International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.4, No.4, pp 1471-1485, Oct-Dec 2012

Immediate Release Drug Delivery System Of Poorly Soluble Aceclofenac By Using Betacyclodextrin

Shahebaz Sheikh[1]*, A.V.Chandewar[1], Sameer Sheaikh[1], Amit Bhople

[1]Depatment Of Pharmaceutics, P.Wadhwani College Of Pharmacy, Yavatmal,-445001 M.S.India.

Corres.author: sheikh.shahebaz14@gmail.com
Phone:+919860208788

Abstract: Today, 35-40% of all new chemical entities suffer from poor aqueous solubility. Aceclofenac Biopharmaceutical classification system (BCS Class II drug) Shows poor solubility and high permeability Aceclofenac comes under Non Steroidal Anti- Inflammatory Drugs and widely used as an analgesic. Aceclofenac is poorly soluble in water and aqueous buffers in the gastrointestinal pH range (1.2 – 7.5), which leads to the failure of dissolution of aceclofenac. The formation of inclusion complexes with guest molecules is one of the most interesting properties of cyclodextrins. A guest molecule experiences changes in the physicochemical properties when it gets incorporated within the cyclodextrin cavity And shows Enhancement of its solubility. physical blending is the easiest way to form the complex with drug to enhance the solubility of the drug.
Keywords: Solubility, Aceclofenac, Cyclodextrin, Complex, BCS Class.

INTRODUCTION

Today, 35-40% of all new chemical entities suffer from poor aqueous solubility; hence the enhancement of the solubility of poorly water-soluble drug is one of the most challenging aspects of modern drug development.[1] This is the case for most poorly soluble compounds in immediate release (IR) formulations whose solubility is less than 1 to 2 mg/Liter in the pH range of 2 to 8. Aceclofenac (BCS Class II drug) comes under Non Steroidal Anti- Inflammatory Drugs and widely used as an analgesic. Aceclofenac is poorly soluble in water and aqueous buffers in the gastrointestinal pH range (1.2 – 7.5), which leads to the failure of dissolution of aceclofenac.[2]

APPROCHES TO ENHANCE THE SOLUBILITY

Poor aqueous solubility leads to poor dissolution and ultimately poor oral bioavailability The enhancement of solubility of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Although, complexation, solubilization, solid dispersion and particle size reduction have commonly been used to increase solubility, dissolution rate and thereby oral absorption and bioavailability of such drugs.[3]

The chief objective of a formulator is to design and formulate a dosage form possessing optimum therapeutic efficacy of drug, economical production on large scale and prolonged shelf life of the drug. Drugs with optimum intrinsic solubility or dissolution rate pose no problem, while poorly soluble drugs are a challenge to the formulator to be appropriately dispensed.

Different techniques have been developed. The methods employed to enhance the drug solubility can be summarizes as follows[4]

- Particle size modification.
- Polymorphs.

- Use of surfactant.
- Co-solvency.
- Hydrotrophy.
- Complexation.
- pH modification.
- Solid dispersion.
- Salt formation.
- Use of cyclodextrin.

Cyclodextrins (CDs) are cyclic oligosaccharides containing six (α-CD), seven (β-CD) or eight (γ-CD) α-1,4-linked glycopyranose units, with a hydrophilic hydroxyl group on their outer surface and a hydrophobic cavity in the center. Owing to lack of free rotation about the bonds connecting the glucopyranose units,[5]the cyclodextrins are not perfectly cylindrical molecules but are toroidal or cone shaped. Based on the architecture, the primary hydroxyl groups are located on the narrow side of the torus while the secondary hydroxyl groups are located on the wider edge[6,7]

Among the different technique of solubility enhancement betacyclodextrin is the one of the easiest and economical.[8]

APPROCHES FOR MAKING OF INCLUSION COMPLEXES

1. Physical blending method
2. Kneading method
3. Co-precipitation technique
4. Solution/solvent evaporation method
5. Neutralization precipitation method
6. Milling/Co-grinding technique
7. Atomization/Spray drying method
8. Lyophilization/ Freeze drying technique

PHYSICAL BLENDING METHOD

A solid physical mixture of drug and CDs are prepared simply by mechanical trituration. In laboratory scale CDs and drug are mixed together thoroughly by trituration in a mortar and passes through appropriate sieve to get the desired particle size in the final product. In industry scale, the preparation of physical mixtures is based on extensive blending of the drug with CDs in a rapid mass granulator usually for 30 minutes. These powdered physical mixtures are then stored in the room at controlled temperatures and humidity conditions.[9]

EXPERIMENTAL

PREFORMULATION STUDY

Preformulation studies are the first step in the development of dosage form of a drug substance. The objectives of preformulation studies are to develop a portfolio of information about the drug substance, so that this information is useful to develop formulation. Preformulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients.[10]

Preformulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product. Followings are the test performed for the preformulation study.[11]

CHARACTERIZATION OF DRUG

1) Determination of solubility
2) Description
3) Bulk density
4) Tapped density
5) Carr's index & Hausner's ratio
6) Flow property (Angle of Repose)
7) FT IR Spectra
8) Drug –Excipient Compatibility study

DETERMINATION OF SOLUBILITY:

An excess quantity of aceclofenac or size enlarged granules was placed in the flask containing 10 ml of distilled water. The flask were agitated in a shaking water bath (100 agitations/min) for 24 h at room temperature. Finally, it was filtered through a No. 41 Whatman filter paper and amount of the drug dissolved was analyzed spectro-photometrically (U.V spectrophotometer Analytic gena) at 274 nm. The samples were analyzed in triplicate.[12]

DETERMINATION OF BULK DENSITY:

Weighed quantity of the powder blend (W) was taken in a graduated measuring cylinder and volume (V_0) was measured and bulk density was calculated using formula[13]

Bulk density = Weight of powder / Bulk volume

DETERMINATION OF TAPPED DENSITY

Weighed quantity of blend, and transferred in 100 mL graduated cylinder. Then mechanically tapped

the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14± 2 mm at a nominal rate of 300 drops per minute. Tapped the cylinder for 500 times initially and measure the tapped volume to the nearest graduated units, repeat the tapping an additional 750 times and measure the tapped volume to the nearest graduated units. If the difference between the two volume is less than 2 % then final the volume.[14]

Tapped density =

Weight of powder / Tapped volume of packing

Carr's Compressibility index & Hausner's Ratio: The compressibility index and Hausner ratio are measures of the propensity of powder to be compressed. Carr's compressibility index and Hausner's ratio can be calculated as follows[15]

Carr's index = Tapped density - Bulk density / Tapped density X 100

Hausner's ratio = Tapped density / Bulk density

FTIR SPECTRA:

IR spectra of bulk drugs were taken using FTIR Spectrophotometer (FTIR-Shimadzu). FTIR spectrum of drug was taken by using single point measurement method. Fraction quantity of sample were taken in sample holder (it needs less than 0.5 gm). There were no need to prepare KBR pallets and sample were analyzed in FTIR spectrophotometer.[16]

DRUG-EXCIPIENTS COMPATIBILITY STUDY:

The primary objective of this investigation was to identify a stable storage condition for drug in solid state and identification of compatible excipients for its formulation.

In this method different excipients were selected and mixed separately with drug in proportion generally used for tablet formulation. the samples are observed visually for change of color or its appearance in powder form. From these two sets of samples, one set is analyzed using DSC study that clarifies if any interaction is occurred between drug-excipient.[17]

UV CHARACTERIZATION:

Standard calibration curve of Aceclofenac in 7.5 pH Phosphate Buffer at λmax 274nm

Calibration curve of Aceclofenac was prepared in 7.5 pH Phosphate Buffer at different dilutions. Different dilutions of Concentration 10,20,30,40 &50 µg/ml were prepared and their respective absorbance were taken by using double beam UV-Spectrophotometer (Table.14.).Using those absorbance standard curve was prepared. [18,19]

$Y=0.023x$,$R^2=0.999$

Where,

Y is absorbance

X is Concentration

R^2 is coefficient of regression.

ASSAY:

Chromatographic condition

Instrument: HPLC (Hitachi)

Column: Stainless steel column packed with octadecylsilane stationary phase for chromato graphy, 15X4.6 mm, 5µm(Hypersil ODS is suitable)

Mobile Phase : A mixture of 55 volumes of buffer solution prepared by adding 1.0 ml of glacial acetic acid in 1000ml of water and 45 volume of acetonirile.

Flow **rate** **:** 1.5 ml / min.

Wavelength **:** 275 mn

Injection volume **:** 20 µl

Solvent Mixture: A mixture of 55 volume of acetonitrile and 45 volume of water.

Standard Solution:

For Drug :- 25 mg of Drug Aceclfenac of was weighed accurately and add acetonitrile to dissolve and make up the volume to 25ml with acetonitrile. Dilute 5ml of above solution to 50ml with solvent mixture.

Sample Solution:

20 tablet were weighed and transfered. Tablet were triturated in mortar and pestle. Triturated powder was taken which was equivalent to about 100 mg of Aceclofenac, add to 60ml of acetonitrile and sonicated further for about 10 min. make up the volume to 100ml with acetonitrile. Dilute 5ml of the solution to 50ml with solvent mixture.[20]

Formulation of Immediate Release Tablet

The tablets were formulated by-

A) Direct Compression, (Batch F1 – F7).

Procedure:

1) Weighed quantity of Aceclofenac was passed through # 40 mesh.
2) Weighed quantity of Beta cyclodextrin were passed through # 40 mesh. Added it above blend in Octagonal blender for 5 minute at 16 rpm.

3) Weighed quantity of Microcrystalline cellulose, was passed through # 40 mesh, it was mixed with the above blend in Octagonal blender for 5 min at 16 rpm.

(In trial 2 Weighed quantity of aerosil was passed through # 40 mesh, it was mixed with the above step 2)

a) In trial F2 Aerosil was added to improve the flow.

b) In trial F3 Avicel pH102 is used which is granular form of of Microcrystalline cellulose having nominal mean particle size 100 (µm)

c) In trial F4 Ac-di-sol was added to improve the drug release.

4) Weighed quantity of Magnesium Stearate were passed through # 60 mesh, it was lubricated the above blend with Magnesium Stearate Octagonal blender for 3 min at 16 rpm.

5) Blend was ready for compression.

6) Compression was done using 8 Station B-tooling machine using 9.5 Standard Concave punch plain on both side.

Procedure:

1) Weighed quantity Aceclofenac & Betacyclodextrin was passed through #40 mesh.
2) The above blend was shifted in to the Rapid Mixing Granulator(RMG) mixing was done done at impeller speed 150 rpm & chopper speed 1500 rpm up to 30 min.
3) Weighed quantity of Avicel PH 102, was passed through #40 mesh. Added it above blend for 5 min in V blender.
4) Lubricated the above blend with Magnesium Stearate (which is passed through # 60 mesh) in V blender for 3 min at 16 rpm.
5) The blend was ready for compression.
6) Compression was done using 8 Station B-tooling machine using 9.5 Standard Concave punch plain on both side.

COATING

Weigh the following material & keep ready for preparation of coating solution

Coating material 9mg per tablet and sufficient amount of water to make dispersion.

Start mixing the purified water to form a vortex at centre. Add coating material to the water and stir for 45min.

Coating Material Wincoat WT-QCAQ-1003 Contains-

1) Hydroxy Propyl Methyl Cellulose I.P. 44-51 %
2) Polyethylene Glycol 400 N.F. 6-13 %
3) Titanium Dioxide I.P. 30-38 %
4) Talcum I.P. 1-7 %

RESULT AND DISCUSSION

SOLUBILITY

Solubility of the drugs is determined in 4 different media which is given below.

DENSITY AND FLOW PROPERTIES

The above observation indicates that the drugs have Appreciable flow property.

UV CHARACTERIZATION

Determination of λ max

Aceclofenac shows λmax 275 nm, (IP 1996), in present study 274 nm is taken as its λ max, where the Aceclofenac shows maximum absorbance.

COMPATIBILITY STUDY

Drug –Excipient mixture was incubated in fixed ratio at condition of 30^{o}/65%RH and 40^{o}/75 %RH. Physical observation of sample was done after period of 15 days and 1 month. As there was no changes in physical characteristic of mixture it was concluded that API is compatible with different excipients.

DSC STUDY

It was confirmed by Differential scanning calorimetry (DSC) studies. From above Figure shows the DSC data. The thermogram of Aceclofenac showed by first line was Sharp peak given at 153.00 ^{0}C corresponding to its melting Point. The DSC thermogram of Drug ,excipient & formulation was characterized by peak near about 148-154^{0}C. these systems indicates the formation not contain any interaction between Drug and Excipient.

FTIR STUDY

Infra-Red spectroscopy is used to estimate the interaction between cyclodextrin and the guest molecules in the solid state. Cyclodextrin bands often change only slightly upon complex formation and if the fraction of the guest

molecules encapsulated in the complex is less than 25%, bands which could be assigned to the included part of the guest molecules are easily masked by the bands of the spectrum of cyclodextrin.

***In-vitro* Dissolution Profile**

Dissolution Summary*:*

Medium **:** 7.5pH Phosphate Buffer

Apparatus **:** Paddle

RPM **:** 50

Volume **:** 900ml

OPTIMIZATION

Here, Aceclofenac tablets were prepared by Direct compression . Betacyclodextrin was used for the dissolution enhancement of Aceclofenac **In trial F1,** Microcrystalline cellulose used as direct compression diluents & magnesium stearate used as lubricant, but formulation did not show flow proper during the compression.

In trial F2 Aerosil was added to enhance the flow but final blend did not show the proper flow.

In trial F3, the Mirocrystalline cellulose was replaced with avicel pH102 which is granular form of Microcrystalline cellulose.

In trial F4, Croscarmellose sodium was added to imrove the drug release.

In trial F5, Aceclofenac & Betacyclodextrin were mixed in High Shear Mixer to form the inclusion between the drug and cyclodextrin.

Evaluation of Post-compression parameters of tablets formulated by Direct Compression

Appearance: White to off white coloured, binconvex circular shaped, film coated tablet, plain on both side.

Average Weight, Thickness, Hardness

Container Closure System

Selection of Packaging material

Tablets were packed in the Aluminium-Aluminium (Alu-Alu) Strip pack.

Justification: Alu-Alu Strip pack complete protection against light, water vapor, gases etc.

STABILITY STUDY

Batch No.: F5,F6,F7 was put on stability as below mentioned condition.

Batch No.: F5,F6,F7 at 25°C ± 2°C / 60% RH ± 5 % RH ,30°C ± 2°C / 65% RH ± 5 % RH 40°C ± 2°C / 75% RH ± 5 % RH

Packaging: Aluminum Strip Pack.

From the above stability data at it reveals that the product is stable at Room temperature and elevated temperature for 12 Weeks. (3 months).

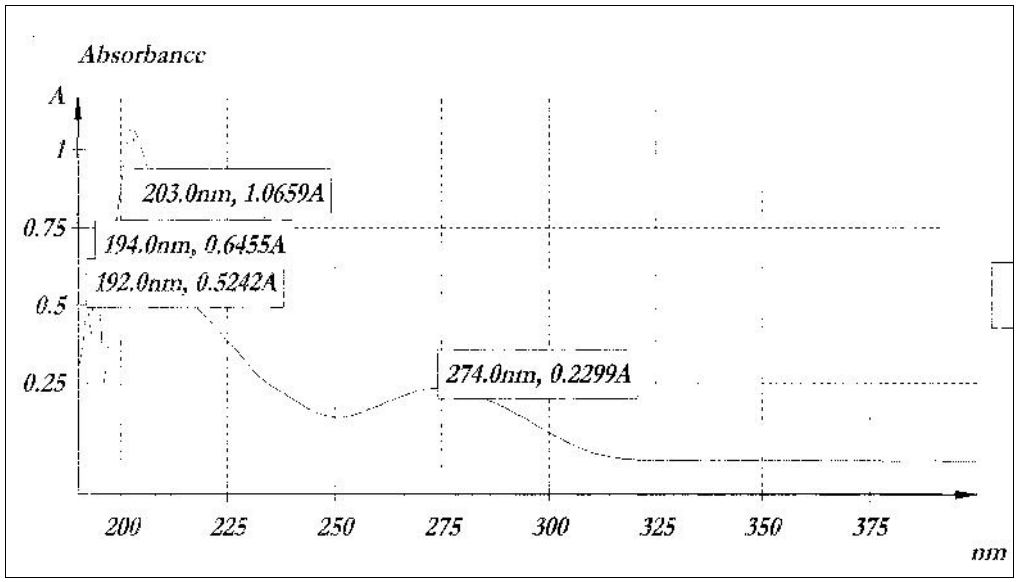

Fig1:UV-Spectral analysis

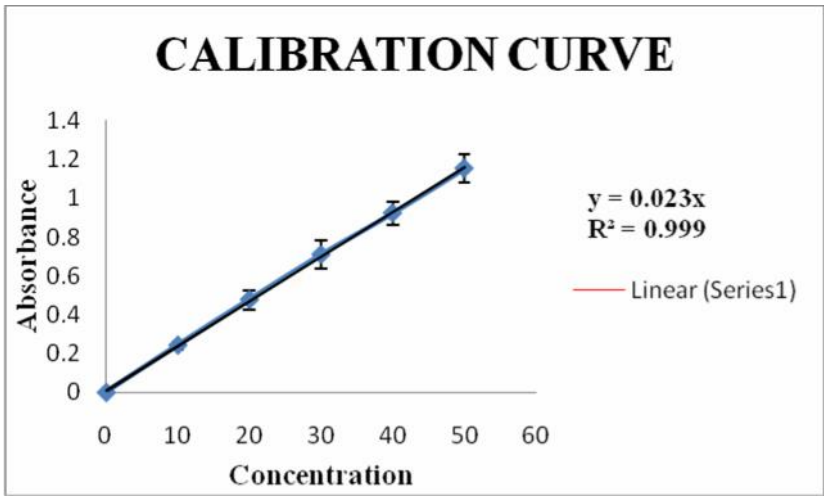

Figure-2 Standard calibration curve of Aceclofenac in pH 7.5 Phosphate Buffer at 274nm

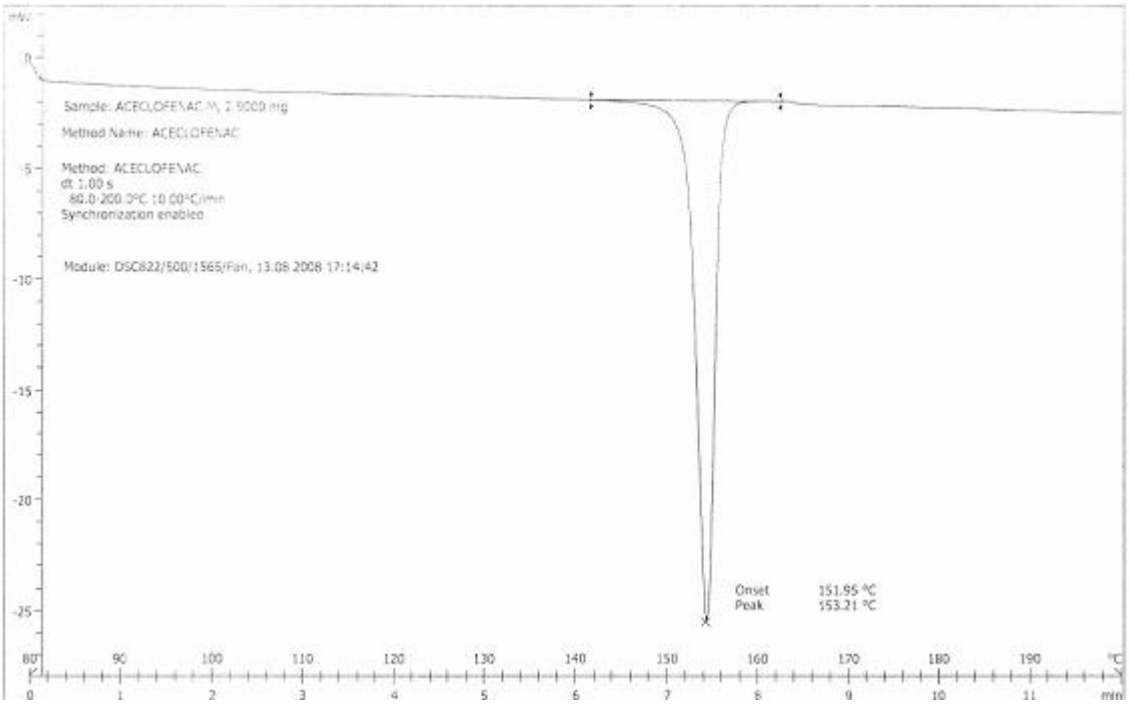

Figure-3. DSC of Drug Aceclofenac

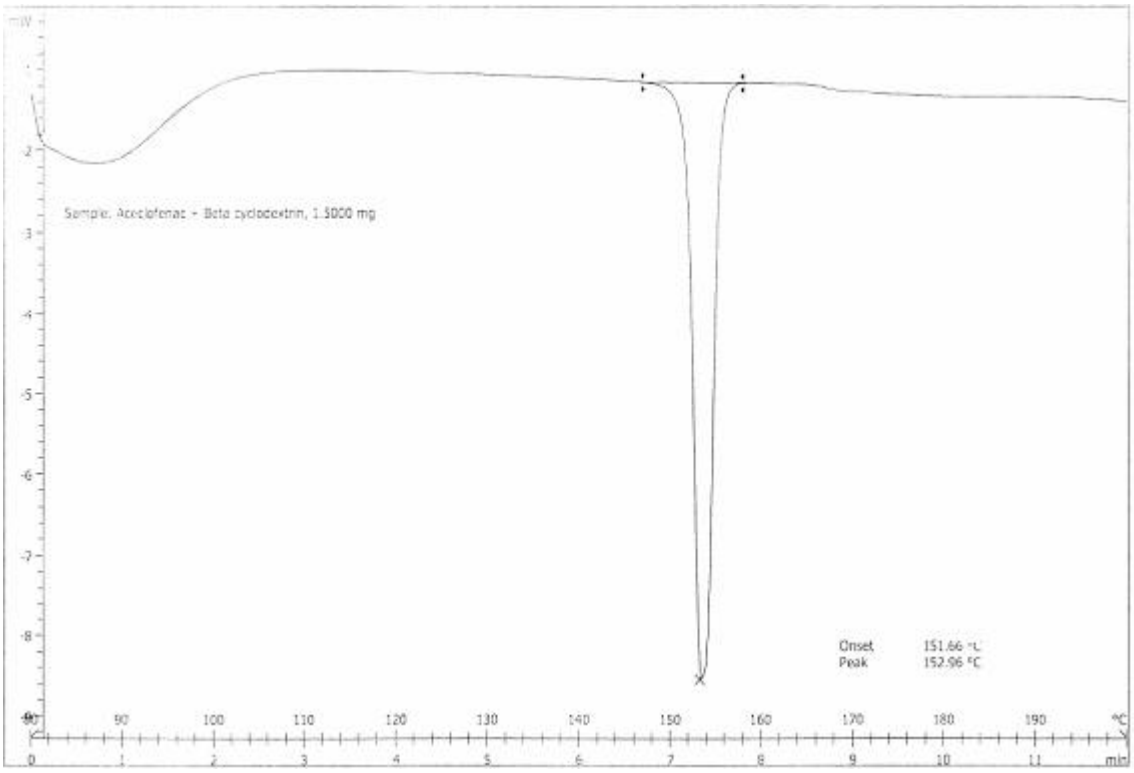

Figure-4. DSC Of Aceclofenac And Betacyclodextrin

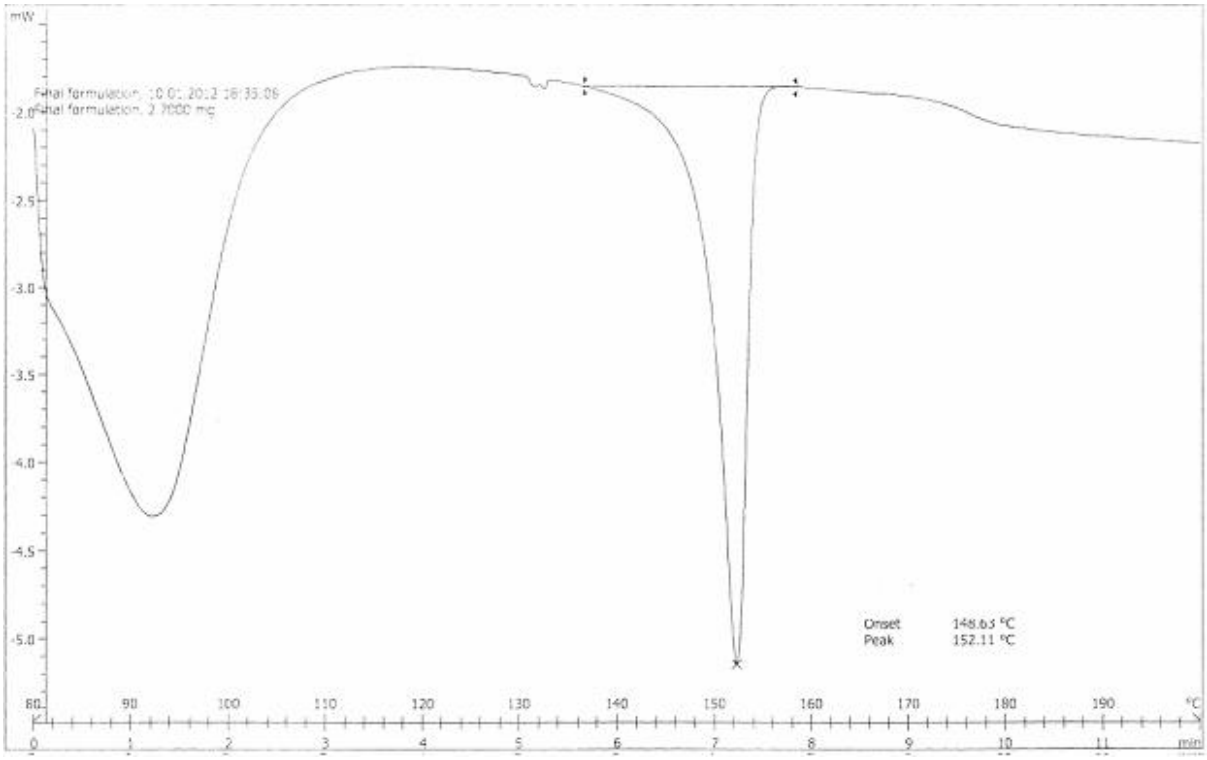

Fig.5.DSC of Final formulation

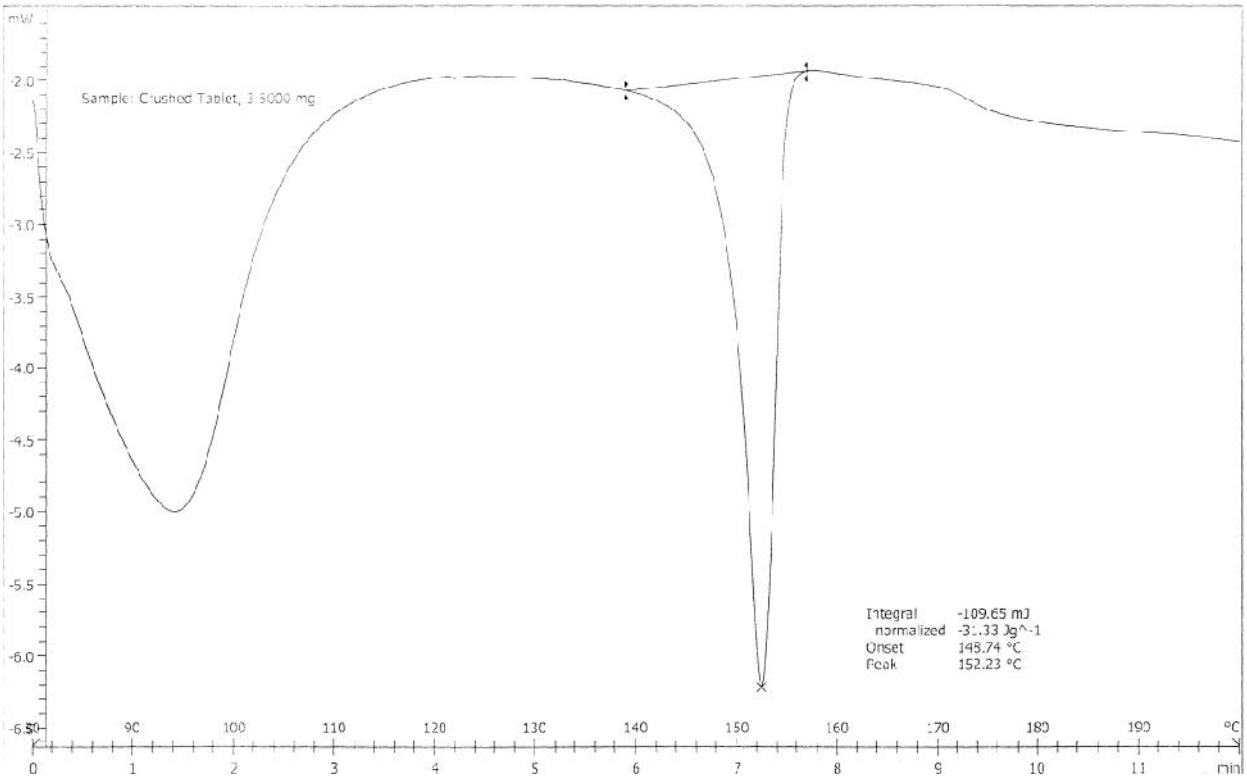

Figure-6. DSc of Crushed table

FTIR spectra.

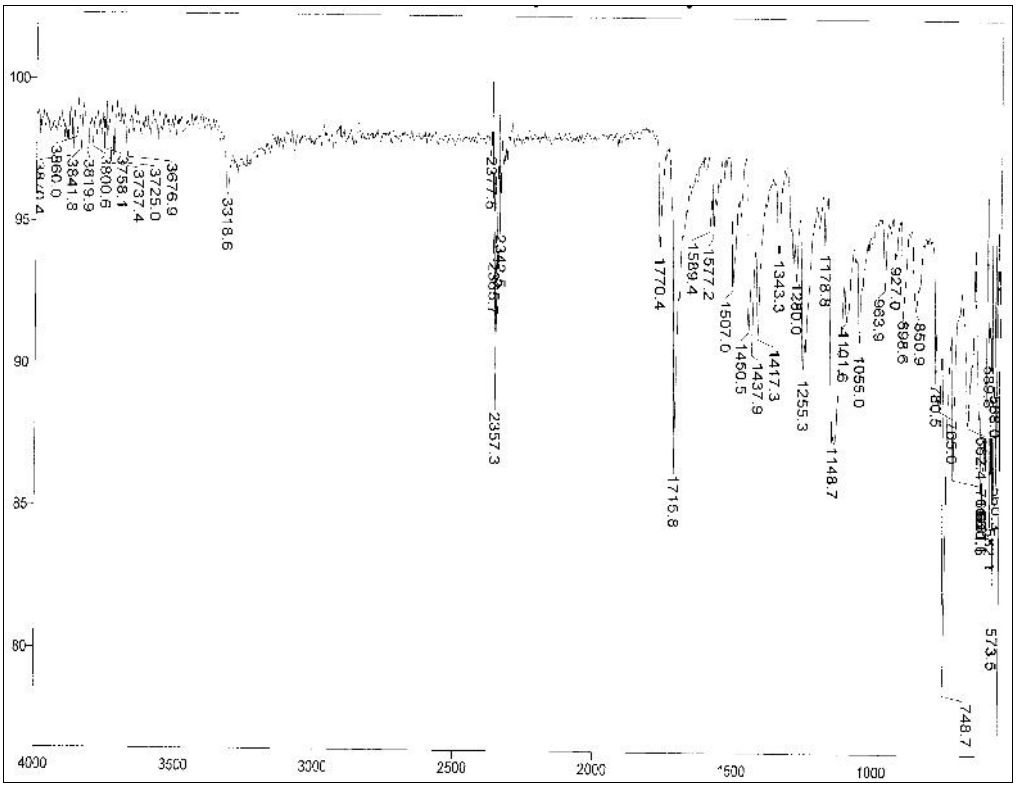

Figure-7 FTIR Spectrum of Aceclofenac

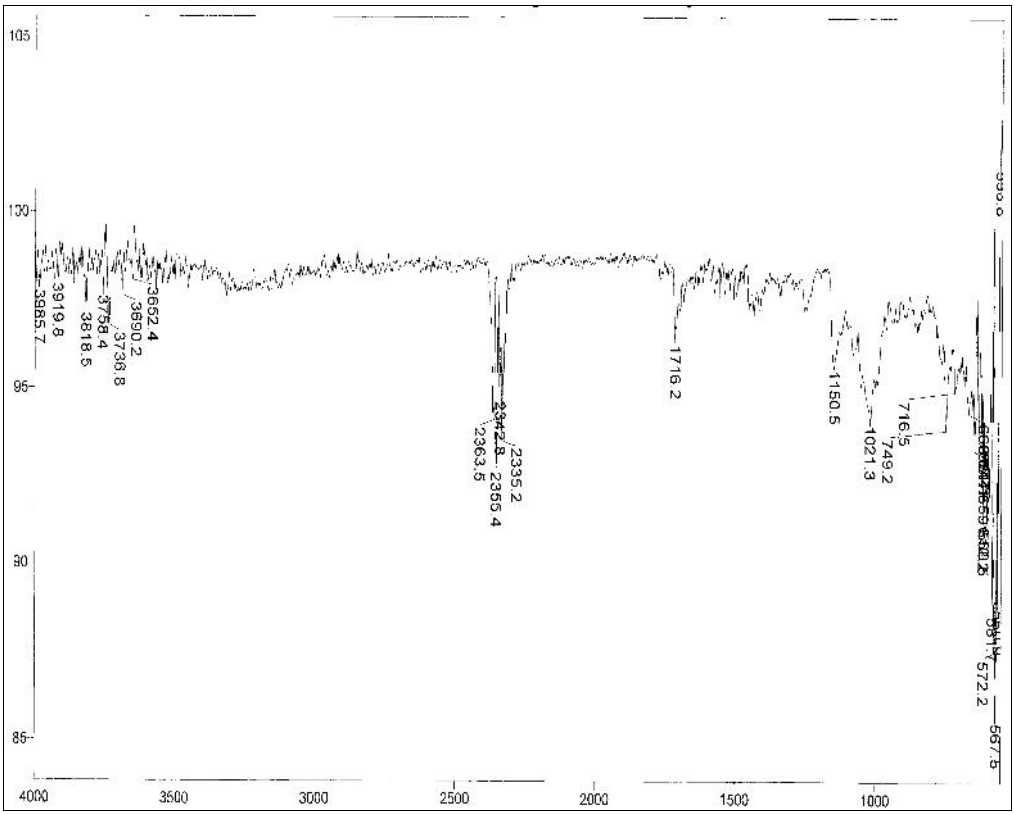

Figure- 8 FTIR Spectrum of Betacyclodextrin

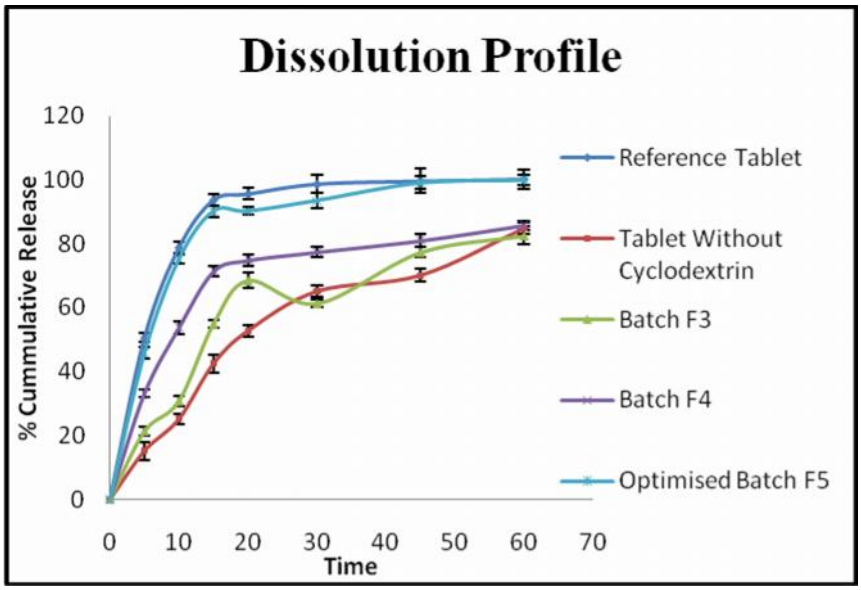

Fig.9.Dissolution Profile of different formulation in pH 7.5 Phosphate Buffer , 900 ml, Paddle, 50 rpm

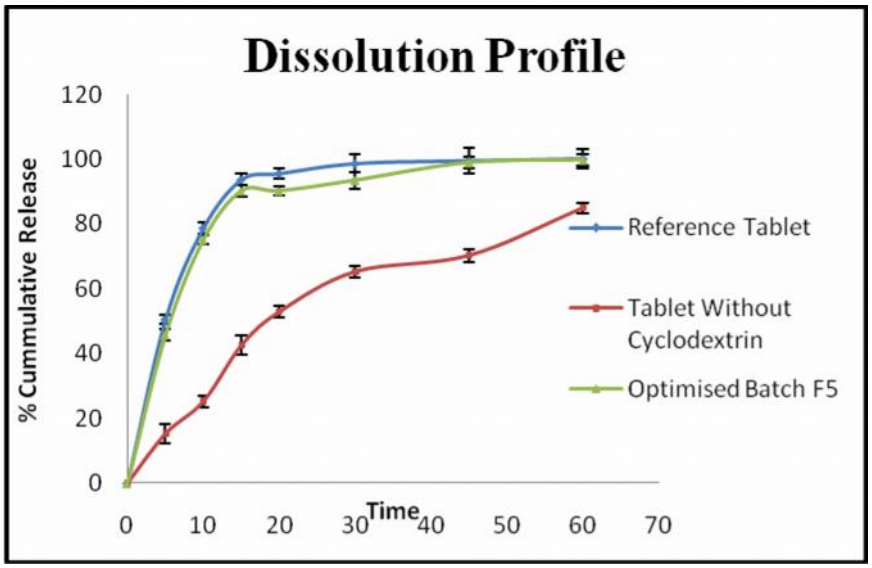

Fig.10.Dissolution Profile of Aceclofenac Tablets in pH 7.5 Phosphate Buffer , 900 ml, Paddle, 50 rpm

Table 1: Characterization of Drug

Sr. No.	Parameter	Discription
1	Description of drug	white crystalline powder
2	Bulk Density	0.54± 0.21g/ml
3	Tapped Density	0.71± 0.15g/ml
4	Assay	100.1±0.33%
5	LOD	0.31±0.25%

Table 2: Composition of tablets batches (F4-F4)

Ingredients	Quantity / Tablet (mg)			
	F1	F2	F3	F4
Aceclofenac	100	100	100	100
Beta cyclodextrin	100	100	100	100
MCC	97	94	-	-
Avicel pH 102	-	-	97	94
Aerosil	-	3	-	-
Ac-di-sol	-	-	-	3
Magnisium sterate	3	3	3	3
Total	**300**	**300**	**300**	**300**

Table 3: Composition of tablet batches (F5-F7)

Ingredients	Quantity / Tablet (mg)		
	F5	F6	F7
Aceclofenac	100	100	100
Betacyclodextrin	100	100	100
Avicel pH 102	97	97	97
Magnisium sterate	3	3	3
Total	**300**	**300**	**300**

Table 4:Coating Parameter:

1	Distance between gun & tablet bed	6 to 12 cm
2	Inlet air temperature	60 to 70 ^{o}C
3	Exhaust air temperature	40 to 50 ^{o}C
4	Tablet bed temperature	25 to 35 ^{o}C
5	Pan speed	5 to 10 RPM
6	Spray rate	2 to 4 g/ min

Table 5: Details of solubility of Aceclofenac And Aceclofenac+Betacyclodextrin

Solvent/Media	Solubility (mg/ml) of Aceclofenac	Solubility(mg/ml) Aceclofenac+Betacyclodextrin
Water	0.082 ± 0.08	0.68 ± 0.11
pH 4.5 Acetate Buffer	0.032 ± 0.14	0.28 ± 0.26
pH 6.8 Phosphate Buffer	1.56 ± 0.15	5.20 ± 0.14
pH 7.5 Phosphate Buffer	1.70 ± 0.07	6.58 ± 0.09
0.1 N HCl	0.018 ± 0.25	0.34 ± 0.12

Table- 6:Observation of density and flow parameter for Drug Aceclofenac .

Sr. No.	Density (g/cm^3)		Flow properties	
	Bulk	Tapped	Carr's index	Hausner Ratio
Drug A	0.557 ± 0.04	0.717 ± 0.02	22.31 ± 0.02	1.28 ± 0.04

Table 7: Standard calibration curve of Aceclofenac in pH 7.5 Phosphate Buffer at 274nm

Sr No	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.2435 ± 0.02
3	20	0.4782 ± 0.05
4	30	0.7102 ± 0.07
5	40	0.924 ± 0.06
6	50	1.154 ± 0.07

Table 8:Drug + Excipients compatibility study

Sr. No.	Sample	Ratio	Condition	Appearance
1	API	1	Initial	White crystalline powder
			30^{o}C/65%RH	No Change
			40^{o}C 75%RH	No Change
2	API+Betacyclodextrin	1:1	Initial	White crystalline powder
			30^{o}C/65%RH	No Change
			40^{o}C 75%RH	No Change
3	API + Avicel PH 102	1:1	Initial	White crystalline powder
			30^{o}C/65%RH	No Change
			40^{o} /75%RH	No Change
4	API + Magnisium sterate	1:0.25	Initial	White crystalline powder
			30^{o}C/65%RH	No Change

			40°C/75%RH	No Change
5	API + Coating agent	1:0.5	Initial	White powder
			30°C/65%RH	No Change
			40°C/75%RH	No Change
6	Placebo	1	Initial	White crystalline powder
			30°C/65%RH	No Change
			40°C/75%RH	No Change
7	API + Placebo	1:3	Initial	White crystalline powder
			30°C/65%RH	No Change
			40°C/75%RH	No Change

Table 9:Functional group of Acelofenac

Peak (cm^{-1})	Absorbance Of Chemical Group
1716/1770	C=O
1055	OH
3319	NH
717	C-Cl

Table 10: Dissolution profiles of trials formulated by direct compression

Time in min	*% Cumulative Drug Released For Drug Aceclofenac*						
	Reference	**Marketed tablet Without Betacyclodextrin**	**F3**	**F4**	**F5**	**F6**	***F7***
5	50.5±1.42	15.2±1.48	21.3±1.39	33.1±1.32	45.8±1.75	44.7±1.18	*45.2±1.29*
10	78.8±1.49	25.2±2.36	30.8±1.45	53.7±1.61	75.2±1.94	74.2±1.29	*76.5±1.45*
15	93.7±1.55	42.5±1.26	54.9±2.16	71.3±2.22	90.2±0.18	89.7±1.32	*90.2±0.94*
20	95.6±1.37	52.8±2.54	68.5±1.64	74.8±1.47	90.2±1.42	90.4±1.20	*92.2±1.93*
30	98.7±1.44	65.2±1.69	61.3±1.24	79.3±0.36	93.5±0.98	91.8±2.29	*93.2±1.37*
45	99.6±1.20	70.2±1.27	77.3±1.44	81.0±1.46	99±0.51	99.5±0.93	*99.4±1.24*
60	100.2±1.77	82.9±1.28	82.5±2.34	85.8±1.22	99.8±1.13	100.2±0.72	*100.4±1.43*
F1 Value							*3.31*
F2 Value							*70.18*

Table 11:Assay

Trial	Assay of Drug
F1	99.80± 0.17
F2	101.4± 0.26
F3	101.3± 0.12
F4	99.80± 0.14
F5	100.2± 0.09
F6	99.80± 0.28
F7	99.60± 0.15

Table 12: Post-compression parameters of tablets

Trials	Avg. Tab Wt. (mg)	Thickness (mm)	Diameter (mm)	Hardness (Kg/cm^2)
F1	299.85± 0.29	4.1± 0.28	9.50± 0.10	5.9± 0.10
F2	298.45± 0.24	4.0± 0.15	9.52± 0.20	7.0± 0.14
F3	298.24± 0.19	4.2± 0.10	9.50± 0.17	7.5± 0.20
F4	297.80± 0.32	4.2± 0.26	9.48± 0.10	7.2± 0.19
F5	298.00± 0.10	4.2± 0.29	9.51± 0.18	7.5± 0.10
F6	301.25± 0.21	4.2± 0.15	9.52± 0.36	7.5± 0.26
F7	301.50± 0.15	4.2± 0.10	9.50± 0.07	7.4± 0.28

Table 13: Coated tablet parameters

Trials	Avg. Tab Wt. (mg)	Thickness (mm)	Diameter (mm)	Hardness (Kg/cm^2)
F1	308.52± 0.10	4.42± 0.14	9.60± 0.24	5.9± 0.12
F2	307.45± 0.16	4.37± 0.23	9.62± 0.09	8.0± 0.25
F3	310.25± 0.15	4.42± 0.25	9.58± 0.12	8.5± 0.12
F4	308.78± 0.24	4.45± 0.16	9.63± 0.14	8.8± 0.16
F5	309.23± 0.18	4.41± 0.17	9.61± 0.18	8.7± 0.24
F6	310.45± 0.13	4.43± 0.18	9.62± 0.16	8.8± 0.23
F7	309.98± 0.24	4.42± 0.26	9.58± 0.19	8.9± 0.26

Table 14: Physical Parameter after stability

Trials	Avg. Tab Wt. (mg)	Thickness (mm)	Diameter (mm)	Hardness (Kg/cm^2)
F1	308.52± 0.10	4.42± 0.14	9.60± 0.24	5.9± 0.12
F2	307.45± 0.16	4.37± 0.23	9.62± 0.09	8.0± 0.25
F3	310.25± 0.15	4.42± 0.25	9.58± 0.12	8.5± 0.12
F4	308.78± 0.24	4.45± 0.16	9.63± 0.14	8.8± 0.16
F5	309.23± 0.18	4.41± 0.17	9.61± 0.18	8.7± 0.24
F6	310.45± 0.13	4.43± 0.18	9.62± 0.16	8.8± 0.23
F7	309.98± 0.24	4.42± 0.26	9.58± 0.19	8.9± 0.26

Table 15: First, Second & Third month Stability Data of Tablet at 25°C ± 2°C / 60% RH ± 5 % RH ,30°C ± 2°C / 65% RH ± 5 % RH , 40°C ± 2°C / 75% RH± 5 % RH

Parameters	Initial	1 Months	2 Months	3 Months
Description	White to off white coloured,binconvex, circular shaped,film coated tablet, plain on both side.	White to off white coloured,binconvex, circular shaped, film coated tablet, plain on both side.	White to off white coloured, inconvex circular shaped, film coated tablet, plain on both side.	White to off white coloured,binconvex circular shaped, film coated tablet, plain on both side.
Assay	99.80± 0.18%	99.60± 0.2%	99.30± 0.14%	99.30± 0.18%
Dissolution : Medium: 900 ml of pH 7.5 Phosphate Buffer, paddle, 50 rpm	100.2± 0.12%	100.1± 0.20%	99.8± 0.19%	99.5%± 0.10
Thickness (mm)	4.38± 0.26	4.38± 0.22	4.36± 0.17	4.38± 0.14
Hardness (Kp)	8.9± 0.24	9.2± 0.15	9.1± 0.33	9.1± 0.35
Friability : 100 Revolutions	0.18± 0.14%	0.16± 0.08%	0.18± 0.24%	0.18± 0.10%

REFERENCES

1. Hite, M., Turner, S., Federici, C.,. Part 1: Oral delivery of poorly soluble drugs, Pharmaceutical Manufacturing and Packing Sourcer Summer, 2003,38-40.
2. Sachin Kumar Singh et al /Int.J. Pharmtech Res.2010,2(4)
3. Amidon, G.L., Lennernas, H., Shah, V.P., Crison, J.R.,. A theoretical base for a biopharmaceutic drug classification: the correlation of in-vitro drug product dissolution and in vivo bioavailability. Pharm. Res., 1995, 12,413-420.
4. Nadendla, R.R., Sudhakar, G., Srinath, N.,. Current status of dispersible dosage forms, Int. J. Pharma. Excip, 2002, 1, 25.
5. Cunha-Filho, MSS, Dacunha-Marinho B, Torres- Labandeira JJ, Martinez-Pacheco R, Landin M. Characterization of β-Lapachone and Methylated β- Cyclodextrin Solid-state Systems. AAPS Pharm Sci. Tech. 2007: 8:1-10.
6. Moyano JR, Blanco MJA, Gines JM, Giordano F.Solid State Characterization and Dissolution Characteristics of Gliclazide Beta-Cyclodextrin Inclusion Complexes. Int. J. Pharm. 1997: 48:211-214
7. Raymond C Rowe, Paul J Sheskey, Marian E Quinn Handbook of Pharmaceutical Excipient, 6th edition, Pharmaceutical Press and American Pharmacists Association 2009
8. Patil J.S.*, Kadam D.V., Marapur S.C., Kamalapur M.V. Inclusion complex system; a novel technique to improve the Solubility and bioavailability of poorly soluble drugs International journal of pharmaceutical sciences review and research 2010; 006; 29-32
9. Moyano Jr, Blanco Mja, Gines Jm, Giordano F.Solid State Characterization and Dissolution Characteristics of Gliclazide Beta-Cyclodextrin Inclusion Complexes. Int. J. Pharm., 1997: 48:211-217
10. Amidon, G.L., Lennernas, H., Shah, V.P., Crison, J.R.,. A theoretical base for a biopharmaceutic drug classification: the correlation of in-vitro drug product dissolution and in vivo bioavailability. Pharm. Res., 1995, 12,413-420.
11. Ansel H., Allen L. and Jr. Popovich N. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. 8th Edition: 227-259.
12. Naidoo NT, Beare MA, Kanfer I, Sparrow N. Effect of lubricating excipients on the dissolution characteristics of theophylline tablets prepared by direct compression. South African Pharmaceutical Journal, 1986 : 53: 100-103.

13. Martin,A.,Swarbrick,J.,Cammarata,A., Physical chemical principle in the pharma ceutical sciences. 3rd edition. Varghese publication house.Bombay40014
14. Ramnik Singh *et al*/ Journal of Pharmaceutical Science and Technology, 2010, 2 (3), 171-183
15. Vekama K. Design and Evaluation of Cyclodextrin- Based Drug Formulation. Chem.Pharm.Bull. 2004: 52:900-15.
16. Rajewski RA, Stella VJ. Pharmaceutical applications of cyclodextrins. 2. in vivo drug Delivery. J. Pharm. Sci. 1996: 85:1142-69. Rajewski RA, Stella VJ. Pharmaceutical applications of cyclodextrins. 2. in vivo drug Delivery. J. Pharm. Sci. 1996: 85:1142-69.
17. Johansen H, Moller N. Solvent deposition method for enhancement of dissolution rate: Importance of drug to excipient ratio. *J Pharm Sci* 1978; 67: 135-136.
18. Dhamane SP, Aher D, Shinde KK. Solubility enhancement of diloxanide furoate by adsorption on excipient. Int J Pharm Excip 2005; 117-120.
19. Pinnamaneni S., Das N. And Das S.K., Formulation approaches for orally administened poorly soluble drug, pharmazie, 2002, 57, 291 – 300.
20. Indian Pharmacopoeia Volume I, & II Controlled of Publication, Delhi, 2010.

*****