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LIQUISOLID COMPACTS OF CLOFIBRATE: AN APPROACH TO ENHANCE THE DISSOLUTION AND BIOAVILABILITY OF POORLY WATER SOLUBLE DRUGS

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ABSTRACT

The aim of this study was to improve the dissolution and bioavailability 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 and Lactose are used as coating materials. Sodium starch glycolate and Cross carmellose sodium are used as a Super disintegrants. The different attempted formulations (F1-F9) were evaluated for pre- and post-compressional properties. All the prepared formulations shown good flow properties. All the prepared formulations shown hardness in the range of 3.4±0.34kg/cm^2 to 4.1±0.37834kg/cm^2 and friability values in the range of 0.315±0.121% to 0.495±0.171% indicated that tablets had a good mechanical strength. 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 results showed no change in the crystallinity of the drug and no interaction between excipients. The dissolution studies for the liquisolid formulation tablets and the directly compressible tablets were carried out in a pH 7.4 buffer. The dissolution efficiency of Clofibrate at 60 min was increased from 51.2% for directly compressible tablets to 100.47% for the liquisolid formulation tablets. The increase in the dissolution rate was found to be significant in liquisolid tablets when compared to directly compressible tablets. Furthermore, the AUC value of liquisolid formulation was twofold greater than that of the directly compressible formulation, indicating this formulation greatly improved the oral bioavailability of drug in rats. The liquisolid technique appears to be a promising approach for improving the dissolution and bioavailability of poorly soluble drugs like Clofibrate.

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

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.

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

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].

Components of Liquisolid Compact Formulation

1. Non-volatile solvent
2. Super Disintegrants
3. Carrier material
4. Coating material

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].

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].

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].

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].

GENERAL METHOD OF PREPARATION OF LIQUISOLID COMPACTS

As shown in the figure liquid lipophilic drugs (Chloramphenicol, Simvastatin, Norfloxacin and Clofibrate etc.) can be converted into a liquisolid system without being further modified. On the other hand, if solid water –insoluble drug (hydrochlorothiazide, prednisolone etc.) is formulated, it should be initially dissolved or suspended in a suitable non-volatile solvent system to produce 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 excipients 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].

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:

Solubility Studies: To select the best non-volatile solvent to dissolve Clofibrate, Solubility studies of Clofibrate were studied in six different Non-volatile solvents i.e., Glycerine, Tween 20, Tween 80, PEG 200 and Propylene Glycol. Saturated Solutions were prepared by adding excess drug to the vehicles and Shaking it on the incubator Shaker for 48 hrs at 37 ± 2°C. After shaking the solutions were filtered through filter paper and diluted with distilled water and analysed by UV-Visible Spectrophotometer at a

wavelength of 290 nm against blank. The results are shown in Table 4 and Figure 3.

Preparation of Calibration Curve of Clofibrate in pH 7.4 buffer

The100 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 5. The absorbance was plotted against concentration as shown in the Figure 4. This calibration curve was used in the estimation of Clofibrate in the present study.

Method of preparation of liquisolid compacts

1. Clofibrate was initially dissolved in the non-volatile solvent, Propylene Glycol as liquid vehicles to produce a drug solution.
2. Then carrier material microcrystalline cellulose is added to the Drug solution by continuous mixing in a rapid mixer granulator.
3. To the above blend add calculated amount of coating material i.e Starch and Lactose to get a fine and absorptive particle.
4. Before compression of the mixture add required amount of disintegrants like sodium starch glycolate and Cross carmellose sodium mix it well.
5. The remaining additives like lubricant Magnesium sterate are added and mixed for a period of 10 to 20 min in a rapid mixer granulator.
6. The final mixture is passed through sieve to get fine powder
7. The fine powder is compressed by tablet Press to get the liquisolid tablets.

Evaluation of precompressional 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]. 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 whereas above 25% indicates poor flowability [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 flowability.

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].

$$Ø = \tan^{-1} h/r$$

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 and Composition of different formulations of Liquisolid Compacts tablets are shown in Table 3.

Evaluation of Liquisolid compact Tablets[13-16]

All the prepared Tablets were evaluated for the following parameters as per IP and results are shown in Table 7.

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 tablet hardness tester.

Friability: Friability of tablets was determined using the Roche friabilator (USP). Preweighed 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. 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[17]. The results are given in Table 8.

***In – Vitro* dissolution studies:** Dissolution rate of Clofibrate from all formulations was performed using dissolution testing apparatus (paddle). The dissolution fluid was 900ml of P^H 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 (5,10,20,30,45,60min and 120mins), 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 9-13 and shown in Figures 5, 6.

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 pure drug and optimized batches are shown in Figures 11, 12.

DSC studies: DSC thermo gram of the optimized Liquisolid Compacts (10mg sample) was recorded the using automatic thermal analyser[16]. The DSC is used to evaluate the drug –excipient interaction and results are shown in Figures 13, 14.

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 9, 10.

SEM studies: The external surface morphology and diameter of Liquisolid Compacts were studied by scanning electron microscopy. The surfaces of Liquisolid Compacts were 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 7, 8.

***In vivo* pharmacokinetics**

***In vivo* experiments[17-18]**

Male Wistar albino rats weighing 280 ± 20 g were used. The rats were fasted for 10–12 h prior to the experiments, but were allowed free access to water and kept at a temperature of 20 ± 2°C and a relative humidity of 50 ± 5%. All animal care and experimental procedures were in accordance with the Guiding Principles in the Use of Animals in Toxicology, as adopted by the Institutional Animal ethical committee. Oral administration and blood collecting twelve rats were divided into two groups and administered with directly compressiable Clofibrate tablets powder (control) or powder of liquisolid compacts at a Clofibrate dose of 10 mg/kg. Each rat, anaesthetized in an ether-saturated chamber, was secured in the supine position on a surgical board with threads. A polyethylene tube was inserted into the right femoral artery and a three-way stopcock was fitted at the other end to enable easy collection of the blood. The rats in each group were orally administered with directly compressiable Clofibrate tablets powder or optimized liquisolid compacts powder suspended in 1 mL of water. After oral dosing in the rats, 250 µl of blood was collected from the right femoral artery at predetermined time intervals (0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 22 h). The blood samples were centrifuged at 3000rpm for 10 min and the plasma (100 µl) was immediately stored at −20°C until further analysis.

Plasma drug concentration analysis Plasma (50 µl) was mixed with 50 µl of acetonitrile solution containing 100 µg/mL of clofibrate as an internal standard. Then, 0.5 mL of acetonitrile was added, vortexed for 5 min, and centrifuged at 10,000 rpm for 10 min. 50 µl of the supernatant layer was taken and clofibric acid, a major active metabolite of clofibrate was analysed by HPLC. The mobile phase consisted of 0.02 M phosphoric acid and acetonitrile (45:55, volume ratio), followed by adjustment of the pH to 3.0 using 10% w/v phosphoric acid. The eluent was monitored at 290 nm with a flow rate of 1.2 mL/min. The pharmacokinetic data like Area Under Curve from zero to infinity (AUC), half-life (t1/2), the maximum plasma concentration of drug (Cmax), the time taken to reach the maximum plasma concentration (Tmax) and the elimination rate constant (Kel) were determined by HPLC.

3.2. DISCUSSION

The present research work was aimed to prepare and evaluate liquisolid compacts using Propylene Glycol as a Non-volatile solvent and Clofibrate as a drug. Nine batches of formulations (F1-F9) were prepared by liquisolid compact technique with different Carrier, Coating materials and Super disintegrants. 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 glycolate is super disintegrant. For F5–F9 formulations varying concentrations of Microcrystalline Cellulose is used as Carrier material, Silica and Lactose as a coating material and cross Carmellose sodium as super disintegrant. All the formulations were prepared by normal direct compression method. Solubility of Clofibrate in Distilled water, propylene glycol, polyethylene glycol 200, Tween 20 and Tween 80 were performed. Drug solubility was very poor in Distilled water.

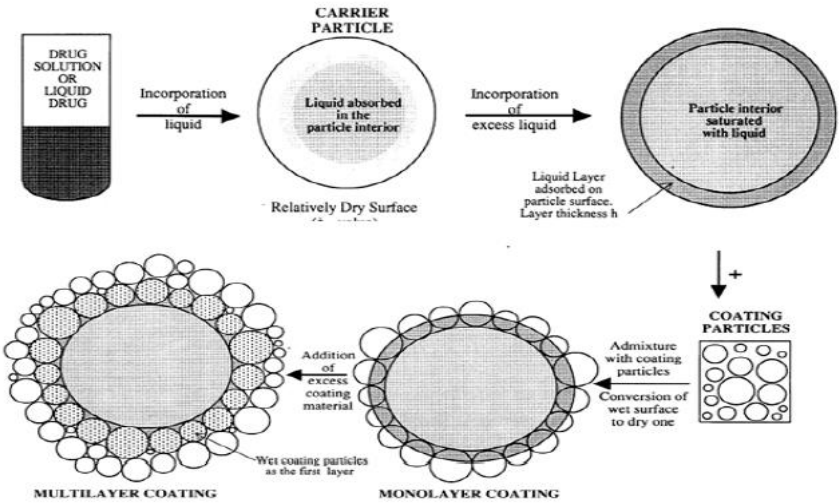

Fig-1: Schematic representation of liquisolid systems

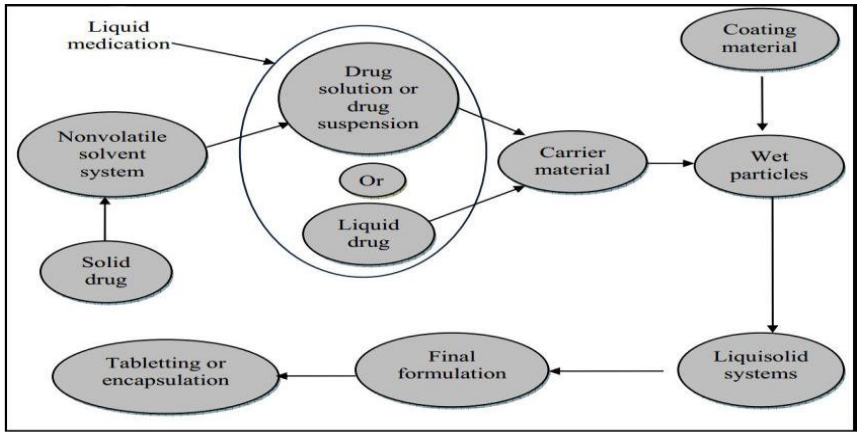

Fig-2: Steps involved in the preparation of liquid solid systems

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	CrossCarmellose 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

Table 4: Solubility Data of Clofibrate in Various Solvents

Solvent	Solubility(mg/ml)
Water	0.05±4.32
Tween 20	24±2.78
Tween 80	29±4.32
Glycerine	44±3.86
PEG 200 (Poly Ethylene Glycol)	68±1.65
PG (Propylene glycol)	73±2.29

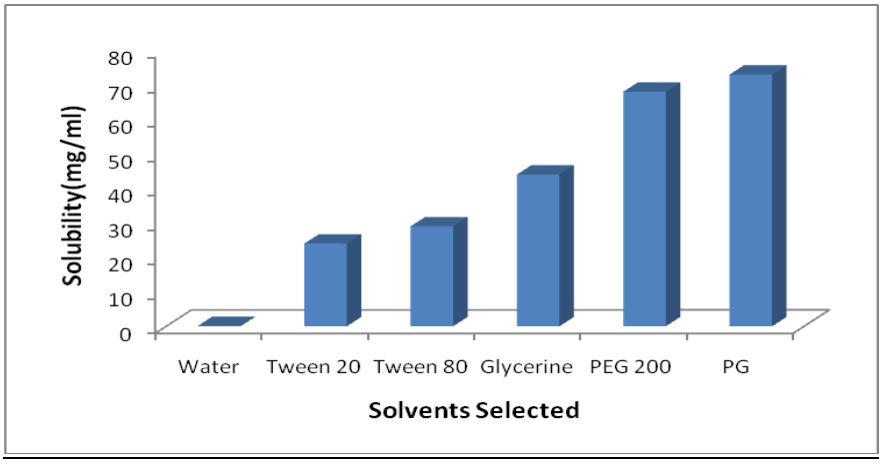

Fig-3: Solubility Data of Clofibrate in Various Solvents

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

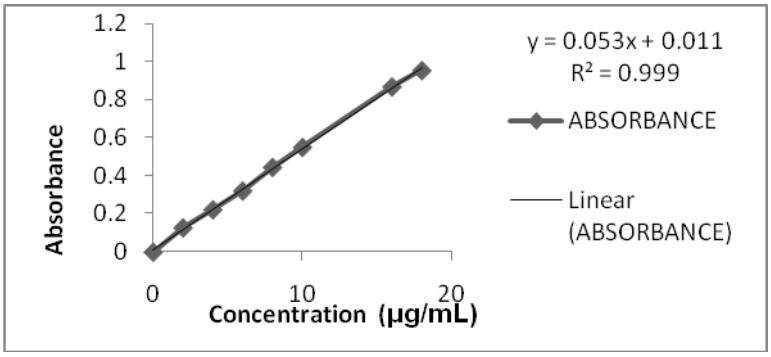

Fig-4: Calibration Curve of Clofibrate in pH 7.4 buffer at 290nm

Table 6: Evaluation of Flow properties of liquisolid compact Formulations (F1-F9)

Formulation Batch	Bulk density (g/cc)	Tapped Density (g/cc)	Carr's Index (%)	Hausners 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 liquisolid compact Formulations (F1-F9)

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±0.31	0.395±0.171	34.13
F6	300±0.18	3.4±0.34	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±0.378	0.422±0.122	21.98
F9	300±0.79	4.0±0.322	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 (mins)	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	56.36±5.9	54.2±1.5	58.5±4.2
90	60.95±7.8	60±4.3	59.8±3.9
120	71.96±7.2	63.2±2.2	73.7±7.2

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

Time (mins)	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	22.2±0.9	34.7±2.6
15	18.4±6.6	33.9±1.6	51.2±5
20	20.1±2.5	45.6±0.44	62.6±5.2
30	31.6±3.1	57.6±1.1	78.4±4.7
45	43.2±2.6	69.9±1	96.2±4.2
60	56.1±5.5	73.2±2.8	100.2±1.5
90	67.5±2.9	77.2±7.2	-
120	72.7±2.5	81.7±6.3	-

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

Time (mins)	Cumulative % Drug Dissolved ±SD (n=3)		
	F7	F8	F9
0	0	0	0
5	16.12±1.1	12±1.8	11±1
10	24.2±1.3	18.9±1.5	21.6±0.6
15	36.14±1.4	22.8±3.3	33.2±.4
20	49.2±3.3	30.6±4.7	40.9±1.5
30	60.4±2.1	44.6±4.5	50.3±3
45	71.3±1.7	51.2±3.8	63.1±3.8
60	78.7±2	63.9±6	71.3±6.1
90	83.2±3.4	72.5±1.6	80.2±7.1
120	89.2±3.3	83.9±1.5	85±5.5

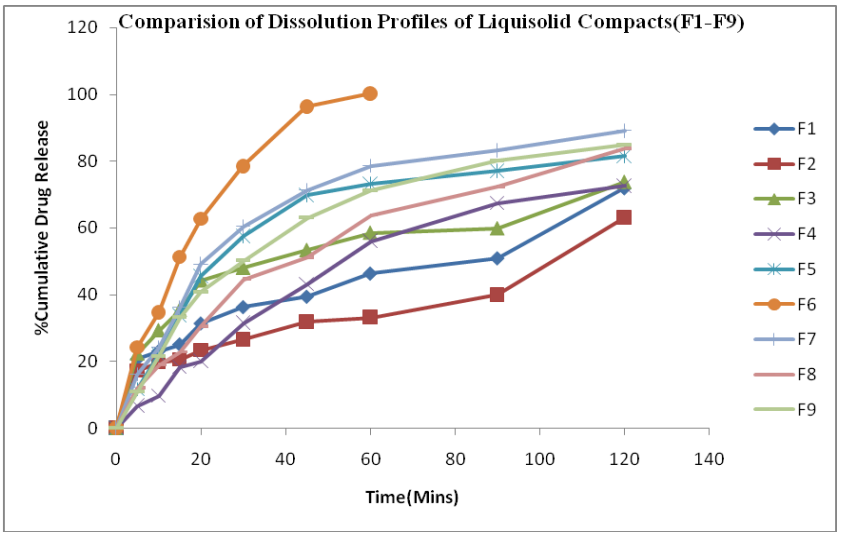

Fig-5: Comparison of dissolution profiles of liquisolid compact Formulations in pH 7.4 buffer (F1-F9)

Table 12: Dissolution Profile of Directly Compressible Tablets (DCTs) in pH 7.4 buffer

Time (mins)	Cumulative % Drug Dissolved ±SD(n=3)(DCTs)
0	0
5	5.6±3.1
10	14.3±2.1
15	19.3±1.5
20	23.8±3.3
30	37.3±2.1
45	49.5±0.5
60	51.2±2.5
90	62.4±1.9
120	69.86±1.5

Table 13: Comparison of Dissolution Profile of optimized formulation (F6) and Directly Compressible Tablets (DCTs) in pH 7.4 buffer

Time (mins)	Cumulative % Drug Dissolved ± SD (n=3)	
	F6 (Optimized Formulation)	DCTs (Directly Compressible Tablets)
0	0	0
5	24.2±1.2	5.6±3.1
10	34.7±2.6	14.3±2.1
15	51.2±5	19.3±1.5
20	62.6±5.2	23.8±3.3
30	78.4±4.7	37.3±2.1
45	96.2±4.2	49.5±0.5
60	100.2±1.5	51.2±2.5
90	-	62.4±1.9
120	-	69.86±1.5

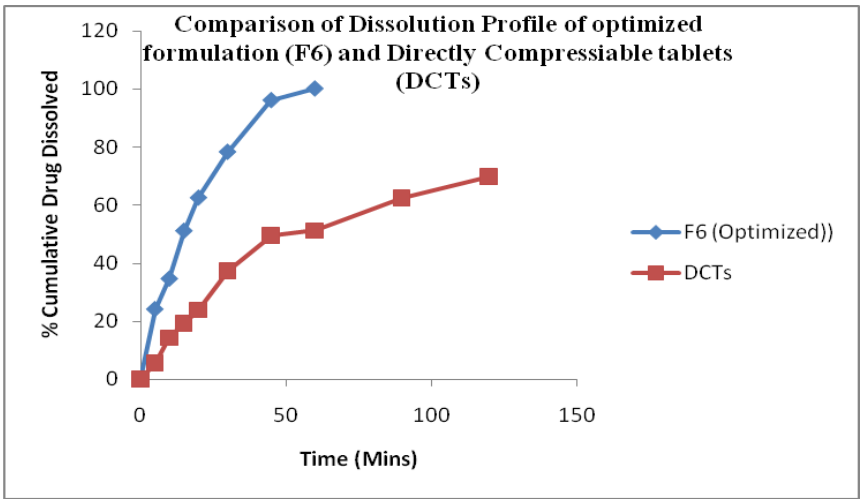

Fig-6: Comparison of Dissolution Profile of optimized formulation (F6) and Directly Compressible Tablets (DCTs) in pH 7.4 buffer

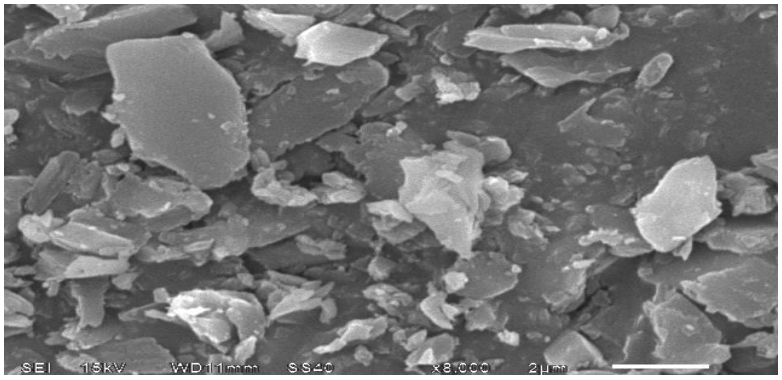

Fig-7: SEM Image of Pure Drug (Clofibrate)

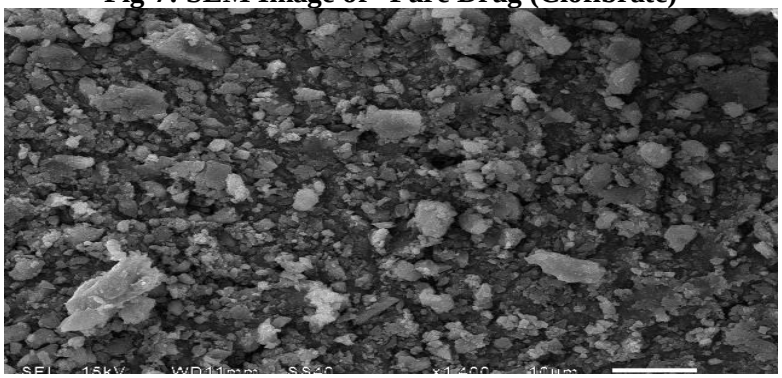

Fig-8: SEM Image of Optimized formulation (F6)

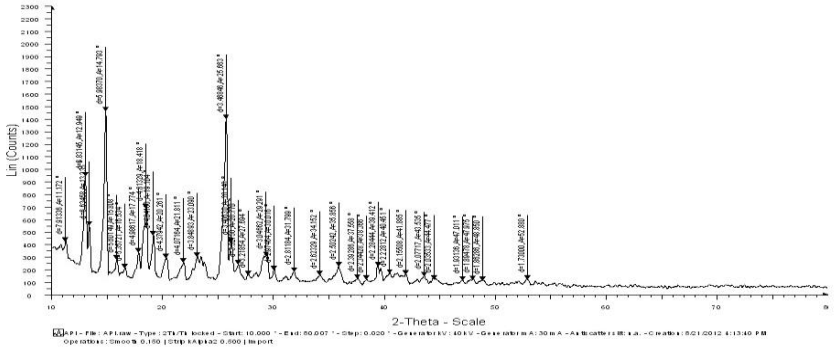

Fig-9: XRD of Pure Drug (Clofibrate)

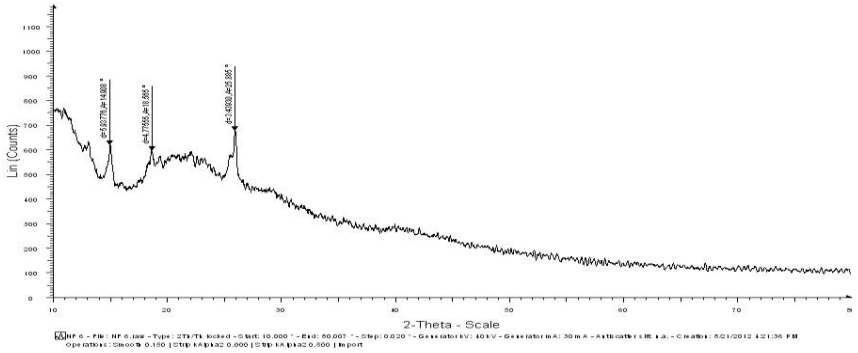

Fig-10: XRD of optimized formulation (F6)

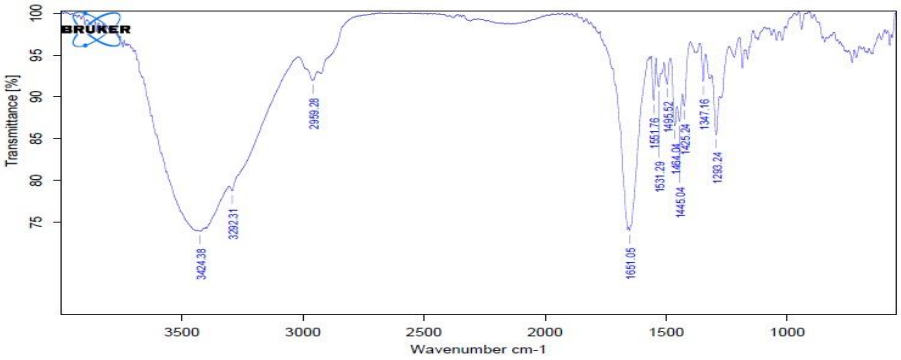

Fig-11: FT-IR Spectrum of Pure drug (Clofibrate)

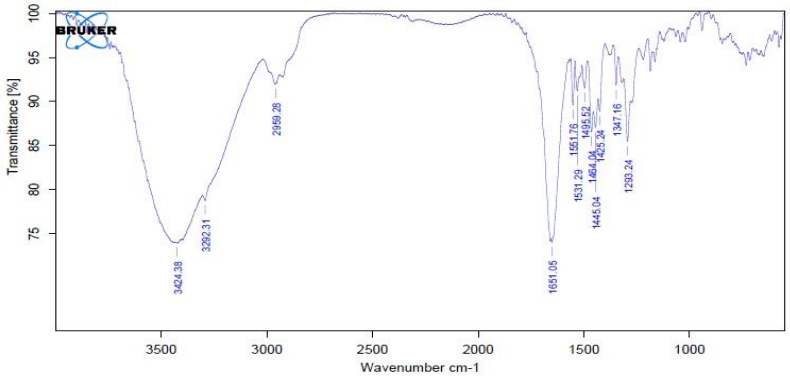

Fig-12: FT-IR Spectrum of optimized formulation F6

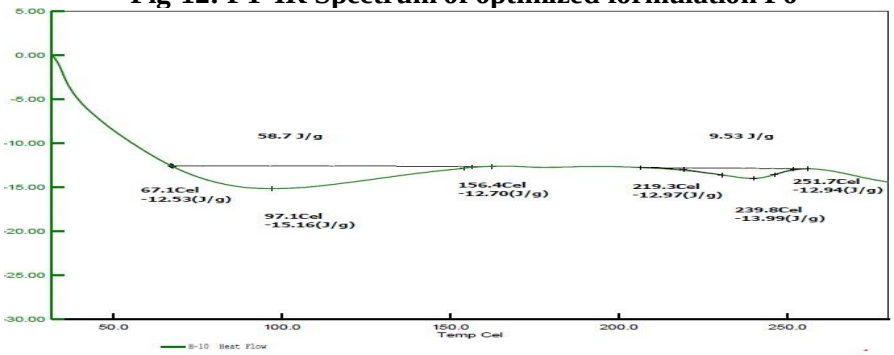

Fig-13: DSC thermo gram of Pure Drug (Clofibrate)

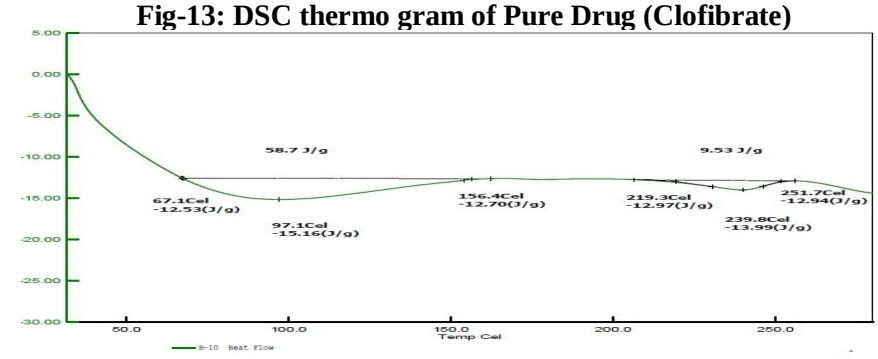

Fig-14: DSC thermo gram of optimized formulation F6

Table 14: Plasma concentration-time profiles of clofibrate after oral administration of directly compressible tablets (DCTs) powder and optimized liquisolid compact tablets (LSTs) powder at a dose of 10mg/kg to rats

Time (Hrs)	Plasma Drug Concentration values (µg/mL)	
	(DCTs)	Optimized LSTs (F6)
0	0	0
0.5	1.5	16
1	2.8	26.2
1.5	6.32	22.31
2	6.11	15.76
3	6	12
4	5.8	8.36
6	5.5	7.11
8	4.2	6.8
10	3.5	5.8
22	3	3.76

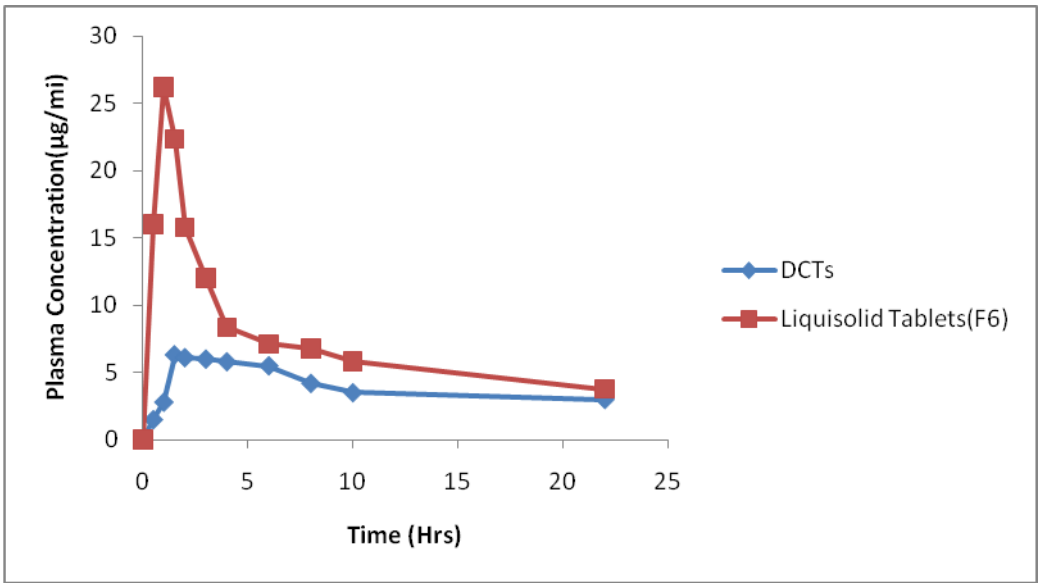

Fig-15: Plasma concentration-time profiles of clofibrate after oral administration of directly compressible tablets (DCTs) powder and optimized liquisolid compact tablets (LSTs) powder at a dose of 10mg/kg to rats

Table 15: Pharmacokinetic parameters of clofibrate after oral administration of Directly Compressible tablets (DCTs) powder and optimized liquidsolid compact tablets (LSTs) formulation powder to rats

Parameters	Directly Compressible Tablets (DCTs) powder	Optimized liquisolid Tablets (F6) powder
C_{max} (µg/mL)	6.32± 0.58	22.31±2.02
T_{max} (h)	1.5	1
AUC (h·µg/mL)	70.15 ± 11.29	158.85 ± 18.14
K (h^{-1})	0.101 ± 0.006	0.048 ± 0.007

Each value represents the mean ± SD (*n* = 4).

Clofibrate drug was very highly soluble in Propylene glycol as compared to other solvents such as Glycerine, polyethylene glycol 200, Tween 20 and Tween 80. Thus, among the solvents tested, Propylene glycol was found to be a better choice as a solvent. 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 excipients 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. All the prepared formulations shown good flow properties. All the prepared formulations shown hardness in the range of 3.4±0.34kg/cm2 to 4.1±0.37834kg/cm2 and friability values in the range of 0.315±0.121% to 0.495±0.171% indicated that tablets had a good mechanical strength. Dissolution studies were carried out for all the prepared liquisolid formulations (F1-F9) and directly compressible tablets (DCTs). From the dissolution study it was clear that liquisolid formulations showed good drug release then that of directly compressible tablets (DCTs). The drug release from the directly compressible tablets (DCTs) is less that is only 51.2% drug was released in dissolution media at 60 mins and the drug release from liquisolid formulations is more that is in the range of 54.2% to 100.2% drug was released in dissolution medium at 60 mins. From the dissolution study it was clear that among all the liquisolid formulations, F6 liquisolid formulation shown more drug release that is 100.2% in 60mins, so F6 selected as optimized formulation. Pharmacokinetic parameters of clofibrate were determined after oral administration of the clofibrate directly compressible tablets (DCTs) powder and optimized liquisolid formulation powder (F6). The total plasma concentration of the drug in optimized liquisolid formulation was significantly higher than those in clofibrate directly compressible tablets (DCTs) powder. Our results suggest that the higher initial plasma concentrations of clofibrate might have been due to the increased initial dissolution rate of the drug in the liquisolid formulations. The liquisolid formulations gave significantly higher AUC and Cmax for the drug than did clofibrate directly compressible tablets (DCTs) powder. In particular, the AUC values of liquisolid formulations were two fold greater than that of the directly compressible tablets powder, indicating this formulation greatly improved the oral bioavailability of drug. However Tmax value of a liquisolid formulation was faster than the clofibrate directly compressible tablets powder. These results showed that it is possible to improve the bioavailability of clofibrate if given in the liquisolid formulations. The enhanced oral bioavailability of drug from these liquisolid formulations might have contributed to the marked increase in the absorption rate of clofibrate due to the increased rate of dissolution of the drug from the liquisolid formulation

CONCLUSION

In the present work nine (9) formulations of Clofibrate tablets were successfully developed by using 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. Dissolution studies were carried out for all the prepared liquisolid formulations (F1-F9) and directly compressible tablets (DCTs). From the dissolution study it was clear that liquisolid formulations showed good drug release then that of directly compressible tablets (DCTs). F6 has shown the more drug release that is 100.2% in 60mins, so F6 selected as optimized formulation among all other liquisolid formulations. *In vivo* pharmacokinetic studies in rats

showed that liquisolid formulation gave a significant increase in the bioavailability of clofibrate compared to the directly compressible formulation. Thus, this liquisolid drug delivery system may provide a useful oral solid dosage form for the poorly water soluble drug, clofibrate. Finally it was concluded that the Liquisolid compact technique can be used for increasing the dissolution rate and bioavailability of Clofibrate and also for other BCS Class-II drugs.

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