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Enhancement of Dissolution Rate of Fenofibrate by Using Liqui-Solid Technique

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ABSTRACT:

Now a days Globally, hyperlipidemia has been shown to be an independent predictor of many cardiovascular and cerebrovascular events, which led to recent advocacy towards hyperlipidemia prevention and control as a key risk factor and its significance to reduce the burden of stroke and myocardial infarction (MI). Fibrates have played a major role in the treatment of hyperlipidemia for more than two decades (Miller and Spence 1998). The first member of this class, clofibrate, was identified in 1962 by Thorp and Waring (1962) and became available in the US in 1967. The third-generation fibric acid derivative Fenofibrate was synthesized in 1975 and was introduced. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability. To enhance these properties like absorption, dissolution which are rate limiting step for lipophilic or poorly soluble drugs, the "**Liquisolid Technique"** was introduced. It is the most **promising & novel** techniques to improve the dissolution rates of the poorly water soluble drugs. Formulations with Fenofibrate, PEG 200, Crosspovidone, Aerosil, Magnesium stearate, Talc, Microcrystalline cellulose are prepared and evaluated.

According to the results it revealed that liquisolid compacts containing PEG200 produced higher dissolution rates compared to other liquisolid compacts containing Tween 80 of the same concentration. It can be concluded that the non-volatile vehicle plays a major role in design of liquisolid compact tablets in the dissolution enhancement. Increasing the concentration of liquid medication the dissolution rate of Fenofibrate was increased. Based on the *in-vitro* dissolution studies the formulation F7 was observed as optimal formulation. The optimized formulation F7 showed the 90.34 ± 0.58 drug release in 100min. Thus the formulation F7 was considered better among all formulations to produce fast release of Fenofibrate.

Keywords: Hyperlipidemia, Fenofibrate, Liquisolid technique, Dissolution

INTRODUCTION:

HYPERLIPIDEMIA:

- In medicine, combined hyperlipidemia (or -aemia) (also known as "multiple-type hyperlipoproteinemia") is a commonly occurring form of hypercholesterolemia (elevated cholesterol levels) characterised by increased LDL and triglyceride concentrations, often accompanied by decreased HDL.
- Hyperlipidemia, hyperlipoproteinemia, or hyperlipidaemia involves abnormally elevated levels of any or alllipids and/or lipoproteins in the blood. It is the most common form of dyslipidemia (which includes any abnormal lipid levels).

- Lipids (fat-soluble molecules) are transported in a protein capsule. The size of that capsule, or lipoprotein, determines its density. The lipoprotein density and type of apolipoproteins it contains determines the fate of the particle and its influence on metabolism.

Fredrickson classification of hyperlipidemias:

- **Type I** **(** increased lipoprotein-Chylomicrons)
- **Type II** **(** LDL & VLDL **)**
- **Type III** (IDL **)**
- **Type IV** (VLDL **)**
- **Type V** (VLDL & Chylomicrons **)**

Hyperlipoproteinemia type I :

Type I hyperlipoproteinemia exists in several forms:

- Lipoprotein lipase deficiency (type Ia), due to a deficiency of lipoprotein lipase (LPL) or altered apolipoprotein C2, resulting in elevated chylomicrons, the particles that transfer fatty acids from the digestive tract to the liver
- Familial apoprotein CII deficiency (type Ib) a condition caused by a lack of lipoprotein lipase activator.
- Chylomicronemia due to circulating inhibitor of lipoprotein lipase (type Ic)

Type I hyperlipoproteinemia usually presents in childhood with eruptive xanthomata and abdominal colic. Complications include retinal vein occlusion, acute pancreatitis, steatosis and organomegaly, and lipaemia retinalis.

Type II a : It is a rare genetic disorder characterized by increased levels of LDL cholesterol in the blood due to the lack of uptake (no Apo B receptors) of LDL particles.

- This pathology, however, is the second-most common disorder of the various hyperlipoproteinemias, with individuals with a heterozygotic predisposition of one in every 500 and individuals with homozygotic predisposition of one in every million.
- These individuals may present with a unique set of physical characteristics such as: xanthelasmas (yellow deposits of fat underneath the skin often presenting in the nasal portion of the eye), tendon and tuberous xanthomas, arcus juvenilis (the graying of the eye often characterized in older individuals), arterial bruits, claudication, and of course atherosclerosis.

Type II b :

The high VLDL levels are due to overproduction of substrates, including triglycerides, acetyl CoA, and an increase in B-100 synthesis. They may also be caused by the decreased clearance of LDL. Prevalence in the population is 10%.

- Familial combined hyperlipoproteinemia (FCH)
- Lysosomal acid lipase deficiency, often called (Cholesteryl ester storage disease)
- Secondary combined hyperlipoproteinemia (usually in the context of metabolic syndrome, for which it is a diagnostic criterion)

Hyperlipoproteinemia type III :

- This form is due to high chylomicrons and IDL (intermediate density lipoprotein). Also known as broad beta disease or dysbetalipoproteinemia, the most common cause for this form is the presence of ApoE E2/E2 genotype.
- It is due to cholesterol-rich VLDL (β-VLDL). Its prevalence has been estimated to be approximately 1 in 10,000.
- It is associated with hypercholesterolaemia (typically 8-12 mmol/L), hypertriglyceridaemia (typically 5-20 mmol/L), a normal ApoB concentration, and two types of skin signs (palmar xanthomata or orange discoloration of skin creases, and tuberoeruptive xanthomata on the elbows and knees).
- It is characterized by the early onset of cardiovascular disease and peripheral vascular disease. Remnant hyperlipidaemia occurs as a result of abnormal function of the ApoE receptor, which is normally required for clearance of chylomicron remnants and IDL from the circulation.
- The receptor defect causes levels of chylomicron remnants and IDL to be higher than normal in the blood stream.
- The receptor defect is an autosomal recessive mutation or polymorphism.

Hyperlipoproteinemia type IV :

- Familial hypertriglyceridemia is an autosomal dominant condition occurring in approximately 1% of the population.
- This form is due to high triglyceride level. Other lipoprotein levels are normal or increased a little.
- Treatment include diet control, fibrates and niacins. Statins are not better than fibrates when lowering triglyceride level.

Hyperlipoproteinemia type V :

- Hyperlipoproteinemia type V, also known as mixed hyperlipoproteinemia familial or mixed hyperlipidemia, is very similar to type I, but with high VLDL in addition to chylomicrons.
- It is also associated with glucose intolerance and hyperuricemia.

On lipoprotein electrophoresis (a test now rarely performed) it shows as a hyperlipoproteinemia type IIB. It is the most common inherited lipid disorder, occurring in about one in 200 persons. In fact, almost one in five individuals who develop coronary heart disease before the age of 60 have this disorder. The elevated triglyceride levels (>5 mmol/l) are generally due to an increase in very low density lipoprotein (VLDL), a class of lipoprotein prone to cause atherosclerosis.

1. 11: THERAPY OF HYPERLIPIDEMIA:

- Fibrates have played a major role in the treatment of hyperlipidemia for more than two decades (Miller and Spence 1998). The first member of this class, clofibrate, was identified in 1962 by Thorp and Waring (1962) and became available in the US in 1967.
- Many other fibrates including ciprofibrate, bezafibrate, etofibrate, beclofibrate, and pirifibrate, are available in Europe, where the use of such agents is more extensive (Miller and Spence 1998; Guay 1999). The third-generation fibric acid derivative Fenofibrate was synthesized in 1975 (Keating and Ormrod 2002) and was introduced into clinical practice in France the same year (Blane 1989; Keating and Ormrod 2002).

- The original generic name procetofene was changed to Fenofibrate to comply with World Health Organization nomenclature guidelines. Fenofibrate is marketed in 86 countries and is one of the most commonly used fibrates worldwide, with more than 6 million patient-years of experience (Brown 1988).
- More than 80 clinical trials of Fenofibrate have involved more than 9000 patients and more than 31 000 patient-years of drug exposure (Blane 1989; Keech et al 2005). Its indications include hypercholesterolemia, combined dyslipidemia, remnant hyperlipidemia, endogenous hyperlipemia (hypertriglyceridemia), and mixed hyperlipemia (Frederickson types IIa, IIb, III, IV, and V dyslipidemia, respectively) (Keating and Ormrod 2002).
- Fenofibric acid is metabolized by the hepatic cytochrome P (CYP)-450 3A4 isozyme and has a half-life of 20 hours, which allows once-daily administration.

INTRODUCTION OF TABLETS:

- Tablets are the solid dosage form which are most accepted and widely used in the medical therapy. As per IP 2007 tablet may be defined as tablets are solid dosage forms each containing a unit dose of one or more medicaments.
- They are intended for oral administration. A tablet consist of active medicament along with excipients which are in powder form are compressed or pressed into a solid dosage form.
- Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage forms.
- They vary in shape and differ greatly in size and weight, depending on the amount of medicinal substances and the intended mode of administration.
- It is the most popular dosage form and 70% of the total medicines are dispensed in the form of Tablet.
- Solid medicaments may be administered orally as powders, pills, cachets, capsules or tablets . These dosage forms contain a quantity of drug which is given as a single unit and they are known collectively as solid unit dosage forms.

1. 1. 1: Classification:

Tablets are majorly classified into following :

1. Uncoated tablets
2. Coated tablets
3. Dispersible tablets
4. Effervescent tablets
5. Modified-release tablets :
   - Enteric-coated tablets
   - Prolonged released tablets
6. Soluble tablets
7. Tablets for use in the mouth :
   - buccal tablets
   - sublingual tablet
   - Troche/lozenges
8. Tablets for other routes of administration:
   - Implantable tablets
   - vaginal tablets

1. Uncoated tablets:

These are a single layer or morethan one layer tablet consisting of active ingredient with the excipients, no additional cover is applied on to it after the compression.

2. Coated tablets:

These tablets have an additional coating layer on it after the tablet is compressed, the coating layer may be applied with sugar,gums,resins,insoluble/inactive fillers,plasticisers,waxes.

3. Dispersible tablets:

These are the film coated/uncoated tablets which form an uniform dispersion when suspended in water.

4. Effervescent tablets:

These are the tablets which are uncoated and are intended to be dissolved &produce a dispersion before they are administered the dissolution is achieved by the reaction between an organic &bicarbonate which produce Co_2, thus produced Co_2 will disintegrate the tablet so which dissolves in the solution to produce an suspension which is rapidly absorbed.

5. Modified-release tablets:

These are the coated/uncoated tablets which are designed in such a way that the rate (or) location of the active ingredient released is modified if includes enteric coated tablets, prolong release tablet,delay release tablet.

- **Enteric coated tablets:**

These are also called as gastro resistant tablets as they are resistant to the gastric juices, these are formulated by coating the tablet with anionic polymer of methylacrylic acid & their esters(or)by coating with cellulose acetyl pthylate .

Example: Erythromycin,NSAIDS.

- **Prolonged –release tablets:**

These are also called as sustain release tablets (or) extended release tablets is formulated in such a way that the active ingredient is released for a prolonged duration of time &is available in systemic circulation after administration.

6. Soluble tablets:

These are coated/uncoated tablets which are dissolved in water before they are administered.

7. Tablets for use in the mouth:

These are the tablet formulations which are intended to be show local action in the buccal cavity.

- **Buccal tablets:**

Buccal tablets are placed in between in cheek & gingival.

- **Sublingual tablets:**

Sublingual tablets are placed underneath the tongue.

Example:Glyceryltrinitrate

8. Tablets for other routes of administration:

These include implantable tablets,vaginal tablets.

- **Vaginal tablets:**

These are inserted into the rectum(or) vagina for their local/action systemic.

1. 1. 2: The advantages of solid dosage forms:

The tablet formlations have the following advantages:

- They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.

- Cost is lowest of all oral dosage form.
- Lighter and compact.
- Easiest and cheapest to package and strip.
- Easy to swallowing with least tendency for hang-up.
- Objectionable odour and bitter taste can be masked by coating technique.
- Suitable for large scale production.
- Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.
- Unstable API, bitter tasting tablets can be formulated as coated tablets which mask the bitter taste and are safe guard the API.
- Modified drug release rate and duration tablets can increase the therapeutic effect and increase the patient compliance by reducing the frequency of drug administration.
- The physical stability,microbial stability ,and chemical stability of tablet are superior to other dosage forms.

1. 1. 3: The disadvantages of solid dosage forms are:

- The systemic availability of the drug depend on many physiological factors.
- The onset of action is less when compared to IV route (except sublingual tablets).
- Geriatric and unconcious patients cannot swallow the tablets.
- Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
- Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
- Bitter tasting drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating. In such cases, capsule may offer the best and lowest cost.

1. 1. 4: General properties of Tablet dosage forms:

- A tablet should have elegant product identity while free of defects like chips, cracks, discoloration, and contamination.
- Should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
- Should have the chemical and physical stability to maintain its physical attributes over time
- The tablet must be able to release the medicinal agents in a predictable and reproducible manner.
- Must have a chemical stability over time so as not to follow alteration of the medicinal agents.

1. 1. 5: Tablet Ingredients:

In addition to active ingredients, tablet contains a number of inert materials known as additives or excipients. Different excipients are:

1. Diluent
2. Binder and adhesive
3. Disintegrents
4. Lubricants and glidants
5. Colouring agents
6. Flavouring agents
7. Sweetening agents

1. Diluent: Diluents are fillers used to make required bulk of the **tablet** when the drug dosage itself is inadequate to produce the bulk. Secondary reason is to provide better tablet properties such as improve cohesion, to permit use of direct compression manufacturing or to promote flow. A diluent should have following properties:

- They must be non toxic.
- They must be commercially available in acceptable grade.
- There cost must be low.
- They must be physiologically inert.
- They must be physically & chemically stable by themselves & in combination with the drugs.
- They must be free from all microbial contamination.
- They should not alter the **bioavailability** of drug.
- They must be color compatible.

Commonly used tablet diluents:

- Lactose-anhydrous and spray dried lactose
- Directly compressed starch- Rx 1500
- Hydrolyzed starch-Emdex and Celutab
- Microcrystalline cellulose-Avicel (PH 101and PH 102)
- Dibasic calcium phosphate dehydrate
- Calcium sulphate dihydrate
- Mannitol
- Sorbitol
- Sucrose- Sugartab, DiPac, Nutab
- Dextrose
- Microcrystalline cellulose, having trade name Avicel is used for direct compression. These are two types: PH101 (Powder) and PH102 (Granules).
- Dibasic calcium phosphate and calcium sulphate used as diluents but reduce bioavailability of tetracycline tablet.

2. Binders and Adhesives: These materials are added either dry or in wet- form to form granules or to form cohesive compacts for directly compressed tablet.

Example:

- Acacia, tragacanth- Solution for 10-25% Conc.
- Cellulose derivatives- Methyl cellulose, Hydroxy propyl methyl
- cellulose, Hydroxy propyl cellulose
- Gelatin- 10-20% solution
- Glucose- 50% solution
- Polyvinylpyrrolidone (PVP)- 2% conc.
- Starch paste-10-20% solution
- Sodium alginate
- Sorbitol

3. Disintegrants: Added to a tablet formulation to facilitate its breaking or disintegration when it contact in water in the GIT.

Example:

- Starch- 5-20% of tablet weight.
- Starch derivative – Primogel and Explotab (1-8%)
- Clays- Veegum HV, bentonite 10% level in colored tablet only
- Cellulose
- Cellulose derivatives- Ac- Di-Sol (sodium carboxy methyl
- cellulose)
- Alginate
- PVP (Polyvinylpyrrolidone), cross-linked

4. Lubricant and Glidants: Lubricants are intended to prevent adhesion of the tablet materials to the surface of dies and punches, reduce inter particle friction and may improve the rate of flow of the tablet granulation.

Glidants are intended to promote flow of granules or powder material by reducing the friction between the particles.

Example: Lubricants

- Stearic acid,
- Stearic acid salt - Stearic acid,
- Magnesium stearate,
- Talc,
- PEG (Polyethylene glycols),
- Surfactants

Glidants-

- Corn Starch – 5-10% conc. ,
- Talc-5% conc. ,
- Silica derivative - Colloidal silicas such as Cab-O-Sil,
- Syloid,
- Aerosil in 0. 25-3% conc.

5. Coloring agent: The use of colors and dyes in a tablet has three purposes:

- Masking of off color drugs
- Product Identification
- Production of more elegant product

All coloring agents must be approved and certified by FDA. Two forms of colors are used in tablet preparation – FD &C and D & C dyes. These dyes are applied as solution in the granulating agent or Lake form of these dyes. Lakes are dyes absorbed on hydrous oxide and employed as dry powder coloring.

Example:

- FD & C yellow 6-sunset yellow
- FD & C yellow 5- Tartrazine
- FD & C green 3- Fast Green
- FD & C blue 1- Brilliant Blue
- FD & C blue 2 - Indigo carmine
- D & C red 3- Erythrosine.
- D & C red 22 – Eosin Y

6. **Flavouring agents**: For chewable tablet- flavour oils are used
7. **Sweetening agents:** For chewable tablets: Sugar, mannitol.

- Saccharine (artificial): 500 time's sweeter than sucrose

Disadvantage: Bitter after taste and carcinogenic

- Aspartame (artificial)

Disadvantage: Lack of stability in presence of moisture.

1. 2: INTRODUCTION OF LIQUISOLID TECHIQUE

- Major rate limiting step for class II and IV is dissolution
- The term "water-insoluble drugs" are the drugs which are known as "Sparingly water-soluble" (1 part solute to 100 parts of water),
- "Slightly water soluble" (1 into 100 to 1000 parts of water)
- "Very slightly water soluble" (1 part solute into 1000 to 10,000 parts of water).
- To enhance these properties like absorption, dissolution which are rate limiting step for lipophilic or poorly soluble drugs, different approaches have been designed with required modification such a
- Solid Dispersions
- Inclusion complex using β-cyclodextrins
- Micronization
- Microwave induced dissolution rate improvement
- Adsorption onto silica gels
- New technique "Liquisolid Technique"
- Solid dispersions prepared by melting technique may leads to stability problems.
- Salt formation leads to hygroscopicity and May causes stability problems.
- By the use of co solvents precipitation may occurs upon dilution.
- To overcome all these types of problems the "**Liquisolid Technique"** was introduced. Liquisolid technology also called as "**Powder Solution Technology".**
- It is the most **promising & novel** techniques to improve the dissolution rates of the poorly water soluble drugs.
- The concept of powder solution technology is to convert the liquid drug into free flowing readily compressible powder.
- Here the liquid drug (or) liquid medication is the water insoluble drug and it is dissolved in a non-volatile solvent.
- These liquid drugs are converted to free flowable& compressible powder by the addition of suitable excipients like carriers, coating materials, lubricants, disintegrants &glidants etc.
- The compression can be proceeded by direct compression and slugging method.
- Liquid medication includes liquid lipophilic drugs and drug suspensions or solutions of solid water insoluble drugs in suitable non-volatile solvent systems.
- Liquisolid systems refers to powdered forms of liquid medications formulated by converting liquid lipophilic drugs, or drug suspensions or solutions of water insoluble solid drugs in suitable nonvolatile solvent systems, into dry, non-adherent, free-flowing and readily compressible powder admixtures by blending with selected carrier and coating materials.

- Carrier material refers to a preferably porous material possessing sufficient absorption properties, such as microcrystalline and amorphous cellulose, which contributes in liquid absorption.
- Coating material refers to a material possessing fine and highly adsorptive particles, such as various types of silica, which contributes in covering the wet carrier particles and displaying a dry looking powder by adsorbing any excess liquid.

1. 2. 1: COMPONENTS IN THE LIQUISOLID COMPACT TECHNIQUE:

Drug:

- The drug used in liquisolid systems must be water insoluble, low dose drugs.
- It must be in BCS class II and IV.

Example:Digoxin,Digitoxin,Prednisolone,Hydrocortisone,Water insoluble vitamins,Fish oil etc.

Non-volatile solvent:

It must be inert water miscible, not highly viscous and should have high boiling point.

Example:Polyethyleneglycol 200 and 400,Glycerin,N, N dimethyl acetamide,Span 80 &19,Tween 80&19,Propylene glycol,Fixed oils etc.

Carrier materials:

These are highly porous materials & have a wide surface area and the recommended to absorb the drugs on to them.

Example:Cellulose(microcrystalline&amorphous),starch,sorbitol,Lactose,(AvicelPH102),Eudragit RS&RL etc. ,

Coating materials:

- There are fine materials having a particle size range from 10 nm to 4560 mm in diameter.
- These must be highly adsorptive to cover the carrier particles and show dry look.

Example: Silica of various grades like cab-o-sil M5,Aerosil200,Syloid 244 etc. ,

Disintegrants*:*

- These are used to break the compacts to smaller particles.

Example:Crosscarmellosesodium,Crosspovidone,Explotab,Pre gelatinized starch etc.

Lubricants:

- These are intended to reduce the friction.

Example:Stearicacid,Stearic acid salts,Talc etc. ,

Glidants:

- Intended to promote the flow between particles by reducing the friction.

Example:Silicaderivatives,Talc,Corn starch etc. ,

1. 2. 2: ADVANTAGES OF LIQUISOLID TECHNIQUE:

- Huge number of Bio-Pharmaceutical classification class II drugs with high permeability, slightly or very slightly water soluble and practically insoluble liquids and solid drugs can be formulated into liquisolid systems.
- This principle governs or administers the mechanism of drug delivery from liquisolid systems of powdered drug solutions and it is mainly responsible for the improved dissolution profiles exhibited by this preparations.
- Drug is formulated in a tablet form or encapsulated dosage form and is held in solubilized liquid state, which confers developed or improved drug wetting properties thereby improving drug dissolution

profiles.

- Greater drug surface area is exposed to the dissolution medium.
- This liquisolid system is specifically for powdered liquid medications.
- Drug can be molecularly dispersed in the formulation.
- Less production cost compared to soft gelatin capsules.
- Suitable for industrial production.
- Drug release can be modified by changing suitable ingredients.
- Rapid release liquisolid tablets (or) capsules exhibit enhanced *in vitro & in vivo* drug release compared to their commercial products.
- Sustained released tablets (or) capsules of water insoluble drugs exhibit zero order release.
- It can be used to formulate liquid medications.
- Used in controlled drug delivery.

1. 2. 3: DISADVANTAGES OF LIQUISOLID TECHNIQUE:

- Liquisolid system requires low drug loading capacities.
- Requires more efficient excipients and it should provide faster drug release with smaller tablet size.
- In order to achieve acceptable flowability and compactability for liquisolid powder formulation higher amounts of carrier and coating materials are required.

1. 2. 4: LIMITATIONS:

- Not suitable for formulation of high dose water insoluble drugs.
- If more amounts of carrier is added it increase the flow properties of powder, it may increases the tablet weight too, hence it is difficult to swallow.
- It does not require chemical modification of drugs.
- Acceptable compression may not be achieved because the liquid drug may be squeezed out during compression resulting in unsatisfactory tablet weight .

1. 2. 5: APPLICATIONS:

- This technology is powerful tool to improve the bioavailability of poorly water soluble drugs.
- Rapid release rate.
- Suitable for controlled release.
- Applicable in probiotics.

1. 3: CLASSIFICATION OF LIQUISOLID SYSTEMS :

The liquisolid systems are classified into **two** types. They are

1. Based on the formulation technique used. These are of two categories :

1. Liquisolid compacts
2. Liquisolid Microsystems

2. Based on the type of liquid medication contained therein. These are of four different formulation systems namely

1. Powdered drug solutions (e. g: prednisolone solution in propylene glycol)
2. Powdered drug suspensions (e. g: gemfibrozil suspension in polysorbate 80)
3. Powdered liquid drugs (e. g: clofibrate, vitamins, etc.)
4. Non-volatile solvents are used to dissolve the drug the liquid vehicle does not evaporate so the drug carried as it is throughout the product.

1. 4: THEORY OF LIQUISOLID SYSTEMS:

- The powder can retain only certain limited amount of liquid while maintaining the flowability& compressibility.
- To calculate the quantities of powder excipients required for the formulation of liquisolid system, a mathematical approach is required. It has been developed by Spireaset. al. This approach is based on *flowable* (Ø-value) and *compressible* (Ψ-number) liquid retention potential.
- The **flowable liquid retention potential** of a powder defined as the maximum amount of a given non-volatile liquid that can be retained inside the bulk (w/w) while maintaining acceptability.
- The **compressible liquid retention potential** of a powder defined as the maximum amount of liquid that can be retained inside its bulk (w/w) while maintaining acceptable compatability to produce suitable hardness & friability.
- The Ψ number of powders may be determined using new method called 'pactisity theories' to evaluate compaction properties of powders.
- Depending on the excipients ratio (R) or carrier: coating ratio.

$$R = Q/q$$

Where,
R= ratio between carrier & coating materials
Q=weight of carrier
q= weight of coating material

- The free flowing and compressible liquisolid systems can be prepared if the liquid on the carrier should not exceed the maximum amount and is termed as liquid load factor.
- The **Liquid load factor** (lf) defined as the ratio of liquid medication and weight of carrier powder .

$$Lf = W/Q$$

Where,
W = weight of liquid medication
Q = weight of carrier.

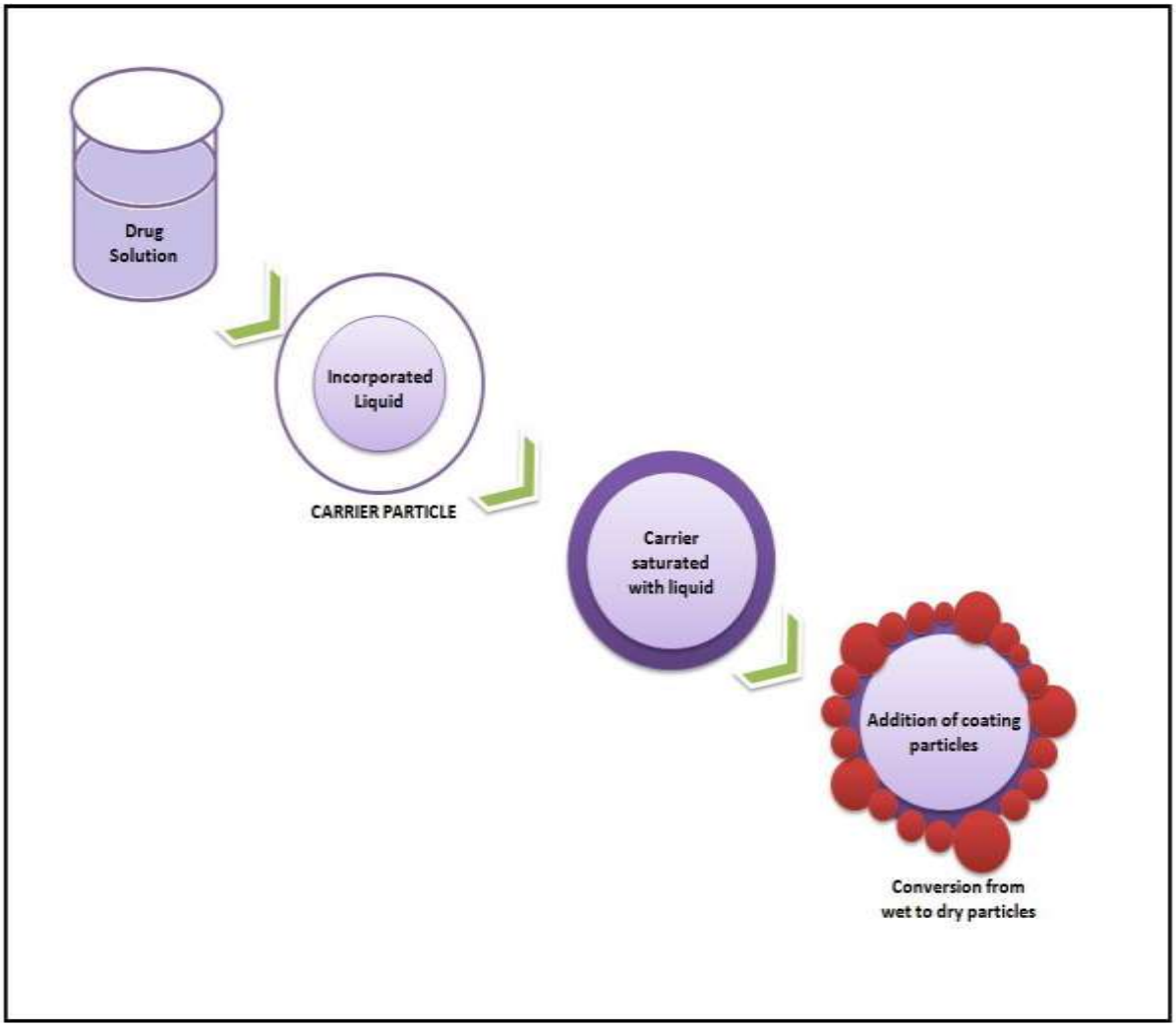


Figure no. 1: Schematic representation of Liquisolid systems

1. 5: MECHANISMS OF ENHANCED DRUG RELEASE FROM LIQUISOLID SYSTEMS:

Several mechanisms are developed to enhance the drug release. **Three** important mechanisms include an increase in drug surface area, an increase in aqueous solubility and an improved wettability of drugs .

1. **Increased surface area:**

- By increasing the surface area of drug the dissolution of drug with the liquid vehicle is increased.
- Accordingly with increasing the limit of solubility the undissolved amount is also increases.
- Hence the drug release rate decreases.

2. **Increased aqueous solubility:**

- A relatively small amount of liquid vehicle is not sufficient to solubilize the total amount of drug.
- But at the solid liquid interface between the particles and dissolution medium, it is possible that a small amount of liquid vehicle diffuses from the total amount along with drug .
- This less amount of liquid is sufficient to increase the aqueous solubility of drug if it acts as a co-solvent.

3. **Improved wetting properties:**

- The liquid vehicle can improve the wettability of liquisolid primary particle by acting as a surface active agent (or) by reducing the surface tension.

- Wettability of liquisolid systems has been demonstrated by measurement of contact angles and water rising times.

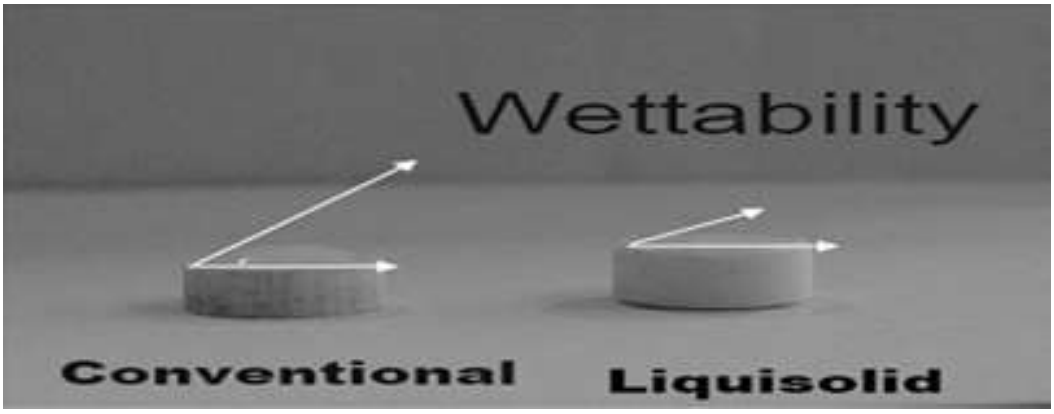


Figure no. 2: Difference between wettability of conventional and liquisolid tablets

1. 6: OPTMIZATION OF LIQUISOLID FORMULATIONS:

- The liquisolid technology was successfully applied to low dose, poorly water soluble drugs.
- The major limitation of liquisolid technology is high dose, poorly soluble drugs.
- The drugs release rates are directly proportional to the fraction of molecularly dispersed drug in liquisolid formulation.
- To obtain acceptable flowability& compressibility high levels of carriers and coating materials are required.
- This will leads to increased tablet weight and it is difficult to swallow. Therefore, to overcome this and other various problems of liquisolid technology several formulation parameters should be optimized .

Table no. 1 : Optimization of formulation parameters for liquisolid systems

Parameters	Optimization	Effect
Liquid vehicle	High drug solubility	Increased fraction of molecularly dispersed drug (FM)
Carrier & coating materials	High specific surface area	Increased liquid load factor(Lf)
Addition of excipients	Poly vinyl pyrrolidone (PVP)	Increased liquid load factor, increased viscosity of liquid vehicle, inhibition of precipitation
Excipients ratio (R)	High R-value	Fast disintegration, inhibition of precipitation

1. 7: PREPARATION OF LIQUISOLID COMPACTS :

- A drug substance was initially dispersed in the nonvolatile solvent systems (Polysorbate 80, Polyethylene glycol-200) termed as liquid vehicles with different drug: vehicle ratio.
- Then a mixture of carrier or different polymers and excipients were added to the above liquid medication under continuous mixing in a mortar. These amounts of the carrier and excipients are enough to maintain acceptable flow and compression properties.
- To the above binary mixture disintegrant like sodium starch glycolate and other reaming additives were added according to their tion and mixed for a period of 10 to 20 min. in a mortar
- The final mixture was compressed using the manual tableting machine to achieve tablet hardness.
- Characterize the final liquisolid granules for solubility, dissolution, flowability, compressibility and other physicochemical properties.

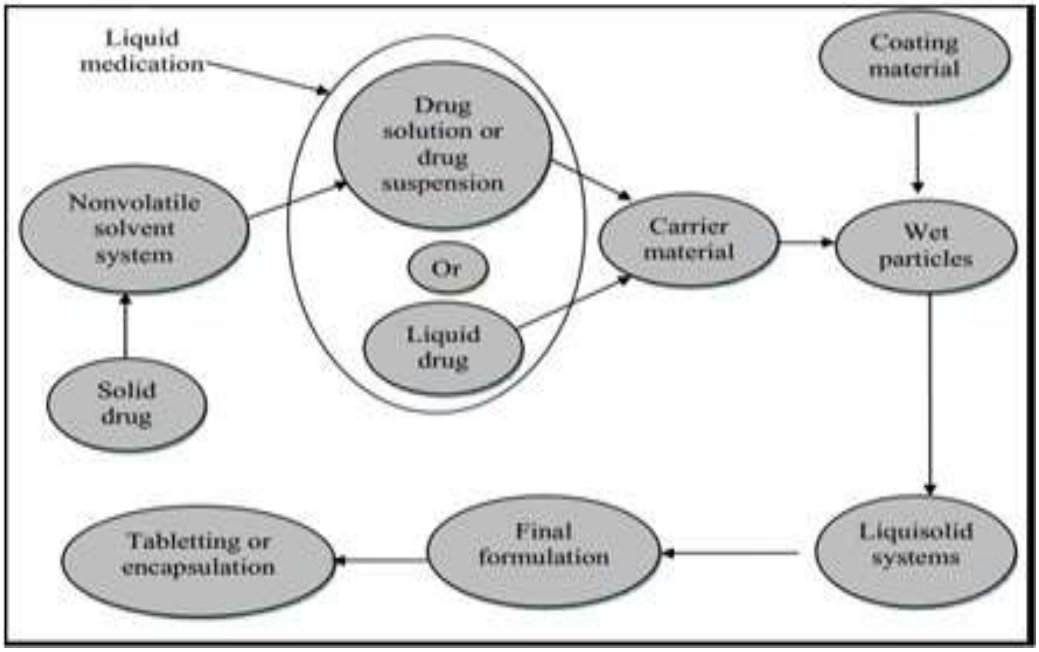


Figure no. 3: Schematic representation of preparation of liquisolid tablets

1. 8 : DRUGS THAT CAN BE INCORPORATED INTO LIQUISOLID SYSTEMS :

- **Antihistaminic** :Chlorpheniramine
- **Antiarrthymic** : Digoxin, Digitoxin
- **Antihypertensive** :Nifedipine
- **Antilipidemics** :Clofibrate, Gemfibrozil
- **Antiepileptic** : Carbamazepine, Valproic acid.
- **Chemotherapeutic agent** :Etoposide.
- **Diuretics** : Hydrochlorothiazide, Methylchlorthiazide, Polythiazide, Spironolactone.
- **Glucocorticoids** : Prednisolone, Hydrocortisone, Prednisone
- **NSAIDS** :Piroxicam, Indomethacin, Ibuprofen.
- **Water-insoluble vitamins** : Vitamin A, D, E, and K

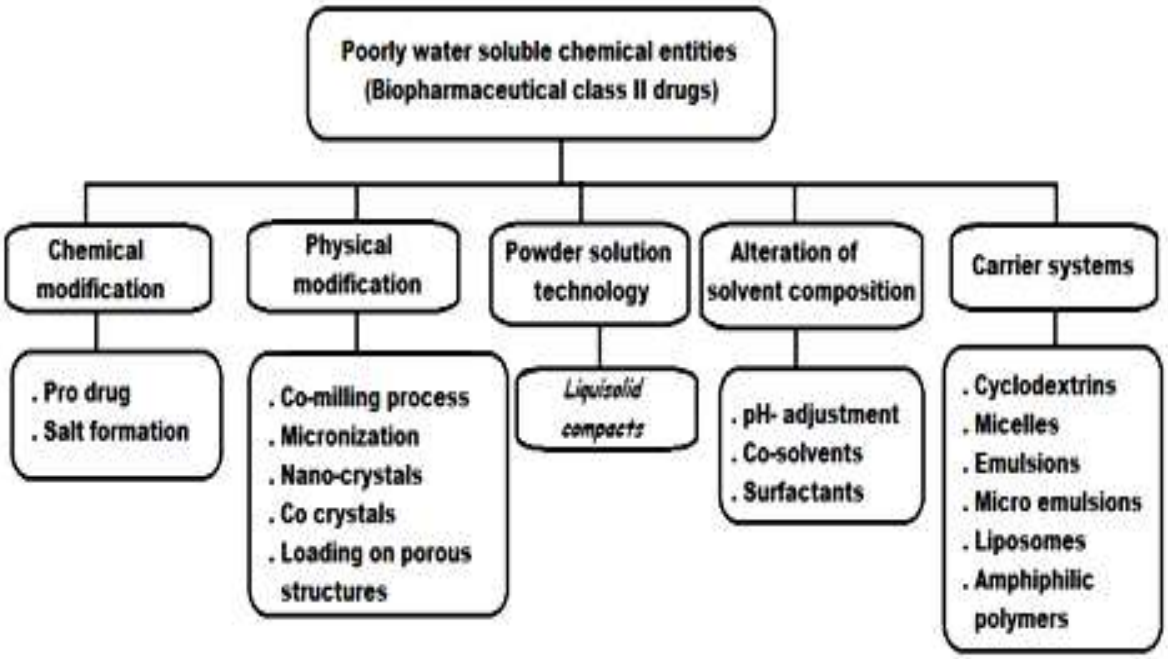


Figure no. 4 : Techniques for poorly water soluble chemical entities

1. 9: COMPARISON WITH OTHER ALTERNATIVE TECHNOLOGY AND THEIR ADVANTAGES AND DISADVANTAGES:

The liquisolid technology can be used both for the enhancement and the retardation of drug release. It is a promising technique because of the simple manufacturing process, low production costs, and the possibility of industrial production due to good flow and compaction properties of the liquisolid formulations.

Technologies for the enhancement of drug release : Release enhancement of poorly soluble drugs may be achieved by an increase of the drug surface area, the drug solubility, or by formulating the drug in its dissolved state. Several methodologies such as micronization, adsorption onto high surface area carriers, co-grinding, formulation of inclusion complexes, solid dispersions and lipid based formulations (e. g. SEDDS) are used for enhancement of drug release.

Micronisation: A simple method for increasing the surface area of the drug is micronization. However, in practice the effect of micronization is often disappointing, especially if the drugs are encapsulated or tableted. Micronized drugs have the tendency to aggregate as a result of their hydrophobicity and electrostatic charge, thus, reducing their available surface area.

Adsorption of poorly soluble drugs : Adsorption of poorly soluble drugs on hydrophilic silica aerogels was found to enhance drug dissolution. This can be explained by both an increase in the specific surface area of the drug adsorbed to the aerogel and an at least partial amorphisation of the drug. However, drug adsorption is dependent on the selected drug and sometimes only low drug loads are achieved. Another disadvantage of this technique is the complex manufacturing process: Silica aerogels are loaded with drugs by adsorption from their solutions in supercritical carbon dioxide.

Co-grinding : Co-grinding of poorly soluble drugs with different excipients may also result in an morphisation of the drug and thus improved dissolution characteristics. Eg; Crospovidone, olyvinylpyrrolidone, and different types of silica, are suitable for that purpose. Co-grinding is another straight forward procedure to achieve drug release enhancement.

Complexation: Complexes of a lipophilic drug with cyclodextrin, commonly known as inclusion complexes, can be easily formulated by mixing the drug with the carrier. The most commonly used carrier β-cyclodextrin acts as a solubilizer and stabilizer consisting of a truncated cone type structure with an outer hydrophilic and an inner hydrophobic surface. However, the maximum possible drug load of these systems is relatively low and the inclusion complexation only works with drugs that fit into the cavities of the cyclodextrin molecule.

Solid dispersions : Solid dispersions consist of one or more active ingredients dispersed in a readily soluble solid hydrophilic matrix prepared by a melting (fusion) or solvent method. With the melting method the drug is added to the molten carrier and the mixture is stirred until a homogenous melt is obtained. With the solvent method drug and carrier are dissolved in small amounts of solvent with final solvent evaporation. Number of factors which include formation of the amorphous form of the drug, reduction of particle size to nearly the molecular level, improved wetting properties, and solubilisation of the drug by the carrier. The advantages of this methodology are the molecular dispersion of the drug within the hydrophilic carrier and the comparably high drug stability. However, for the preparation of solid dispersions usually special equipment is needed such as a spray dryer or a fluid bed apparatus.

Self-emulsifying drug delivery systems : Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of oil, surfactant, co solvent and drug, which emulsify spontaneously to produce oil in water emulsions when introduced into an aqueous phase under gentle agitation. Generally, SEDDS are either administered as liquid dosage forms or as soft gelatin capsules. Basically, solid dosage forms are preferred over liquid preparations for many reasons including ease of manufacture, patient compliance, dosage uniformity, and stability. Liquid SEDDS may be transformed to solid self-emulsifying systems (SSEDDS) by addition of powder carriers. The liquisolid technology may be used to transform liquid SEDDS into acceptably flowing and compressible powders. One of the drawbacks of this technique is the high surfactant concentration.

LITERATURE REVIEW

Spiro Spireas et al(1999)studied the effects of powder substrate composition on the in vitro release properties of methyclothiazideliquisolid compacts were evaluated. The dissolution patterns of this water-insoluble drug formulated in liquisolid tablets were also compared to those of commercial products. According to the new liquisolid technique, liquid medications such as solutions or suspensions of water-insoluble drugs in suitable nonvolatile liquid vehicles can be converted into acceptably flowing and readily compressible powders by a simple admixture with certain powder substrates, which are selected powders referred to as the carrier and coating materials. Enhanced release profiles may be exhibited by such systems due to the increased wetting properties and surface of drug available for dissolution. Liquisolid tablets of methyclothiazide containing a 5% w/w drug solution in polyethylene glycol 400 were prepared using powder substrates of different excipient ratios. The release rates of such products were assessed using the USP dissolution test and were compared to those of their commercial counterparts. It was observed that maximum drug dissolution rates can be exhibited by systems that have powder substrates with optimum carrier-to-coating ratios. In addition, liquisolid tablets displayed significantly enhanced dissolution profiles compared to those of marketed products.

YousefJavadzadehet al(2007) studied different liquisolid formulations of carbamazepine were accomplished by dissolving the drug in the non-toxic hydrophilic liquids, and adsorbing the solution onto the surface of silica. In order to reduce the amounts of carrier and aerosil in liquisolid formulations, some

additives namely polyvinylpyrrolidone (PVP), hydroxypropyle methylcellulose (HPMC) and polyethylene glycol (PEG 35000) were added to liquid medication to increase loading factor. The effects of various ratios of carrier to coating material, PVP concentration, effect of aging and type of the carrier on dissolution rate of liquisolid compacts were studied. X-ray crystallography and differential scanning calorimetery (DSC) were used for evaluation of physicochemical properties of carbamazepine in liquisolid formulations. The results showed that the drug loading factor was increased significantly in the presence of additives. Liquisolid formulations containing PVP as additive, exhibited significantly higher drug dissolution rates compared to the compacts prepared by the direct compression technique. It was shown that microcrystalline cellulose had more liquid retention potential in comparison with lactose, and the formulations containing microcrystalline cellulose as carrier, showed higher dissolution rate. By decreasing the ratio of microcrystalline cellulose to silica from 20 to 10, an improvement in dissolution rate was observed. Further decrease in the ratio of microcrystalline cellulose:silica from 10 to 5 resulted in a significant reduction in dissolution rate. Increasing of PVP concentration in liquid medication caused a dramatic increase in dissolution rate at first 30 min. The results showed that the dissolution rate of liquisolid tablets was not significantly affected by storing the tablets at 25 °C/75% relative humidity for a period of 6 months. The results of DSC and X-ray crystallography did not show any changes in crystallinity of the drug and interaction between carbamazepine and exipients during the process.

Gubbi Sanjeev et al(2009)studied the in vitro dissolution property of slightly water soluble Bromhexine hydrochloride (BXH) was improved by exploring the potential of Liquisolid system (LS). The in vitro release pattern of LS compacts and directly compressed tablets were studied using USP-II apparatus. Different LS compacts were prepared using a mathematical model to calculate the required quantities of powder and liquid ingredients to produce acceptably flowable and compressible admixture. Avicel PH 102, Aerosil 200 and Explotab were employed as carrier, coating material and disintegrant respectively for preparing LS compacts. The prepared LS compacts were evaluated for their flow properties such as bulk density, tapped density, angle of repose, Carr's compressibility index and Hausner's ratio. The interaction between drug and excipients in prepared LS compacts were studied by differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD). The drug release rates of LS compacts were distinctly higher as compared to directly compressed tablets, which show significant benefit of LS in increasing wetting properties and surface area of drug available for dissolution. The LS-1 of LS powder system showed acceptable flowability, Carr's compressibility index and Hausner's ratio. The DSC and XRD studies conforms the no significant interaction between the drug and excipients used in LS compacts. From this study it concludes that the LS technique is a promising alternative for improvement of dissolution property of water-insoluble drugs

EvelyneChaputet al(2000) Activators of peroxisome proliferator activated receptors (PPARs) are effective drugs to improve the metabolic abnormalities linking hypertriglyceridemia to diabetes, hyperglycemia, insulin-resistance, and atherosclerosis. We compared the pharmacological profile of a PPARα activator, Fenofibrate, and a PPARγ activator, rosiglitazone, on serum parameters, target gene expression, and body weight gain in (*fa/fa*) fatty Zuckerratsand *db/db* mice as well as their association in *db/db* mice. Fenofibrate faithfully modified the expression of PPARα responsive genes. Rosiglitazone increased adipose tissue aP2 mRNA in both models while increasing liver acyl CoA oxidase mRNA in *db/db* mice but not in fatty Zucker rats. Both drugs lowered serum triglycerides yet rosiglitazone markedly increased body weight gain while Fenofibrate decreased body weight gain in fatty Zucker rats.

KRP 297, which has been reported to be a PPARα and γ co-activator, also affected serum triglycerides and insulin in fatty Zucker rats although no change in body weight gain was noted. These results serve to clearly differentiate the metabolic finality of two distinct classes of drugs, as well as their corresponding nuclear receptors, having similar effects on serum triglycerides.

M. D. Feher et al(2002)studied assess the short-term urate-lowering effect of Fenofibrate in men on long-term allopurinol therapy for hyperuricaemia and gout.

(i) baseline, (ii) after 3 weeks of once-daily therapy with micronized Fenofibrate. Ten male patients (38–74 yr) with a history of chronic tophaceous or recurrent acute gout with hyperuricaemia and on established allopurinol at 300–900 mg/day for ≥3 months were studied in an open-crossover study of Fenofibrate therapy. Allopurinol at the established dose was continued throughout the study. Clinical and biochemical assessments (serum urate and creatinine, 24-h urinary excretion of urate and creatinine, liver function tests, creatine kinase and fasting serum lipids) were undertaken at 200 mg and (iii) 3 weeks after Fenofibrate was withdrawn.

Fenofibrate was associated with a 19% reduction in serum urate after 3 weeks of treatment (mean±S. E. 0. 37±0. 04 *vs* 0. 30±0. 02 m/ml;*P*=0. 004). The effect was reversed after a 3-week Fenofibrate withdrawal period (0. 30±0. 02 *vs* 0. 38±0. 03 mM/l). There was a rise in uric acid clearance with Fenofibrate treatment of 36% (7. 2±0. 9 *vs* 11. 4±1. 6 ml/min, normal range 6–11; *P*=0. 006) without a significant change in creatinine clearance. Both total cholesterol and serum triglycerides were also reduced. No patient developed acute gout whilst taking Fenofibrate.

Fenofibrate has a rapid and reversible urate-lowering effect in patients with hyperuricaemia and gout on established allopurinol prophylaxis. Fenofibrate may be a potential new treatment for hyperuricaemia and the prevention of gout, particularly in patients with coexisting hyperlipidaemia or those resistant to conventional therapy for hyperuricaemia.

Maryse Guerinet al (2005) studied effect of Fenofibrate on plasma cholesteryl ester transfer protein (CETP) activity in relation to the quantitative and qualitative features of apoB- and apoA-I–containing lipoprotein subspecies was investigated in nine patients presenting with combined hyperlipidemia. Fenofibrate (200 mg/d for 8 weeks) induced significant reductions in plasma cholesterol (−16%; *P*<. 01), triglyceride (−44%; *P*<. 007), VLDL cholesterol (−52%; *P*=. 01), LDL cholesterol (−14%; *P*<. 001), and apoB (−15%; *P*<. 009) levels and increased HDL cholesterol (19%; *P*=. 0001) and apoA-I (12%; *P*=. 003) levels. An exogenous cholesteryl ester transfer (CET) assay revealed a marked decrease (−26%; *P*<. 002) in total plasma CETP-dependent CET activity after Fenofibrate treatment. Concomitant with the pronounced reduction in VLDL levels (37%; *P*<. 005), the rate of CET from HDL to VLDL was significantly reduced by 38% (*P*=. 0001), whereas no modification in the rate of cholesteryl ester exchange between HDL and LDL occurred after Fenofibrate therapy. Combined hyperlipidemia is characterized by an asymmetrical LDL profile in which small, dense LDL subspecies (LDL-4 and LDL-5, *d*=1. 039 to 1. 063 g/mL) predominate. Fenofibrate quantitatively normalized the atherogenic LDL profile by reducing levels of dense LDL subspecies (−21%) and by inducing an elevation (26%; *P*<. 05) in LDL subspecies of intermediate density (LDL-3, *d*=1. 029 to 1. 039 g/mL), which possess optimal binding affinity for the cellular LDL receptor. However, no marked qualitative modifications in the chemical composition or size of LDL particles were observed after drug treatment. Interestingly, the HDL cholesterol concentration was increased by Fenofibrate therapy, whereas no significant change was detected in total plasma HDL mass. In contrast, the HDL subspecies pattern was modified as the result of an increase in the total mass (11. 7%) of HDL, HDL, and HDL(*d*=1. 091 to 1. 156 g/ml) at the expense of reductions in the total mass

(−23%) of HDL (*d*=1. 063 to 1. 091 g/ml) and HDL (*d*=1. 156 to 1. 179 g/mL). Such changes are consistent with a drug-induced reduction in CETP activity. In conclusion, the overall mechanism involved in the Fenofibrate-induced modulation of the atherogenic dense LDL profile in combined hyperlipidemia primarily involves reduction in CET from HDL to VLDL together with normalization of the intravascular transformation of VLDL precursors to receptor-active LDLs of intermediate density.

Melanie G. Creeet al(1999) Multiple studies have documented hyperglycemia and insulin resistance following trauma, myocardial infarction, stroke, or surgery. Both are of serious clinical concern, as hyperglycemia is associated with increased morbidity and mortality of critically ill, surgical, and burned patients. These outcome studies emphasize the importance of better understanding insulin resistance in this large patient population. Pediatric burns provide a unique model for studying acute onset insulin resistance, since the nature of the injury is severe and quantifiable and the timing of onset is exactly known. Further, lean children are much less likely to have preexisting comorbid conditions such as diabetes, or to have been taking medications prior to injury.

We have recently demonstrated that mitochondrial oxidative function is impaired in burned children by more than 70% at 1 week postburn. A limited number of animal studies have found that mitochondrial genes, protein, and function are also decreased in skeletal muscle, liver, and cardiac muscle following burn injury. Similar findings were reported from the liver of patients who died after prolonged stays in intensive care for nonsurgical illness. In patients with type II diabetes, correlations between mitochondrial function and insulin sensitivity have been documented. These studies indicate that improving mitochondrial function may be a potential treatment target for improving insulin sensitivity.

There are limited proven therapies for treating acute injury-induced insulin resistance. Insulin therapy to prevent hyperglycemia has been shown to reduce mortality and/or morbidity in intensive care patients, patients undergoing surgical procedures and in burns. However, intensive insulin therapy requires constant vigilance and does not alter the underlying pathology. One study found that metformin decreased muscle loss after burn, but other medications that are typically prescribed for treatment of insulin resistance have not been tested in these populations.

PPAR-γ agonists, or thioglitazones, have been shown to improve insulin sensitivity in patients with diabetes. [14] The mechanism of action apparently involves suppression of peripheral lipolysis and redistribution of triglyceride stores to subcutaneous fat cells. However, burned children often have a large amount of their subcutaneous triglyceride stores destroyed or removed, decreasing the availability for redistribution sites. Further, burn patients may be treated with the beta-blocking agent propranolol to reduce myocardial stress, which also suppresses lipolysis. Therefore, a PPAR-γ agonist would be anticipated to be redundant in children given propranolol.

PPAR-α agonists have been shown in numerous animal studies and a few human studies to improve insulin sensitivity by enhancing mitochondrial function. We therefore hypothesized that PPAR-α agonism would stimulate mitochondrial function and improve insulin sensitivity in pediatric burn patients.

Devalina Law et al(2003) Poly(ethylene glycol) or PEG is an ideal inactive component for preparing simple binary eutectic mixtures because of its low entropy of fusion (~0. 0076 J/mol-K), lower melting point (~62°C) compared to most pharmaceuticals, miscibility with drugs at elevated temperatures, and its covalent crystalline lattice. Implication of these physicochemical properties on eutectic crystallization and size reduction of the drug is discussed. Enhancement of the dissolution rate of a poorly soluble compound through the formation of PEG–drug eutectics was investigated using Fenofibrate. Solid dispersions of PEG–Fenofibrate when characterized, revealed that PEG and Fenofibrate form a simple

eutectic mixture containing 20–25%(w/w) Fenofibrate at the eutectic point. Eutectic crystallization led to the formation of an irregular microstructure in which Fenofibrate crystals were found to be less than 10 μm in size. Dissolution rate improvement of Fenofibrate correlated with the phase diagram, and the amount of Fenofibrate released from the dispersions that contained Fenofibrate as a eutectic mixture was at least10-fold higher compared to untreated Fenofibrate. On aging, the dissolution rate of the dispersion containing 15%(w/w) Fenofibrate in PEG remained unaltered. The results indicate that PEG–drug eutectic formation is a valuable option for particle size reduction and subsequent dissolution rate improvement.

Michel Farnier et al(1994) Few studies have been performed to compare Fenofibrate, a second-generation fibrate, and simvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. This study was aimed to compare the efficacy of both drugs in reducing atherogenic risk factors in type IIa or IIb hyperlipidemia. Sixty-three patients entered this singlecenter, double-blind, crossover trial. Sixty patients (32 with type IIa and 28 with type lib hyperlipidemia) were randomized to treatment for 3 months with a single daily 200-mg dose of micronized Fenofibrate or 20 mg of simvastatin and then changed to the alternative treatment for a further 3-month period. After the first treatment period, in both types IIa and IIb, Fenofibrateand simvastatin produced similar significant reductions in levels of total cholesterol and low-density lipoprotein cholesterol; high-density lipoprotein cholesterol levels were increased with both drugs in type IIb. Only Fenofibrate decreased total triglyceride levels in type lib, Lp(a) lipoprotein levels in patients with high baseline values, and fibrinogen. After the second period of treatment, in both types IIa and IIb, switching from Fenofibrate to simvastatin resulted in a further reduction in total cholesterol and low-density lipoprotein cholesterol levels. The difference in the response of the two treatments on levels of total triglycerides, Lp(a) lipoprotein, and fibrinogen was confirmed after changing over to the alternative treatment. This short-term study showed few adverse effects for both drugs.

Fenofibrate and simvastatin provide similar variations on total cholesterol and low-density lipoprotein cholesterol levels after a 3-month treatment period, with simvastatin having the capacity to decrease these measures further when administered after Fenofibrate. However, Fenofibrate exhibits a significant effect on other established risk factors, such as total triglyceride, fibrinogen, and Lp(a) lipoprotein levels, and accordingly has a broader spectrum of activity than simvastatin.

Vranikova B et al(2008) Liquisolid systems are an innovative dosage form used for enhancing dissolution rate and improving in vivo bioavailability of poorly soluble drugs. These formulations require specific evaluation methods for their quality assurance (e. g. , evaluation of angle of slide, contact angle, or water absorption ratio). The presented study is focused on the preparation, modern in vitro testing, and evaluation of differences of liquisolid systems containing varying amounts of a drug in liquid state (polyethylene glycol 400 solution of rosuvastatin) in relation to an aluminometasilicate carrier (Neusilin US2). Liquisolid powders used for the formulation of final tablets were prepared using two different methods: simple blending and spraying of drug solution onto a carrier in fluid bed equipment. The obtained results imply that the amount of liquid phase in relation to carrier material had an effect on the hardness, friability, and disintegration of tablets, as well as their height. The use of spraying technique enhanced flow properties of the prepared mixtures, increased hardness values, decreased friability, and improved homogeneity of the final dosage form.

Patel T et al(2009) Liquisolid technique has been widely used to enhance the dissolution of poorly water soluble drugs. The present investigation is on formulation of liquisolid tablets of Fenofibrate, a lipid lowering agent. Liquisolid formulation was prepared by applying central composite design (CCD) to optimize various formulation parameters. Amounts of PEG 600 (X1), Avicel PH 102 (X2), and Aerosil

200 (X3) were selected as independent variables while the angle of repose, hardness, disintegration time, and T90% (time required to release 90% drug) of liquisolid tablets were selected as dependent variables. Optimization of formulation was done by multiple linear regression analysis. The results indicated amounts of PEG 600 and Aviel PH 102 show greater effect on dependant variables. In vitro dissolution of Fenofibrate in liquisolid formulations was enhanced compared to the pure form. To conclude, Liquisolid technique is a promising strategy in improving dissolution of poorly water soluble Fenofibrate.

Kamble PR, et al (2001) Rosuvastatin is a poorly water soluble drug and the rate of its oral absorption is often controlled by the dissolution rate in the gastrointestinal tract. Hence it is necessary to increase the solubility of the Rosuvastatin. Several liquisolid tablets formulations containing various drug concentrations in liquid medication (ranging from 15% to 25% w/w) were prepared. The ratio of Avicel PH 102 (carrier) to Aerosil 200 (coating powder material) was kept 10, 20, 30. The prepared liquisolid systems were evaluated for their flow properties and possible drug-excipient interactions by Infrared spectra (IR) analysis, differential scanning calorimetry (DSC) and X- ray powder diffraction (XRPD). The liquisolid system showed acceptable flow properties. The IR and DSC studies demonstrated that there is no significant interaction between the drug and excipients. The XRPD analysis confirmed formation of a solid solution inside the compact matrix. The tabletting properties of the liquisolid compacts were within the acceptable limits. Liquisolid compacts demonstrated significantly higher drug release rates than those of conventional and marketed tablet due to increasing wetting properties and surface area of the drug. This study shows that liquisolid technique is a promising alternative for improvement of the dissolution rate of water insoluble drug.

Gajdziok J et al(2010) Many modern drugs are poorly water soluble substances, which causes difficulties in the development of solid dosage forms with sufficient bioavailability. Preparation of liquisolid systems (LSS) is a novel technique for improving solubility, dissolution and bioavailability of such drugs. The basic principle of LSS preparation is conversion of the drug in liquid state into a free-flowing, compressible, dry powder through its absorption into suitable excipients - porous carriers (aluminometasilicates, microcrystalline cellulose), subsequently coated with material having high absorption capacity (silicon dioxide commonly known as colloidal silica). LSS exhibit advantages such as lower production costs compared to soft capsules, simple processing and enhanced drug release. The main benefit is higher bioavailability of the liquid drug, caused by a large surface area available for absorption. The article tries to clarify specific aspects connected with the formulation of LSS: properties of excipients (surface area, absorption capacity), variables related to the processing (solubility, liquid load factor) and dosage form evaluation.

Khames A et al(2004) investigate the photoprotective effect of liquisolid technique on amlodipine, a calcium channel blocker antihypertensive drug, representing a photosensitive drug model. Several liquisolid formulations were prepared using propylene glycol as a water-miscible nonvolatile vehicle at drug/solvent ratio (1:1), Avicel PH 102 as a carrier, nanometer-sized amorphous silicon and titanium dioxide either alone or in combination as coating materials. The carrier/coat ratio (R) was varied from 5 to 50. The prepared liquisolids, coated, noncoated tablets and drug substance were irradiated with a light dose of 0. 5 W/m(2)/h visible light, 55. 1 W/m(2)/h UVA, and 0. 247 W/m(2)/h UVB for 8 h. The effect of coating material type and (R) value on the drug dissolution rate and photostability was studied. Results were statistically analyzed by post hoc two-way ANOVA at a probability level ($\alpha = 0.05$). The results indicated that liquisolid technique not only improved the dissolution rate, but also significantly

inhibited the photodegradative effect of different light energies in all prepared liquisolid formulations. The residual drug percentage reached 97. 37% in comparison to 73. 8% for the drug substance after 8 h of irradiation. The residual drug percentage was affected by the (R) value. Statistically; the detected difference was significant at the selected probability level (α = 0. 05). It can thus be concluded that this liquisolid technique is a promising alternative to conventional coating procedures in formulations containing photosensitive drugs.

Nokhodchi Aet al(2007)studied properties of many new chemical entities have shifted towards higher molecular weights and this in turn increases the lipophilicity hence decreasing aqueous solubility. The low solubility of drugs usually has in vivo consequences such as low bioavailability, increased chance of food effect and incomplete release from the dosage form. The present review discusses the advantages of the liquisolid technology in formulation design of poorly water soluble drugs for dissolution enhancement and highly water soluble drugs for slow release pattern. With the advent of high throughput screening and combinatorial chemistry, it has been shown that most of the new chemical entities have a high lipophilicity and poor aqueous solubility, hence poor bioavailability. In order to improve the bioavailability, the release rate of these drugs should be enhanced. Although there are multiple technologies to tackle this issue, they are not cost effective due to the involvement of sophisticated machinery, advanced preparationtechniques and complicated technology. As the liquisolid technology uses a similar production process as the conventional tablets, this technology to improve the release rate of poorly water soluble drugs will be cost effective. This technology also has the capability to slow down drug release and allows preparing sustained release tablets with zero order drug release pattern. The excipients required for this technology are conventional and commonly available in the market. The technology is in the early stages of its development with extensive research currently focused on. It is envisaged that the liquisolidcompacts could play a major role in the next generation of tablets.

DRUG AND EXCIPIENT PROFILE

5. 1 DRUG PROFILE :

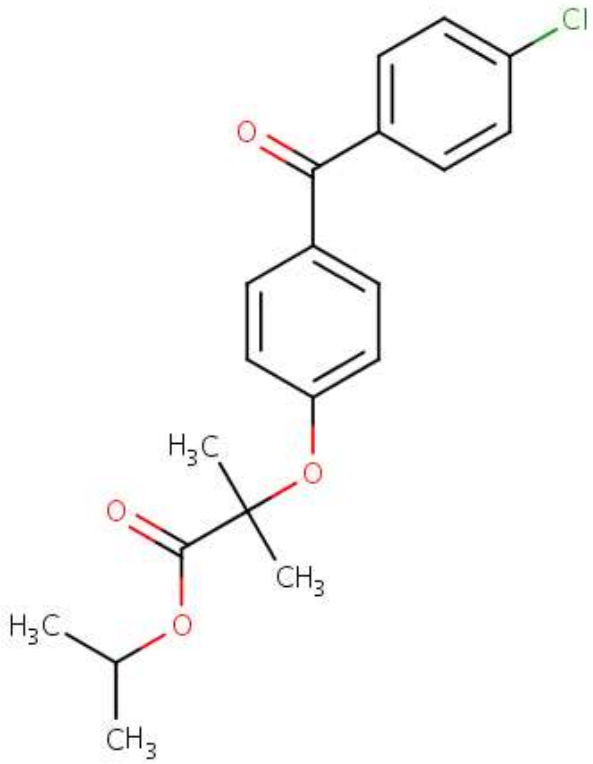
5. 1. 1 Fenofibrate is a poorly water - soluble drug.

Fenofibrate (INN), marketed as Tricor and under several other brand names, is a drug of the fibrate class. It is a class of amphipathic carboxylic acids.

Fibrates have played a major role in the treatment of hyperlipidemia for more than two decades (Miller and Spence 1998). The first member of this class, clofibrate, was identified in 1962 by Thorp and Waring (1962) and became available in the US in 1967. Many other fibrates, including ciprofibrate, bezafibrate, etofibrate, beclofibrate, and pirifibrate, are available in Europe, where the use of such agents is more extensive (Miller and Spence 1998; Guay 1999). The third-generation fibric acid derivative Fenofibrate was synthesized in 1975 and was introduced into clinical practice in France the same year. The original generic name procetofene was changed to Fenofibrate to comply with World Health Organization nomenclature guidelines. Fenofibrate is marketed in 86 countries and is one of the most commonly used fibrates worldwide, with more than 6 million patient-years of experience (Brown 1988). More than 80 clinical trials of Fenofibrate have involved more than 9000 patients and more than 31 000 patient-years of drug exposure.

It is used alone or along with statins in the treatment of hypercholesterolemia and hypertriglyceridemia. Fenofibrate has been used since 1975, is one of the most commonly prescribed fibrates, and has a well known efficacy and tolerability profile.

Category: Anti hyperlipidemic (or) hyperlipidemic agent.
IUPAC name : Propan-2-yl -2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoate
Molecular formula : $C_{20}H_{21}ClO_4$
Molecular weight : 360. 831 g/mol
Trade names : Fenoglide, lipofen, tricor, trilipix.
λ_{max} : 287nm
Molecular structure :



Physical properties:
Appearance : crystalline
State : solid
Density : 1. 18 g/cm^3
Melting point : 79 -83°c
Boiling point : 469. 77°c @760mm Hg
Solubility :
Insoluble in water . Water solubility – 0. 25mg/ml @ 25°c.
Soluble in acetone,benzene,chloroform,ether, ethanol (1mg/ml).
Slightly soluble in methanol.
Usage volume :
Oral administration : 100 mg /3 times / day
for three months a treatment significantly decreased blood lipid question after maintenance doses 100 mg / time, two times / day.

Pharmacokinetic parameters:

Administration : oral
Bioavailability : 1 hour
Protein binding : 99%
Metabolism : Glucuronidation (Fenofibric acid is metabolized by the hepatic cytochrome P(CYP)-450 3A4 isozyme)
Half life ($t^{1/2}$) : 20 hours
Excretion : Urine (60%), Faeces (25%)

Mechanism of action:

"In summary, enhanced catabolism of triglyceride-rich particles and reduced secretion of VLDL underlie the hypotriglyceridemic effect of fibrates, whereas their effect on HDL metabolism is associated with changes in HDLapolipoprotein expression. "

Fenofibrate is a fibric acid derivative, a prodrug comprising fenofibric acid linked to an isopropyl ester. It lowers lipid levels by activating Peroxisome proliferator-activated receptor alpha (PPARα). PPARα activates lipoprotein lipase and reduces apoprotein CIII, which increases lipolysis and elimination of triglyceride-rich particles from plasma.

PPARα also increases apoproteins AI and AII, reduces very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) containing apoprotein B, and increases high-density lipoprotein (HDL) containing apoprotein AI and AII.

Medical uses:

Fenofibrate is mainly used for primary hypercholesterolemia or mixeddyslipidemia. Fenofibrate appears to decrease the risk of cardiovascular disease and possibly diabetic retinopathy in those with diabetes mellitus, and firstly indicated for the reduction in the progression of diabetic retinopathy in patients with Type 2 diabetes and existing diabetic retinopathy in Australia. It also appears to be helpful in decreasing amputations of the lower legs in this same group of people. Fenofibrate also has an unlabeled use as an added therapy of high blood uric acid levels in people who have gout.

It is used in addition to diet to reduce elevated low-density lipoprotein cholesterol (LDL), total cholesterol, triglycerides (TG), and apolipoprotein B (Apo B), and to increase high-density lipoprotein cholesterol (HDL) in adults with primary hypercholesterolemia or mixed dyslipidemia.

- Severe hypertriglyceridemia type IV or V

It is used in addition to diet for treatment of adults with severe hypertriglyceridemia. Improving glycemic control in diabetics showing fasting chylomicronemia will usually decrease the need for pharmacologic intervention.

Statins remain first line for treatment of blood cholesterol. AHA Guidelines from 2013 did not find evidence for routine use of additional medications

Interactions:

The following drug interactions with Fenofibrate is considered major and may need therapy modifications:

- Bile acid sequestrants (e. g. cholestyramine, colestipol, etc.): If taken together, bile acid resins may bind to Fenofibrate, resulting in a decrease in Fenofibrate absorption. In order to maximize absorption, patients need to separate administration by at least 1 hour before or 4–6 hours after taking the bile acid sequestrant.

- Immunosuppressants (e. g. cyclosporine or tacrolimus): There is an increased risk of renal dysfunction with concomitant use of immunosuppressants and Fenofibrate. Please approach with caution when coadministering additional medications that decrease renal function.
- Vitamin K antagonists (e. g. warfarin): As previously mentioned, Fenofibrate interacts with coumarin anticoagulants to increase the risk of bleeding. Dosage adjustment of Vitamin K antagonist may be necessary.
- Statins: Combination of statins and Fenofibrate may increase the risk of rhabdomyolysis or myopathy.

Contraindications:

Fenofibrate is contraindicated in:

- Patients with severe renal impairment, including those receiving dialysis (2. 7-fold increase in exposure, and increased accumulation during chronic dosing in patients with estimated glomerular filtration rate (eGFR)<30mL/min)
- Patients with active liver disease, including those with primary biliary cirrhosis and unexplained persistent liver function test (LFT) abnormalities
- Patients with preexisting gallbladder disease
- Nursing mothers
- Patients with known hypersensitivity to Fenofibrate or fenofibric acid

Adverse effects:

The most common adverse events (>3% of patients with coadministered statins) are

- Headache
- Back pain
- Nasopharyngitis
- Nausea
- Myalgia
- Joint pain or arthralgia
- Diarrhea
- Upper respiratory tract infection

Precautions:

Musculoskeletal

Myopathy and rhabdomyolysis; increased risk when coadminstered with a statin, particularly in the elderly and patients with diabetes, renal failure, hypothyroidism.

Hepatotoxicity

Can increase serum transaminases; liver tests should be monitored periodically.

Nephrotoxicity

Can increase serum creatinine levels; renal function should be monitored periodically in patients with renal insufficiency.

Biliary

Can increase cholesterol excretion into the bile, leading to risk of cholelithiasis; if suspected gallbladder studies are indicated. See "Interaction" section under Bile Acid Sequestrant

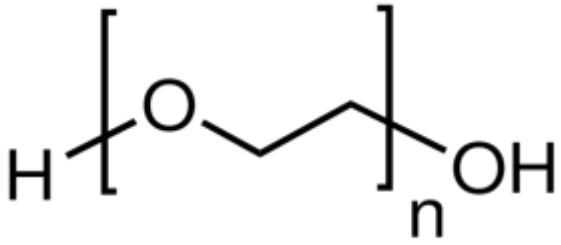
Coagulation/Bleeding

Exercise caution in concomitant treatment with oral coumarin anticoagulants (e. g. Warfarin). Adjust the dosage of coumarin to maintain the prothrombin time/INR at desired level to prevent bleeding complications.

Specifications :
capsules: 100mg / tablets, 200 mg / tablets, 300 mg / tablets.

5. 2 EXCIPIENT PROFILE:

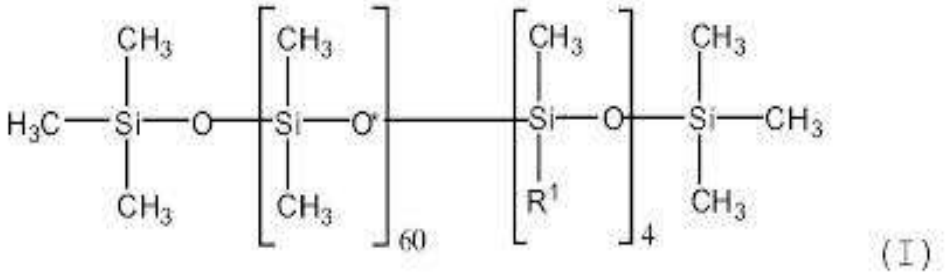
5. 2. 1. Polyethylene glycol 200:



Chemical Formula: $(C_2H_4O)_nH_2O$
IUPAC names: Poly(oxyethylene), Poly(ethylene oxide)
Synonyms: Carbowax, Macrogol, Nycoline.
Physical and chemical properties:
Appearance : clear viscous liquid
Melting point : -55 - -40°C
Boiling point : >250°C
Flash Point : 180°C
Specific density : 1. 124 g/cm^3 (20°C)
Specific Gravity : 1. 125 at 77. 0 ° F
Water Solubility : Soluble (>= 10 mg/ml at 70° F) (NTP, 1992)
Chemical uses:

- Polyethylene glycol has a low toxicity and is used in a variety of products. The polymer is used as a lubricating coating for various surfaces in aqueous and non-aqueous environments.
- PEG is the basis of many skin creams (as *cetomacrogol*) and personal lubricants (frequently combined with glycerin).
- PEG is used in a number of toothpastes as a dispersant. In this application, it binds water and helps keep xanthan gumuniformly distributed throughout the toothpaste.
- Since PEG is a flexible, water-soluble polymer, it can be used to create very highosmotic pressures (on the order of tens of atmospheres). It also is unlikely to have specific interactions with biological chemicals. These properties make PEG one of the most useful molecules for applying osmotic pressure in biochemistry and bio membranes experiments, in particular when using the osmotic stress technique.
- Polyethylene glycol is also commonly used as a polar stationary phase for gas chromatography, as well as a heat transfer fluid in electronic testers.
- PEG is often used (as an internal calibration compound) in mass spectrometry experiments, with its characteristic fragmentation pattern allowing accurate and reproducible tuning.
- PEG derivatives, such as narrow range ethoxylates, are used as surfactants.
- PEG has been used as the hydrophilic block of amphiphilic block copolymers used to create some polymersomes.
- PEG is used as a binder in the preparation of technical ceramics.

5. 2. 2. Aerosil:



(I)

Description:

- Fumed silica , also known as pyrogenic silica because it is produced in a flame, consists of microscopic droplets of amorphous silica fused into branched, chainlike, three-dimensional secondary particles which then agglomerate into tertiary particles.
- The resulting powder has an extremely low bulk density and high surface area.
- Its three-dimensional structure results in viscosity-increasing, thixotropic behavior when used as a thickener or reinforcing filler.

IUPAC name : Dioxosilane
Chemical name : Quartz, silica, silicon dioxide
Chemical formula : O_2Si
Molecular weight : 60. 0843g/mol
Synonyms :Aerosol silica; amorphous fumed silica; hydrophilic sillica
CAS number : 112945-52-5

Physical and chemical Properties:

pH : 3. 6-4. 5
Melting point : 1700°C
Surface area : 50–600 m^2/g.
Density : 160–190 kg/m^3.
Particle size : 5–50 nm.
Refractive index : 1. 45

Hazards and safety:

- Inhalation may cause silicosis; use dust mask.
- Particles can irritate eyes.
- Non-flammable. Inert.

Properties:

- Fumed silica has a very strong thickening effect.
- The particles are non-porous .
- The Free flow and anti-caking agent to improve powder properties
- Improves tablet properties such as hardness and friability
- Used as viscosity increasing agent to thicken and thixotropize liquids
- Dessicant for moisture-sensitive actives
- Improves distribution of active pharmaceutical ingredients
- Used as anti-setting, thickening and anti-sagging agent

- High purity, low humidity content
- No influence on taste
- Does not alter natural colour of powder formulations

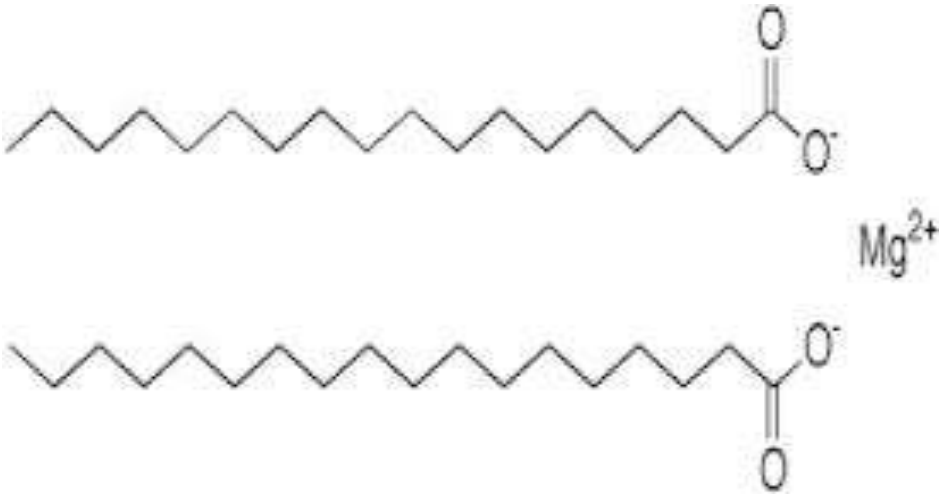
Applications:

- Fumed silica serves as a universal thickening agent and an anticaking agent (free-flow agent) in powders.
- Like silica gel, it serves as a desiccant.
- It is used in cosmetics for its light-diffusing properties.
- It is used as a light abrasive, in products liketoothpaste.
- Other uses include filler in silicone elastomer and viscosity adjustment in paints, coatings, printing inks, adhesives and unsaturated polyester resins.
- It is also used in the production of cat litter box filler.

Storage:

We recommend to store the product in closed containers under dry conditions and to protect the material from volatile substances. AEROSIL® 200 Pharma should be used within 2 years after production.

5. 2. 3. Magnesium stearate



Synonyms: Stearic acid magnesium salt, magnesium salt, magnesium octadecanoate

Description : If is a fine, white, precipitated of milled, impalpable powder of low bulk density having a faint odour of stearic acid & a characteristic taste.

Structural Formula: [$CH_3(CH_2)_{16}$ COO]$_2$Mg

Molecular Weight: 591. 34 g/mol

Solubility: It is insoluble in water, ethanol & ether, slightly soluble in warm benzene & war m ethanol

Functional categories: Tablet & capsule lubricant

Melting point **:** 117- 150°C

Density (bulk) **:** 0. 159gm/cm3

Density (tapped) **:** 0. 286gm/cm3

Stability and storage conditions:

- It should be stored in well-closed container in a cool, dry place. It is stable no. compound.

Incompatibilities:

- It is incompatible with strong oxidizing agents, strong acids, alkalis & iron salts. It cannot be used in products containing aspirin, some vitamins, & most alkaloid salts.

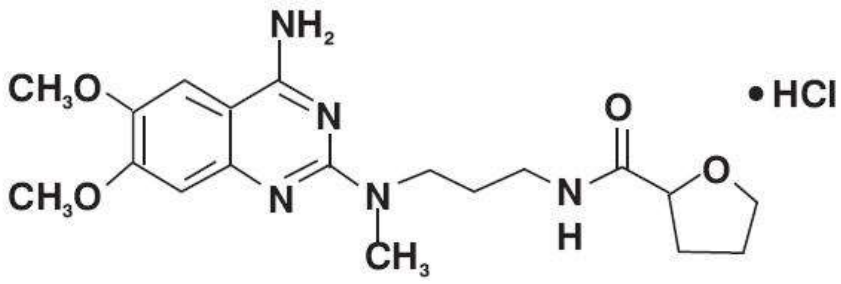
Safety:

- It is nontoxic. However, oral consumption of large quantity may result in some laxative effect or **mucosal** irritation.

Applications:

- Used in cosmetics, food & pharmaceutical formulations and as a lubricant in capsule & table no. at concentration between 0. 25-5. 0%.

5. 2. 4. Talc:



IUPAC name : Hydroxy-oxido-oxo-silane
Chemical formula : $H_2Mg_3(SiO_3)_4$
Molecular weight : 379.26568 g/mol
Chemical names : Mussolinite, Soapstone, Snowgoose

Description:

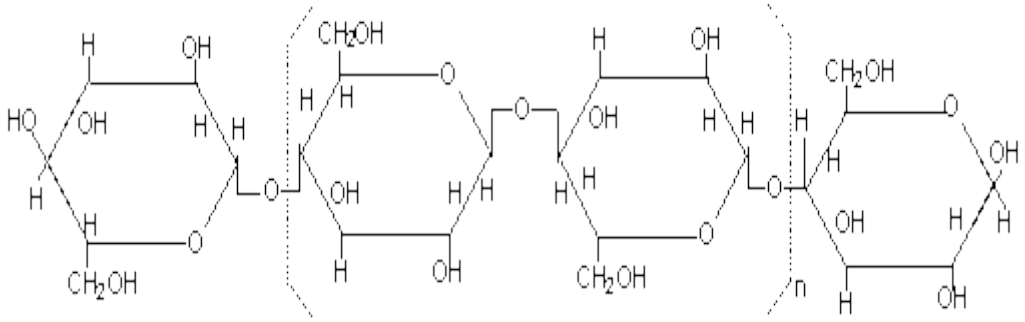
- Talc derived from the Persian 'talc' is a mineral composed of hydrated magnesium silicate
- It is a very fine, white to grayish-white, odorless, oily, Crystalline powder used as both lubricant and glidant.

Uses:

- Talc is used in many industries such as paper making, plastic, paint and coatings, rubber, food, electric cable, pharmaceuticals, cosmetics, ceramics, etc.
- A coarse grayish-green high-talc rock is soapstone or steatite and has been used for stoves, sinks, electrical switchboards, crayons, soap, etc.
- It is often used for surfaces of lab counter tops and electrical switchboards because of its resistance to heat, electricity and acids. Talc finds use as a cosmetic (talcum powder), as a lubricant, and as a filler in paper manufacture.
- Talc is used in baby powder, an astringent powder used for preventing rashes on the area covered by a diaper. It is also often used inbasketball to keep a player's hands dry.
- Most tailor's chalk, or French chalk, is talc, as is the chalk often used for welding or metalworking.
- Talc is also used as food additive or in pharmaceutical products as aglidant. In medicine talc is used as a pleurodesis agent to prevent recurrent pleural effusion or pneumothorax. In the European Union the additive number is E553b.

- Due to its low shear strength, talc is one of the oldest known solid lubricants. There is also a limited use of talc as friction-reducing additive in lubricating oils.

5. 2. 5. Microcrystalline cellulose:



N: Polymer degree

Synonyms :Cellulose gel, Avicel PH.
Chemical name : cellulose
Description : white or almost white, fine or granular powder.
Structural Formula : $(C_6H_{10}O_5)_n$
Solubility:practically insoluble in water, freely soluble in acetone, soluble in diethylene glycol, practically insoluble in ethanol and in methylene chloride. It dissolves in dilute Solutions of alkalis.
Viscosity : 45 mPa·s to 90 mPa·s for the apparentViscosity determined at 25°C.
PH : 5. 0 to 7. 5 for the supernatant liquid
Functional categories : Tablet & capsule lubricant
Melting point : 160°C
Boiling point : 667. 9°C
Density :1. 76gm/cm^3

MATERIALS AND METHODS

6. 1: MATERIALS:

6. 1. 1: MATERIALS USED IN THE STUDY:

Table no. 2: List of materials

Name of the chemical	Specification	Suppliers
Fenofibrate	USP	Dr. Reddy's lab - Hyderabad
PEG 200	USP	Lobachemiepvt. ltd - Mumbai
Crosspovidone	USP	Loba chemie private limited - Mumbai

Aerosil	USP	Luzenac - Italy
Magnesium stearate	USP	Sd fine chem. Limited -Mumbai
Talc	USP	Qualikems fine chem. private limited-India
Microcrystalline cellulose	USP	Lobachemie private limited - Mumbai

6. 2: METHODS:

6. 2. 1 PREFORMULATION STUDIES:

Table no. 4: Characterization of Fenofibrate

TEST	SPECIFICATIONS	RESULTS
Colour	White	White
Physical state	Solid	Conform
Appearance	Crystalline	Conform
Identification	UV- spectroscopy,DSC	Positive
Melting point	79-83°C	80°C
Solubility	Insoluble in water	0. 25mg/ml
λ_{max}	287nm	287nm

Solubility:

Fenofibrate was insoluble in water. solubility of Fenofibrate was determined by visible method. Water solubility was 0. 25mg/ml at room temperature. Soluble in acetone,benzene, chloroform, ether, ethanol (1mg/ml). Slightly soluble in methanol, ethyl acetate, acetonitrile, hexane. The Fenofibrate was taken and added into different solvents and solubility was determined.

Melting point:

Drug melting point was determined by using melting point apparatus. Drug melting point was compared with reference melting point value.

Identification of drug :

- **Uv visible spectroscopy:**

Specific amount of drug was added in methanol, λmax of Fenofibrate was determined by using U. V visible spectrophotometer. λmax of test drug was compared with reference. And that was 287nm.

- **Differential scanning calorimetry:**

DSC is a thermoanalytical technique in which the difference in the amount of heat required to increase the temperature of a sample and reference is measured as a function of temperature. Both the sample and reference are maintained at nearly the same temperature throughout the experiment. Generally, the temperature program for a DSC analysis is designed such that the sample holder temperature increases

linearly as a function of time. The reference sample should have a well-defined heat capacity over the range of temperatures to be scanned.

Preparation of standard graph of Fenofibrate:

Fenofibrate (5 to 25 µg/mL) concentrations were prepared in methanol and 6. 8 pH phosphate buffer solutions. The absorbances of above solutions were recorded at λ_{max} (287nm in 6. 8 pH phosphate buffer) using double beam UV-Visible spectrophotometer. Standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis).

Preparation of stock solution:

- 5mg of Fenofibrate drug was dissolved in 50ml of **methanol** in 100ml volumetric flask i. e. ,100µg/ml.
- Fenofibrate (5-30µg/ml) concentrations were prepared in methanol.
- The absorbances of above solutions were recorded at λ_{max} 287nm in 6. 8 pH phosphate buffer using double beam UV-Visible spectrophotometer.
- Standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis).

PREPARATION OF LIQUISOLID COMPACTS:

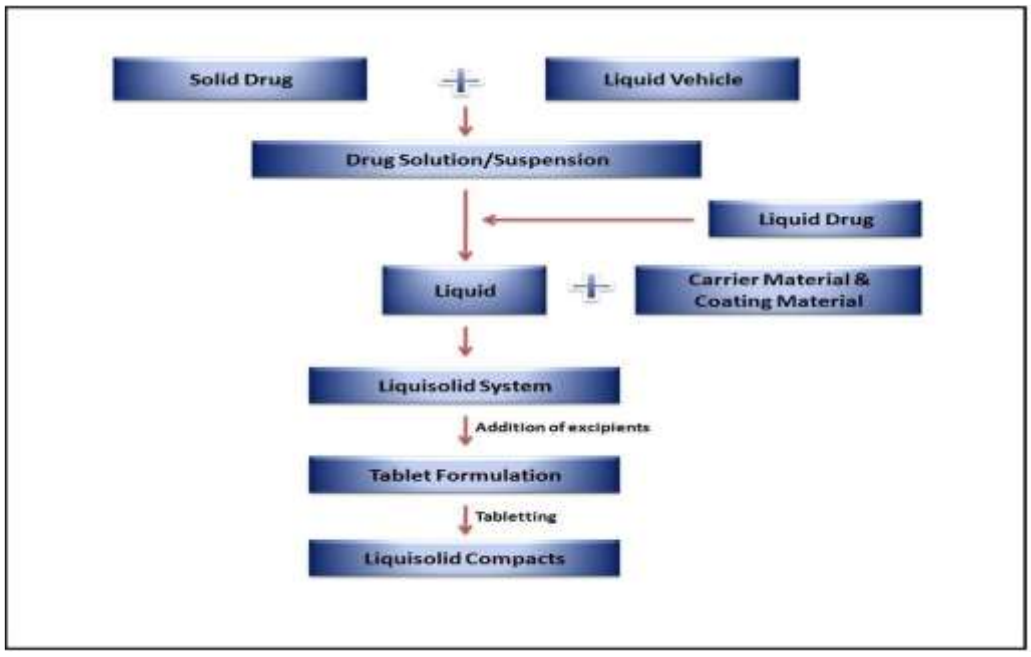


Figure no 5: Flow chart of the steps involved in the preparation of liquisolid compacts.

- The required components were weighed accurately.
- The drug was slightly heated and the non volatile solvent was added to this.
- This hot medication was added into carrier and coating material to be spread.
- This was continuously mixed in a mortar involves 3 steps as following below:

Step 1:

- This mixture was rotated for 1 rotation per second for 1 minute for complete mixing of liquid medication in powder.

Step 2:

- This mixture was spread over the mortar for 5 minutes so that drug get absorbed in the interior of

powder.

Step 3:

- Powder was scraped off.
- Disintegrant was added and left for 10-20 minutes.
- Other additives were added and then compressed directly into tablets.

FORMULATION OF FENOFIBRATE TABLET :

Table no. 5 : Formulation table for Fenofibrate

S. No.	Ingredients (w/w) in mg	F1	F2	F3	F4	F5	F6	F7	F8	*DCT
1	Fenofibrate	100	100	100	100	100	100	100	100	100
2	PEG 200	0. 1	0. 1	0. 1	0. 2	0. 3	0. 4	0. 2	0. 4	-
3	Aerosil	40	45	55	55	55	55	75	75	-
4	Crosspovidone	-	-	-	10	10	10	10	10	10
5	Talc	5	5	5	5	5	5	5	5	5
6	Magnesium stearate	5	5	5	5	5	5	5	5	5
7	Microcrystalline cellulose (Q. S)	220	220	220	220	220	220	220	220	220

***DCT**= Direct compressible tablet

Preformulation studies of tablets:

Angle of Repose (θ):

The frictional force in a loose powder can be measured by the angle of repose. Funnel method was used to measure the angle of repose of powder. The accurately weighed powders were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder (2. 0 cm above hard surface). The powders were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

$$\mathbf{Tan\theta = h/r}$$
$$\mathbf{\theta = Tan^{-1}(h/r)}$$

Where,

H = Height of the powder cone.

R = Radius of the powder cone

Table no. 6: correlation between angle of repose and flow properties of powder

Angle of repose	Type of flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk Density (ρ_b) :

Density is defined as weight per unit volume. It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume was called the bulk volume. From this the bulk density was calculated according to the formula mentioned below. It is expressed in gm/cm^3 and is given by

$$\rho_b = M/ V_b$$

Where,

M =mass of powder

V_b= bulk volume of the powder

Tapped Density (ρ_{tap}):

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in gm/ml and is given by

$$\rho_{tap} = M/V_t$$

Where,

M= mass of powder

V_t =tapped volume of the powder

Hausner's Ratio:

Hausner'sRatio is an ease of index of powder flow. It is calculated by using the following formula:

Hausner's Ratio = Tapped Density/ Bulk Density

Compressibility Index: The compressibility index of the power was determined by Carr's/ index. It is a measure of the flow property of a powder to be compressed. It is calculated by using the following formula:

$$\text{Carr's index (\%)} = \{(\rho_{tap} - \rho_b) \text{ X } 100\}/ \rho_{tap}$$

Table no. 7: Correlation between Carr's index values and flow properties of powders

Carr's Index	Type of flow
5-15	Excellent
15-18	Good
18-23	Fair to passable
23-35	Poor
35-38	Very poor
>40	Extremely poor

6. 3. 2 EVALUATION OF TABLETS:

1. Appearance
2. Colour
3. Taste
4. Size and shape
5. Thickness
6. Hardness
7. Friability
8. Weight variation
9. *Invitro* drug release - Content uniformity, Disintegration test,Dissolution test
10. Release kinectics
11. Accelerated stability studies

Appearance :

The tablet appearance is considered as one of the important factor in evaluation, based on the patient acceptance.

Colour :

The colour of the tablet should be uniform and not vary from lot to lot.

Taste :

It is an important criteria for consumers acceptance.

Size and shape :

The size and shape of the tablet is designed to allow rapid production and also to enable good consumer acceptance.

Thickness :

The tablet thickness is influenced by the amount of fill-material in the die-cavity, die-diameter and the compaction force applied. In general the tablet thickness is required to be within +or -5% of the prescribed value.

Measurement of tablet thickness:

- Micrometer
- Digital readout caliper.
- Sliding caliper scale method.

Hardness :

The hardness of the tablet is also termed as its crushing strength. The hardness of the tablet may be defined as the compressional force required to break the tablet when such force is applied. A tablet that gives a minimum test reading of about4kg/inch is considered to have appreciable strength.

Measurement of tablet hardness:

- Monsanto hardness tester.
- Pfizer hardness tester.
- Erweka hardness tester.

Friability :

Friability in addition to hardness gives the measurement of the tablets strength. The friability of a tablet may be defined as its resistance to shock and abrasion encountered during the process of the manufacture ,packing, transport. The tablets which are compressed conventionally, acceptable friability value is 0. 5to1% of their original weight.

Measurement of friability:

- Shipping test
- Roche friabilator.

Weight variation test (USP):

Take 20 tablet and weighed individually. Calculate average weight and compare the individual tablet weight to the average. The tablet pass the U. S. P. test if no more that 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Preparation of Buffers :

1. Preparation of 1. 2 pH HCl buffer:

- 8. 5ml of concentrated hydrochloric acid was diluted with distilled water and volume was adjusted to 1000ml.

2. Potassiumdihydrogen phosphate solution, 0. 2 M:

27. 218g of Potassium dihydrogen phosphate was dissolved in distilled water and adjusted to 1000 ml to give 0. 2M Potassium dihydrogen phosphate solution.

3. Sodium hydroxide solution, 0. 2 M:

8grams of sodium hydroxide was dissolved in distilled water and diluted to1000 ml with distilled water**.**

4. Phosphate buffer solution, pH 6. 8:

250ml of 0. 2M Potassium dihydrogen phosphate was placed in a 1000ml volumetric flask, 112ml of 0. 2M sodium hydroxide was added and then volume was adjusted with distilled water up to 1000 ml. pH was adjusted to 6. 8 with dilute NaOH**.**

In vitro drug release study:

Content uniformity :

Randomly select 30 tablets. 10 of these assayed individually. The Tablet pass the test if 9 of the 10 tablets must contain not less than 85% and not more than 115% of the labeled drug content and the 10th tablet may not contain less than 75% and more than 125% of the labeled content. If these conditions are not met, remaining 20 tablet assayed individually and none may fall out side of the 85 to 115% range.

Disintegration test (USP):

The U. S. P. device to test disintegration uses 6 glass tubes that are 3" long; open at the top and 10 mesh screen at the bottom end. To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid at 37 ± 20 C such that the tablet remain 2. 5 cm below the surface of liquid on their upward movement and not closer than 2. 5 cm from the bottom of the beaker in their downward movement. Move the basket containing the tablets up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. Floating of the tablets can be prevented by placing perforated plastic discs on each tablet. According to the test the tablet must disintegrate and all particles must pass through the 10 mesh screen in the time specified. If any residue remains, it must have a soft mass. Disintegration time: **5-30** minutes for uncoated tablets and 1-2 hours for coated tablets.

Dissolution test :

Dissolution apparatus types –

There are many types of dissolution apparatus which are classified as per **United States Pharmacopoeia, Indian Pharmacopoeia or British Pharmacopoeia.**

Types of Dissolution Apparatus as per USP (Official):

- Basket Type
- Paddle Type
- Reciprocating Cylinder
- Flow Through Cell
- Paddle Over Disc
- Rotating Cylinder
- Reciprocating Disc

Types of Dissolution Apparatus as per IP (Official):

- Paddle Type
- Basket Type

Types of Dissolution Apparatus as per BP (Official):

- Basket Type Apparatus
- Paddle Type Apparatus
- Flow Through Cell

Apparatus-1:

A single tablet is placed in a small wire mesh basket attached to the bottom of the shaft connected to a variable speed motor. The basket is immersed in a dissolution medium (as specified in monograph) contained in a 100ml flask. The flask is cylindrical with a hemispherical bottom. The flask is maintained at 37±0. 50C by a constant temperature bath. The motor is adjusted to turn at the specified speed and sample of the fluid are withdrawn at intervals to determine the amount of drug in solutions.

Apparatus-2:

It is same as apparatus-1, except the basket is replaced by a paddle. The dosage form is allowed to sink to the bottom of the flask before stirring. For dissolution test U. S. P. specifies the dissolution test medium and volume, type of apparatus to be used, rpm of the shaft, time limit of the test and assay procedure for. The test tolerance is expressed as a % of the labeled amount of drug dissolved in the time limit.

Table no. 8 :Dissolution test parameters

Dissolution parameters	Details
Dissolution apparatus	USP -Type II (paddle)
Medium	pH 6. 8 phosphate buffer
Volume	900 ml
Rotation speed	50 rpm
Temperature	37± 0. 5 ºC
Sample volume withdrawn	5ml
Time points	10,20,40,60,80, 100,120minutes
λ max	287 nm

Dissolution testing and Interpretation can be done in three stages:

Stage 1: Six tablets are tested and are acceptable if all of the tablets are not less than the monograph tolerance limit (Q) plus 5% if fail.
Stage 2: Another six tablets are tested. The tablets are acceptable Take 6 tablets, test individually, Avg. weight 12 tablets is greater or equal to but no one less than (Q-15) % If the average of the twelve is greater than or equal to Q and no unit is less than (Q-15) % if fail.
Stage 3: Another 12 tablets are tested. The tablets are acceptable if the average of all 24 tablets is greater than or equal to Q and if no more than 2 tablets are less than (Q-15) % if fail.

Release kinetics:
The analysis of drug release mechanism from a pharmaceutical dosage form is important but complicated process and is practically evident in the case of matrix systems. The order of drug release from FDDS was described by using zero order kinetics or first order kinetics. The mechanism of drug release from FDDS was studied by using Higuchi equation and the Peppa's-Korsemeyer equation.
Zero order release kinetics:
It defines a linear relationship between the fractions of drug released versus time.

$$Q=k_0t$$

Where,
Q = The fraction of drug released at time t
k_o = The zero order release rate constant.
A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.
First order release kinetics:
Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that the drug release from most of the slow release tablets could be described adequately by the first-order kinetics. The equation that describes first order kinetics is

$$\mathbf{logC= logC_0-k_t / 2.303}$$

Where,
C = The amount of drug dissolved at time t
C_o= The amount of drug dissolved at t=0
k_t = The first order rate constant.
A graph of log cumulative of log % drug remaining vs time yields a straight line. Will be linear if the release obeys the first order release kinetics.
Higuchi eqation:
It defines a linear dependence of the active fraction released per unit of surface (Q) and the square root of time

$$\mathbf{Q=K_2\sqrt{t}}$$

Where,

K2 = release rate constant.

A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependent.

Peppa's –korsemeyereqation(power law):

In order to define a model, which would represent a better fit for the formulation, dissolution data was further analysed by Peppa's-Korsemeyer equation (Power Law).

$$\mathbf{Mt/\ M\infty = Kt^n}$$

Where,

Mt = The amount of drug released at time t

M∞= The amount released at time ∞

Mt/M∞= The fraction of drug released at time t

K =The kinetic constant

n = The diffusion exponent

To characterize the mechanism for both solvent penetration and drug release n can be used as abstracted. A plot between log drug release upto 60% against log of time will be linear if the release obeys Peppa's-Korsemeyer equation and the slope of this plot represents "n" value. the kinetic data of the formulations were included.

Nature of release of the drug from the designed tablets was inferred based on the correlation coefficients obtained from the plots of the kinetic models. The data were processed for regression analysis using Ms-excel.

Accelerated stability studies:

The stability studies of selected tablet batches were carried out according to ICH guidelines 25 ± 2°C and 60±5% RH (or) 40±2°C and 75±5% RH conditions for three months. The effects of temperature and time on the physical characteristics of the tablet were evaluated for assessing the stability of the prepared formulations. The tablets were evaluated for their physicochemical parameters(such as hardness, thickness, friability,drug content, and *invitro*dissolution) after 1 month, 2 month, and 3 months.

RESULTS

7. 1: PREFORMULATION STUDIES:

Determination of Fenofibrate solubility:

Table no. 9 : Solubility data of Fenofibrate in various liquid vehicles.

Sl no	Name of liquid	Drug dissolved (mg/ml)
1	Propylene glycol	2. 4

2	PEG 200	1. 7
3	Distilled water	0. 08
4	0. 1N Hcl	0. 9

Melting point:

The melting point of Finofibrate was found to be 81°C. The obtained melting point of Finofibrate matched with reference(Reference M. P is 79-83°C).

The standard graph of Fenofibrate:

Table no. 10: Standard graph ofFenofibratein pH 6. 8 phosphate buffer

Concentration(µg/ml)	Absorbance
	pH 6. 8 phosphate buffer
0	0
5	0. 266
10	0. 435
15	0. 629
20	0. 831
25	1. 060
30	1. 219

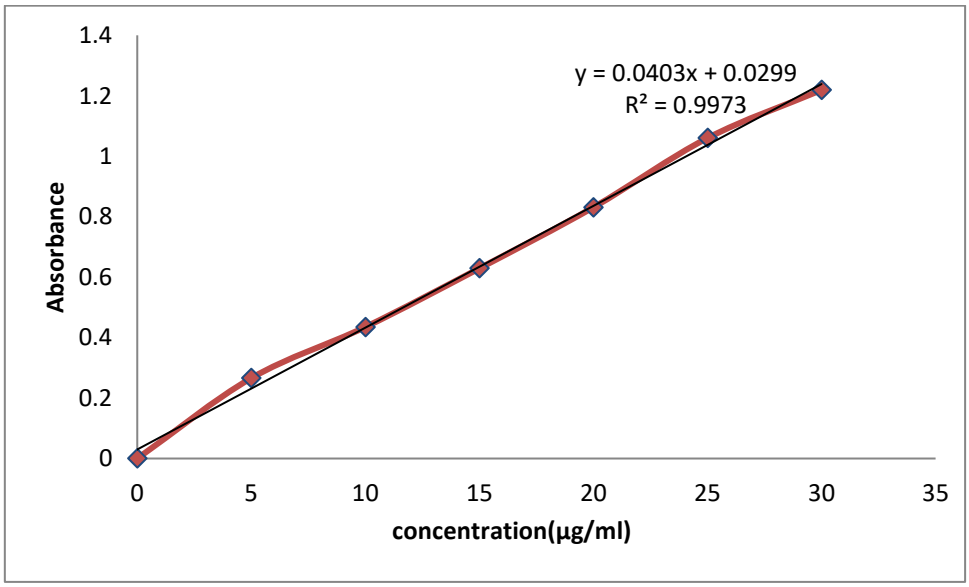


Fig 6-:Standard graph of Fenofibrate in pH 6. 8 phosphate buffer

Precompression parameters:

Table no. 11: Pre-compression parameters of powder blends of Fenofibrate

Formulation code	Bulk density	Tapped density	Angle of repose	Compressability index	Hausner's ratio
F1	0. 31	0. 38	28. 7	18. 4	1. 22
F2	0. 36	0. 42	26. 5	14. 28	1. 16
F3	0. 35	0. 42	25. 7	16. 66	1. 2
F4	0. 39	0. 45	28. 9	13. 33	1. 15
F5	0. 45	0. 52	26. 7	13. 46	1. 15
F6	0. 49	0. 58	28. 6	18. 36	1. 18
F7	0. 38	0. 45	28. 9	15. 55	1. 18
F8	0. 44	0. 55	28. 3	20. 0	1. 25

7.EVALUATION OF TABLETS :

Post compression parameters:

Table no. 12: Post compression parameters of Fenofibrate

Formulation code	***Weight variation**	****Hardness (kg/cm^2)**	****Thickness(mm)**	****Friability(%)**	****Drug content(%)**	****Content uniformity (%)**
F1	355±0. 8	3. 9	4. 1±0. 2	0. 08	98	97
F2	359±1. 1	4. 1	4. 1±0. 1	0. 19	99	97
F3	361±1. 1	3. 8	3. 9±0. 2	0. 09	99	97
F4	386±0. 8	3. 9	4. 0±0. 2	0. 09	99	98
F5	385±1. 2	4. 2	5. 4±0. 3	0. 10	98	96
F6	389±0. 8	3. 9	5. 1±0. 2	0. 11	100	96
F7	416±0. 8	4. 5	4. 9±0. 3	0. 11	100	98
F8	419±0. 9	4. 1	5. 3±0. 1	0. 20	99	98

Data represented Mean±S. D (*n=20; **n=5)

***In-vitro* dissolution studies:**

Table no. 13: % drug release profile of formulations F1-F8

Time (Min)	Formulation code							
	F1	F2	F3	F4	F5	F6	F7	F8
10	14. 16	10. 497	28. 69	13. 365	16. 449	9. 75	24. 673	12. 729
20	17. 847	17. 53	32. 277	27. 9	33. 573	17. 94	28. 026	20. 577
40	20. 997	21. 027	39. 05	43. 515	36. 549	32. 082	51. 475	33. 573
60	22. 94	29. 85	53. 161	44. 64	49. 95	59. 625	71. 52	43. 995
80	27. 279	49. 227	63. 899	55. 8	58. 881	66. 327	73. 804	50. 694
100	28. 518	49. 227	68. 075	65. 88	64. 836	70. 794	88. 29	58. 137

120	-	-	-	-	-	76. 74	91. 665	67. 815
150	-	-	-	-	-	78. 96	94. 653	80. 46
180	-	-	-	-	-	85. 68	98. 259	92. 38

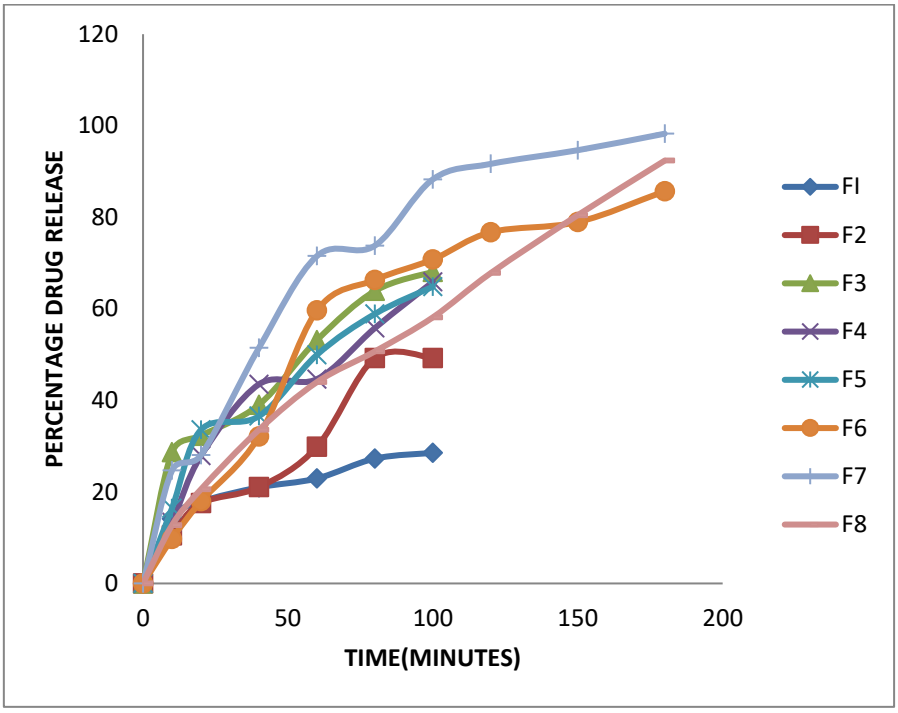


Fig-7 :*In-vitro* % drug release of Fenofibrate tablet

Disintegration of Fenofibrate:

Table no. 14: Table of disintegration

Formulation code	Time(min)
F1	4
F2	2
F3	1
F4	1
F5	2
F6	2
F7	1
F8	1

Kinetic analysis of dissolution data:

Table no. 15: Release kinetics of dissolution data of Fenofibrate

Formulation code	Zero order		First order		Higuchi		Peppas-korsemeyer	
	K	R^2	K	R^2	K	R^2	n	R^2

F1	0. 2287	0. 7762	-0. 0008	0. 968	2. 6942	0. 9514	0. 2992	0. 9843
F2	0. 4891	0. 9518	-0. 0055	0. 9173	5. 1179	0. 9208	0. 6722	0. 9524
F3	0. 4719	0. 9807	-0. 0042	0. 9769	6. 6294	0. 9797	0. 3976	0. 9325
F4	0. 6023	0. 9233	-0. 004	0. 9636	6. 5963	0. 978	0. 6658	0. 9563
F5	0. 593	0. 9129	-0. 004	0. 975	6. 5456	0. 9826	0. 5503	0. 9462
F6	0. 4857	0. 8732	-0. 0047	0. 965	7. 2879	0. 9516	0. 7826	0. 9563
F7	0. 5195	0. 8497	-0. 0094	0. 9824	7. 9735	0. 9688	0. 5395	0. 9569
F8	0. 4827	0. 9784	-0. 0055	0. 9713	6. 9418	0. 9793	0. 6786	0. 9977

7. 3: Compatability studies of drug and polymer interaction (DSC STUDY):

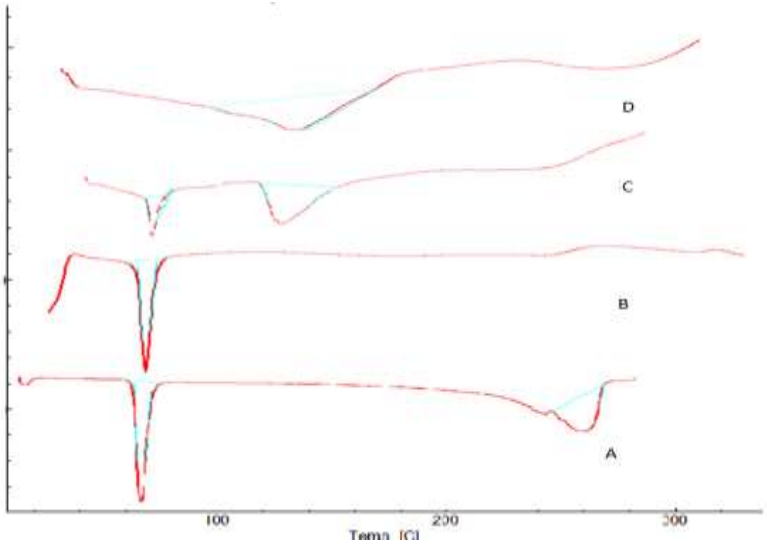


Fig no.8:DSC of A.Fenofibrate(pure drug) B.Physical mixture C.formulation containing drug and other excipients. D.Blank formulation

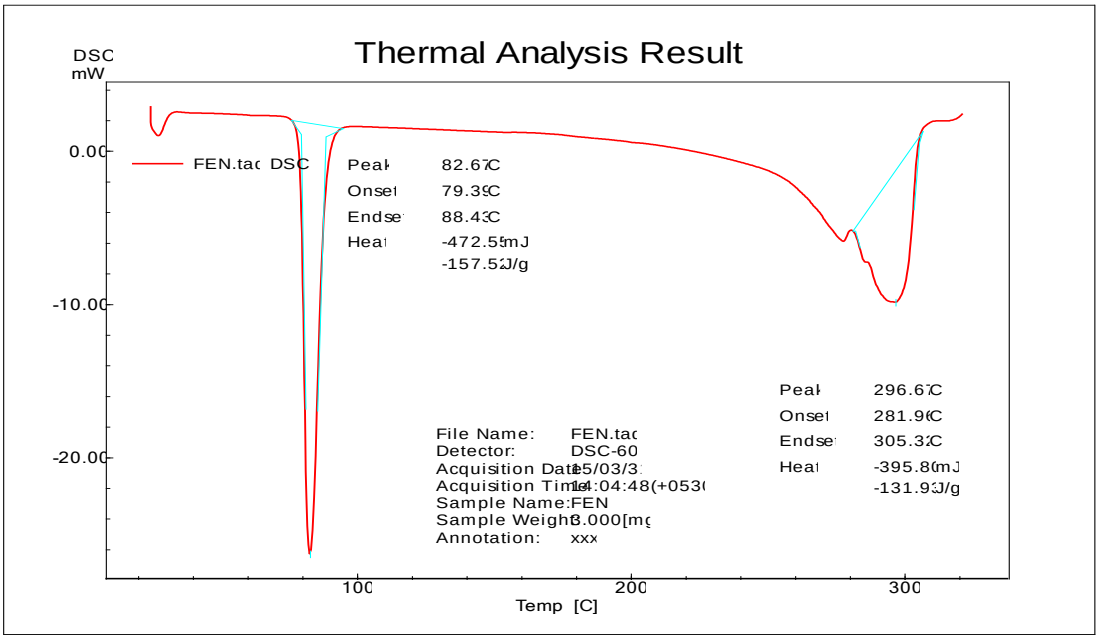


Fig no.9: DSC of Fenofibrate

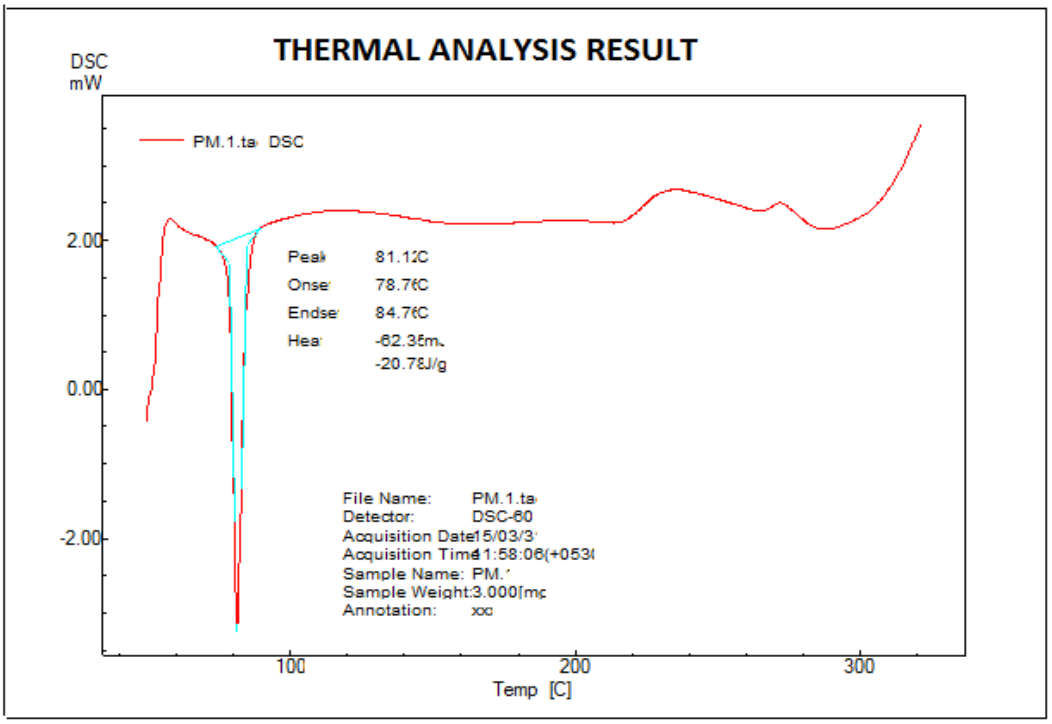


Fig no.10: DSC of physical mixture

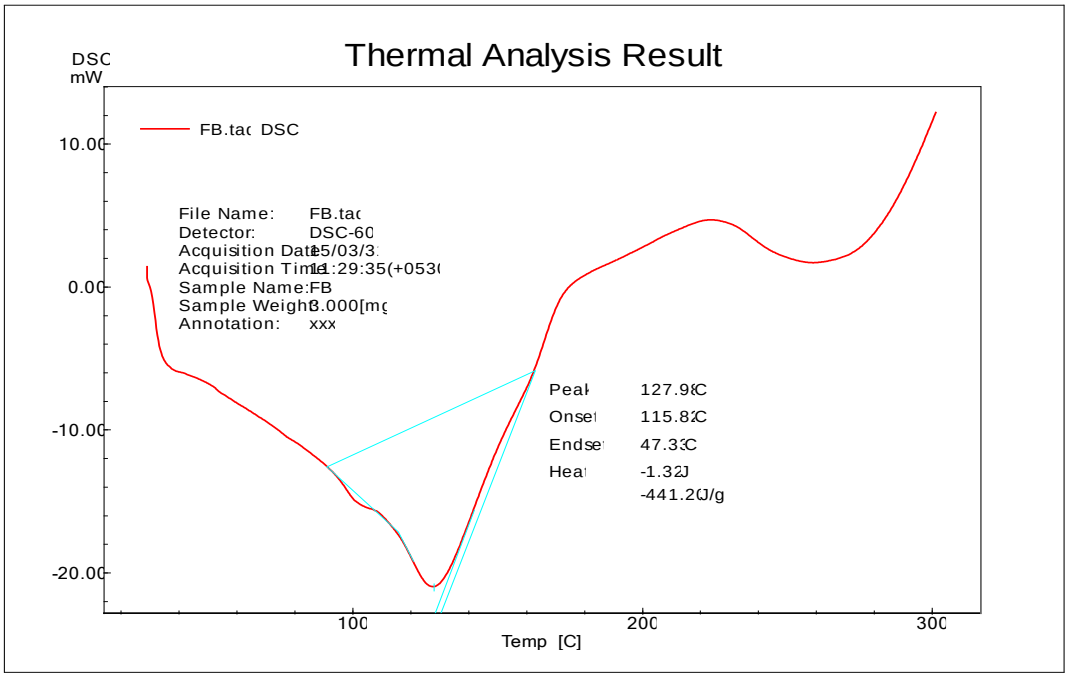


Fig no:11 - DSC of blank formulation

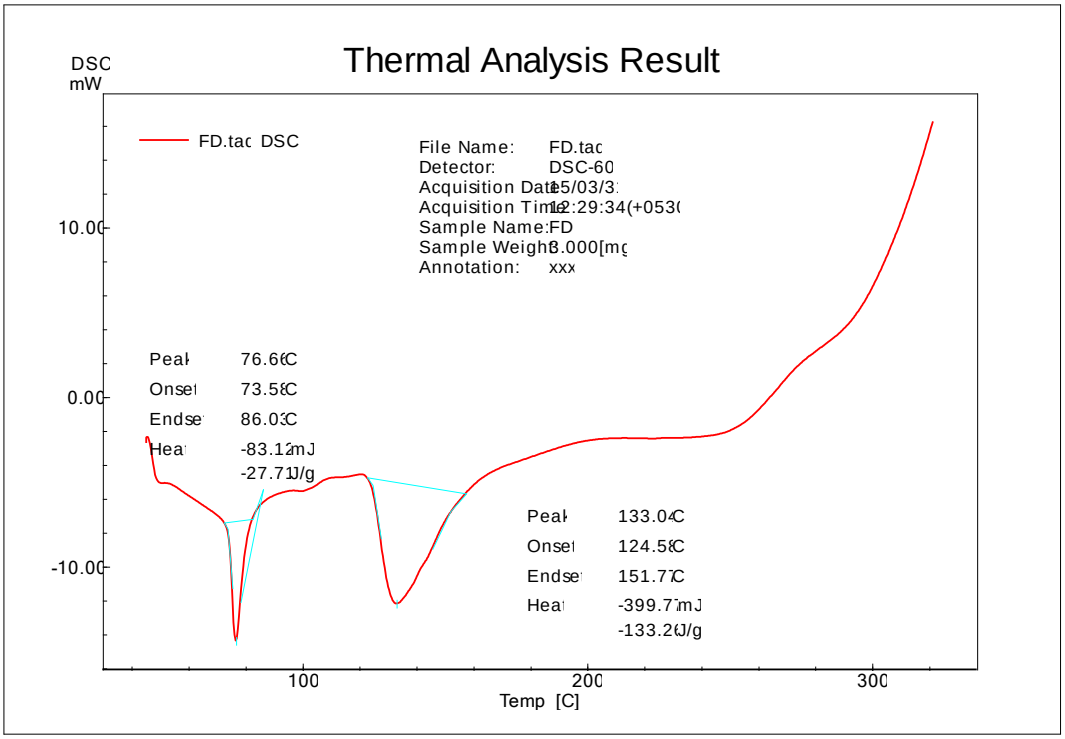


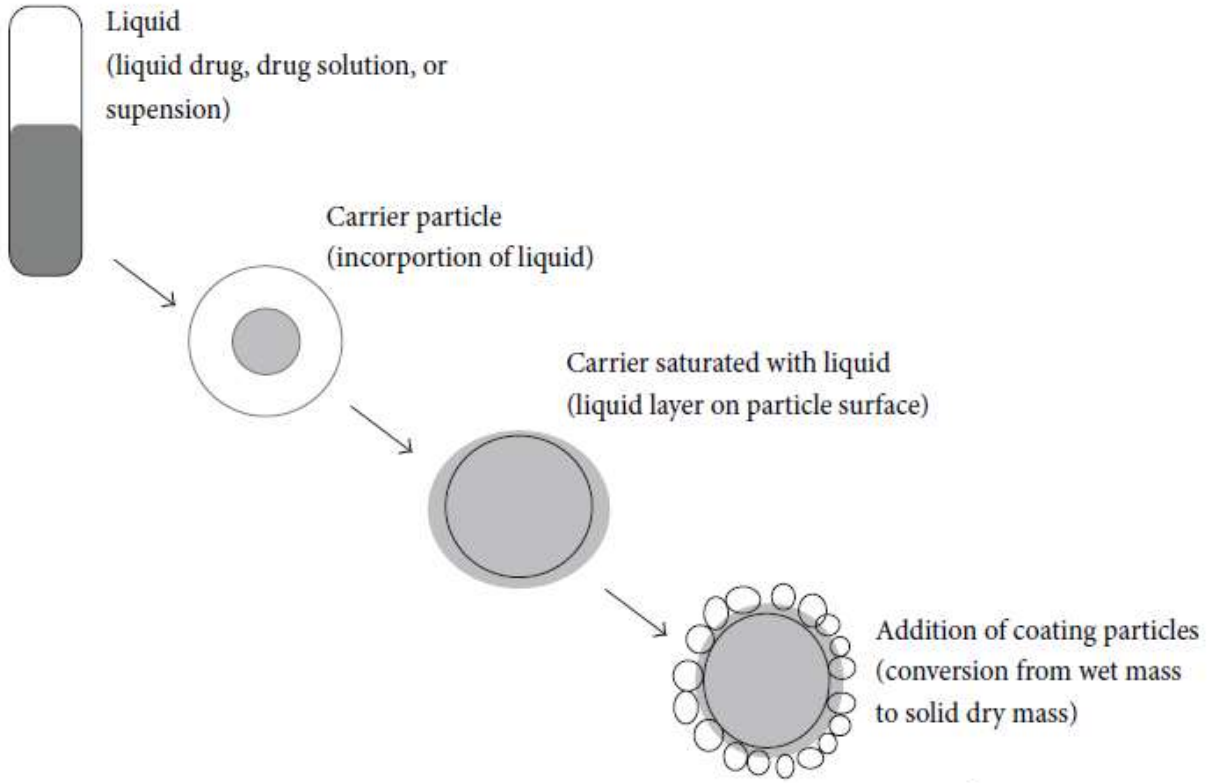
Fig no: 12 - Formulation containing drug with other excipients

7. 4 : ACCELERATED STABILITY STUDIES FOR OPTIMIZED FORMULATION:

Table no. 16: Stability study of optimized formulation(F7) at 40˚c / 75%RH

Condition	40˚c / 75%RH		
Time	1 month	2 months	3 months
Hardness(kg/cm^2)	4. 1	3. 9	3. 8
Thickness (mm)	4. 9±0. 3	4. 7±0. 3	4. 7±0. 3
Friability(%)	0. 11	0. 9	0. 9
Drug content	100	98	98

DISCUSSION



Schematic representation of liquisolid systems.

For the preparation of liquisolid compacts of Fenofibrate, propylene glycol as non-volatile solvent chosen for dissolving the drug (Fenofibrate 100 mg). MCC as carrier and colloidal silica(aerosol) as the coating material was selected for the preparation of liquisolid compacts. Various ratios of carrier and coating materials were selected. According to solubility of Fenofibrate desired quantities of drug and Propylene glycol were accurately calculated. The weighed quantity of drug dispersed/mixed with non-volatile vehicle. Selected amounts (W) of the resultant liquid medication were incorporated into calculated quantities of carrier contained in a mortar. The mixing procedure was conducted in three stages. During the first stage, the system was blended at an approximate mixing rate of one rotation/sec for approximately one minute in order to evenly distribute the liquid medication into the powder. In the second mixing stage,

calculated quantities of coating material was added to the system and blended for 2 min. The liquid powder admixture was evenly spread as a uniform layer on the surfaces of the mortar and left standing for approximately 5min to allow the drug solution to be absorbed in interior of the powder particles. In the third stage, the powder was scraped off from mortar surfaces by means of aluminium spatula, and then the powder was compressed as tablets.

The composition of Fenofibrate liquisolid formulations is given in table no. 5.

The solubility of Fenofibrate in Propylene glycol, PEG-200, 0. 1 N HCl and distilled water, was given in the table no. 9. The results shows that the Fenofibrate has highest solubility in PEG200 then followed by propylene glycol, 0. 1 N HCl and finally in distilled water.

Powder flow is a complicated matter and is influenced by so many interrelated factors includes physical, mechanical as well as environmental factors. Powder flowability is crucial in the industrial production of tablet dosage forms, as a uniform powder stream through hopper confirms uniformity of both tablet weight and drug content. Therefore, The powder mixtures of different formulations were evaluated for angle of repose, bulk density (apparent and tapped), compressibility index and their values were shown in Table 11. The apparent bulk density and tapped density values ranged from 0. 31 to 0. 44 and 0. 40 to 0. 55 respectively. The results of angle of repose and compressibility index (%) ranged from25to 28. 9 and 14-19 respectively. The results of angle of repose (<30) and compressibility index (<20) indicates fair to passable flow properties of the powder mixture. Finally, formulations were proven to be acceptably flowing according to either the angle of repose, Carr's index and Hausner's ratio.

Post-compression Parameters:

The physical properties of Fenofibrate aregiven in table no. 12. In weight variation test, the pharmacopoeial limit for the tablets of not more than7. 5% of the average weight. The average percentage deviation of all tablet formulations was found to be within the above mentioned limit and hence all formulations passed the uniformity of weight as per official requirements (India Pharmacopoeia, 1996). The hardness of the tablets was found to be in the range of 3. 9±0. 42 to 4. 6±0. 52 kg/cm2. Another measure of tablets strength is friability. Conventional compressed tablets that loss less than1% of their weight are generally considered acceptable. The percentage friability for all formulations was below 1%, indicating that the friability is within the prescribed limits. The tablets were found to contain 96. 0±1. 32 98. 0±1. 06 % of the labeled amount indicating uniformity of drug content.

To investigate the effect of vehicle type on the rate of Fenofibrate dissolution from liquisolid compacts, several formulations were prepared with different % W/W of polyethylene glycol 200 containing 100 mg of Fenofibrate in liquid. The dissolution profiles of these liquisolid compacts are shown in figure no. 7. It can be seen from liquid medicationie. PEG 200used in liquid solid compacts, are able to increase the dissolution rate of Fenofibrate from liquisolid compacts in comparison with the conventional tablet According to the results it revealed liquisolid compacts containing PEG200 produced higher dissolution rates compared to other liquisolid compacts containing Tween 80 of the same concentration. Increasing the concentration of liquid medication the dissolution rate of Fenofibrate was increased. The percent of Fenofibrate released from liquisolid compacts containing varying amounts of carrier and coating materials (from F1 to F8) was found in 10 min and that was given in table no. 13 . The optimized formulation F7 showed the 90.34 ± 0.58 drug release in 100min. Thus the formulation F7 was considered better among other formulations to produce fast release of Fenofibrate. The percentage drug released after 15min (Q)and the time required for the release of 50% of the drug (t)were determined. From the dissolution profiles, it can be seen that all iquisolid formulations significantly improved drug dissolution compared to

conventional tablets. Due to significantly increased wetting properties and surface area of the drug particles available for dissolution, liquisolid tablets were expected to enhance drug release characteristics. It was found that the % drug release is always (with both R-values and all liquid vehicles used) higher from liquisolid tablets with lower drug concentration. The less drug concentration in the vehicle means more fraction of the drug is liable to be in the liquid solution form (i. e. , molecularly dispersed), which is a prerequisite for fast drug dissolution. Moreover, the more vehicle available means an even distribution of the vehicle over the remaining un dissolved drug particles that will help in good wetting of the drug during the dissolution step.

Differential Scanning Calorimetry (DSC).

DSC was used for the investigation of any interaction between the drug and its excipients. Fenofibrate showed an endothermic peak around its melting point. Figure no. 8,9,10,11 and 12 showed the thermogram for Fenofibrate and liquisolid mixture. The thermogram showed a sharp endothermic peak at 81. 12ºC corresponding to its melting point. For liquisolid mixture, the endothermic peak of the drug completely disappeared indicating that the drug is completely solubilized and molecularly dispersed with excipients within liquisolid system. This would explain the improved drug dissolution from liquisolid compared to conventional preparations. DSC thermograms confirmed the above findings .

Kinetic analysis of dissolution data:

To evaluate the release profile of Fenofibrate ,drug release was subjected to various kinetic models such as zero order, first order, higuchi and korsemeyer-peppa's. Among all the formulations F1,F4,F5,F6,F7 follows first order release as the concentration varies and the remaining formulations such as F2,F3 and F8 follows zero order release. All the formulations follows Higuchi model.

SUMMARY AND CONCLUSIONS

Fenofibrate is one of the widely prescribed anti-hyper lipidemic agent which is used to lowering the cholesterol levels in the body.

In the present study, Fenofibrate was formulated into various formulations by using liquislid compact technique. According to solubility of Fenofibrate, desired quantities of drug and Propylene glycol were accurately calculated. The weighed quantity of drug dispersed/mixed with non-volatile vehicle. Selected amounts (W) of the resultant liquid medication were incorporated into calculated quantities of carrier contained in a mortar. The mixing procedure was conducted in three stages. During the first stage, the system was blended at an approximate mixing rate of one rotation/sec for approximately one minute in order to evenly distribute the liquid medication into the powder. In the second mixing stage, calculated quantities of coating material was added to the system and blended for 2 min. The liquid powder admixture was evenly spread as a uniform layer on the surfaces of the mortar and left standing for approximately 5min to allow the drug solution to be absorbed in interior of the powder particles. In the third stage, the powder was scraped off from mortar surfaces by means of aluminium spatula, and then the powder was compressed into tablets.

The average percentage deviation of all tablet formulations was found to be within the above mentioned limit and hence all formulations passed the uniformity of weight as per official requirements (India Pharmacopoeia, 1996). The hardness of the tablets was found to be in the range of 3.9±0.42 to 4.6±0.52 kg/cm^2.

It can be seen from liquid medicationie. PEG200 used in liquid solid compacts, are able to increase the dissolution rate of Fenofibrate from liquisolid compacts in comparison with the conventional tablet

According to the results it revealed liquisolid compacts containing PEG200 produced higher dissolution rates compared to other liquisolid compacts containing Tween 80 of the same concentration.
Similarly the drug release was decreased in F8 compared to F7. Based on the *in-vitro* dissolution studies the formulation F7 was observed as optimal formulation. The optimized formulation F7 showed the 90.34 ± 0.58 drug release in 100min. Thus the formulation F7 was considered better among all formulations to produce fast release of Fenofibrate.
DSC has shown a significant decrease in the melting point in the optimal formulation. The thermogram showed a sharp endothermic peak at 81.12ºC corresponding to its melting point. For liquisolid mixture, the endothermic peak of the drug completely disappeared indicating that the drug is completely solubilized and molecularly dispersed with excipients within liquisolid system. This would explain the improved drug dissolution from liquisolid compared to conventional preparations. DSC thermograms confirmed the above findings .

CONCUSION:

It can be concluded that the non-volatile vehicle plays a major role in design of liquisolid compact tablets in the dissolution enhancement Among all the formulations F1,F4,F5,F6,F7 follows first order release as the concentration varies and the remaining formulations such as F2,F3 and F8 follows zero order release. All the formulations follows Higuchi model. The study reveals that the release of drug was found to be 90.34±0.58 *in vitro* drug release within 100minutes and thus the formulation F7 was considered better among other formulations to produce fast release of Fenofibrate.

SCOPE FOR FURTHER WORK

- The present investigation was done by using liquisolid compact technique. The *in-vitro* studies can be further extended to correlate with *in-vivo* studies.
- The present study can be extended to further improvement of the drug release profile by using other carrier and coating materials.
- Controlled and drug delivery can also be achieved by using liquisolid compact technique by using various polymers.
- Huge number of Bio-Pharmaceutical classification class II drugs can be formulated into liquisolid systems.
- Rapid release liquisolid tablets (or) capsules exhibit enhanced *in vitro* & *in vivo* drug release compared to their commercial products.

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