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ENHANCEMENT OF DISSOLUTION RATE OF CLOFIBRATE BY USING VARIOUS SOLID DISPERSION TECHNIQUES

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Abstract:

The aim of the present research work, Clofibrate a BCS class II Anti-hyperlipidemic drug belongs to fibrate class was formulated as solid dispersions by using various hydrophilic carriers to enhance the solubility, dissolution rate and oral bioavailability. Kneading technique is used to prepare solid dispersions of Clofibrate. Solid state characterization of solid dispersions is done by Differential Scanning Calorimetry, Fourier-Transform Infrared spectrometry and X-ray powder Diffraction studies, Scanning electron microscopy. The solid dispersions can be evaluated by in-vitro dissolution studies. To develop the solid oral dosage form (Tablets) with Clofibrate solid dispersions. To study the physical parameters of tablets prepared by direct compression, which includes hardness, friability, weight variation, and disintegration. To estimate the % drug content in the solid dispersions and the fabricated formulations. To evaluate the drug release from the tablets by in-vitro dissolution studies and to compare in-vitro dissolution profile of fabricated formulation with marketed formulation.

Key words: *FT-IR, SEM Studies, Clofibrate, Hydroxyl propyl β-Cyclodextrin, β- Cyclodextrin, Solid dispersion, BCS class II Anti-hyperlipidemic drug.*

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INTRODUCTION:

The progress in treatment of diseases has been evident with the upsurge in development of new drugs. An estimated 40% of these drugs are poorly water soluble. The enhancement of oral bioavailability of such poorly water soluble drugs remains one of the most challenging aspects of drug development. The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcome the limitations of previous approaches such as salt formation, solubilization by co solvents, and particle size reduction. Much of the research that has been reported on solid dispersion technologies involves drugs that are poorly water-soluble and highly permeable to biological membranes as with these drugs dissolution is the rate limiting step to absorption. Solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs [1].

The Biopharmaceutics Classification System (BCS):

According to the BCS, drugs are classified as follows [2]:

BCS classification of Drugs

Class I	**High Permeability, High Solubility**
Class II	**High Permeability, Low Solubility**
Class III	**Low Permeability, High Solubility**
Class IV	**Low Permeability, Low Solubility**

SOLID DISPERSION

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particle [3]. Chiou and Riegelman defined solid dispersions as "The dispersion of one or more active ingredients in an inert excipient or matrix, where the active ingredients could exist in finely crystalline, solubilized, or amorphous states".

Advantages of Solid Dispersion [4]:

- To reduced particle size
- To improve wettability
- To improve porosity of drug
- To decrease the crystalline structure of drug in to amorphous form
- To improve dissolvability in water of a poorly water-soluble Drug in a pharmaceuticals.
- To mask the taste of the drug substance.
- To prepare rapid disintegration oral tablets.

Methods of Preparation of Solid Dispersion [4-7]

a) Melting method (fusion method): The melting or fusion method, first proposed by Sekiguchi involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved.

b) Melt Extrusion Method: Melt extrusion method is same as the melt method except that intense mixing of drug/carrier mix is typically processed with a twin-screw extruder. Then drug/carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermo labile to be processed.

c) Solvent Evaporation Method: In this method, the first step is formation of solution containing physical mixture of the drug and carrier dissolved in a common solvent and second step involve the removal of solvent resulting the formation of solid dispersion. First to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. An important prerequisite for the manufacture of a solid dispersion using the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent. The solvent can be removed by various methods like by spray-drying or by freeze-drying. Temperatures used for solvent evaporation generally lie in the range 23-65 °C. Solvents used for solid dispersions.

d) Melting Solvent Method (Melt Evaporation): It involves preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical standpoint, it is only limited to drugs with a low therapeutic dose. E.g. below 50 mg.

e) Physical Mixture Method: The physical mixtures were prepared by weighing the calculated amount of drug and carriers and then mixing them in a glass mortar by triturating. The resultant physical mixtures were passed through 44-mesh sieve and stored in desiccators until used for further studies.

f) Co-Grinding Method: The calculated amounts of drug and carriers where weighed and mixed together with one ml of water. The damp mass obtained was passed through a 44-mesh sieve; the

resultant granules were dispersed in Petri dishes and dried at 60°C under vacuum, until a constant weight was obtained. The granules obtained were stored in desiccators until used for further studies.

g) Electro Spinning: Electro spinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle. This process involves the application of a strong electrostatic field over a conductive capillary attaching to a reservoir containing a polymer solution or melt and a conductive collection screen. This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest, the cheapest this technique can be utilized for the preparation of solid dispersions in future.

Site and Mode of Action of Clofibrate

Clofibrate belongs to fibrate class. It is used to reduce low-density lipoprotien (LDL) and very low density lipoprotein (VLDL) levels, as well as increasing high-density lipoprotein (HDL) levels. Clofibrate exerts its therapeutic effects through activation of peroxisome proliferator activated receptor a (PPARa). This increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III. The resulting fall in triglycerides produces an alteration in the size and composition of LDL and thereby it reduces the LDL and VLDL levels [8,9],

MATERIALS AND METHOD:

Materials Used

Clofibrate, Hydroxyl propyl β Cyclodextrin, β Cyclodextrin, Ethanol, Lactose anhydrous

Talc, Magnesium stearate, Triton x -100, Sodium cmc.

Methods Used

Preparation of Physical Mixtures:

Physical mixtures of Clofibratee with β-Cyclodextrin and Hydroxy propyl-β-Cyclodextrin were prepared in the ratio of 1:2 separately. Clofibrate and β-Cyclodextrin were accurately weighed, pulverized and then mixed thoroughly by light trituration for 5 min in a glass mortar until homogenous mixture was obtained. Similarly physical mixtures of Clofibrate and Hydroxy propyl-β-Cyclodextrin containing drug: carrier (1:2) were prepared.

Preparation of Solid Dispersions by Kneading Method:

Dispersions were prepared in the ratios of 1:0.5, 1:1, 1:2 (Drug: carrier) withβ-Cyclodextrin and Hydroxy propyl-β-Cyclodextrin. Initially weighed amount of drug and carrier (β-Cyclodextrin or Hydroxy propyl-β-Cyclodextrin) were placed in a mortar and were ground with pestle for few minutes. Then few ml of alcohol: water (1:1) was added and then triturated until alcohol: water gets evaporated. Then the obtained dry dispersions were preserved in a desiccator for overnight. The dry dispersion was then passed through the 100# mesh sieve and is stored in moisture free area till further use.

Formulation of Immediate release tablets of Clofibrate:

The solid dispersion equivalent to 145 mg of drug was taken then mixed with directly compressible diluent in a plastic bag. Magnesium stearate, talc and lactose were passed through sieve no. 60, mixed and blended with initial mixture in the plastic container followed by compression of the blend using a single punch CADMACH punching machine

Evaluation of Solid Dispersions

Drug Content Uniformity:

Drug equivalent to 20 mg of the dispersions was weighed transferred into a 100ml volumetric flask, the dispersion was solubilized in 20ml alcohol and finally the volume was adjusted to 100ml with 0.2% w/v SLS. From the obtained stock, dilutions were made such that we finally obtain 10µg/ml solution. The obtained solution was assayed for drug content using a U.V. spectrophotometer at 290nm. The drug content is calculated from the absorbance obtained with the help of the calibration curve. The results are given in Table no.2.

In – Vitro Dissolution Studies:

Dissolution rate of Clofibrate from all the dispersions was performed using dissolution testing apparatus with paddle [10]. The dissolution fluid was 900ml of 0.1N HCl with Containing 0.0072% w/v SLS, a sp

37±0.5°C

dissolution medium (5ml) were withdrawn at different time intervals (5, 10, 15,20,30,45 and 60min), suitably diluted and assayed for Clofibrate by measuring the absorbance at 290nm. The dissolution experiments were conducted in triplicate and the results are tabulated in Tables 3, 4, 7 and shown in Figs 1, 2, 3.

Evaluation of Immediate Release Tablets

All the prepared tablets were evaluated for the following parameters as per the I.P guidelines and the results are given in the Table 5, 6.

Weight Variation:

Twenty tablets were randomly selected from each batch, individually weighed, the average weight and the standard deviation of 5 tablets was calculated.

Hardness:

Hardness or tablet crushing strength (F_c), the force required to break a tablet in a diametric compression was measured using a MONSANTO tester.

***In – Vitro* Dissolution Studies:**

Dissolution rate of Clofibrate from all formulations was performed using dissolution testing apparatus (paddle) [10]. The dissolution fluid was 900ml of 0.1N HCL Containing 0.0072% w/v SLS, a speed of 50 rpm and a temperature of 37±0.5°C was used in each test. Samples of dissolution medium (5ml) were withdrawn at different time intervals (5,10,20,30,45 and 60min), suitably diluted and assayed for Clofibrate by measuring the absorbance at 290nm by using U.V. spectrophotometer. The dissolution experiments were conducted in triplicate and the results are tabulated in Tables 3, 4, 7 and shown in Figs 1, 2, 3.

Characterization of Clofibrate Solid Dispersions

X-Ray Diffraction [9]: Powder X-ray diffraction can be used to qualitatively detect material with long range order. Sharper diffraction peaks indicate more crystalline material. Recently developed X-ray equipment is semi quantitative and the results are shown in Fig no.14 to 16.

FTIR Spectroscopy studies [10]:

FTIR Spectra of the optimized batches of solid dispersions of Clofibrate were studied to confirm the compatibility of the API with the excipients. FTIR spectroscopy was obtained by the FTIR spectrophotometer (Brucker) using the potassium bromide pellets and the scanning range used was 4400 to 400 cm^{-1} at a scan period of 1min.Spectra of the optimized batches are shown in Fig 4 to 10.

DSC studies [11]: DSC thermo gram of the optimized solid dispersion (10mg sample) was recorded the using automatic thermal analyzer. The DSC is used to evaluate the drug – excipient interaction and are shown in Fig 11 to 12.

SEM studies [12]:

The external surface morphology and diameter of solid dispersions were studied by scanning electron microscopy and the results are shown.

Saturation Solubility Studies

Saturation solubility studies were carried out using distilled water as a solvent by using shake flask method. Each excessive quantity (50mg) of Clofibrate and equivalent prepared solid dispersions were taken in conical flask plugged with cotton with fixed volume (25ml) of deionized water [13]. The resultant suspension was treated at 37° C with 200 rpm in incubator shaker for 48hrs. After 48 hrs samples were taken from rotary shaker and allowed to stand for 24hrs .After 24 hrs samples were withdrawn and filtered through whatman no.1filter.The filtrate was suitably diluted with deionized water and analyzed at 290 nm by UV-visible spectrophotometer and the results are shown in the Table no 8 and Fig 23.

Phase Solubility Studies [14]

Phase solubility studies on pure drug (Clofibrate) with different concentrations of cyclodextrins (β CD / HP β -CD) (0.25%, 0.5%, 0.75%, 1%) were performed by the Shake flask method [14,15]. Excess amount of the drug is added to 25ml distilled water containing various concentrations of cyclodextrins (β -CD, HP β -CD) taken in a series of 25ml stopped conical flask and the mixture was shaken for 48 hours at 37°C on a rotary flask shaker at 200rpm. After 48 hrs of shaking, allowed to stand for 24hrs, after that sample were filtered through whatman no.1 filter paper. The concentrations of the sample are estimated by U.V Spectrophotometer at 290nm and the results are shown in the Table no 9 and Fig 23.

RESULTS AND DISCUSSIONS

Table 1: Composition of Solid Dispersion Samples

BATCH CODE	COMPOSITION
SD 1	Clofibrate:β cyclodextrin (1:0.5) solid dispersions
SD 2	Clofibrate:β cyclodextrin (1:1) solid dispersion
SD 3	Clofibrate:β cyclodextrin (1:2) solid dispersion
PM 1	Clofibrate:β cyclodextrin (1:2) physical mixture
SD 4	Clofibrate:HP-β cyclodextrin (1:0.5) solid dispersion
SD 5	Clofibrate:HP-β cyclodextrin (1:1) solid dispersion
SD 6	Clofibrate:HP-β cyclodextrin (1:2) solid dispersion
PM 2	Clofibrate:HP-β cyclodextrin (1:2)Physical mixture
D	PURE DRUG
B	BRAND

Table 2: Assay Values of Different Solid Dispersion Formulations

Formulation	%Drugcontent± Sd (n=3)
SD 1	98.2±3.65
SD 2	100±2.09
SD 3	100.1±3.79
PM 1	100.1±3.39
SD 4	99.94±1.6
SD 5	100.1±3.83
SD6	100.2±1.72
PM 2	99.9±4.5
BRAND	100±2.6

Table 3: Dissolution Profiles of Clofibrate solid dispersions in 0.1N HCl Containing 0.0072% w/v SLS

Time (min)	Cumulative % drug dissolved ±Sd(n=3)			
	SD 1	SD 2	SD 3	PM 1
5	15.15±0.5	27..1± 2.7	53.3± 1.46	13.35± 2.17
10	19.02±0.9	31.4± 3.47	58.9± 4.12	24.5± 4.02
15	21.9± 14.8	40.7± 3.18	68.3± 1.8	31.4± 2.17
20	24.3± 1.41	46±7.5	75.1± 3.37	42.7± 4.88
30	26.3± 0.77	55±7.8	83.8± 2.33	47.6± 2.67
45	32.02± 2.23	69.7± 2.71	93.5± 1.77	62.4± 1.58
60	39.75± 1.52	75.36± 2.22	106± 1.6	72.1± 3.1

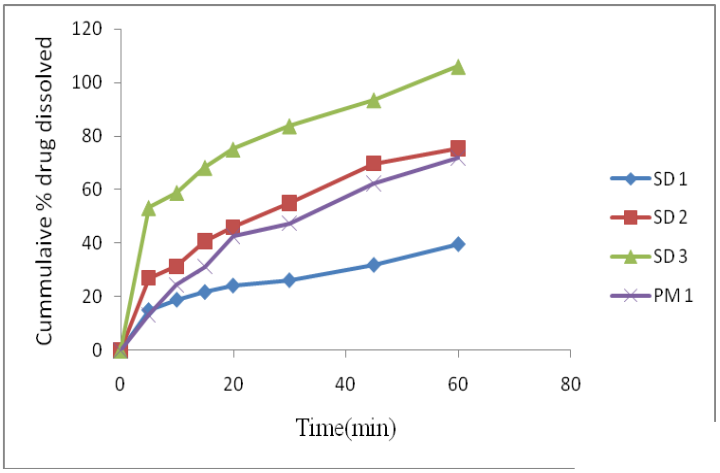

Fig 1: Dissolution Profiles of Clofibrate solid dispersions in 0.1N HCL with 0.0072%w/v SLS

Table 4: Dissolution Profiles of Clofibrate solid dispersions in 0.1N HCl Containing 0.0072% w/v SLS

Time (min)	Cumulative % drug dissolved ±Sd(n=3)			
	SD 4	*SD 5*	*SD 6*	*PM 2*
5	24.3± 1.87	47.7± 3.82	65.4± 7.7	18.15± 2.02
10	32.9± 1.27	55.8± 0.85	80.98± 6.3	30.4± 1.48
15	34.87±0.80	61.3± 0.36	86.25±4.41	37± 0.86
20	37.5± 0.63	69.2± 0.75	93.4± 0.55	46.1± 1.48
30	40.53± 0.60	76.8± 2.72	97.4± 1.8	54.8±3.93
45	43.3± 1.1	82.3± 2.5	103.7± 1.6	63.7± 0.77
60	46.5± 2.19	93.7± 3.3	109.95±3.5	72.28± 1.18

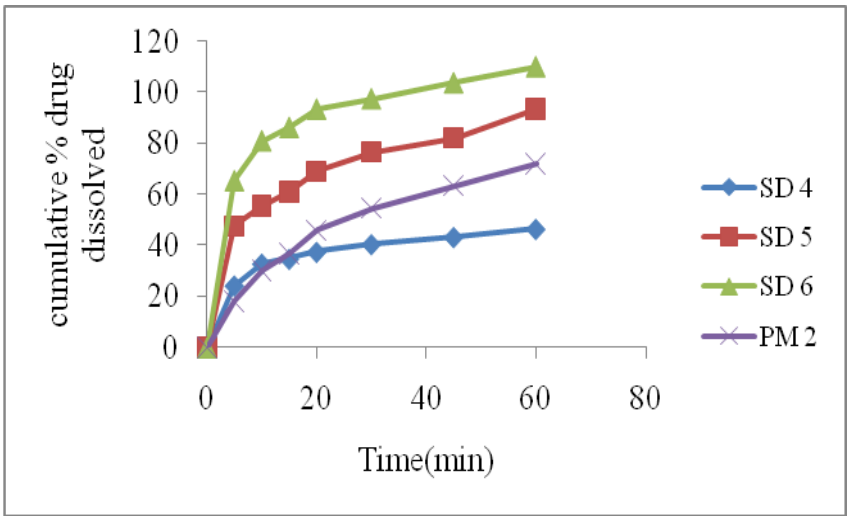

Fig 2: Dissolution Profiles of Clofibrate solid dispersions in 0.1N HCl Containing 0.0072% w/v SLS

Table 5: Formulae for Immediate Release Tablets of Clofibrate

Ingredients	F1	F2
SD 3	435 mg	-
SD 6	-	435 mg
Lactose	5 mg	5 mg
Talc	5 mg	5 mg
Magnesium stearate	5 mg	5 mg

Table 6: Evaluation of Immediate Release Tablets of Clofibrate

Parameter	F1	F2
Avg.wt(mg)±SD (n=3)	457±0.54	452±0.32
Hardness(Kg/cm^2) (n=3)	4.5±0.12	4.5±0.34
Friability(n=3)	0.42±0.22%	0.66±0.13%
Drug content (%) (n=3)	100.1±3.315	100.15±2.702

Table 7: Dissolution Profiles of Clofibrate tablets in 0.1N HCl Containing 0.0072% w/v SLS

TIME (min)	CUMULATIVE % DRUG DISSSOLVED±Sd(n=3)			
	D	B	F 1	F 2
5	9.46±0.96	10.5±1.2	15.5±1.8	17.8±0.8
10	12.71±0.49	13.89±0.28	22.6±1.5	23.5±2.7
15	13.2±0.11	15.09±0.08	43.4±2.72	45±0.9
20	14±0.08	17.3±1.8	51.5±0.77	56±1.46
30	14.5±0	19.98±2	70.24±0.6	69±1.77
45	15.1±0.1	22.5±1.12	80.2±1.1	92±2.22
60	16.4±0.2	25.3±3.8	101.3±2.19	110.8±0.12

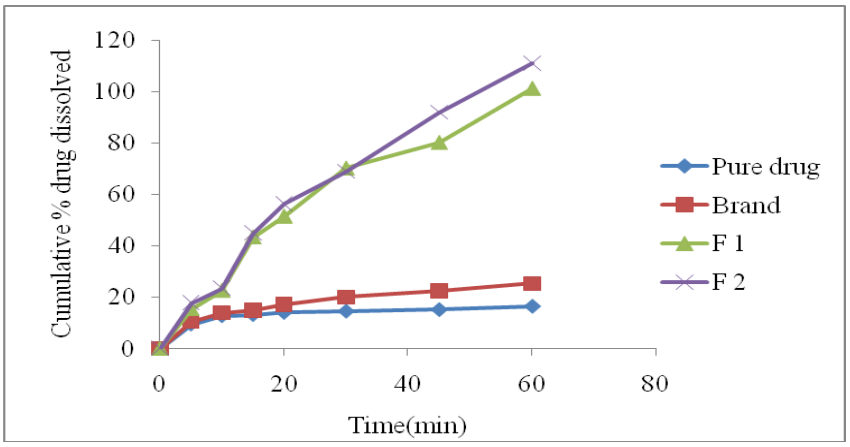

Fig 3: Dissolution Profiles of Clofibrate tablets in 0.1N HCl Containig 0.0072% w/v SLS

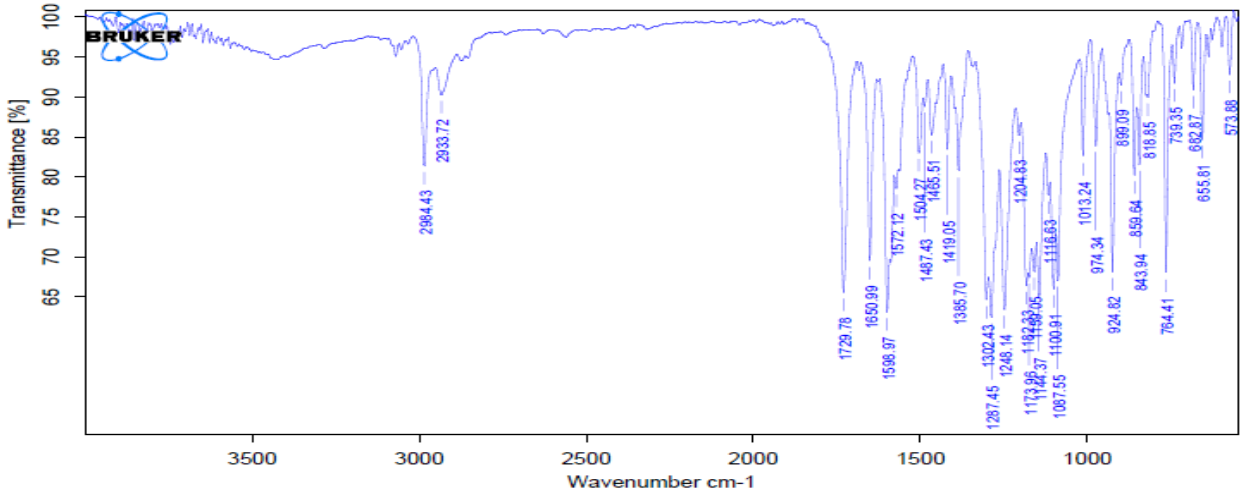

Fig 4: FTIR Spectrum of Clofibrate

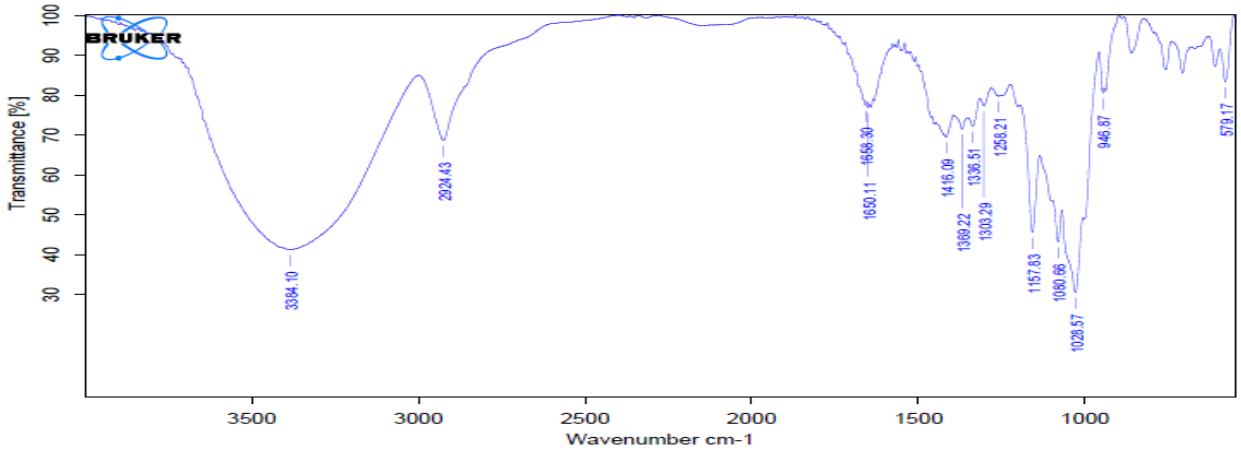

Fig 5: FTIR Spectrum of ß cyclodextrin

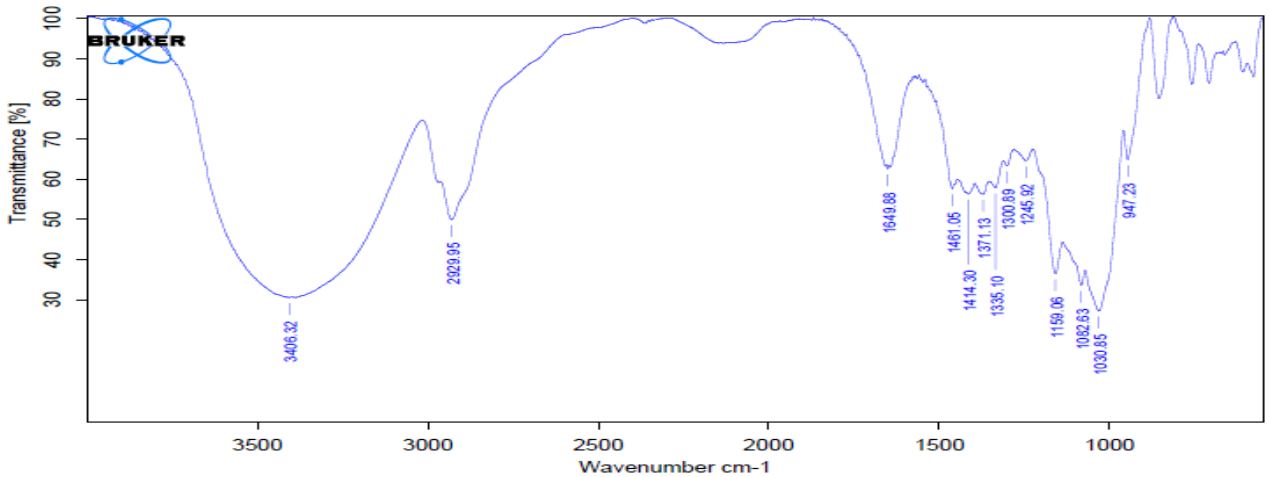

Fig 6: FTIR Spectrum of HP- ß cyclodextrin

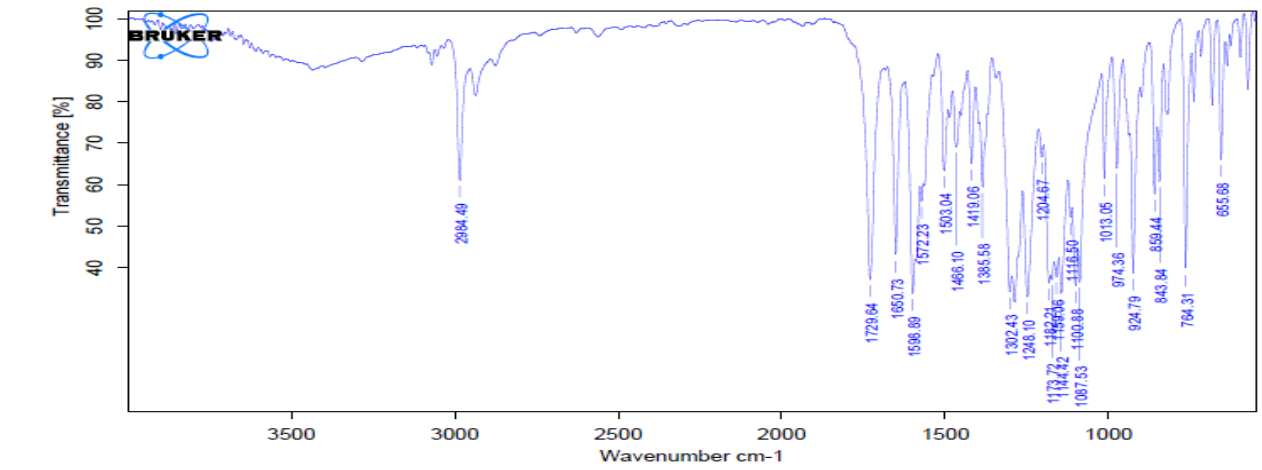

Fig 7: FTIR Spectrum of 1:2 physical mixture of Drug: HP ß cyclodextrin

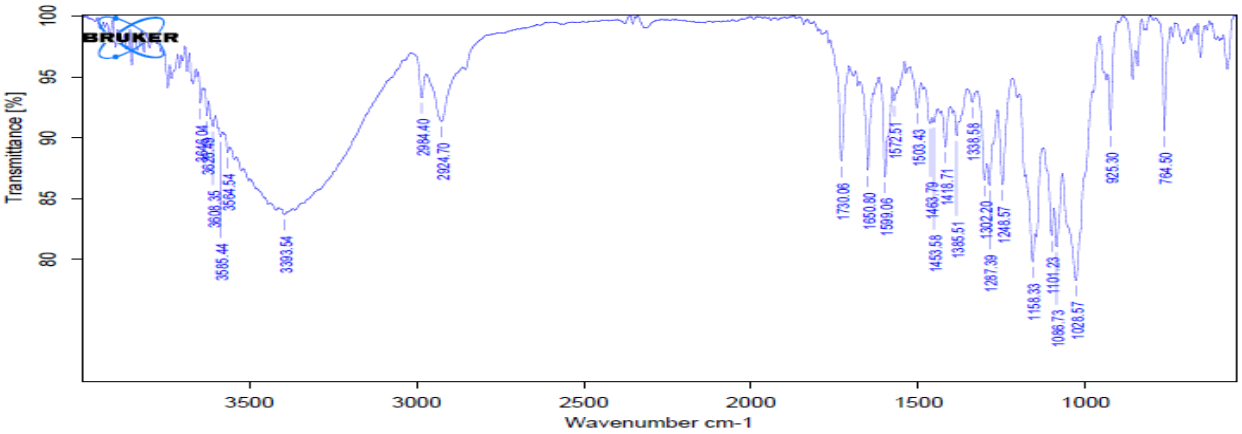

Fig 8: FTIR Spectrum of 1:2 physical mixture of Drug: ß cyclodextrin

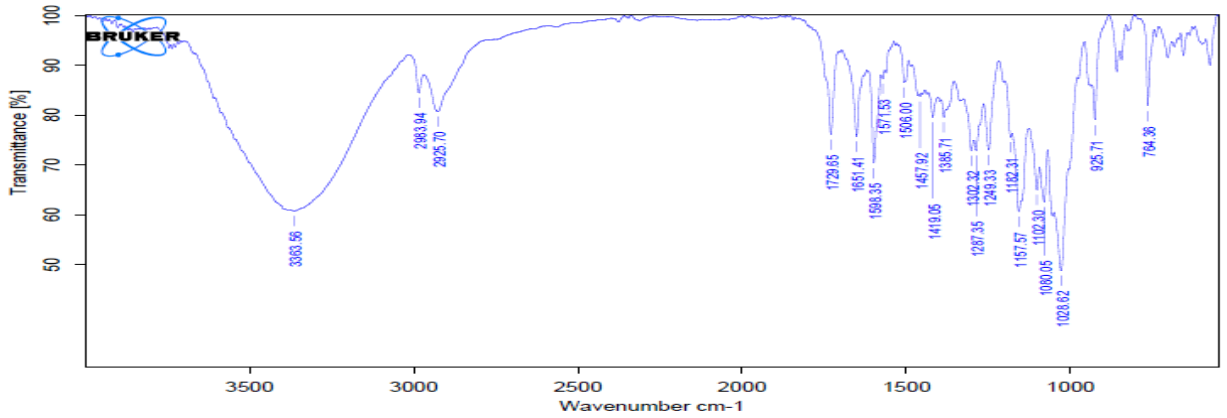

Fig 9: FTIR Spectrum of 1:2 Solid dispersion of Drug: ß cyclodextrin

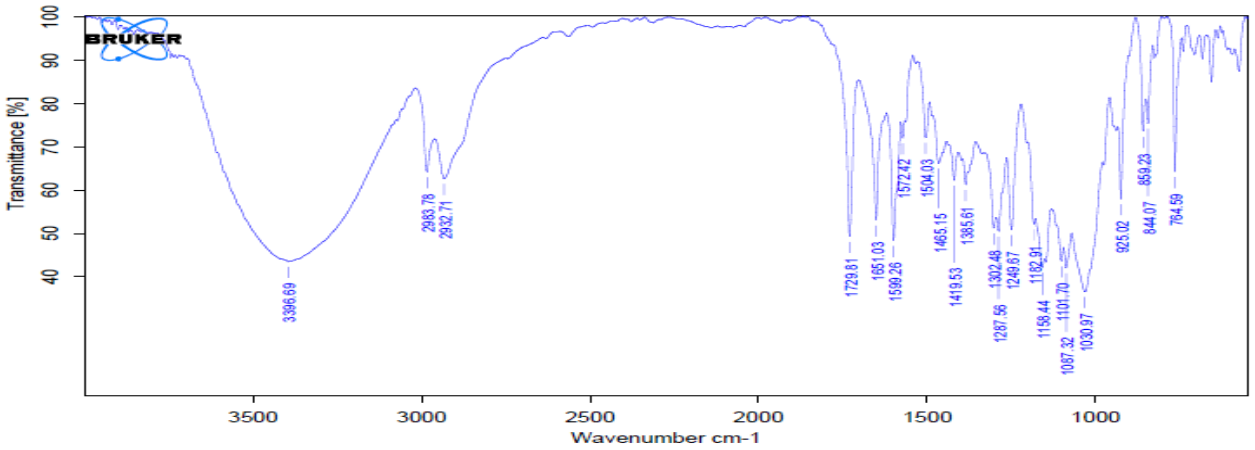

Fig 10: FTIR Spectrum of 1:2 Solid dispersion of Drug: HP ß Cyclodextrin

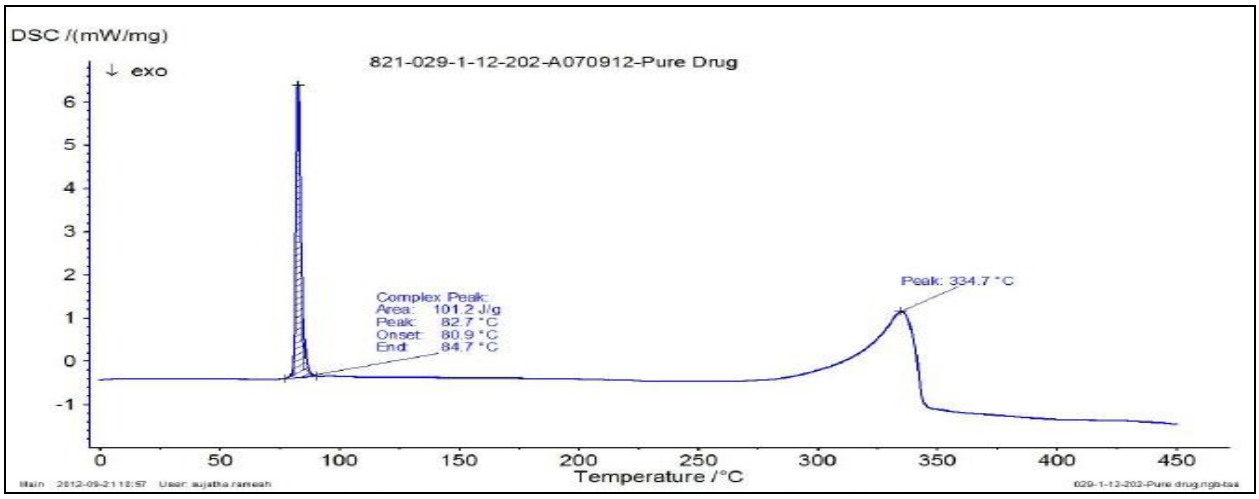

Fig 11: DSC thermo gram of Clofibrate

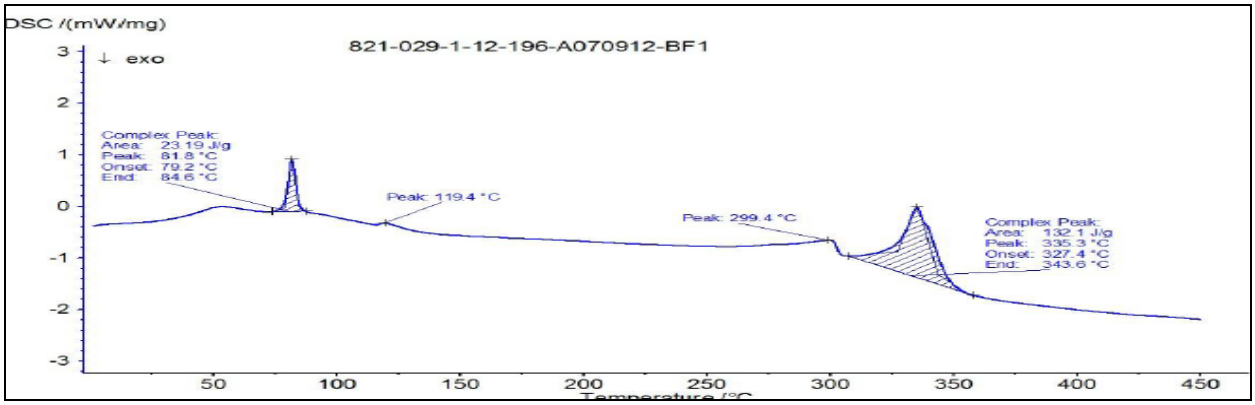

Fig 12: DSC thermo gram of 1:2 Solid dispersion of Drug: HP β Cyclodextrin

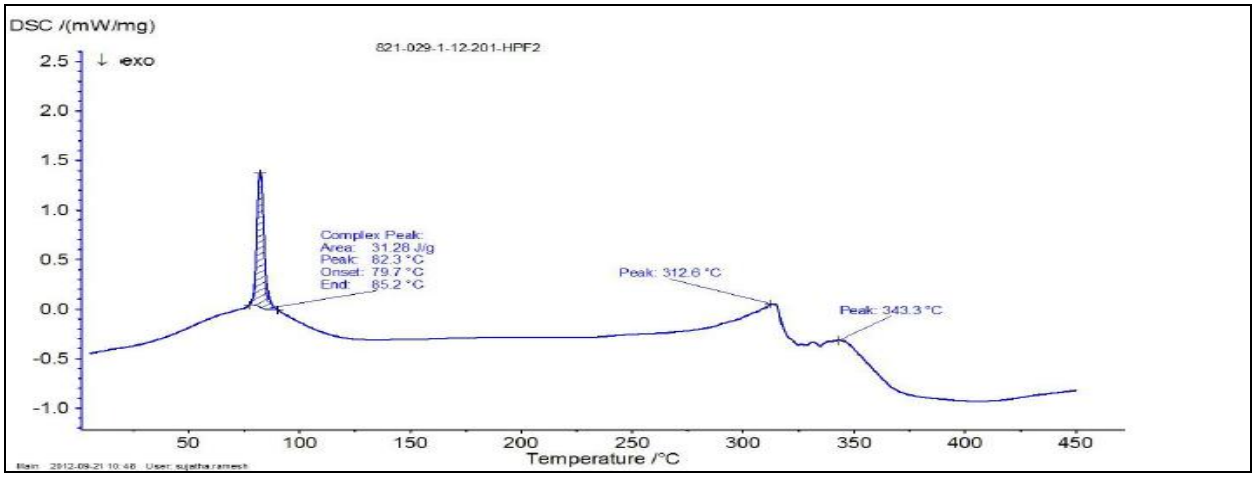

Fig 13: DSC thermo gram of 1:2 Solid dispersion of Drug: β Cyclodextrin

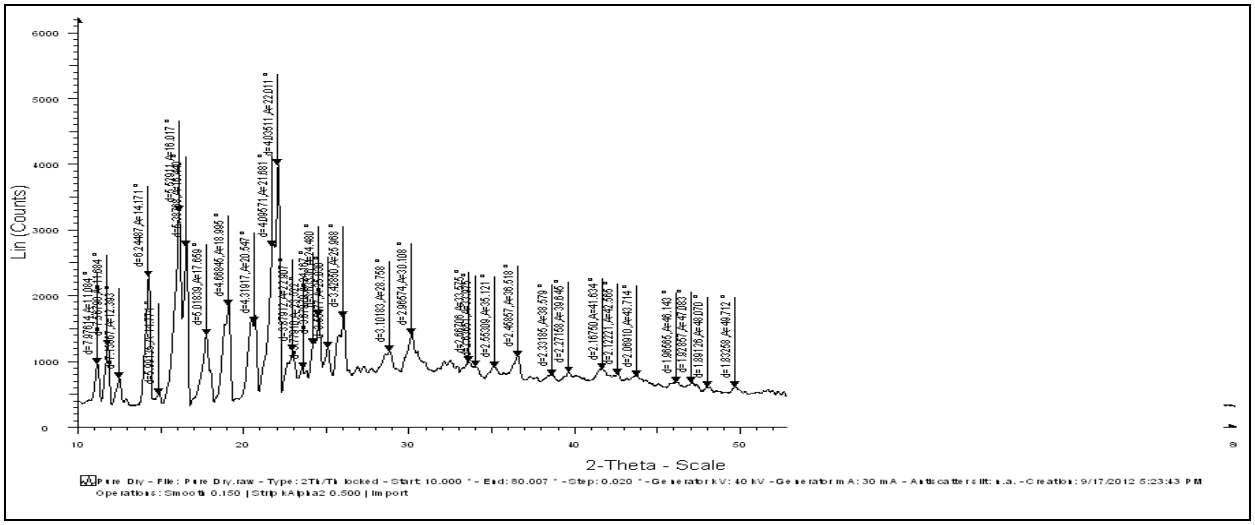

Fig 14: X-ray Diffractogram of Clofibrate

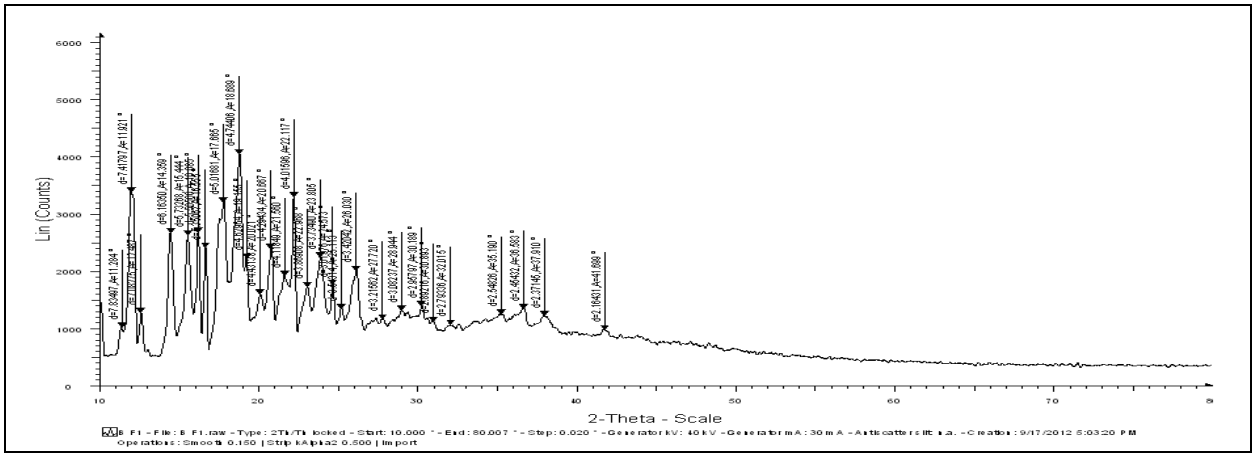

Fig 15: X- ray Diffractogram of 1:2 Solid dispersion of Drug: β Cyclodextrin

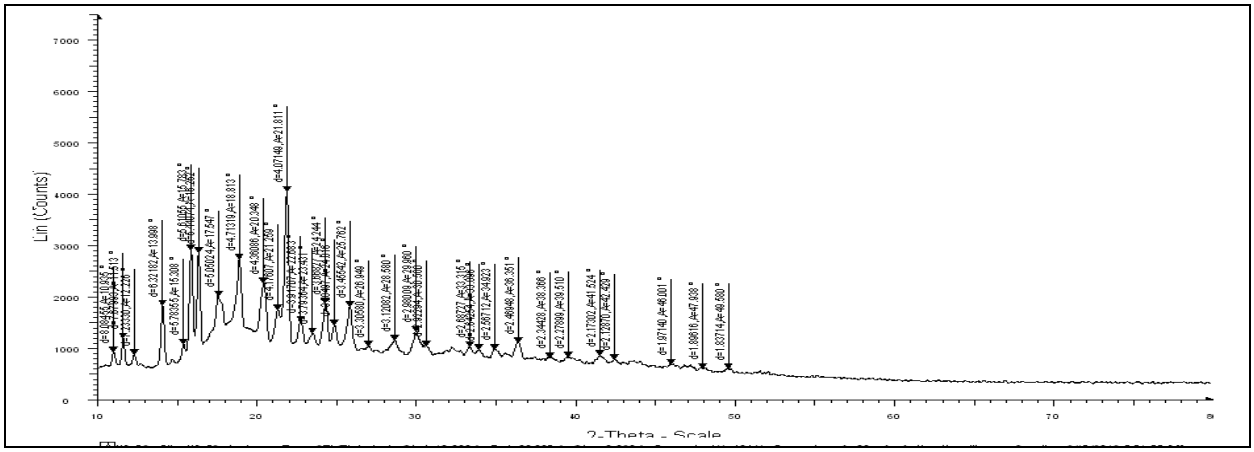

Fig 16: X- ray Diffractogram of 1:2 Solid dispersion of Drug: HP β Cyclodextrin

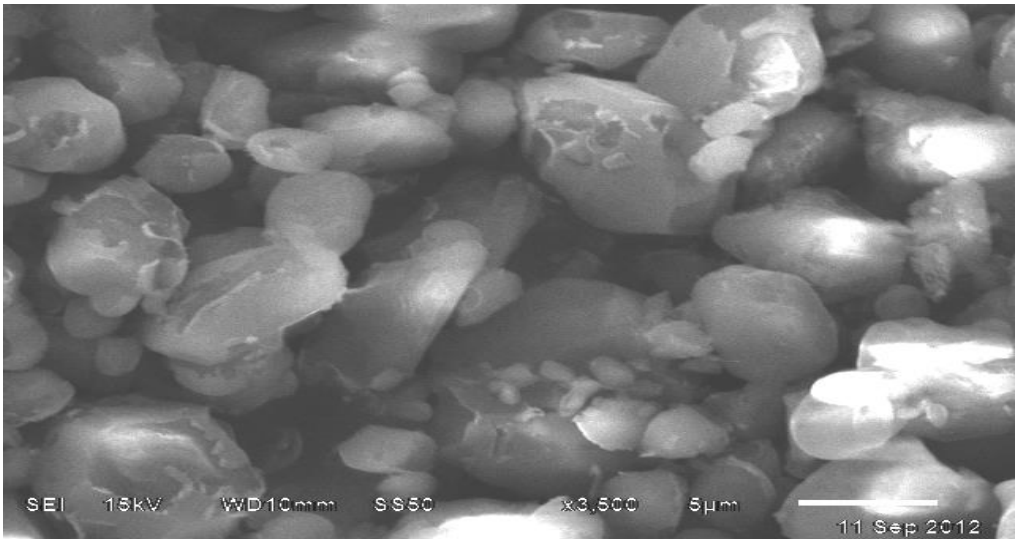

Fig 17: SEM Studies of Clofibrate

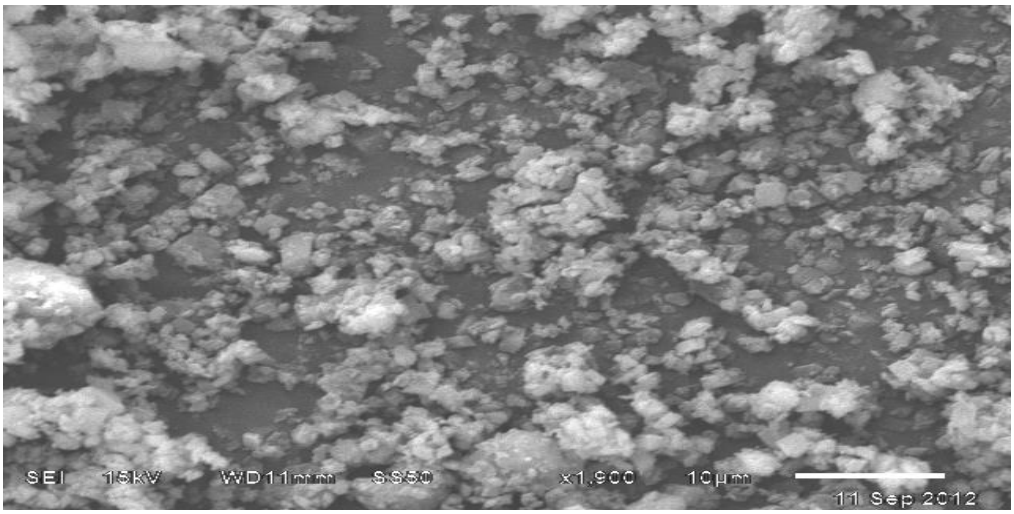

Fig 18: SEM Studies of 1:2 Solid dispersion of Drug: β Cyclodextrin

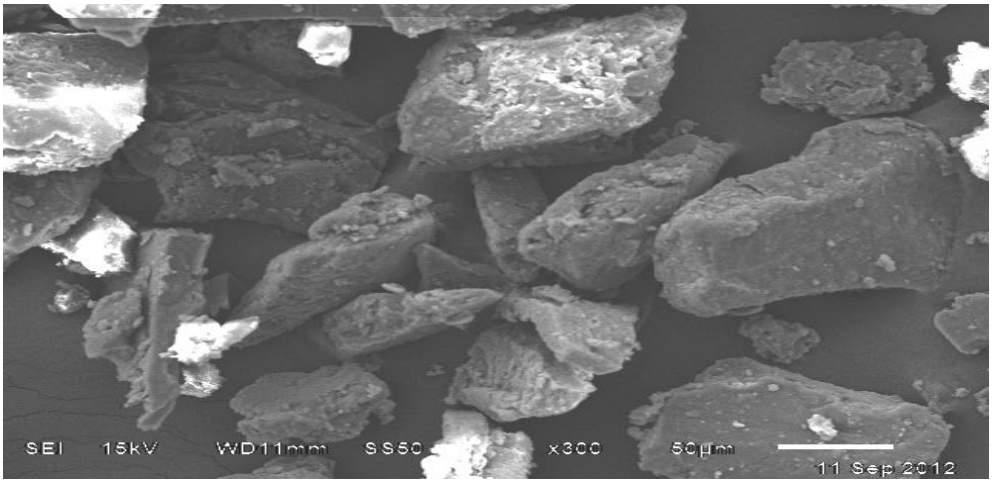

Fig 19: SEM Studies of 1:2 Solid dispersion of Drug: HP β Cyclodextrin

Table 8: Saturation solubility studies of optimised formulations

Formulation	Solubility(mg/ml)
Pure drug	2.28
SD 3	3.38
SD 6	3.76

Table 9: Phase solubility studies

% Concentration of β and HP β - cyclodextrin	Solubility of drug (mg/ml) in βcyclodextrin solution	Solubility of (mg/ml) in HP- β cyclodextrin solution
0.25	4.36	5.86
0.5	6.23	7.72
0.75	8.36	17.38
1	10.8	22.22

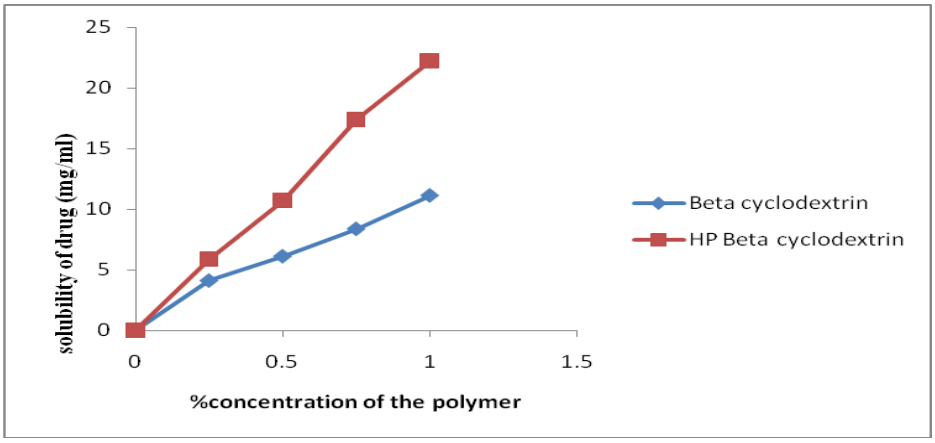

Fig 20: Phase solubility studies

DISCUSSION:

The objective of present study was to improve the dissolution rate of Clofibrate by solid dispersion method and formulate it into immediate release tablets. In the present study ß and HP-ß Cyclodextrins are employed in the preparation of solid dispersions as they act as hydrophilic carriers, there by enhancing the dissolution rate of the drug. As physical mixtures that are prepared at 1:2 ratio shown good dissolution profile, solid dispersion technique was employed.

Totally, six solid dispersions were prepared (Sd1, Sd2, Sd3, Sd4, Sd5, and Sd6) with varying drug: excipient ratios (Table no 1). For the prepared dispersions drug content (Table no.2) and In-vitro dissolution studies (Table no.3, 4, & 7) were performed. All the prepared dispersions showed satisfactory dissolution rate. SD 3 and SD 6 were selected for further study.

FTIR indicated the absence of drug-excipient interactions, as all the peaks of drug were present in the physical mixture and in the solid dispersion. Similarly, DSC ruled out the no drug-excipient interaction, as the original exotherm of the drug was clearly evident in the physical mixture and in the solid dispersion and the SD 6 shows the decrease in the crystalline nature and heat of enthalpy than SD 3 .The XRD shows less intense peaks of SD 6 formulation compared to SD 3 and the pure drug. SEM results show the particle size and surface morphology of the Clofibrate SD3 and SD6 formulations (Fig 17 to 19).

The faster dissolution rate of the drug from the solid dispersions is attributed to the enhancement of wettability (as hydrophilic carriers were used) and decrease in the aggregation of the hydrophobic drug particles. Also, the decrease in the particle size and the increase in the surface area of the hydrophobic drug particles (in the solid dispersions) may contribute to the enhancement of the dissolution rate of the drug.

Totally, two different tablets (F1,F2) of Clofibrate were formulated using SD3 and SD6 .Out of the prepared two formulations, F1 showed lower dissolution profile (Table no.7 and Figure no 3) than formulation F2 .The result obtained was satisfactory. There is a fourfold increase in the % Cumulative drug dissolved for F1 & F2 when compared with the brand.

CONCLUSION:

The optimized formulations were SD3 and SD6.The study shows that the dissolution rate of Clofibrate can be enhanced to a great extent by solid dispersion technique using an industrially feasible Kneading method. Hence, Clofibrate-β cyclodextrin, Clofibrate- HP-β cyclodextrin systems could be considered for formulations of immediate release tablets of Clofibrate. The tablets of Clofibrate (F1 and F2) were showed higher drug release when compared to the brand and the pure drug.

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