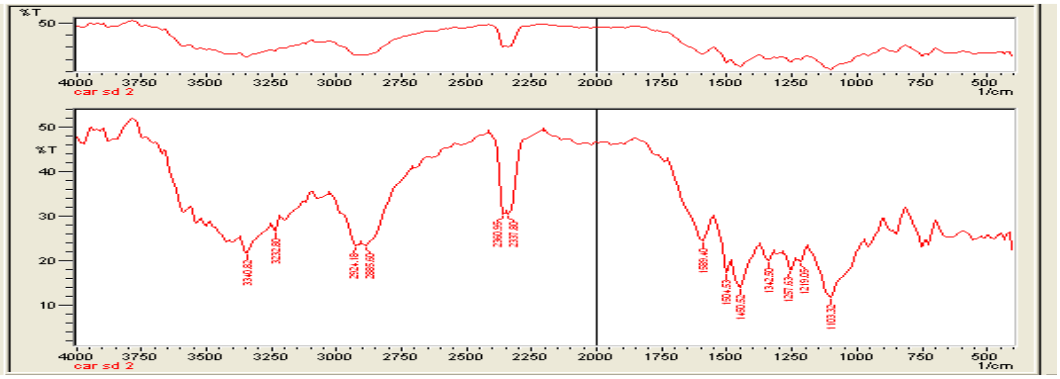

Figure 2.9: FTIR Studies of Solid Dispersion

Table 3.4: Interpretation of FTIR Spectrum of Kneading Method

Sr.no.	Reference Peak Wavenumber(cm^{-1})	Observed Peak Wavenumber(cm^{-1})	Functional Group
1	3300-3350	3340	N-H stretching
2	3500 – 3000	3232.80	O –H Stretching
3	3000-2500	2885.60	O –H Bending
4	1600 – 1450	1589.40	C = C Stretching
5	1500 -1000	1103.39	C = O Stretching

In IR spectrum of solid dispersion of Kneading method showed in figure 3.9. In above IR spectra the peak of drug and polymer are showed in Table 3.4. All principal peaks have appeared in formulation its indicating no chemical interaction between Carvedilol and polymer.

FORMULATION OF FAST DISINTEGRATING TABLET OF CARVEDILOL

According to comparative dissolution study showed in figure 2.8 it is concluded that the solid dispersion prepared by Kneading method containing Carvedilol+ PEG 6000 (1:3) was shown maximum percent drug release as compared to other solid dispersion. Hence the solid dispersion F3 Formulation was selected for preparation of fast disintegrating tablets.

EVALUATION OF TABLET BLEND FOR FAST DISINTEGRATING TABLETS

The tablet blend was evaluated for various precompression parameter like are angle of repose, bulk density, tapped density, hausner's ratio and compressibility index. Results are as follows.

Table 3.5: Evaluation of Tablet Blend For Fast Disintegrating Tablets

Formulations	Angle of repose (Θ)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Hausner's Ratio (H_R)	Carr's Compressibility index (%)
FD1	24.44±1.88	0.44±0.12	0.48±0.023	1.09±0.47	8.33±0.86
FD2	22.52±0.95	0.48±0.16	0.55±0.059	1.14±0.32	12.72±0.50
FD3	24.42±1.78	0.47±0.04	0.50±0.026	1.06±0.38	6±0.30
FD4	23.40±1.27	0.42±0.10	0.47±0.012	1.11±0.20	10.63±0.88
FD5	25.46±1.45	0.43±0.09	0.49±0.021	1.13±0.16	12.24±0.36
FD6	22.43±1.18	0.45±0.12	0.50±0.021	1.11±0.22	10±0.16

Results are the mean of three determinations

Angle of Repose

Table 3.5. indicates the results obtained for angle of repose of all the formulations. The values were found to be in the range of 23.44 θ˚ to 25.46 θ˚ all formulations showed the angle of repose within 30˚. It indicates that all formulations showed good flow properties.

Bulk Density

Bulk density is reported in Table 3.5. The bulk density of mixed blend varies between 0.48 to 0.42 gm/ml, indicating good packaging capacity of tablets.

Tapped Density

The tapped density results are reported in table 3.5. The tapped density of mixed blend was found in the range of 0.47 to 0.55 gm/ml, indicating good packing capacity of tablets.

Compressibility Index

The percent compressibility of powder mixture was determined. Table 3.5. indicates result obtained for percentage compressibility. The percent compressibility for all the six formulations lies within the range of 8.33 – 12.72 %. all the formulations showing good compressibility

Hausner's Ratio

Hauser's ratio of the powder was determined from bulk density and tapped density. Hauser's ratio of all the formulation lies within the acceptable range. The Hauser's ratio of all the formulations in the range of 1.09 – 1.13. All the formulations showed good flow property.

From the results of precompression studies of the blend from formulations FD1-FD6 it is concluded that all the formulations blend possesses good flow property and compressibility.

EVALUATION OF FAST DISINTEGRATING TABLETS

All the formulations were subjected to postcompression evaluation in which various parameters like weight variation, thickness, hardness, friability, drug content, in vitro disintegration time,and in vitro dissolution studies were evaluated. The results obtained are as follows.

Table 3.6: Evaluation of Fast Disintegrating Tablets

Formulations	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Drug Content (%)	Weight variation (mg)	Disintegration time (sec)
FD1	2.50±0.10	3.26±0.45	0.69±0.15	92.64±0.11	199± 0.93	49±3.28
FD2	2.53±0.17	3.36± 0.11	0.75±0.15	94.39±0.01	201±0.32	53±1.41
FD3	2.55±0.25	3.22± 0.15	0.79±0.18	96.92±0.15	199±0.51	48±1.41
FD4	2.56±0.10	3.34± 0.15	0.76±0.13	91.73±0.13	203±0.47	50±1.89
FD5	2.52±0.17	3.40± 0.25	0.80±0.07	95.76±0.06	201± 0.85	49±1.41
FD6	2.51±0.10	3.32± 0.10	0.83±0.09	98.10±0.23	200±0.56	48±1.91

Results are mean of three determinations

Appearance

The tablets were visually observed for capping, chipping and lamination.

Thickness

The measured Thickness of tablets of each batch ranged between 2.50–2.56mm. This ensures good handling and transportation of all tablets.

Weight Variations

All the formulated (FD1 to FD6) tablets passed weight variation test as the % Weight variation was within the pharmacopeial limit of ±7.5 of the weight. The weight of all the tablets were found to be uniform with low standard deviation values.

Hardness

The measured hardness of tablets of each batch ranged between 3.2 to 3.4 Kg/cm^2. This ensures good handling and transportation of all tablets.

Friability

The % Friability was less than 1% in all formulations ensuring that the tablets were mechanically strong.

Drug Content of FDT

The percentage of Drug content for FD1 to FD6 was found to be between 91.73 - 98.10% of Carvedilol, it complies with official specifications.

Disintegration Time

The measured disintegration time of tablets of each batch ranged between 47 to 53 seconds This ensures as concentration of superdisintigrants increased, decreased in disintegration time. The formulation batch FD6 containing crosspovidone showed less disintegration time i.e. 48 seconds. So formulation batch FD6 was optimized batch.

***In vitro* Drug Release of Drug from Tablet**

All the nine formulations were subjected for the *in vitro* dissolution studies using tablet dissolution apparatus (USP). The 0.1N HCl was used as dissolution medium. The sample were withdrawn at different time intervals, Filtered, diluted and analyzed at 242 nm. Cumulative % drug release was calculated on the basis of mean amount of tablet present in respective table. The results obtained in the in vitro drug release for all formulations FD1 to FD6 are as follows.

Table 3.7: *In vitro* Cumulative Drug Release from Tablets

Time(min)	Cumulative % Drug Release					
	FD1	FD2	FD3	FD4	FD5	FD6
0	00	00	00	00	00	00
5	30.07±0.46	30.31±0.92	32.20±0.88	31.01±0.16	33.27±0.11	35.11±0.23
10	42.88±0.65	44.93±0.54	48.15±0.17	43.17±0.89	46.32±0.94	48.53±0.89
15	54.34±0.49	56.55±0.98	69.83±0.97	56.53±0.35	59.20±0.56	62.14±0.35
20	67.59±0.33	67.61±0.17	72.00±0.05	69.05±0.78	71.18±0.35	73.45±0.51
25	75.70.±0.34	79.05±0.43	82.17±0.07	78.68±0.20	84.84±0.34	86.29±0.76
30	83.84±0.53	85.05±0.78	87.30±0.93	87.37±0.88	89.33±0.17	90.39±1.27
40	89.54±0.22	91.06±0.12	92.14±0.33	91.24±0.17	92.08±0.89	94.87±0.82

Results are the mean of three determinations.

The rapid dissolution was observed in formulation FD6 which was 94.87% at the end of 40 minutes. Formulations FD1, FD2 and FD3 had shown releases 89.54%, 91.06% and 92.14% of drug respectively at the end of 40 min were as formulations FD4, FD5 and FD6 had shown releases 91.24%, 92.08% and 94.87% of drug respectively at the end of 40 min.

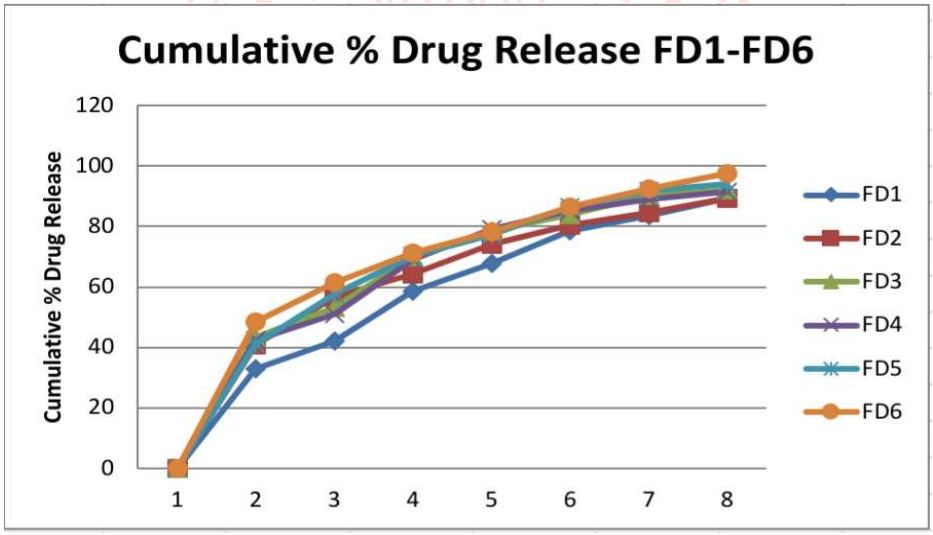

Figure 2.1: Cumulative % Drug Release of FD1-FD6 Formulations

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