International Journal of Biomedical and Advance Research
ISSN: 2229-3809 (Online); 2455-0558 (Print)
Journal DOI: 10.7439/ijbar
CODEN: IJBABN

Original Research Article

Enhancement of dissolution rate of clofibrate (BCS Class –II drug) by using liquisolid compact technology

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Abstract

The aim of this study was to improve the dissolution rate of the poorly soluble drug Clofibrate by delivering the drug as a liquisolid compact. Liquisolid compacts were prepared using propylene glycol as solvent, microcrystalline cellulose as carrier, Starch, Silica and Lactose are used as coating materials. Sodium starch glycolate and Cross carmellose sodium are used as a Super disintigrants. The crystallinity of the newly formulated drug and the interaction between excipients was examined by X-ray powder diffraction and Fourier-transform infrared spectroscopy, respectively. The dissolution studies for the liquisolid formulation and the Conventional tablet were carried out at a pH 6.8 buffer. The results showed no change in the crystallinity of the drug and no interaction between excipients. The dissolution efficiency of Clofibrate at 60 min was increased from 71.02% for plain drug and 81.3% for Conventional Tablet to 100.47% for the liquisolid formulation. The increase in the dissolution rate was also found to be significant compared to the pure drug and Conventional Tablet at pH 6.8 buffer. The liquisolid technique appears to be a promising approach for improving the dissolution of poorly soluble drugs like Clofibrate.

Keywords: Liquisolid compact Technology, FT-IR, X-RD, SEM, Solubility, Dissolution rate.

1. 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 Liquisolid Compact Technology as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcome the limitations of previous approaches such as salt formation, solubilisation by co solvents, and particle size reduction and other methods. Much of the research that has been reported on Liquisolid Compact 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. Liquisolid Compact technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs [1].

The Bio pharmaceutics Classification System (BCS)[2]: According to the BCS, drugs are classified as follows:

Table 1: 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

Table 2: Terms of Approximate Solubility According to USP [3]

Term	Parts of solvent required for part of solute
Very soluble	Less than 1 part
Freely soluble	1 to 10 parts
Soluble	10 to 30 parts
Sparingly soluble	30 to 100 parts
Slightly soluble	100 to 1000 parts
Very slightly soluble	1000 to 10,000 parts
Practically insoluble	≥10, 000 parts

1.1 Liquisolid Compact Technology

The new developed technique by Spireas liqui-solid system improves the dissolution properties of water insoluble or poorly soluble drugs. The term 'liqui-solid systems' (LS) is a powdered form of liquid drug formulated by converting liquid lipophilic drug or drug suspension or solution of water-insoluble solid drug in suitable non-volatile solvent systems, into dry looking, non-adherent, free-flowing and readily compressible powdered mixtures by blending with selected carrier and coating materials. Since drug dissolution is often the rate limiting step in gastrointestinal absorption, the significant increase in wetting properties and surface area of drug particles available for dissolution from liquisolid compacts may be expected to display enhanced drug release characteristics and, consequently, improved oral bioavailability[4].

1.2 Components of Liquisolid Compact Formulation

1.2.1 Non volatile Solvent

Non volatile Solvent should be Inert, high boiling point, preferably water-miscible and not highly viscous organic solvent systems and compatible with having ability to solubilise the drug. The non volatile solvent acts as a binding agent in the liquisolid formulation Various non-volatile solvents Used for the formulation of liquisolid systems include Polyethylene glycol 200 and 400, glycerin, polysorbate 80 and propylene glycol[5].

1.2.2 Super Disintegrants

Super disintegrate increases the rate of drug release, water solubility and wet ability of liquisolid granules. Mostly super disintegrates like sodium starch glycolate, Cross Carmellose Sodium and crosspovidone[6].

1.2.3 Carrier Materials

Carrier material should be porous material possessing sufficient absorption properties which contributes in liquid absorption. The carrier and coating materials can retain only certain amounts of liquid and at the same time maintain acceptable flow and compression properties hence, increasing moisture content of carrier's results in decreased powder flow ability. These include grades of microcrystalline cellulose such as avicel PH 102 and avicel PH 200 [7].

1.2.4 Coating Materials

Coating material should be a material possessing fine and highly adsorptive particles which contributes in covering the wet carrier particles and displaying a dry looking powder by adsorbing any excess liquid. Coating material is required to cover the surface and maintain the powder flow ability. Coating material includes silica (Cab-O-Sil) M520, 35, Aerosil 2003, syloid, Starch and Lactose [8].

1.3 General method of preparation of liquisolid compacts

As shown in the figure a liquid lipophilic drugs (chloramphenicol, simvastatin and Clofibrae etc..) can be converted into a liquisolid system without being further modified on the other hand, if a solid water –insoluble drug (hydrochlorothiazide, prednisolone etc) is formulated, it should be initially dissolved or suspended in a suitable non-volatile solvent system to produced a drug solution or drug suspension of desired concentration next a certain amount of the prepared drug solution or suspension, or the liquid drug itself incorporated into a specific quantity of carrier material which should be preferably of a porous nature and possessing sufficient absorption properties, such as power and granular grades of microcrystalline and amorphous cellulose are most preferred as carriers .the resulting wet mixture is then converted into a dry –looking, non adherent, free-flowing and readily compressible power by the simple addition and mixing of a calculated amount of coating materials and excepients possessing fine and highly adsorptive particles, such as various type of amorphous silicon dioxide (silica), are most suitable for this a step. before compression or encapsulation, various adjuvant such as lubricants and disintegrates (immediate) or binder (sustained-released) may be mixed with the finished liquisolid system to produce liquisolid compact i.e. tablets or capsule[9,10].

Fig-1: Mechanism represents formulation of Liquid-solid system

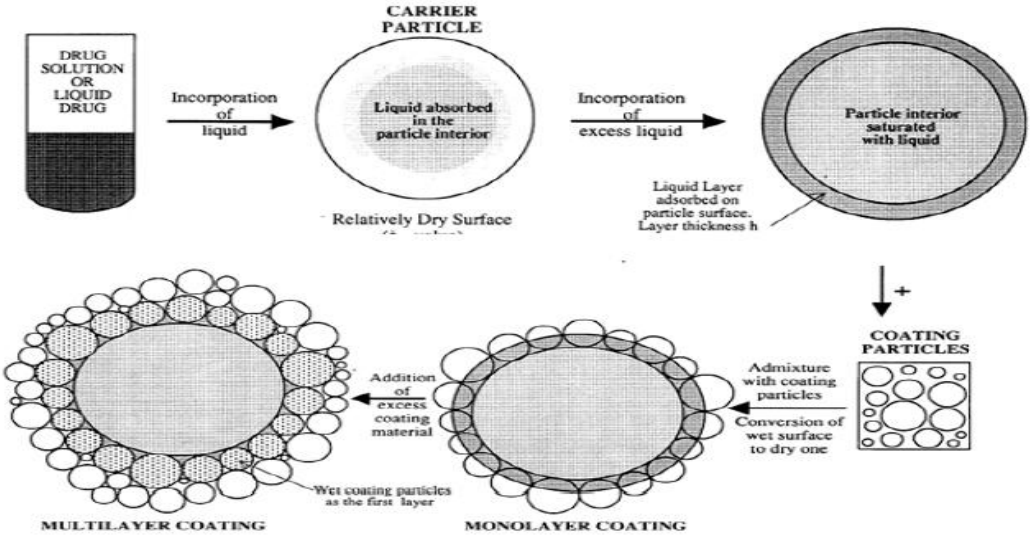


Figure-2: Schematic representation of liquisolid systems

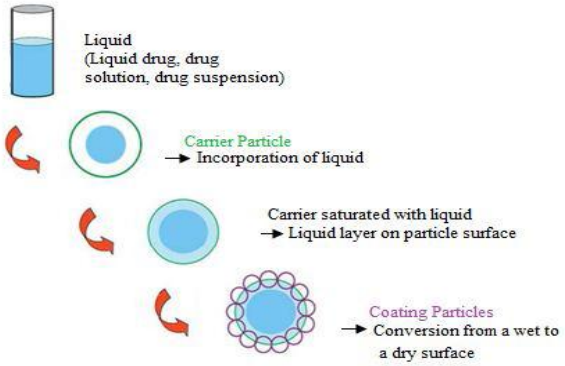
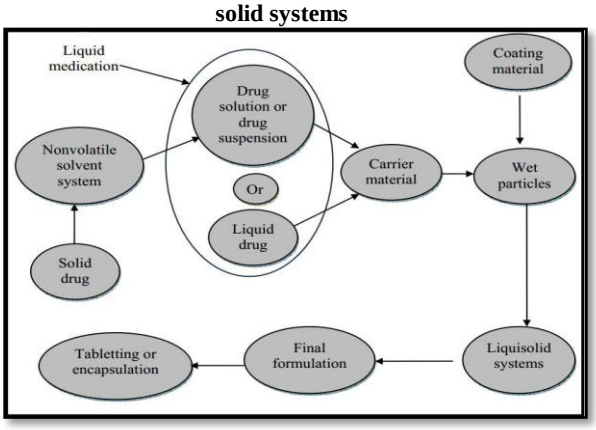


Figure-3: Steps involved in the preparation of liquid solid systems



2. Materials and Methods

2.1 Materials Used: Clofibrate, Micro Crystalline Cellulose, Starch, Silica, Lactose, Talc, Sodium starch Glycolate, Cross Carmellose Sodium and Propylene glycol.

2.2 Methods used

2.2.1 Calibration Curve of Clofibrate

Preparation of Calibration Curve of Clofibrate in pH 7.4 buffer: The 100 mg of Clofibrate was accurately weighed and dissolved in 20 mL of 0.1N NaOH in a 100 mL volumetric flask and finally the volume was adjusted to 100 mL with pH 7.4 buffer (1000 µg/mL). The standard solution of Clofibrate was subsequently diluted with pH 7.4 buffer to obtain a series of dilutions containing 2,4,6,8,10 µg/mL. The absorbance of the above dilutions was measured on a spectrophotometer at 290 nm using pH 7.4 buffer as the blank. The concentration of Clofibrate used and the corresponding absorbance is given in Table. The absorbance was plotted against concentration as shown in the Figure. This calibration curve was used in the estimation of Clofibrate in the present study.

Method of preparation of liquisolid compacts

i. Clofibrate was initially dissolved in the non-volatile solvent, PEG-400 as liquid vehicles to produce a drug solution.
ii. Then carrier material microcrystalline cellulose is added to the Drug solution by continuous mixing in a rapid mixer granulator.
iii. To the above blend add calculated amount of coating material i.e Starch, Silica and Lactose to get a fine and absorptive particle.
iv. Before compression of the mixture add required amount of disintegrant like sodium starch glycolate and Cross carmellose sodium mix it well.
v. The remaining additives like lubricant Magnesium sterate are added and mixed for a period of 10 to 20 min in a rapid mixer granulator.
vi. The final mixture is passed through sieve
vii. The granules obtained are dried in vacuum tray Drier at 60^0c for one hour.
viii. The Resultant dried granules are compressed by Tablet Press.

2.2.2 Evaluation of pre compressional and post compressional parameters of oral Dispersible tablets

Bulk density: Apparent bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder was determined[11].

$$\text{Bulk density} = M / V_b$$

Tapped density: The measuring cylinder containing a known mass of powder blend was tapped for a fixed number of times as per USP apparatus-11. The minimum volume occupied by the powder after tapping was measured.

Tapped density = weight/tapped volume

Compressibility index: Compressibility index is calculated as follows

Tapped density- Bulk density/ Tapped density*100

The value below 15% indicates a powder with good flow characteristics where as above 25% indicates poor flow ability[12].

Haussner's ratio: It is an indirect index of ease of powder flow, it is calculated as follows:

Tapped density / Bulk density

Haussner's ratio <1.25 indicates good flow properties, where as >1.5 indicates poor flow ability.

Angle of Repose: Angle of repose was determined using funnel method. The blend was poured through funnel that can rise vertically until a maximum cone height (h) was obtained. Radius of the heap(r) was measured and angle of repose was calculated as follows[13].

$$Ø = \tan^{-1} h/r$$

2.2.3 Compression of Tablets: To the mixed blend of powder and excipients finally add magnesium stearate then mixed for 5 min. The mixed blend was compressed with twelve (12) station tablet punching machine using 7 mm flat punches with break line. A minimum of 10 tablets for each batch were prepared.

2.2.4 Evaluation of Liquisolid compact Tablets

All the prepared Tablets were evaluated for the following parameters as per IP.

Weight variation: Twenty tablets were randomly selected from each batch, individually weighed, the average weight and the standard deviation of 5 tablets was calculated [14].

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

Friability: Friability of tablets was determined using the Roche friabilator (USP). Pre weighted sample of tablets was placed in the friabilator and was subjected to 100 revolutions at 25 rpm. Tablets were de dusted using a soft muslin cloth and reweighed[15].

Percent friability = [initial wt- final wt/ initial wt] × 100

Drug content: Three tablets from each formulation were weighed accurately and powdered. Powder equivalent to 100mg of Clofibrate was dissolved in 20ml alcohol and the volume was adjusted to 100ml with 0.2% w/v SLS. The resultant solution was then subsequently diluted with distilled water assayed for the drug by using UV 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

***In – Vitro* dissolution studies:** Dissolution rate of Clofibrate from all formulations was performed using dissolution testing apparatus (paddle). The dissolution fluid was 900ml of Ph 7.4 Buffer Containing 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 Table and shown in Figure.

FTIR Spectroscopy studies: FTIR Spectra of the optimized batches of Liquisolid Compacts 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 Figures.

DSC studies: DSC thermo gram of the optimized Liquisolid Compacts (10mg sample) was recorded the using automatic thermal analyzer. The DSC is used to evaluate the drug –excipient interaction[16].

X-Ray Diffraction: 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 Figures.

SEM studies: The external surface morphology and diameter of Liquisolid Compacts were studied by scanning electron microscopy. The surface of Liquisolid Compacts was observed under a scanning electron microscope. They were mounted directly on to the SEM sample stub using double sided sticking tape and coated with gold film (thickness 200nm) under reduced pressure (0.0001 mm of Hg) and the results are shown in Figures.

3. Results and Discussion

Table 3: Composition of different formulations of Liquisolid Compacts

S.No	Ingredients in mgs	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Clofibrate	50	50	50	50	50	50	50	50	50
2	Propylene glycol(ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
3	MCC	10	10	5	5	10	10	5	5	10
4	Starch	35	50	75	80	-	-	-	-	-
5	Lactose	-	-	-	-	35	50	75	80	200
6	Silica	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
7	Sodium Starch Glycolate	100	120	150	160	-	-	-	-	-
8	Cross Carmellose Sodium	-	-	-	-	100	120	150	160	25
9	Talc	50	40	10	-	50	40	10	-	5
10	Mg.Stereate	50	25	5	-	50	25	5	-	5
	Total Weight(mgs)	300	300	300	300	300	300	300	300	300

3.1Solubility Studies

Table 4: Solubility Data of API, and Optimized Formulation (F6)

Drug(mg)	50
Volume (mL)	20
Medium	Water
Temperature	37^0C
Solubility of API	10µg/mL
Solubility of F6	49µg/mL

The results revealed that Clofibrate is poorly water soluble drug, so it can be formulated into F6. It is stated that F6 is more soluble in water compared to API.

Table 5: Calibration Curve of Clofibrate in pH 7.4 buffer at λ max 290 nm

Concentration (µg/mL)	Absorbance
0	0
2	0.128
4	0.223
6	0.322
8	0.446
10	0.551
16	0.869
18	0.955

Figure-4: Calibration Curve of Clofibrate in pH buffer 7.4 at 290nm

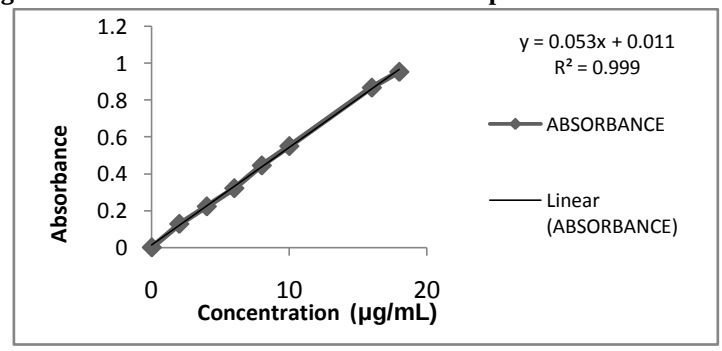


Table 6: Flow properties of liquisolid compacts

Formulation Batch	Bulk density (g/cc)	Tapped Density (g/cc)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (Degrees)
F1	0.56	0.65	13.84	1.14	33
F2	0.66	0.74	10.8	1.12	34
F3	0.69	0.79	9.12	1.08	29
F4	0.55	0.64	13.16	1.15	26
F5	0.64	0.72	11.31	1.16	28
F6	0.68	0.76	12.34	1.08	22
F7	0.53	0.84	17.18	1.20	36
F8	0.62	0.96	16.78	1.12	38
F9	0.65	0.78	18.46	1.36	32

Table 7: Evaluation Studies on Formulations

Formulation	Weight Variation (mg)	Hardness (Kg/cm^2)	Friability (percentage)	Disintegration Studies (mins)
F1	300±0.16	3.5±0.127	0.495±0.171	28.76
F2	300±0.10	3.7±0.132	0.365±0.121	25.45
F3	300±0.26	3.6±0.191	0.465±0.161	31.56
F4	299±0.16	3.9±0.221	0.410±0.151	21.68
F5	300±0.06	3.8±0.342	0.395±0.171	34.13
F6	300±0.18	3.4±0.342	0.315±0.112	18.53
F7	300±0.78	3.6±0.342	0.395±0.271	22.65
F8	299±0.26	4.1±0.342	0.422±0.122	21.98
F9	300±0.79	4.0±0.342	0.399±0.161	31.11

Table 8: Assay Values of Different formulations (n=3±sd)

Batch Codes	Drug Content (%)
F1	100.13±0.88
F2	101.84±1.07
F3	99±1.2
F4	98.3±0.52
F5	97.5±0.21
F6	**100.08±0.41**
F7	93.9±0.34
F8	92.6±1.1
F9	99.9±0.7

Table 9: Dissolution Profiles of F1, F2 and F3 in pH 7.4 buffer

Time (min)	Cumulative % Drug Dissolved ±SD (n=3)		
	F1	**F2**	**F3**
0	0	0	0
5	20.7±0.2	17.2±1	22.3±4
10	23±1.84	19.7±3	29.3±1.7
15	25.1±1.84	20.6±2.4	35.4±4.1
20	31.4±5	23.4±5	44.2±6
30	36.3±2.12	26.6±7.8	48±5.7
45	39.4±0.8	31.9±8.7	53.3±4.2
60	46.36±5.9	33.2±1.5	58.5±4.2
90	50.95±7.8	40±4.3	59.8±3.9
120	61.96±7.2	53.2±2.2	63.7±7.2

Fig- 5: Dissolution profile of F1, F2, F3

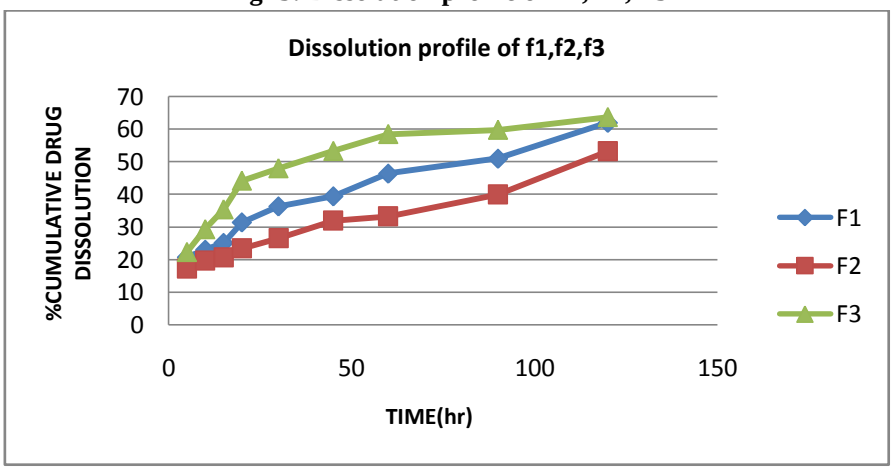


Table 10: Dissolution Profiles of F4, F5, F6 in pH 7.4 buffer

Time (min)	Cumulative % Drug Dissolved ± SD(n=3)		
	F4	F5	F6
0	0	0	**0**
5	6.69±3.1	11.7±0.4	**24.2±1.2**
10	9.75±2.7	12.2±0.9	**34.7±2.6**
15	18.4±6.6	13.9±1.6	**51.2±5**
20	20.1±2.5	15.6±0.44	**62.6±5.2**
30	31.6±3.1	17.6±1.1	**78.4±4.7**
45	43.2±2.6	29.9±1	**96.2±4.2**
60	56.1±5.5	33.2±2.8	**100.2±1.5**
90	67.5±2.9	47.2±7.2	-
120	72.7±2.5	51.7±6.3	-

Fig - 6: Dissolution profile of F4, F5, F6

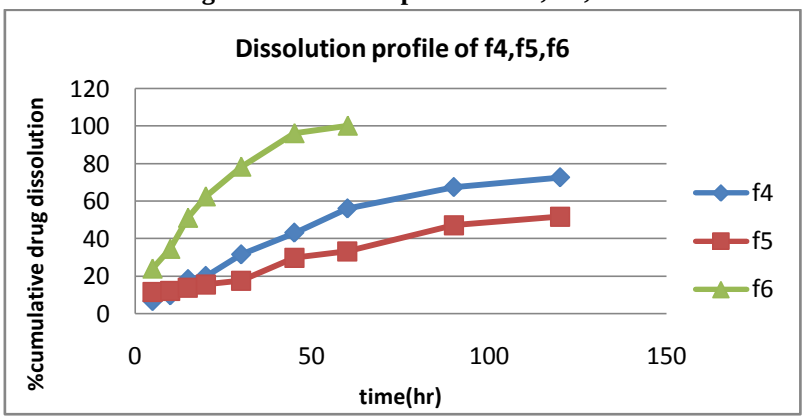


Table 11: Dissolution Profiles of F7, F8 and F9 in pH 7.4 buffer

Time (min)	Cumulative % Drug Dissolved ±SD(n=3)		
	F7	F8	F9
0	0	0	0
5	46.12±1.1	12±1.8	21±1
10	54.2±1.3	18.9±1.5	27.6±0.6
15	56.14±1.4	22.8±3.3	33.2±.4
20	59.2±1.8	24.6±4.7	37.9±1.5
30	60.4±2.1	28.6±4.5	40.3±3
45	61.3±1.7	36.2±3.8	43.1±3.8
60	62.7±2	43.9±6	45.3±6.1
90	63.2±3.4	52.5±1.6	48.2±7.1
120	66.2±3.3	63.9±1.5	55±5.5

Fig -7: Dissolution profile of f7,f 8, f9

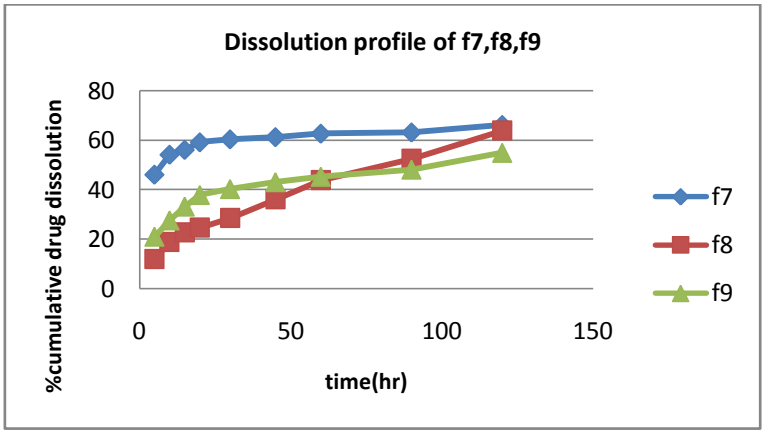


Fig-8: dissolution profile of pure drug, conventional tablets, F6

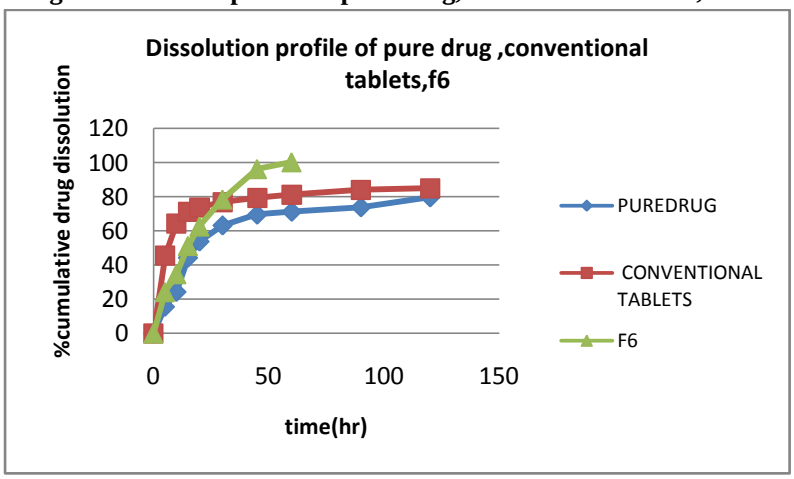


Table 12: Dissolution Profile of Physical Mixture in pH 7.4 buffer

Time (min)	Cumulative % Drug Dissolved ± SD (n=3)
0	0
5	25.6
10	44.3
15	71.3
20	73.8
30	77
45	79.5
60	81.2
90	84
120	85

Fig-9: SEM Image of Pure Clofibrate

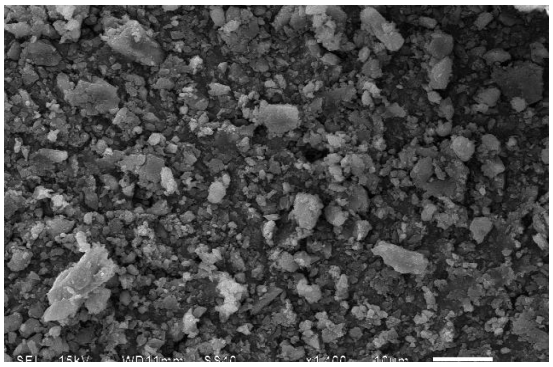


Fig-10: SEM Image of F6

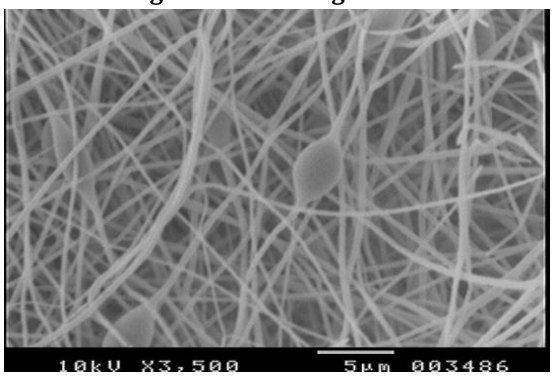


Fig-11: SEM Image of Physical Mixture

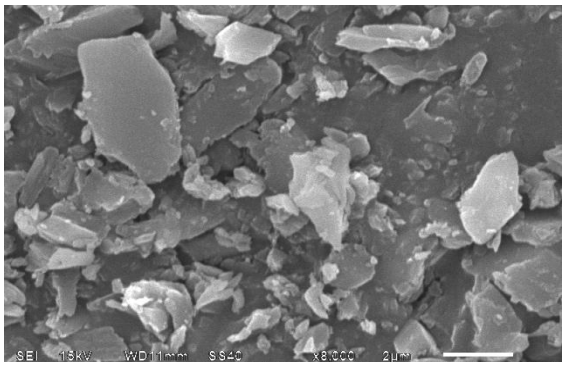


Fig-12: SEM Image of conventional Tablet

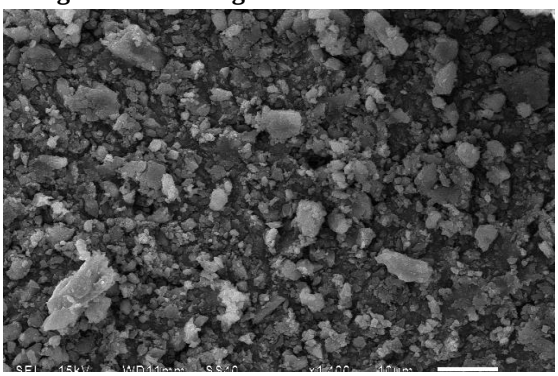


Figure-13: XRD of Pure Drug

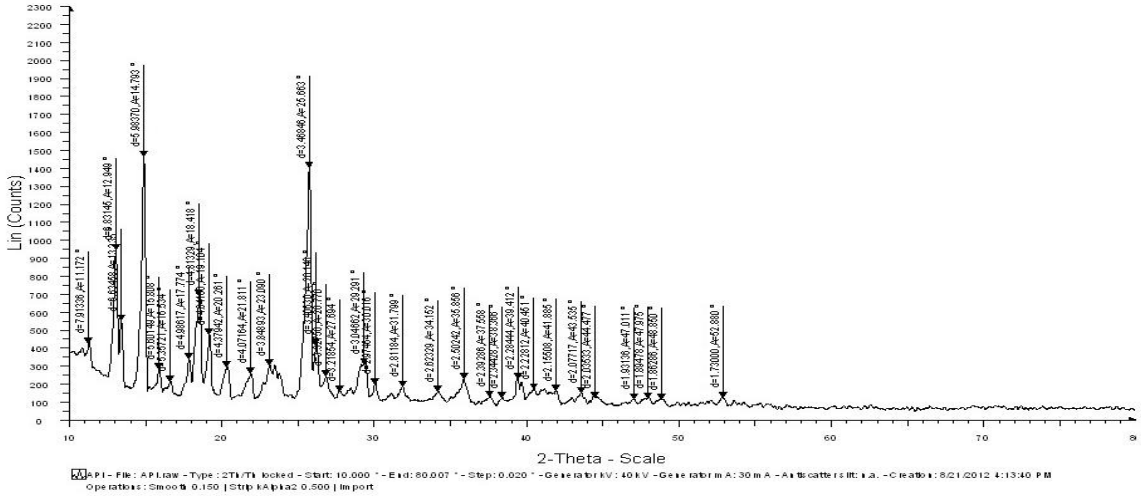


Fig-13: XRD of F6

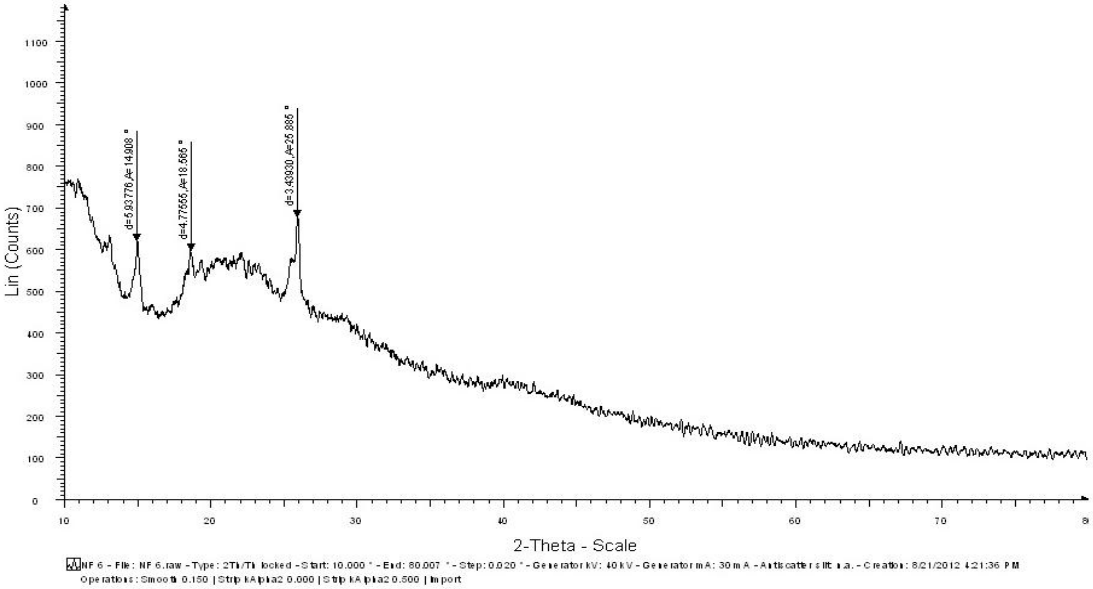


Fig- 14: DSC thermo gram of F6

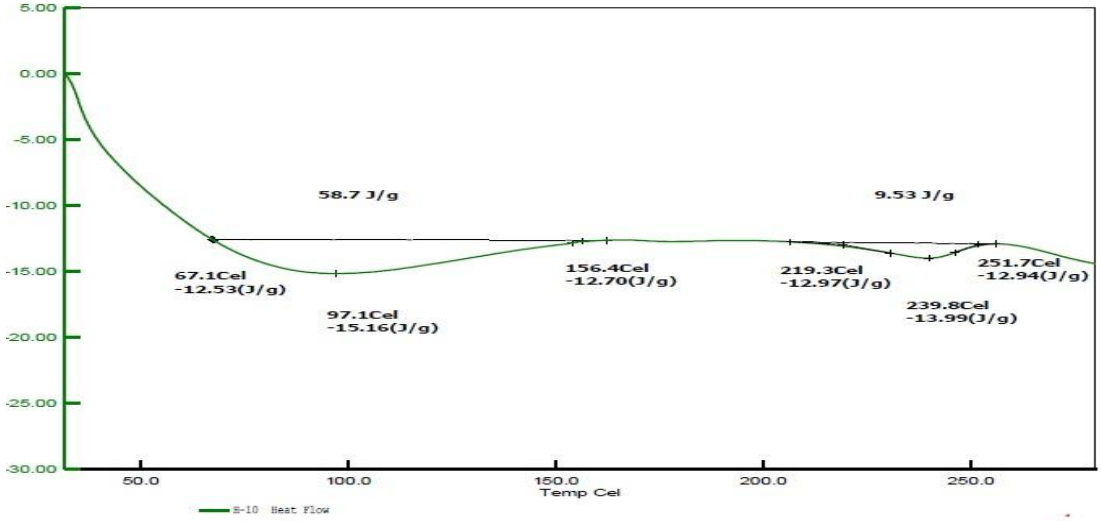


Fig-15: FT-IR Spectrum of Pure drug

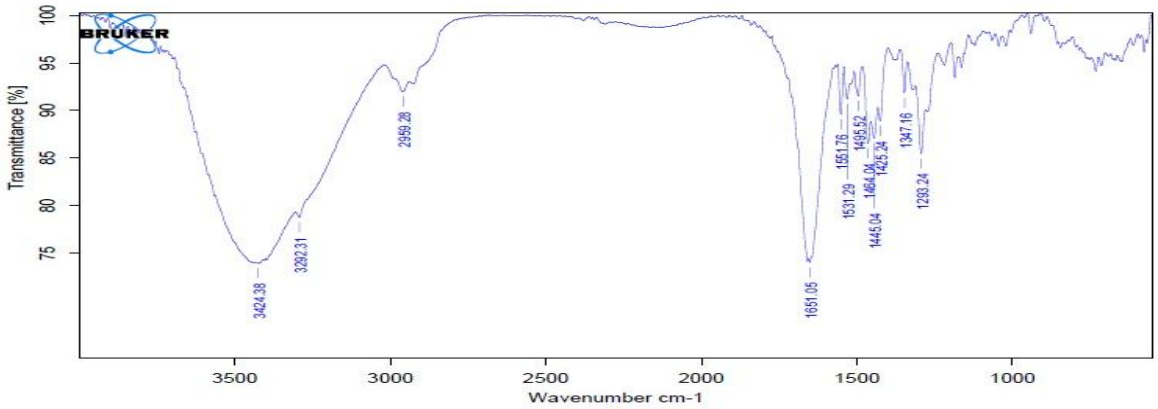
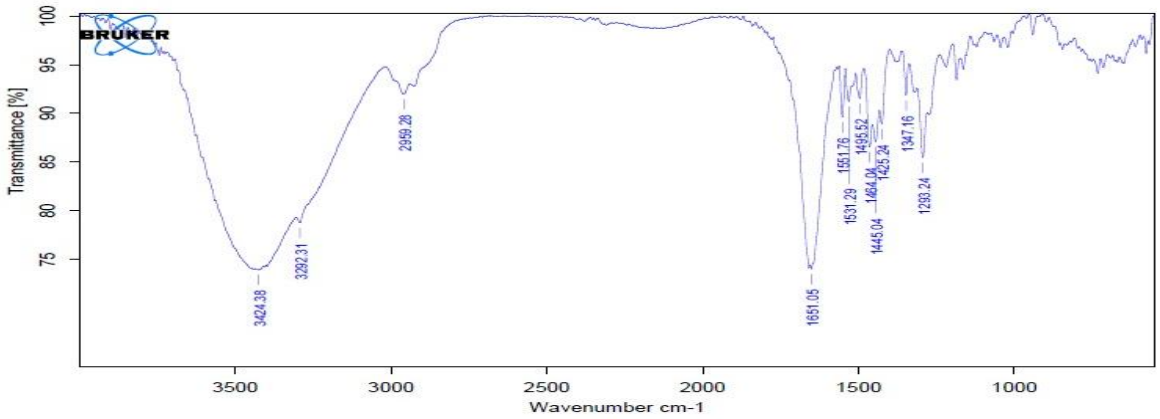


Fig-16: FT-IR Spectrum F6



4. Discussion

The present research work was aimed to prepare and evaluate liquisolid compacts using PEG 400 as a Non volatile solvent and Clofibrate as a drug. Nine batches of formulations were prepared by liquisolid technique with different Carrier, Coating materials and Super disintigrants. For F1–F4 formulations varying concentrations of microcrystalline cellulose is used as a Carrier material, Silica and Starch as a coating material and sodium starch glycol ate is super disintigrant. For F5–F9 formulations varying concentrations of Microcrystalline Cellulose is used as Carrier material, Silica and Lactose as a coating materials and cross Carmellose sodium as super disintigrant. All the formulations were prepared by normal direct compression method. Solubility of Clofibrate in Distilled water, propylene glycol, polyethylene glycol 400 and Tween 80 were performed. Its solubility was very poor in Distilled water. Propylene glycol (PG), the solubility of Clofibrate was found to be slightly greater than that of water. This slight increase in solubility was probably through hydrogen bonding. Clofibrate drug was very highly soluble in PEG 400 as compared to others. PEG 400, with a large polar part and several hydroxyl groups is responsible for the enhanced solubility. Thus, among the solvents tested, PEG400 could be a better choice as a solvent. In Pre formulation studies, it was found that, the wavelength of Clofibrate by spectroscopic method at 290 nm in Distilled water. This complied with IP standards thus indicating purity of obtained drug sample and plot graph of absorbance V/s concentration between 2-18 µg/ml ranges. The IR value of Clofibrate pure drug was observed as no difference between the IR patterns of the liquisolid compact of Clofibrate and polymer it indicates there is no drug and Excepient interactions. The flow properties of the liquisolid granules are vital for the performance of the tablet. Hence the flow properties were analyzed before compression of the tablets. The Hausner's ratio is ≤1.15 and angle of repose ≤25.00 values indicated a fairly good flow ability of granules. As the granules was free flowing, due to uniform filling in the die. Hardness is from 3.4-5.6kg/cm^2 and friability values are 0.35-0.7% indicated that tablets had a good mechanical strength table. The drug release from a conventional Clofibrate tablet is less that is only 65.6% and 79.78% drug was released in dissolution media in 40 and 60 min respectively. The dissolution enhancement of such poorly soluble drug was carried

out by formulating liquisolid compacts. The drug release from a Liquisolid compact Clofibrate tablet is more that is 96.2 to 100.2% drug was released in dissolution medium in a 40 to 60 min respectively. From the dissolution study it is clear that **F6** formulation showed good drug release then that of other respective formulation batches.

5. Conclusion

In the present work nine formulations of Clofibrate tablets were successfully developed by using liquisolid compact technique. Dissolution of Clofibrate tablets were improved by liquisolid compact technique. Clofibrate tablets were prepared by liquisolid technique with different concentrations of Carrier and Coating materials. Starch, Silica and Lactose are used as coating materials and Micro crystalline cellulose was used as carrier material. For F1–F4 formulations varying concentrations of microcrystalline cellulose is used as a Carrier material, starch, Silica as a coating materials and sodium starch glycolate is superdisintigrant. For F5–F9 formulations varying concentrations of microcrystalline cellulose is used as Carrier material, starch, Silica as coating materials and cross Carmellose sodium as superdisintigrant. F6 has showed the best drug release. The *in-vitro* drugs release of Clofibrate compacts showed an increase in dissolution rate. It is concluded that the Liquisolid compact technique can be used for increasing the dissolution rate of Clofibrate tablets.

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