FORMULATION AND EVALUATION OF LOPERAMIDE LIQUISOLID COMPACTS

Dissertation work submitted to The Tamilnadu Dr. M.G.R Medical University, Chennai in partial fulfilment for the award of degree of

MASTER OF PHARMACY

IN

Pharmaceutics

Submitted by

DIBU.S.BABU

Reg no:261510751

Under the guidance of

Institutional Guide:

Mr BARISH MPHARM,Ph.D,FICS,FAGE

Assistant Professor

Department of Pharmaceutics,

RVS College of Pharmaceutica l Sciences,

Sulur, Coimbatore – 641 402

Industrial Guide:

Dr.Jiji chandran

General Manager

Research& Development

Chetan Pharmaceuticals

Mavelikara,Kerala

May – 2017

DEPARTMENT OF PHARMACEUTICS,

RVS COLLEGE OF PHARMACEUTICAL SCIENCES,

SULUR, COIMBATORE - 641402,

TAMIL NADU

Certificate

This is to certify that the dissertation work entitled " Formulation and evaluation of loperamide liquisolid compacts**"** is a bonafide work of **Mr. Dibu.S.Babu** carried out in **Chethan pharmaceuticals pvt ltd,Mavelikara,Kerala** under my guidance and supervision of **Dr. Jiji Chandran.c,General Manager,Chetan Pharmaceuticals,Mavelikara,**in partial fulfilment of the award of degree of Master of Pharmacy in **Pharmaceutics.**

Dr Barish M.Pharm,Ph.D.FICS,FAGE
Assistant professor,
Department of Pharmaceutics,
RVS College of Pharmaceutical Sciences
Sulur, Coimbatore – 641 402

Date:

Place: Sulur

Certificate

This is to certify that the dissertation work entitled **Formulation and evaluation of Loperamide liquisolid compacts "** is a bonafide work of **Mr.Dibu.S.babu** carried out in **Chethan pharmaceuticals pvt ltd,mavelikara, Kerala** under the supervision of **Dr. Jiji chandran.c,** General Manager,Chetan pharmaceuticals, Mavelikkara and the institutional guidance of **Dr. Barish, M.Pharm,PhD,FICS,FAGE** Assistant Professor, Department of Pharmaceutics, in partial fulfilment of the award of degree of Master of Pharmacy in **Pharmaceutics.**

Dr. R. Venkatanarayanan, M.Pharm., Ph.D.,
Principal
RVS College of Pharmaceutical Sciences
Sulur

Date:

Place: Sulur

Evaluation Certificate

Dissertation title	**:**	**Formulation and evaluation of loperamide liquisolid compacts**
Name of the Candidate	**:**	Mr Dibu.S.Babu
Course of Study	**:**	Master of Pharmacy in Pharmaceutics
Institution Name	**:**	RVS College of Pharmaceutical Sciences, Sulur, Coimbatore

INTERNAL EXAMINER **EXTERNALEXAMINER**

Date: **Date:**

Place: Sulur **Place:** Sulur

ACKNOWLEDGEMENT

The secret of success is undaunted ardour, motivation, dedication, confidence on self and above all the blessings of God. I bow in reverence to the Almighty for bestowing upon me all this kindness that has helped me throughout the journey of my life. Success is an outcome of collaborated efforts aimed at achieving different goals. I hereby take this opportunity to acknowledge all those who have helped me in the completion of this dissertation work.

First and foremost I thank to my **God** for my successful completion of this work.

I sincerely acknowledge my deep sense of gratitude and hearty thanks to **Mr. manavalan, M.Pharm., PhD.,** Professor and HOD, Department of Pharmaceutics, RVS College of Pharmaceutical Sciences, Sulur, Coimbatore, for his valuable guidance encouragement and continued support throughout the course of this work.

I express my sincere thanks to Dr**. Jiji chandran.c,** General Manager,Chethan Pharmaceuticals for providing the facilities to carryout my project work in this esteemed organization.

I am highly indebted to **Dr. R. Venkatanarayanan**, **M.Pharm.,Ph.D.,** Principal, RVS College of Pharmaceutical Sciences, Sulur, Coimbatore, for providing necessary laboratory facilities, encouragement and continued support throughout the course of this work.

With great pleasure I am thankful to **Dr Barish Mpharm Ph.D,FICS,FAGE** Professor of Pharmaceutical Analysis, R.V.S. College of Pharmaceutical Sciences,

Sulur, Coimbatore, for their valuable suggestions about advance bio analytical tools, advises and stimulating criticism.

I express my thanks to my **friends**for their help and moral support in the successful completion of this project work.

A dictionary can never define such a great moral that can be felt but can never be described.

Last I thanks with my core of heart to **"MY BELOVEDPARENTS"** my father and mother who gave me constant support and constructive, suggestion, incessant encouragement and positive approach, without which report would not have taken shape.

DIBU.S.BABU

LIST OF SYMBOLS AND ABBREVIATIONS USED

Abbreviation	Full form
API	Active Pharmaceutical Ingredient
DDS	Drug delivery system
HCl	Hydrochloric acid
SSG	Sodium starch glycolate
PG	Propylene Glycol
MCC	Micro crystalline cellulose
Cm	Centimetre
Conc.	Concentration
°C	Degree Celsius
e.g.	Example
FTIR	Fourier Transform Infrared Spectroscopy
Gr	Gram
An	Absorption number
Dn	Dissolution number
LS	Liquisolid system
Kg	Kilogram
Hrs	Hours
IP	Indian Pharmacopoeia
L_f	Loading factor
LSC	Liquisolid compressibility test
L	Litre
λ max	Maximum absorbance
Min	Minutes
µg/ml	Microgram per milliliter
µl	Microlitre
N	Normal
mm	Millimeter
nm	Nanometer

BCS	Biopharmaceutical Classification System
pH	Negative logarithm of hydrogen ion concentration
%	Percentage
Ph.Eur	European Pharmacopoeia
r^2	Correlation factor
RH	Relative humidity
rpm	Revolutions per minute
S.D	Standard deviation
ADRs	Adverse drug reactions
USP	United states Pharmacopoeia
UV	Ultra violet
Wt	Weight
HR	Hausner's ratio
CI	Compressibility index

ABSTRACT

Liquisolid technique is a novel technique. It is used to improve the dissolution rate of the poorly water soluble drugs like loperamide. The liquisolid compacts were prepared by using carrier, coating material & liquid medication. Liquisolid compacts refer to the formulations that are formed by conversion of liquid drugs, drug suspension or solution in non-volatile solvents into dry, non-adherent, free flowing and compressible powder mixture. The crystallanity of the newly formulated drug and the interaction between excipients was examined by X-ray powder diffraction (XRD) and Fourier-transform infrared spectroscopy (FTIR). finally the increased dissolution rate of poorly water soluble drug. Loperamide is a Piperidine derivative, it is used in treatment of Anti diarrheal agent.

Keywords: loperamide, liquisolid compacts, X-RD, FT-IR, dissolution profile.

LIST OF CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

CHETHAN PHARMACEUTICALS PVT.LTD.

Phone: 0469 – 26027872, 26027871
Fax:91-46926027891
E-mail:info@chethanpharma.com

INDUSTRIAL ESTATE, KALLIMEL PO, MAVELIKARA, KERALA -690 510

CERTIFICATE

This is to certify that this dissertation entitled "FORMULATION AND EVALUATION OF LOPERAMIDE LIQUISOLID COMPACTS" submitted by Mr.DibuS Babu to the TamilNadu Dr MGR Medical University, Chennai towards partial fulfillment of the requirements of Master In Pharmacy Pharmaceutics is the bonafide work carried out in Chethan Pharmaceuticals Mavelikara under my supervision and guidance.

Ifound him Honest, Sincere and Hard Working. I wish him all success in his future career.

Certified by:

Dr.JijiChandranC.M.Pharm Ph.D.
General Manager,
Research & Development,
Chethan Pharmaceuticals,
Mavelikara, Kerala.

INTRODUCTION

1. DRUG DELIVERY SYSTEM

Dosage forms are also referred to as "Drug Delivery Systems" or "Finished Drug Products". A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance into the body and improves its efficacy and safety by controlling the rate, time, and site of release of drugs in the body. The goal of any drug delivery system is to provide a therapeutic amount of drug in the proper site in the body to achieve promptly and then to maintain the desired drug concentration. That is, the drug delivery system should deliver drug at a rate dedicated by the needs of the body over a specified period of treatment. Oral route of drug administration is most appealing route for delivery of drugs for various dosage forms. The tablet is one of the most preferred dosage forms, because of its ease of administration, accurate dosing and stability as compared to oral liquid dosage forms.

Tablets may be defined as solid unit pharmaceutical dosage forms containing drug substance with or without suitable excipients and prepared by either compression or molding methods (Aulton M.*et al.*, 2002).

The first step in the development of dosage form is preformulation, which can be defined as investigation of physiochemical properties of drug substances alone and when combined with excipients. The main objective of preformulation studies, is to develop stable and bioavailable dosage form and study of factors affecting such as stability, bioavailability and to optimize so as to formulate the best dosage form. Here, optimization of formulation means finding the best possible composition (Ansel H.*et al.*, 2004). Compressed tablets are formed by applying pressure, for which compression machines (tablet presses) are used and they are made from powdered crystalline or

granular material, alone or in combination with binder, disintegrants, release polymers, lubricants and diluents and in some cases with colorant.

1.1 Tablets

Tablets may be defined as the solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or moulding methods. They have been in wide spread use since the latter part of the 19th century and their popularity continues. The term compressed tablet is believed to have been first used by "JOHN WYETH". Tablets remain popular as a dosage form because of the advantages afforded both to the manufacturer and the patient (Banker GS.*et al.*, 2002).

1.1.1 Properties of tablets

The attributes of an acceptable tablet are as follows:

- The tablet must be sufficiently strong and resistant to shock, abrasion, should withstand handling during manufacturing, packing, shipping, and use. Hardness and friability tests measure this property.
- Tablet must be uniform in weight and in drug content of the individual tablet. This is measured by the weight variation and content uniformity tests.
- The drug content of the tablet must be bioavailable. This property is measured by the dissolution test. Accurate bioavailability can be obtained from the drug levels in the blood after its administration.
- Tablets must be elegant in appearance, characteristic shape, color and other markings necessary to identify the product.
- Tablets must retain all these functional attributes which include drug stability and efficacy (Herbert A.*et al.*, 2003).

1.1.2 Advantages of Tablets

- They are unit dosage forms, so they offer greater capabilities of all oral dosage forms for the greatest dose precision and the least content variability.
- They are easy to administer.
- Large scale manufacturing is feasible in comparison to other dosage forms. Therefore economy can be achieved.
- Accuracy of dose is maintained since tablet is a solid unit dosage form.
- Longer expiry period and minimum microbial spillage owing to lower moisture content.
- As tablet is not a sterile dosage form, stringent environmental conditions are not required in the manufacturing department.
- Ease of packaging (Blister or Strip) and ease of handling over liquid dosage forms.
- In comparison to capsules, tablets are more tamper proof.

1.1.3 Disadvantages of tablets:

- Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low density character.
- Drugs with poor wetting, slow dissolution properties, intermediate to large dosages, and optimum absorption in the gastrointestinal tract or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet that will still provide adequate bioavailability.
- Bitter tasting drugs, drugs with objectionable odour or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation or a special type of coating which may increase the cost of finished product.
- Some drugs may be unsuitable for administration by oral route.
- Difficult to swallow for kids, terminally ill and geriatric patients.

1.2 Types of tablets

Tablets are classified as follows:

1.2.1 According to the drug release rate from the tablet.

1.2.2 According to the method of manufacturing.

1.2.3 According to the route of administration or function.

1.2.1.2 According to the drug release rate from the tablet (USP classification)

(a) Immediate release or conventional tablets: The tablet is intended to be released rapidly after administration or the tablet is dissolved and administered as a solution. It is the most common type and it includes.

- Disintegrating tablet
- Chewable tablet
- Sublingual tablet
- Buccal tablet
- Effervescent tablet

(b) Modified release tablets: They have release features based on time, course or location. They must be swallowed intact.

- Delayed release tablets – Drug release is delayed due to physiological conditions.
- Extended release tablet – Allows the reduction in dosing frequency.

1.2.1.3 According to the method of manufacturing:

(a) Compressed tablet: It is obtained by compressing uniform volume of particles using "Tablet compression machine". It is used for large scale production. e.g. paracetamol tablet.

(b) Moulded tablet: Moulding means shaping, hardening of semisolid mixture of drug and excipients. It is obtained by "tablet mould". It is restricted to small dose tablet and small scale production. e.g. Nitro-glycerine Tablet (Herbert A.*et al.*, 2003).

1.2.1.4 According to the route of administration:

i) Tablets ingested orally: These tablets are to be swallowed intact with sufficient quantity of water. Exception is chewable tablet. Over 99% of the tablets manufactured today are to be ingested orally. This shows that this class of formulation is most popular worldwide.

- **a.** Compressed tablets
- **b.** Multi compressed tablets
- **c.** Multi layered tablets
- **d.** Sustained action tablets
- **e.** Enteric coated tablets
- **f.** Sugar coated tablets
- **g.** Film coated tablets
- **h.** Chewable tablets
- **i.** Targeted tablets

ii) Tablets used in oral cavity: The tablets under this group are aimed to release API in oral cavity or to provide local action in this region. The tablets under this category avoids first-pass metabolism, decomposition in gastric environment, nauseatic sensations and gives rapid onset of action. The tablets formulated for this region are designed to fit in proper region of oral cavity.

a) Buccal tablets

b) Sublingual tablets

c) Lozenge tablets and trouches

d) Dental cones

iii) Tablets administered by other routes: These tablets are administered by other route other than oral cavity and so the drugs are avoided from passing through the gastro intestinal tract. These tablets may be inserted into other body cavities or directly placed below the skin to be absorbed into systemic circulation from the site of application.

a) Implants

b) Vaginal tablets

iv) Tablets used to prepare solutions: The tablets under this category are required to be dissolved first in water or other solvents before administration or application This solution may be for oral ingestion or parenterals application or for topical use depending on the type of medicament used.

eg: Effervescent granules

v) Molded tablets or tablet triturates:

a) Dispersing tablets

b) Hypodermic tablets

1.3 Immediate release drug delivery system

Immediate release drug delivery system is also conventional type of drug delivery system as it is defined as – Immediate release tablets are designed to disintegrate and release their medicaments with no special rate controlling features such as special coatings and other techniques (Syed azeem.*et al.*, 2011).

1.3.1 Advantages of immediate release drug delivery systems:

- Release the drug immediately.
- More flexibility for adjusting the dose.
- It can be prepared with minimum dose of drug.
- There is no dose dumping problem.
- Immediate release drug delivery systems used in both initial stage and final stage of disease.
- At the particular site of action the drug is released from the system.

1.4 Tablet-manufacturing methods

A). Direct compression

B). Granulation

A) Direct compression

➢ The term "direct compression" is defined as the process by which tablets are compressed directly from powder mixture of API and suitable excipients. No pretreatment of the powder blend by wet or dry granulation procedure is required. (G.S.Banker.*et al.*, 2002).

Manufacturing steps for direct compression

Direct compression involves comparatively few steps:

- Milling of drug and excipients
- Mixing of drug and excipients
- Tablet compression

B) Granulation

Granulation may be defined as a size enlargement process which converts small particles into physically stronger and larger agglomerates.

Granulation Techniques

(1) Dry Granulation

(2) Wet Granulation

1.4.1 Dry granulation:

When tablet ingredients are sensitive to moisture or are unable to withstand elevated temperature during drying and when the tablet ingredients have sufficient inherent binding or cohesive properties, slugging may be used to form granules. This method is referred to as dry granulation, pre compression or double compression. When slugging is used, large tablets are made as slugs because fine powders flow better into large cavities. These compressed slugs are comminuted through the desirable mesh screen either by hand or for large quantities through the Fitzpatrick or similar comminuting mills after this the granulation is blended gently with lubricants and then compressed to form tablets. The other method is to pre compress the powder with pressure rolls using a machine such as Chilsonator (Lieberman H.*et al.*, 1986).

Steps in Dry Granulation:

- Milling of drugs and excipients.
- Mixing of milled powders.
- Compression into large, hard tablets to make slugs.
- Screening of slugs.
- Mixing with lubricant and disintegrating agent.
- Tablet compression.

Two main Dry Granulation processes:

a) Slugging process: Granulation by slugging is the process of compressing dry powder of tablet formulation with tablet press having die cavity large enough in diameter to fill quickly. The accuracy or condition of slug is not too important. Only sufficient pressure to compact the powder into uniform slugs should be used. Once slugs are produced they are reduced to appropriate granule size for final compression by screening and milling.

b) Roller compaction: The compaction of powder by means of pressure roll can also be accomplished by a machine called Chilsonator. Unlike tablet machine, the chilsonator turns out a compacted mass in a steady continuous flow. The powder is fed down between the rollers from the hopper which contains a spiral auger to feed the powder into the compaction zone. Like slugs, the aggregates are screened or milled for production into granules. (Remington J. *et al.,* 2005).

1.4.2 Wet granulation:

The most widely used process of agglomeration in pharmaceutical industry is wet granulation. Wet granulation process simply involves wet massing of the powder blend with a granulating liquid, wet sizing and drying the unique portions of wet granulation process involve the wet massing of powders, wet sizing or milling and drying.

Important steps involved in the Wet Granulation:

- Mixing of the drug(s) and excipients.
- Preparation of binder solution.
- Mixing of binder solution with powder mixture to form wet mass.
- Coarse screening of wet mass using a suitable sieve.
- Drying of moist granules.
- Screening of dry granules through a suitable sieve.
- Mixing of screened granules with disintegrant, glidant, and lubricant (Ansel H.*et al.*, 2004).

1.5 Tablet compression

After the preparation of granules (in case of wet granulation) or sized slugs (in case of dry granulation) or mixing of ingredients (in case of direct compression), they are compressed to get final product. The compression is done either by single punch machine (stamping press) or by multi station machine (rotary press).

The tablet press is a high-speed mechanical device. It 'squeezes' the ingredients into the required tablet shape with extreme precision. It can make the tablet in many shapes, although they are usually round or oval. Also, it can press the name of the manufacturer or the product on the top of the tablet. Each tablet is made by pressing the granules inside a die, made up of hardened steel. The die is a disc shape with a hole cut through its centre. The powder is compressed in the centre of the die by two hardened steel punches that fit into the top and bottom of the die.

The punches and dies are fixed to a turret that spins round. As it spins, the punches are driven together by two fixed cams - an upper cam and lower cam. The top of the upper punch (the punch head) sits on the upper cam edge .The bottom of the lower punch sits on the lower cam edge. The shapes of the two cams determine the sequence of movements of the two punches. This sequence is repeated over and over because the turret is spinning round. The force exerted on the

ingredients in the dies is very carefully controlled. This ensures that each tablet is perfectly formed. Because of the high speeds, they need very sophisticated lubrication systems. The lubricating oil is recycled and filtered to ensure a continuous supply (Ansel H.*et al.*, 2004).

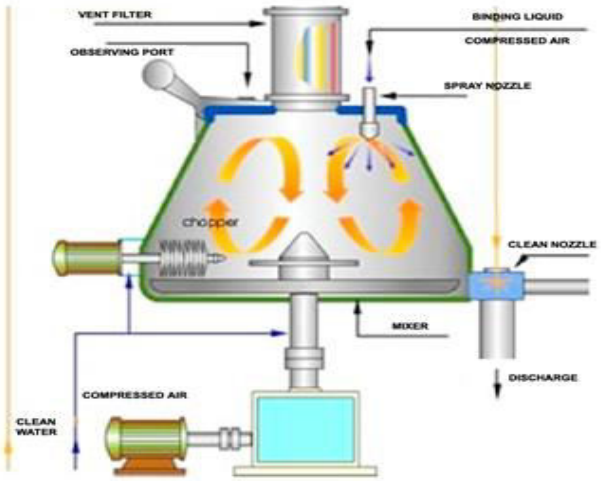


Fig: 1&2 Rotary Punching Machine

LIQUISOLID COMPACTS

In recent years much attention has been focussed on the problem of drug bio-availability. The dissolution rate of a drug from its dosage form is now considered as an important parameter in the bio-availability. Dissolution is the rate limiting step in the absorption of drugs from solid dosage forms, especially when the drug is poorly soluble. Among the various approaches to improve the dissolution of

the drugs, the preparation of solid dispersion has often proven to be very successful.

Because of the limited aqueous solubility it exhibits poor dissolution characteristics and its oral absorption is dissolution rate limited.

I) STUDIES ON SOLUBILITY IMPROVEMENT:

The most important property of a dosage form is its ability to deliver the active ingredient to its site of action at a rate and amount sufficient to elicit the desired pharmacological response. If the drug is administered by an extra vascular route and acts systemically, its potency will be directly related to the amount of drug the dosage form delivers into the blood. Also, if the pharmacological effects of the drug are directly and instantaneously related to the plasma concentration, the rate of absorption will be important because the rate will influence the height of plasma concentration peak and peak time. Thus, the bioavailability of a drug product is defined in terms of the amount of the active drug delivered to the blood and the rate at which it is delivered. The successful transportation of a drug from oral solid dosage form into the general circulation can be considered as a four step process.

1. The delivery of drug to the absorption site.
2. Getting the drug into solution.
3. Movement of the drug through the membrane of the gastrointestinal tract.
4. The movement of the active ingredient from the site of absorption into the general circulation.

The order of the first two steps is not absolute i.e., the drug may dissolve either before or after reaching the site of absorption, but it is imperative that the drug be in solution before it is absorbed.

The slowest of the process determines the rate of availability of the drug from the dosage form. The rate and extent of absorption will be influenced by many factors in all the four of these steps. These factors

related to the physio-chemical properties of the drug, and the design and production of the dosage form are called pharmaceutical variables and those factors arising from the anatomical and physiological characteristics of the patient are called patient variables.

The factors related to the dosage form that can produce profound differences in the drug bioavailability include, formulation and manufacturing variables, such as chemical form and solubility of the drug, the type and quantity of the excipients used and the compaction pressure. Among the patient related factors that control bioavailability include the time of drug administration relative to meals, Co-administration of other drugs which may influence absorption and the compliance of the patient with the instructions of the physician, pharmacist or nurse. Patient related factors which normally cannot be controlled but for which some all owance or adjustment can be made include age, disease state, abnormal genital characteristics and/ or gastrointestinal physiology.

II) DISSOLUTION RATE LIMITED ABSORPTION:

The poor dissolution characteristics of relatively insoluble drugs have long been problem to the pharmaceutical industry. When an insoluble or sparingly soluble drug is administered orally, the rate and extent of absorption are controlled by the dissolution rate in the gastrointestinal fluids.

The process of dissolution is primarily dependent on pharmaceutical variables with the possible exception of ph dependency which may be patient variable.

A quantitative description of dissolution rate is given by the Noyes-Whitney equation based on diffusion layer model.

$$\frac{dc}{dt} = \frac{DS\,(c_s - c)}{h}$$

Where,

dc / dt is the rate of diffusion,

S is the surface area,

D is the diffusion coefficient,

h is the thickness of the diffusion layer,

Cs is the saturation solubility and

C is the concentration of the drug in the solvent at time's'.

In dissolution rate limited absorption 'C' is negligible when compared to 'Cs'. Under these conditions 'D' and 'h' remain constant and cannot be altered to any degree by the product formulation. Hence,

$dc / dt = K.S.C_S$

Thus, the dissolution rate of a poorly soluble drug can be increased by increasing either solubility or surface area or both.

Methods Used For Increasing the Dissolution Rate of Poorly Soluble Drugs:

Noyes–Whitney equation states that the variables to be controlled by formulation are simply the surface area and solubility.

1. Controlling the solubility of a weak acid or base by buffering the entire dissolution medium, the microenvironment of the diffusion layer surrounding a particle through the use of buffers and salts.

2. Controlling the solubility of the drug through the choice of the physical state such as crystal forms, its hydrates, its amorphous form and so on.

3. Controlling the surface area of the drug through control of the particle size.

A solid dispersion is defined as "a dispersion of one or more active ingredients in an inert carrier or matrix of solid state prepared by the melting (fusion), solvent or melting solvent method".

III) METHOD OF PREPARATION:

1. Melting Method:

In the melting Method, a physical mixture of a drug and a water soluble carrier was heated directly until it melted mixture was then cooled and solidified rapidly in an ice bath under vigorous stirring. The final solid mass was then crushed, pulverized and sieved. To facilitate faster solidification, the homogenous melt was poured in the form of a thin layer on to a ferriteplateora stainless steel plate and cooled by following air or water in the opposite side of the plate. The solidified masses of some systems like drug poly ethylene glycol polymer were often found to require storage of one or more days in desiccators at ambient temperatures for hardening and ease of powdering.

The main advantages of this method are its simplicity and economy. It is technically less difficult method of preparing dispersions provided drug and carrier are miscible in the molten state. There is no use of toxic solvents. A modification of the melt process involves spray congealing from a modified spray drier on to cold metal surfaces and has been used for dispersions.

The disadvantages are that many substances, either drugs of carriers may decompose or evaporate during fusion processes at high temperatures. For example some carriers are quite volatile and may partially decompose by dehydration near its melting point that immiscibility and instability may occur during fusion. The other potential problem of carriers such as thermal degradation, sublimation and polymorphic transformation since Meta stable modification of the drug maybe formed which convert to more stable forms during storage..

2. Solvent method:

In the solvent method, solid dispersions are prepared by dissolving of two solid components in a common solvent, followed by evaporation of the solvent .More commonly; the solvent is removed by evaporation under reduced pressure at varying temperatures. The process uses organic solvent as the agent to intimately mix the drug and carrier to prepare solid dispersion. The choice of solvent and its removal rate are critical to the quality of the dispersion. Since the chosen carriers are generally hydrophilic and the drugs are hydrophobic, the selection of a common solvent is difficult and its complete removal necessitated by its toxic nature, is imperative careful control of the temperature and rate of evaporation of solvent is essential in controlling the particle size of the drug, and although low temperatures and in vacuum evaporation may be used for solvent removal, instabilities cannot always be avoided.

The main advantage of the solvent method is that thermal decomposition of drugs or carriers can be prevented because of the low temperatures required for the evaporation of organic solvents. Insolvent method high melting carriers can be used.

However, some disadvantages associated with this methods are the higher cost of preparation, the difficulty incompletely removing the solvent, the possible adverse effects of the supposedly negligible amount of the solvent on the chemical stability of the drug, the selection of common volatile solvent and the difficulty of reproducing crystal forms.

The BCS class II drugs for which the dissolution profile must be clearly defined and reproducible shows high absorption number (an) and low dissolution number (dn).Drugs in this class are expected to have a variable dissolution profile due to the formulation and *in vivo* variables that, in turn, affect the absorption. The poor dissolution rate of such water insoluble drug is a major impediment to the development of pharmaceutical dosage forms. The oral absorption of

drugs is most often controlled by dissolution in the gastrointestinal tract. Different methods are employed to improve the dissolution characteristics of poorly water soluble drugs, like solubilisation, pH adjustment, co-solvents, micro emulsion, self emulsification, polymeric modification, drug complication, particle size reduction, use of a surfactants a solubilising agent, the pro-drug approach, and solid solutions. Amongst these the most promising method for promoting dissolution is the use of the liquisolid (LS) system. Liquisolid systems are acceptably flow inland compressible powdered forms of liquid medications.

The term 'liquid medication' involves oily liquid drugs and solutions or suspensions of water insoluble solid drugs carried in suitable non-volatile solvent systems termed liquid vehicles. Employing this Liquisolid technique, a liquid medication maybe converted into a dry looking, non-adherent, free flowing and readily compressible powder by a simple blending with selected powder excipients referred to as carrier and coating materials. Various grades of cellulose, starch and lactose maybe used as the carriers, where as very fine particle size silica powders may be used as the coating (or covering) materials .In fundamental studies made by Spire as *etal.*, flow and compression issues have been addressed with the use of the new formulation mathematical model of liquisolid systems, which is based on the flow able (Φ-value) and compressible (Ψ-number) liquid retention potentials of the constituent powders. The good flow and compression properties of the liquisolid system are encouraged by the large surface area and fine particle size. Hence, liquisolid compacts containing water-insoluble drugs are expected to display enhanced dissolution characteristics and, consequently, improved oral bioavailability.

Therapeutic effectiveness of a drug depends upon the bioavailability which is dependent on the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of

drug in systemic circulation for pharmacological response to be shown .A number of new chemical entities do not reach the public merely because of their poor oral bioavailability due to in adequate dissolution. For drugs belonging to Biopharmaceutical Classification System (BCS) class II (poor water solubility and high permeability) dissolution rate is often the rate determining step in the drug absorption**.** To increase dissolution rates of such drugs, various methods have been described. These include the use of micronization, modification of the crystal habit, solid dispersions, inclusion complexes using cyclodextrin, Solubilisation by surfactants, Microwave induced dissolution rate improvement etc. Among them liquisolid compacts is one of the most promising and new technique which promotes the dissolution rate of water insoluble drugs.

LIQUID SOLID COMPACTS

Liquisolid Compacts - A Novel Approach

The new Liquisolid technique may be applied to formulate liquid medications (i.e., oily liquid drugs and solutions, suspensions or emulsions of water insoluble solid drugs carried in non-volatile liquid vehicles) into powders suitable for tableting or encapsulation. Simple blending of such liquid medications with calculated quantities of a powder substrate consisting of certain excipients referred to as the carrier and coating powder materials, can yield dry looking, non adherent, free flowing, and readily compressible powders.

Type of Liquisolid compacts based on the liquid medication:-

1. Powdered drug solutions
2. Powdered drug suspensions
3. Powdered drug emulsions
4. Powdered liquid drug

Concept

When the drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted fibres in its interior as cellulose, both absorption and adsorption take place; i.e., the liquid initially absorbed in the interior of the particles is captured by its internal structure and, after the saturation of this process, adsorption of the liquid on to the internal and external surfaces of the porous carrier particles occur. Then, the coating material having high adsorptive properties and large specific surface area gives the liquisolid system the desirable flow characteristics.

In liquisolid systems the drug is already in solution in liquid vehicle, while at the same time, it is carried by the powder particles (microcrystalline cellulose and silica). Thus, due to significantly increased wetting properties and surface area of drug available for dissolution, liquisolid compacts of water-insoluble substances may be expected to display enhanced drug release characteristics and consequently, improved Oral bioavailability. Since dissolution of a non polar drug is often the rate limiting step in gastro intestinal absorption, better bioavailability of an orally administered water-insoluble drug is achieved when the drug is already in solution, thereby displaying enhanced dissolution rates. That is why soft gelatin elastic capsules containing solutions of such medications demonstrate higher bioavailability when compared to conventional

Oral solid dosage forms. A similar principle underlies the mechanism of drug delivery from liquisolid compacts and is chiefly responsible for the improved dissolution profiles exhibited by these preparations. The wettability of the compacts by the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid compacts. Non volatile solvent present in the liquisolid system facilitates wetting of the drug particles by decreasing interfacial tension between dissolution

medium and tablet surface**.**

Mechanism of Liquisolid Compacts

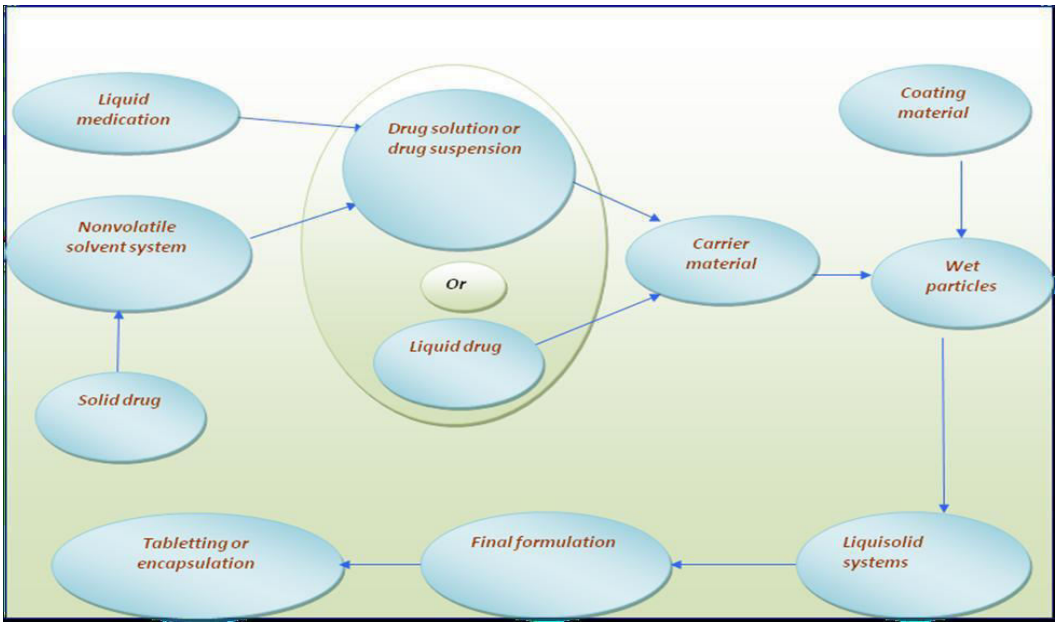
Liquisolid system is a novel concept of drug delivery via oral route. This technique is applied to water insoluble drugs and lipophilic drugs to sustain their release. Formulation and manufacture of the liquisolid tablet is quite simple method according to new mathematical model described by Spires etal**.** The liquisolid tablet preparation method involves, first a mathematically calculated amount of pure drug weighed and dissolved in the suitable amount of solvent in a molecularly dispersed state. For attaining good flow properties trial and error methods were used i.e. changing the carrier: coating material ratio from 50:1 to 5:1 ratios according to new mathematical model expressions proposed by Liao. This liquid medication is poured on the suitable amount of carrier material. The liquid medication is absorbed in to the carrier material internally and externally and then suitable disintegrant was added to this material. Finally, coating material was added for dry looking adherent to the carrier material for achieving good compression properties. As the drug is in the form of liquid medication it is either solubilised or molecularly dispersed state. Due to increased wetting and surface area for dissolution, liquisolid tablet of water insoluble drugs shows improved dissolution properties and in turn increased bioavailability.

Liquid medication is incorporated into carrier medication which has a porous surface and closely matted fibres' in its interior as cellulose. Both absorption and adsorption take place, i.e. the liquid absorbed into the interior of the particles is captured by its internal structure and after saturation of this process, adsorption of the liquid onto the internal and external surface of the porous carrier particles occurs. Excipients possessing fine and highly adsorptive particles such as various types of amorphous silicon dioxide (silica) are most suitable for this step. Before compression

or encapsulation, various ingredients such as lubricants, disintegrates or Polymers, and binders, maybe mixed with the finished liquisolid systems to produce liquisolid compacts in the dosage form of tablets or capsules.

Fig 3: Mechanism of Liquisolid Compacts

Steps involved in the preparation of Liquisolid compacts



Designing of Liquisolid Systems

Before designing the liquisolid, the Pre formulation studies should be performed first, these include:-

1. Determination of drug in different non-volatile solvents
2. Determination of angle of slide
3. Calculation of liquid load factor (L_f)
4. Determination of flowable liquid retention potential (Φ value)
5. Liquid solid compressibility test (LSC)

The flowability and compressibility of liquisolid compacts are addressed concurrently in the new formulation mathematical model of liquisolid systems, which was used to calculate the appropriate

quantities of the carrier and coating materials required to produce acceptably flowing and compressible powders based on new fundamental powder properties called the flow able liquid retention potential (Φ- value) and compressible liquid retention potential (Ψ-number) of the constituent powders. According to the new theories, the carrier and coating powder material can retain only certain amounts of liquid while maintaining acceptable flow and compression properties. Depending on the excipients ratio (R) or the carrier: coating ratio of the powder system used where,

R = Q/q E q..... (1)

As represents the ratio between the weights of carrier (Q) and coating (q) materials present in the formulation.

Determination of Drug in Different Non Volatile Solvents:

These are carried by preparing saturated solutions of drug in non-volatile solvents, and analyzing them spectrophotometrically. Saturated solutions are prepared by adding excess of drug to vehicles and shaking them on shaker for specific time period under steady vibration. After this, the solutions are filtered and analyzed spectrophotometrically.

Determination of Angle of Slide:

The required amount of carrier is weighed and placed at one of a metal plate with a polished surface and it is gradually raised till the plate becomes angular to the horizontal at which powder is about to slide.

It was used to measure the flow properties of powders. The angle of 33° is optimum for flow of powders.

Calculation of Liquid Load Factor (L_f):

It is defined as the ratio of weight of liquid medication (w) to weight of carrier material (Q).

Different concentrations of non-volatile solvents are taken and the drug is dissolved and the carrier coating material is added and blended.

$L_f = W/Q$ e q……. (2)

W = weight of liquid medication

Q = weight of carrier material

Determination of Flowable Liquid Retention Potential (Φ):

It is defined as the maximum weight of liquid that can be retained per unit powder material in order to produce an acceptably flowing liquid/powder admixture. This value of powders maybe determined using a new procedure, the liquisolid flow ability (LSF) test. The Ø value was used to calculate excipients quantities. Equation for this is as follows:

$L_f = Ø + Ø (1/R)$ eq….. (3)

Where **Ø** and Ø are the constant Ø values of carrier and coating materials, respectively. L_f was calculated from the linear relationship of L_f vs $1/R$.

$L_f = (1/R)$ eq…… (4)

Next according to the used liquid vehicle concentration, different weights of the liquid drug solution (W) will be used. By calculating L_f and W, we can calculate the amount of Q and q required for liquisolid systems.

Liquisolid Compressibility Test (LSC):

It was developed to determine Ψ values and involves steps such as preparing carrier coating material admixture systems, preparing several uniform liquid/powder admixtures to tablets, determining average hardness, measuring of average liquid content

SIGNIFICANCE OF LIQUISOLID COMPACTS

1) 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.

2) Improvement of bioavailability of an orally administered water insoluble drugs is achieved.

3) 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.

4) In this technique, production cost is low compared to soft gelatin capsules.

5) Drug is formulated in a tablet form or encapsulated dosage form and is held in solubilised liquid state, which confers developed or improved drug wetting properties thereby improving drug dissolution profiles.

6) Greater drug surface area is exposed to the dissolution medium.

7) This liquisolid system is specifically for powdered liquid medications.

8) These liquisolid systems formulate into immediate release or sustained release dosage forms.

9) Optimized sustained release, liquisolid tablets or capsules of water insoluble drugs demonstrate constant dissolution rates.

10) It is used in controlled drug delivery systems.

11) Drug can be molecularly dispersed in the formulations.

12) Drug release can be modified using suitable formulation

ingredients.

13) Capability of industrial production is also possible.

14) Enhanced bioavailability can be obtained as compared to conventional tablets.

15) Differentiate the dosage form by admixture of colour into liquid vehicle.

16) To minimize excipients in formulation compare with other formulations like solid dispersions.

17) Omit the process approaches like nanonisation, micronization techniques.

Applications of Liquisolid Systems

- Solubility and dissolution enhancement.
- Used efficiently for water insoluble solid drugs or liquidlipophilic drugs.
- Rapid release rates.
- Designed for controlled release tablets.
- Designed for sustained release of water soluble drugs such as Propronolol hydrochloride.
- Application in probiotics.

AIM AND OBJECTIVE OF THE WORK

The aim and objective of the present study is to develop a pharmaceutically stable, cost effective and quality improved robust formulation of Loperamide tablets using **liquisolid technique**.

Oral route still remains the convenient route of drug administration in many diseases. That the major problem in oral drug formulations is low and erratic bioavailability, which mainly results from poor aqueous solubility of certain drugs. Incase of poorly water soluble drugs, dissolution is the rate limiting step in the process of drug absorption. So, bioavailability problems are prevalent with extremely hydrophobic drugs (aqueous solubility <3.4 mg /ml at 37 ˚C). The enhancement of oral bioavailability of poorly water soluble drugs like LOPERAMIDE could be improved by enhancing aqueous solubility. Among numerous ways of enhancing drug dissolution, liquisolid compacts are the promising techniques to enhance the dissolution poorly water soluble drugs.

To achieve this goal various prototype formulation trials will be taken and evaluated with respect to the various quality control parameters such as dissolution, assay. The formula will be finalized by dissolution profile. The objective includes providing a robust formulation for the production of the dosage form for which the influence of various factors like concentration and nature of non volatile solvents along with type of disintegrates used on disintegration time and dissolution parameters are to be studied and also analyzed.

PLAN OF WORK

With the above mentioned aims and objectives, the work is planned as follows:

Survey of literature on Loperamide liquisolid compacts.

1. Solubility studies.
2. Pre formulation studies:

Blend: Bulk Density, Tapped Density, Angle of repose, Carrs' Index.

3. Formulation of the dosage form.
4. Selection of method of preparation of dosage form.
5. Evaluation of dosage form for

i. Hardness
ii. Friability
iii. Disintegration
iv. Weight variation
v. Dissolution
vi. Drug content
vii. Compatibility studies
viii. Powder X-Ray Diffraction
ix. Stability studies.

3. LITERATURE REVIEW

Sanjeev Raghavendra Gubbi [1] Purpose: The solubility and dissolution properties of any drug are vital determinants of its oral bioavailability. The dissolution rate of poorly soluble, highly permeable (BCS-II) drugs, such as atorvastatin calcium, can be improved by application of the liquisolid (LS) technique. Methods: Different liquisolid compacts were prepared using a mathematical model for calculating required quantities of powder and liquid ingredients to produce an acceptably flowable and compressible admixture. Avicel PH 102, Aerosil 200 and Explotab were employed as carrier, coating material and disintegrant, respectively. The prepared liquisolid systems were evaluated for their micromeritic properties and possible drug-excipient interactions by Infrared spectra (IR) analysis, differential scanning calorimetry (DSC) and X- ray powder diffraction (XRPD). Liquisolid compacts were prepared and evaluated for their tabletting properties.

Results: The liquisolid system showed acceptable micromeritic properties. The IR and DSC studies ruled out any 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. The release rates of liquisolid compacts were markedly higher compared with directly compressed tablets, due to increasing wetting properties and surface area of the drug. From the obtained pharmacokinetic parameters, such as the AUC, Tmax and Cmax, the liquisolid compacts demonstrated better bioavailability compared with their conventional formulation.

Tejaswi Annapureddy [2] It is well established that the active ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the GIT. About 40 % of the newly discovered drugs fall into poorly water soluble or water insoluble categories. The aqueous solubility for poorly water soluble drugs is usually less than 100 µg/ml. Liquisolid compact system is a novel concept of drug delivery that can change the dissolution rate of water insoluble drugs. Formulation and manufacture of the Liquisolid compacts is quite simple method according to new mathematical model described by Spire as et al. The technique is based up on dissolving the insoluble drug in the non-volatile solvent and admixture of drug loaded solutions with appropriate carrier and coating materials to convert into acceptably flowing and compressible powders. In this case, even though the drug is in a solid dosage form, it is held within the powder substrate in solution, or in a solubilised, almost molecularly dispersed state, which contributes to the enhanced drug dissolution properties. Liquisolid system is characterized by flow behaviour, saturation solubility, drug content, Fourier transform infra red spectroscopy, in-vitro release, release kinetics and stability studies.

Therefore, the optimum liquid load factor (L_f) required to obtain acceptably flowing and compressible liquisolid systems are equal to either ΦLforΨLf,[3] whichever represents the lower value. As soon as the optimum liquid load factor is determined, the appropriate quantities of carrier (Qo) and coating (qo) material required to convert a given amount of liquid formulation (W) into an acceptable. Several mechanisms of enhanced drug release have been postulated for liqui-solid systems. The three main suggested mechanisms include an increased surface area of drug available for release, an increased aqueous solubility of the drug, and an improved wet ability of the drug particles. Formation of a complex between the drug and excipients or any changes in crystalline of the drug could be ruled out using DSC and XRPD measurements.

Vijasya ranga vital [4] Liquisolid techniques is used in delivery of lipophilic and poorly water soluble drugs through oral route. It involves dissolving water insoluble drugs in nonvolatile solvents and converting into acceptably flowing and compressible powders. The objective of the present work was to enhance the dissolution rate of ketoprofen using microcrystalline cellulose as carrier, Aerosil 200 as coating material, and polyethylene glycol as nonvolatile water miscible liquid vehicle. Materials and Methods: The drug concentration was kept constant in all formulations at 40% w/w. Optimization was carried out using Box-Behnken design by selecting liquid load factor, amount of coating material, and amount of magnesium oxide as independent variables; cumulative percentage drug release and angle of repose were considered as dependent variables. Results: The Fourier transforms infrared (FTIR) and differential scanning calorimetry (DSC) studies revealed that there was no possible interaction between drug and tablet excipients. Prepared ketoprofen liquisolid tablets were evaluated for hardness, weight variation, friability, in-vitro disintegration time, drug content uniformity, and in-vitro dissolution studies. The optimized formulation yielded the response values, which were very close to the predicted values. The accelerated stability studies conducted showed that liquisolid tablets were not affected by ageing and there were no appreciable changes in the drug content.

Abdul jabba [5] Objective: The purpose of the present research was to investigate the in vitro dissolution properties of poorly water soluble piroxicam by utilizing liquisolid technique. Different liquisolid (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. Methods: Avicel PH 102, Aerosil 200 and cros carmellose sodium were employed as carrier, coating material and disintegrant respectively for preparing LS compacts. LS compacts were prepared and evaluated for their tabletting properties.

Fourier transform infrared (FTIR) analysis, differential scanning calorimetry (DSC) and X- ray powder diffraction (XRPD) were performed. Results: The tabletting properties of the liquisolid compacts were within the acceptable limits and drug release rates of all prepared LS compacts were distinctly higher as compared to directly compressed tablets, and marketed capsules. Both DSC and XRPD suggested loss of piroxicam crystalline upon liquisolid preparation indicating that even though the drug existed in a solid dosage form, it is held within the powder substrate in a solubilized, almost molecularly dispersed state, which contributed to the enhanced drug dissolution properties. The FTIR spectra showed disappearance of the characteristic absorption band of piroxicam (3338.78 cm-1) in liquisolid formulations which might be attributed to the formation of hydrogen bonding between the drug and liquid vehicle; this resulted in drug dissolution enhancement. Conclusion: From this study it concludes that the LS technique is an effective approach to enhance the dissolution rate of piroxicam.

V. J. Kapure [6]In present investigation liquisolid compact technique is investigated as a tool for enhanced dissolution of poorly water-soluble drug Rosuvastatin calcium (RVT). The model drug RVT, a HMG-Co A reductase inhibitor was formulated in form of directly compressed tablets and liquisolid compacts; and studied for in-vitro release characteristics at different dissolution conditions. In this technique, liquid medications of water insoluble drugs in non-volatile liquid vehicles can be converted into acceptably flowing and compressible powders. Formulated systems were assessed for Precompression parameters like flow properties of liquisolid system, Fourier transform infra red spectra (FTIR) analysis, X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), and post compression parameters like content uniformity, weight variation, hardness and friability, disintegration test, wetting time, in vitro dissolution studies, effect of dissolution volume on drug release rate, and estimation of fraction of molecularly dispersed drug in liquid

medication. As liquisolid compacts demonstrated significantly higher drug release rates, we lead to conclusion that it could be a promising strategy in improving the dissolution of poor water soluble drugs and formulating immediate release solid dosage forms.

Srinivas Vaskula [7] The present study enlightens to enhance the dissolution rate, absorption efficiency and bioavailability of Nimesulide, a poorly soluble-highly permeable drug by preparing liquisolid compacts. Nimesulide liquisolid tablets were prepared by using polyethylene glycol-400 as a non-volatile liquid vehicle, microcrystalline cellulose, hydroxyl propyl methylcellulose-E15, starch were used as carrier materials and silica gel as coating material in different ratios. They were characterized for different physical parameters to comply with pharmacopoeial limits. In vitro dissolution profiles of the liquisolid formulations were studied and compared with conventional formulation in pH 7.4 phosphate buffer and it was found that liquisolid tablets formulated with microcrystalline cellulose showed significant higher drug release rates than conventional tablets due to increase in wetting properties. DSC study showed that there is no interaction between the drug and excipients. In conclusion, development of nimesulide liquisolid tablets is a good approach to enhance the dissolution rate.

V.N.L. Sirisha[8] At present 40% of the drugs in the development pipelines, and approximately 60% of the drugs coming directly from synthesis are poorly soluble. The limited solubility of drugs is a challenging issue for industry, during the development of the ideal solid dosage form unit. Liqui-solid compacts technique is a new and promising approach to overcome this consequence and that can change the dissolution rate of water insoluble drugs and increase the bioavailability of the drugs. According to the new formulation method of liqui-solid compacts, liquid medications such as solutions or suspensions of water insoluble drugs in suitable non-volatile liquid vehicles can be converted

into acceptably flowing and compressible powders by blending with selected powder excipients. It has been speculated that such systems exhibit enhanced release profiles. In this case, even though the drug is in a solid dosage form, it is held within the powder substratin solution or, in a solubilised, almost molecularly dispersed state, which contributes to the enhanced drug dissolution properties

Vijay kumar Nagaband [9] At present 40% of the drugs in the development pipelines, and approximately 60 % of the drugs coming directly from synthesis are poorly soluble. The limited solubility of drugs is a challenging issue for industry, during the development of the ideal solid dosage form unit. Liquisolid technique is a novel and promising approach to overcome this consequence. The technique is based upon the dissolving the insoluble drug in the non volatile solvent and admixture of drug loaded solutions with appropriate carrier and coating materials to convert into acceptably flowing and compressible powders. The selection of non toxic hydrophilic solvent, carrier, coating materials and its ratios are independent of the individual chemical moieties. The increased bioavailability is due to either increased surface area of drug available for release, an increased aqueous solubility of the drug, or improved Wettability of the drug particles.

Izhar Ahmed Syed [10] The "Liquisolid" technique is a novel and capable addition towards such an aims for solubility enhancement and dissolution improvement, thereby it increases the bioavailability. It contains liquid medications in powdered form. This technique is an efficient method for formulating water insoluble and water soluble drugs. This technique is based upon the admixture of drug loaded solutions with appropriate carrier and coating materials. The use of non-volatile solvent causes improved wet ability and ensures molecular dispersion of drug in the formulation and leads to enhance solubility. By using hydrophobic carriers (non-volatile solvents) one can modify release

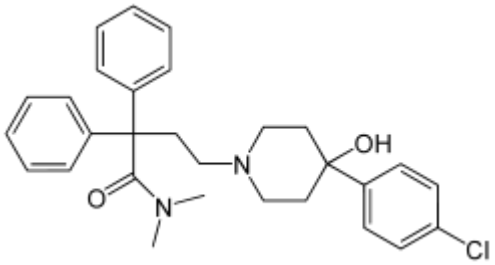
(sustained release) of drugs by this technique. Liquisolid system is characterized by flow behaviour, wettability, powder bed hydrophilicity, saturation solubility, drug content, differential scanning calorimetry, Fourier transform infra red spectroscopy, powder X-ray diffraction, scanning electron microscopy, in-vitro release and in-vivo evaluation. By using this technique, solubility and dissolution rate can be improved, sustained drug delivery systems be developed for the water soluble drugs.

DRUG PROFILE

LOPERAMIDE:

Formula : $C_{29}H_{33}Cl\,N_2O_2$

Fig.4: Structure of Loperamide



IUPAC NAME: 4-[4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl]-*N, N*-dimethyl-2,2-diphenylbutanamide

Routes : oral, insufflations

Pharmacokinetic data:

Bioavailability	0.3%
Protein binding	97%
Metabolism	Hepatic (extensive)
Half-life	7-14 hours
Excretion	Faeces (30-40%), urine (1%)

LOPERAMIDE HYDROCHLORIDE:

Pharmacologic class**:** Piperidine derivative

Therapeutic class**:** Anti diarrheal

Molecular weight**:** 477.038 g/mol

Melting point**:** 223-225^{0} C

Actions

- Slows intestinal motility and affects water and electrolyte movement through the bowel.Inhibits peristaltic activity by a direct effect on circular and longitudinal muscles of the intestinal wall.
- Prolongs the transit time of intestinal contents; reduces fecal volume, increases fecal viscosity and bulk density, diminishes loss of fluid and electrolytes.
    - *Inhibits peristalsis of intestinal wall musculature and intestinal cont ents. Also reduces fecal volume, increases fecal bulk, andminimizes fluid and electrolyte loss.*

Medical uses:

Loperamide is effective for the treatment of a number of types of diarrhea.

This includes control of acute nonspecific diarrhea, mild traveller's diarrhea, irritable bowel syndrome, chronic diarrhea due to bowel resection, and chronic diarrhea secondary to inflammatory bowel disease.

Mechanism of action:

Loperamide is an opioid -receptor agonist and acts on the μ-opioid receptors in the myenteric plexus of the large intestine; by itself it does not affect the central nervous system. It works similarly to morphine, by decreasing the activity of the myenteric plexus, which in turn decreases the tone of the longitudinal and circular smooth muscles of the intestinal wall. This increases the amount of time substances stay in the intestine, allowing for more water to be absorbed out of the fecal matter. Loperamide also decreases colonic mass movements and suppresses the gastrocolic reflex.

Adverse effects:

Adverse drug reactions (ADRs) most commonly associated with loperamide are constipation , dizziness, nausea , and abdominal cramps

Sideeffects: paralyticileus, angioedema,anaphylaxis/allergic reactions, toxic epidermal, necrolysis, Stevens-Johnson syndrome, erythema multiforme, urinary retention, and heat stroke. The most frequent symptoms of loperamide overdose are drowsiness, vomiting and abdominal pain or burning.

Drug interactions:

Loperamide is a substrate of P-Glycoprotein, therefore the concentration of Loperamide will increase when given with a P-Glycoprotein inhibitor. Loperamide is also capable of decreasing the concentration of other P-Glycoprotein substrates. As an example, when saquinavir concentrations can decrease by half when given with loperamide.

Loperamide is an anti-diarrheal agent which decreases intestinal movement. As such, when combined with other anti motility drugs, there is an increased risk of constipation. These drugs include, but are not limited to opiates, antihistamines, antipsychotics, and anticholinergics.

Contraindications:

• Hypersensitivity .
• Abdominal pain of unknown cause (especially with fever).
• Acute diarrhea caused by enteroinvasive Escherichia coli, Salmonella, or Shigella.
• Acute ulcerative colitis.
• Bloody diarrhea with temperature above 38.3° C (101° F) (with OTC pro duct).

• Pseudomembranous colitis associated with broad-spectrum anti-infectives.
• Children younger than age 6.

Warnings/Precautions:

Warnings: Do not use in patients with acute dysentery, characterized by high fever or blood in stools.

Fluid and Electrolyte Replacement Therapy

Fluid and electrolyte depletion may occur in patients with diarrhea; in such cases, administration of appropriate fluid and electrolytes is important. Use of loperamide does not preclude administration of appropriate fluid and electrolyte therapy.

Infectious Diarrhea and Pseudomembranous Colitis

Antiperistaltic agents may prolong and/or worsen diarrhea resulting from some infections (e.g., those caused by *Shigella*, *Salmonella*, toxigenic *Escherichia coli*) and from pseudomembranous colitis associated with broad spectrum antibiotics; do not use in these conditions.

Toxic Megacolon

Toxic megacolon reported with agents that inhibit intestinal motility or prolong intestinal transit time in some patients with acute ulcerative colitis or pseudomembranous colitis associated with broad spectrum antibiotics; discontinue promptly if abdominal distention, constipation, or ileus occurs.

Sensitivity Reactions

Hypersensitivity

Hypersensitivity reactions, including rash, reported.

General Precautions

Use of Fixed Combination

When used in fixed combination with other agents, consider the cautions, precautions, and contraindications associated with the concomitant agents.

Specific Populations

Pregnancy

Category B.

Lactation

Not known whether loperamide is distributed into human milk. Caution advised if used in nursing women.

Pediatric Use: Not recommended for children <2 years of age. Use particular caution in young children due to greater variability of response to the drug; presence of dehydration, especially in younger children, may further influence variability of response.

Not recommended for treatment of travelers' diarrhea in infants, children, or adolescents with HIV infection.

Children may be more sensitive to CNS effects than adults.

Hepatic Impairment: In patients with hepatic impairment, monitor closely for manifestations of CNS toxicity during therapy, since first-pass metabolism may be decreased.

Common Adverse Effects

Abdominal pain/distention/discomfort, constipation, drowsiness, dizziness, fatigue, dry mouth, nausea, vomiting, epigastric pain.

Interactions for Loperamide Hydrochloride

No drug interactions reported during clinical trials.

Loperamide Hydrochloride Pharmacokinetics

Absorption:99%

Bioavailability: Peak *plasma concentrations attained about 2.5 or 4–5 hours after oral solution or capsules, respectively. Oral bioavailability of capsules and oral solution, as determined by AUC, is similar***.**

Peak plasma concentrations of loperamide metabolites are reached 8 hours following oral administration of capsules.

Distribution :**Not known whether loperamide crosses the placenta or is distributed into milk.**

Elimination

Elimination Route : ***Excreted principally in feces.***

Half-life: ***10.8 hours (range 9.1–14.4 hours).***

Stability:well stabled

Storage:oral capsule 20 -25$_0$C

Oral

Capsules: Well-closed containers at 15–30°C.

Solution: 20–25°C.

Tablets: 20–25°C.Protect fixed-combination loperamide and simethicone caplets from light.

Availability

Capsules: 2 mg

Solution: 1 mg/5 ml

Tablets: 2 mg

Tablets (chewable): 2 mg

Indications and dosages

➢ Acute diarrhea

Adults: Initially, 4 mg , then 2 mg after each loose stool. Usual maintena nce dosage is 4 to 8 mg . daily in divided doses,not to exceed 16 mg daily.

Children ages 8 to 12 or weighing more than 30 kg (66 lb): Initially, 2 mg P.O. t.i.d., then 1 mg/10 kg after each loose stool,not to exceed 6 mg daily

Children ages 6 to 8 or weighing 20 to 30 kg (44 to 66 lb): Initially, 2 mg P.O. b.i.d., then 1 mg/10 kg after each loose stool,not to exceed 4 mg daily

Children ages 2 to 5 or weighing 13 to 20 kg (29 to 44 lb): Initially, 1 mg P.O. t.i.d., then 1 mg/10 kg after each loose stool,not to exceed 3 mg daily

➢ Acute diarrhea (treated with over-the-counter loperamide)

Adults and children ages 12 and older: Twocaplets with 4 to 8 oz water after first loose stool, then one caplet (with 4 to 8 ozwater) after each sub sequent loose stool. Don't exceed four caplets in 24 hours. Or give equiva lent dosage in liquid form.

Children ages 9 to 11 who weigh 27 to 43 kg (60 to 95 lbs): One caple t with 4 to 8 oz water after first loose stool, then ½caplet (with 4 to 8 oz w ater) after each subsequent loose stool. Don't exceed three caplets in 24 hours. Or give equivalent dosage in liquid form.

Children ages 6 to 8 who weigh 22 to 27 kg (48 to 59 lbs): One caplet with 4 to 8 oz water after first loose stool, then ½ capletwith 4 to 8 oz waterafter each subsequent loose stool. Don't exceed two caplets in 24 hrs. Or give equivalent dosage in liquidform.

Children younger than age 6: Consult physician.

➢ Chronic diarrhea

Adults: Initially, 4 mg P.O., then 2 mg after each loose stool; reduce dosa ge as tolerated. Don't exceed 16 mg daily for more than10 days.

Precautions

Use cautiously in:

• hepatic disease

• elderly patients

• pregnant or breastfeeding patients
• children.

Administration

• Use patient's weight to determine appropriate dosage (especially in chil dren).

Route	Onset	Peak	Duration
P.O.	1 hr	2.5-5 hr	10 hr

Adverse reactions

CNS: drowsiness, dizziness

GI: nausea; vomiting; constipation; abdominal pain, distention, or disco mfort; dry mouth; **toxic megacolon** (in patients with acuteulcerative coli tis)
Other: allergic reactions
Interactions
Drug-
drug. Antidepressants, antihistamines, other anticholinergics: additive anticholinergic effects
CNS depressants (including antihistamines, opioid analgesics, sedative-hypnotics): additive CNS depression
Drugherbs. Chamomile, hops, kava, skullcap, valerian

Drug-behaviors. Alcohol use: increased CNS depression

5. METHODOLOGY

5.1 MATERIALS

TABLE NO 1 : List of Materials

S.NO	MATERIALS	SUPPLIERS
1	Loperamide	MAYSA LABS PRIVATE LIMITED
2	Propylene Glycol	S.D fine chem. limited
3	Poly Etylene Glycol 200	S.D fine chem. limited
4	Poly Etylene Glycol 300	S.D fine chem. limited
5	Poly Etylene Glycol 400	S.D fine chem. limited
6	Poly Etylene Glycol 600	S.D fine chem. limited
7	Tween 20	S.D fine chem. limited
8	Tween 80	S.D fine chem. limited
9	Span 20	S.D fine chem limited
10	Span 80	S.D fine chem. limited
11	Methanol	S.D fine chem. limited
12	HCl	S.D fine chem. limited
13	Microcrystalline Cellulose	Saraswathi enterprises
14	Aerosil	Saraswathi enterprises
15	Sodium Starch Glycollate	Saraswathi enterprises

Materials Used in Liquisolid Compacts

Drug:

Drugs which are poorly soluble or else insoluble in water. Examples of drugs that can be incorporated into liquisolid systems include: Digoxin, digitoxin, Prednisolone, Hydrocortisone, spironolactone, hydrochlorothiazide, polythiazide and other liquid medications such as chlorpheniramine, water insoluble vitamins, fish oil, etc.

Non volatile Solvent:

These may be hydrophilic or lipophilic in nature based on

selection of type of formulation like immediate or control release. Inert, high boiling point, preferably water miscible and not highly viscous organic solvent systems are most suitable as vehicles. Some of the materials are: Polyethylene glycol, Propylene glycol, Tween 80 & 20, and Span 80 & 20.

Carrier:

These are preferred to be coarse and granular for acceptable flow. These are compress enhancers, relatively large, preferably porous particles possessing a sufficient absorption property which contributes in liquid absorption.

Eg: Various grades of cellulose, lactose, sorbitol, etc.

Coating Material:

These are flow enhancing, very fine(10 nm to 5000 nm in diameter), highly adsorptive coating particles (eg. silica of various grades like Cab-O-SilM5, Aerosil200, Syloid244FPetc) contributes in covering the wet carrier particles and displaying a dry-looking powder by adsorbing any excess liquid.

Super Disintegrants:

Most commonly used disintegrate are Sodium starch glycolate, Crosspovidone, Pumogel, etc.

Chemicals Used:

Drug (loperamide), Methanol, HCl, propylene glycol (PG), PEG200, 300, 400, 600, span 80 & 20, tween 80 & 20, water , potassium bromide.

5.2 EQUIPMENTS

Table No. 2: Equipments Used

S.NO	EQUIPMENTS	MANUFACTURER
1.	Digital balance	SHIMAZDU
2.	Orbital Shaker	LABINDIA
3.	FT-IR	LABINDIA
4.	KBr Press	LABINDIA
5.	Bulk Density Apparatus	LABINDIA
6.	Mixer	LABINDIA
7.	Tablet dissolution apparatus	LABINDIA
8.	U.V visible spectrophotometer	LABINDIA
9.	HPLC	WATERS
10.	Hardness tester	Monsanto hardness tester
11.	Disintegration test apparatus	Campbell Electronics

5.3 . METHODOLOGY:

5.3.1 ESTIMATION OF LOPERAMIDE

5.3.1.1 Development Of Calibration Curve For Loperamide:

A) Loperamide was weighed accurately 10 mg using digital analytical balance and transferred in to100 ml of volumetric flask ,dissolve methanol and the final volume was made up to 100 ml with methanol to get a stock solution A. from the stock solution A, 10 ml was pipette

out in 50 ml volumetric flask and the final volume was made up to 50 ml with hydrochloric acid to get a stock solution B. from the stock solution B, further dilution was made with the hydrochloric acid in 10 ml volumetric flask to get the solutions in the range of 0.2 to 1.8 µg/ml concentration and absorbance was recorded at 214 nm against suitable blank using UV-visible spectrophotometer.

B) Loperamide was weighed accurately 10 mg using digital analytical balance and transferred in to 100 ml of volumetric flask ,dissolve methanol and the final volume was made up to 100 ml with methanol to get a stock solution A. from the stock solution A, 10 ml was pipette out in 50 ml volumetric flask and the final volume was made up to 50 ml with methanol to get a stock solution B. from the stock solution B, 0.1ml was taken further dilution to 10 ml volumetric flask to get a solutions in the range of 0.2-1.8 µg/ml concentration and absorbance was recorded at 214 nm against suitable blank using UV-visible spectrophotometer.

5.3.2 Solubility studies:

Determination of Solubility

The solubility of loperamide in hydrochloric acid, methanol and two liquid vehicles tried to prepare the liquisolid systems, namely, water, tweens & spans, Polyethylene glycol 300, 400, 600, and Propylene glycol were studied by preparing saturated solutions of the drug in these solvents and analysing their drug content spectrophotometrically. Specially, loperamide was mixed in 7ml screw capped vials with such amounts of each of the above solvents in order to produce systems containing an excess of drug. The mixtures were shaken on an automatic test tube shaking machine for 48 hours and then settled for another 2 hours. The screw capped vials were centrifuged at 2500 rpm for further settling of un dissolved crystalline material and thereby obtaining a clear supernatant. After

centrifugation, accurately measured quantities of the filtered supernatant solutions were further diluted with methanol and analysed spectrophotometrically at 214 nm for their drug content. The results were extrapolated to determine the percent mg/ml of loperamide in its saturated solution with the solvents under investigation.

*** Drug concentration in liquid vehicle**

*** Perecent in total weight of the tablet**

5.3.3 FORMULATION OF LIQUISOLID COMPACTS

1. Model drug is initially dispersed in the non volatile solvent systems

(Propylene glycol, PEG 400) termed as liquid vehicles with different drug: vehicle ratio.

2. Then a mixture of carrier (Micro crystalline cellulose pH 102) was added to the above liquid by Continuous mixing for a period of 10 to 20 minutes in a mortar.

3. Then to the above mixture coating material (Aerosil powder) was added and mixed thoroughly. The amount of carrier and coating materials added were based on the R value.

4. To the above binary mixture disintegrant like cross povidone and other additives such as Glidant (magnesium stearate) are added according to their application and mixed in a mortar.

5. The final blend was compressed.

4.3.4 EVALUATION OF POWDER BLEND

The prepared powder blend were subjected to evaluation as per the methods suggested in the Indian Pharmacopoeia like Bulk density, Tapped density, Hausner's ratio, Angle of repose and car's index.

a) Bulk density:

Bulk density of Loperamide was determined by pouring gently 5.00gm through a glass funnel into 20 ml graduated cylinder. The volumes occupied by the samples were recorded. Bulk density was calculated as:

Bulk density *= weight of sample in gram /volume occupied by the sample*

b)Tapped density:

Tapped density was determined by using LABINDIA density tester, which consists of a graduated cylinder mounted on a mechanical tapping device. An accurately weighed sample of powder was carefully added to the cylinder with the aid of a funnel. Typically, the initial volume was noted, and the sample is then tapped (50, 100,150 or 250 tapping) until no further reduction in volume is noted or the percentage of difference is not more than 2%.

A sufficient number of taps should be employed to assure reproducibility for the material in question. Volume was noted and tapped density is calculated using following formula.

Tapped density *= Wt. of sample in gm / Tapped volume*

c) Compressibility Index and Hausner's ratio:

In recent years the compressibility index and the closely related Hausner's ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. Both the compressibility index and the Hausner's ratio were determined by using bulk density and the tapped density of a powder.

$$\text{Carr's index} = \frac{\text{Tapped desnity} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausenr's Ratio *= Tapped Density / Bulk Density*

d) Angle of repose:

The angle of repose of the powder blend was determined by using funnel method. The accurately weighed powder was taken in a funnel. The height of funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The diameter of the powder cone was measured and angle of repose was calculated by using the equation.

$$\text{Tan } \theta = h/r$$

Where ,

h and r are the height of pile and radius of the pile.

TABLE NO 3: The relation between angle of repose and flow properties

Angle of repose θ	Flow
<25	Excellent
25-30	Good
30-40	Passible
>40	Very poor

TABLE.NO 4: Flow property: (Relation of flow property with HR & CI)

Compressibility Index (%)	Flow Character	Hausenr's Ratio
≤10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

5.3.5. CHARACTERIZATION OF LOPERAMIDE LIQUISOLID COMPACTS:

Compatibility Studies: Fourier Transform –Infrared spectroscopy (FT-IR)

The samples of, liquisolid compacts of physical mixture were prepared with KBr in the ratio of 1 : 2 in the form of KBr pellets and subjected for scanning from 4000cm^{-1} to 400cm^{-1} using FT-IR spectrophotometer .the peaks are appeared .

5.3.6 FORMULATION OF IMMEDIATE RELEASE TABLETS OF LOPERAMIDE LIQUISOLID COMPACTS

1. The Lopramide drug was gift sample from MAYSA LABS PVT LTD.

The drug was dispersed in the non volatile solvent systems (Propylene glycol)

Termed as liquid vehicles with different drug: vehicle ratio.

2. Then a mixture of carrier (Micro crystalline cellulose) was added to the above liquid by Continuous mixing for a period of 10 to 20 minutes in a mortar until free flow is obtained.

3. Then to the above mixture coating material (Aerosil powder) was added and mixed thoroughly. The amount of carrier and coating materials added were based on the R value.

4. To the above binary mixture disintegrants like cross povidone and other SSG remaining additives such as Glidant (magnesium stearate) are added according to their application and mixed in a mortar.

5. The final blend was compressed by using 9mm punch.

TABLE NO 5: Formulation Of Loperamide Liquisolid Compacts

Formulations	Drug conc.in PG(%w/w)	R	L_f	MCC (mg)	Aerosol (mg)	Sodium starch glycolate	Total Tablet weight (mg)
F1	2	19.2	0.006	300	15.5	40	380
F2	**2**	**10.5**	**0.009**	**210**	**20**	**40**	**320**
F3	2	20	0.008	200	10	40	300
F4	4	5.6	0.017	225	40	40	330
F5	4	11	0.018	220	20	40	260
F6	4	12	0.017	235	25	40	280
F7	6	10	0.023	260	24	40	310
F8	6	20	0.024	250	12.5	40	330
F9	6	15	0.025	240	15	40	310

Excipient ratio, R=Q/q. Q, weight of carrier; q, weight of coating material.

Liquid load factor, L_f = W/Q . W, weight of liquid medication.

5.3.7. EVALUATION OF TABLETS: (POST COMPRESSION PARAMETER)

1. Weight variation.
2. Hardness.
3. Friability.
4. Disintegration Time.
5. Dissolution.
6. Assay (% of drug content).
7. Compatibility studies.
8. Powder X-Ray diffraction studies.
9. Stability studies.

1. Weight Variation:

20 intact tablets were selected randomly and weighed ,the average weight was calculated. Individual weight of each tablet was determined. According to USP, none of the individual tablet weight should be less than 90% and more than 110% of the average weight.

2.Hardness:

Take 10 tablets from the sample given for analysis, test the Hardness in Kg/Cm^2 for each tablet and note down the results. Calculate the average of the 10 readings and report the average result.

Acceptance criteria: Not less than 4.0 Kg/cm^2.

3. Friability (core tablets):

Take 13 tablets from the sample given for analysis and de-dust. Weigh the tablets and note down the weight. Place the tablets in the drum of the friability apparatus and set the apparatus rotation time for 4 minutes (100 revolutions). Operate the instrument for the specified time or for the rpm. Take out the tablets and de-dust.

Weigh the tablets and calculate the friability by the following formulae.

Friability (%) =

$$\frac{\text{(Initial weight of the tablets – Final weight of the tablets)} \times 100}{\text{Initial weight of the tablets}}$$

Acceptance criteria: Friability is not more than 1.0 %

4. Disintegration Time:

Fill the beakers with water and switch on the Apparatus and wait for some time to reach the desired temperature (37 ^{0} C).When the apparatus reaches to the desire temperature, the siren is coming from the apparatus. Place the 6 tablets in each case of the basket. Press start for disintegration and observe the tablets for disintegration. Note down the time of the last tablet for complete disintegration (No tablet fragments should remain on the mesh of the cases of the basket)

Acceptance criteria: Not more than 30 minutes.

5. Dissolution Studies (In Vitro Drug Release Studies):

The Model drug release from different formulations was determined using aUSP-type2 (paddle type) apparatus under sink condition. The dissolution medium was 900ml 0.01M HCl. 37 ± 0.5°C; at 50rpm, to simulate *in vivo* conditions. The formulation prepared was subjected to dissolution tests for 2hrs. Sample (5ml) was withdrawn at predetermined time intervals (5, 10, 15, 30, 45, 60, 90 & 120), filtered through Whatmann filter paper and replaced by an equal volume of dissolution medium.

Drug content in the dissolution sample was determined by UV spectrophotometer at 214 nm.

Apparatus : USP-2, paddle method

Dissolution Medium : 0.01 N HCl

rpm : 50

Time intervals : 5, 10, 15, 30, 45, 60, 90 & 120

Temperature : 37 ± 0.5^0 C

6. Assay:

Each un coated Tablet Contains

Loperamide BP 2 mg

Method of analysis : HPLC

Chromatographic Conditions :

Column : C18 (4.6 X 15 cm) BDS

Wave length : 214 nm

Flow rate : 1.2 ml

Mobile phase: Buffer: Acetonitrile (50: 50)

Buffer: Weigh and transfer 2.95 gms of Potassium Di Hydrogen Orthophosphate into a 1000 ml VF. Add about 500 ml of Water and shake well to dissolve. Add 0.53 gms of Di potassium Hydrogen Orthophosphate dissolve and makeup the volume with Water.

Standard Preparation: Weigh about 25 mg of working standard transfer to 25 ml VF and make up with Mobile Phase. Transfer 2 ml of this solution to 25 ml and make up with Mobile Phase..

Test Preparation: Weigh equivalent to about 20 mg of the active substance and transfer to a 50 ml VF , shake well to dissolve and make up the volume with Mobile Phase. Filter the solution and reject the first few ml of the filtrate. Transfer 5 ml of the filtrate into a 25 ml VF and makeup the volume with Mobile Phase.

Calculation: Assay = % Tab.

$$\frac{\text{Test Area}}{\text{Std Area}} \times \frac{\text{Std Wt.}}{25} \times \frac{2}{25} \times \frac{50}{\text{Test Wt}} \times \frac{25}{5} \times \frac{\text{Std. purity}}{100} \times \frac{100}{2} \times \text{Avg. Wt.} =$$

Acceptance criteria: Not less than 90 % and not more than 110 % of the label claim.

7. **Compatability studies**:

Compatibilitystudies were carried out using Fourier Transform Infra red spectroscopy to detect any possible interaction of loperamide with the excipient used in the formulation.

The FTIR spectra of the formulations were compared with the FTIR spectra of the pure drug.(400 cm^{-1} - 4000cm^{-1}). The results indicated that the characteristic absorption peaks due to pure loperamide have appeared in the formulated liquisolid compact, without any significant change in their position after successful encapsulation.

8.Powder Analysis XRD:

Powder Analysis of loperamide, physical mixture and liquisolid formulation were studied by using X-ray diffractometer .

X-ray diffraction is based on constructive interference of monochromatic X-rays and a crystalline sample. These X-rays are

generated by a cathode ray tube, filtered to produce monochromatic radiation, collimated to concentrate, and directed toward the sample. The interaction of the incident rays with the sample produces constructive interference (and a diffracted ray) when conditions satisfy Bragg's Law ($n\lambda=2d \sin\theta$). This law relates the wavelength of electromagnetic radiation to the diffraction angle and the lattice spacing in a crystalline sample. These diffracted X-rays are then detected, processed and counted. By scanning the sample through a range of 2θangles, all possible diffraction directions of the lattice should be attained due to the random orientation of the powdered material. Conversion of the diffraction peaks to d-spacings allows identification of the mineral because each mineral has a set of unique d-spacings. Typically, this is achieved by comparison of d-spacings with standard reference patterns.

All diffraction methods are based on generation of X-rays in an X-ray tube. These X-rays are directed at the sample, and the diffracted rays are collected. A key component of all diffraction is the angle between the incident and diffracted rays. Powder and single crystal diffraction vary in instrumentation beyond this.

9. Stability studies: (Accelerated Stability Studies: Temperature 40 ± 2˚C & Relative Humidity 75 ± 5%**)**

The stability studies were carried out according to ICH guidelines by exposing the formulations F1 to F9 in their final packing mode to the temperature 40 ± 2 ˚C and relative humidity 75 ± 5% in programmable environmental test chamber. Aliquot were withdrawn at 30 and 60 days and analyzed for change in drug content, hardness, friability, disintegration time, and in-vitro dissolution profile.

5.0 RESULTS

TABLE N0:6 Standard Calibration Curve of Loperamide In 0.01NHCl at (λ_{max}=214nm)

S.NO	Concentration µg/ml	Absorbance
1	0.2	0.1347
2	0.4	0.2481
3	0.6	0.3541
4	0.8	0.4645
5	1.0	0.5643
6	1.2	0.6723
7	1.4	0.7892
8	1.6	0.8723
9	1.8	0.9921

Standard graph of Loperamide in 0.01N HCl at (λ_{max} = 214nm)

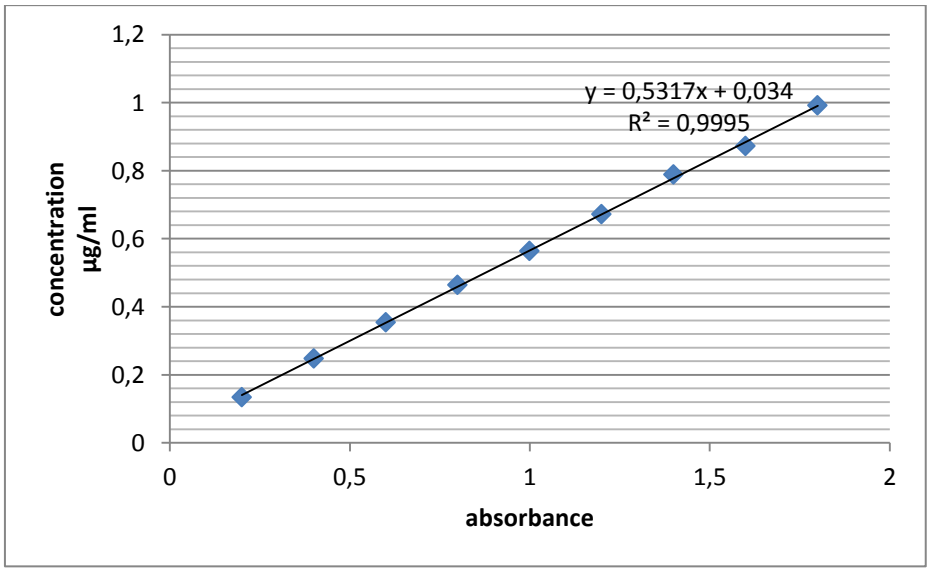


TABLE NO 7: Standard Calibration Curve of Loperamide In Methanol At (λ_{max} = 214nm)

S.NO	Concentration µg/ml	Absorbance
1	0.2	0.1321
2	0.4	0.2489
3	0.6	0.3511
4	0.8	0.4621
5	1.0	0.5689
6	1.2	0.5689
7	1.4	0.7661
8	1.6	0.8801
9	1.8	0.9854

Standard graph of Loperamide in Methanol at (λ_{max} = 214nm)

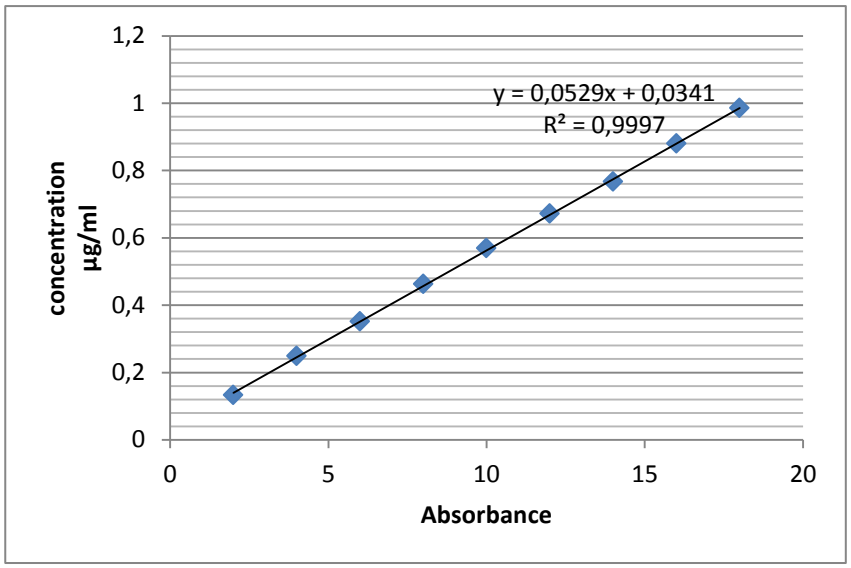
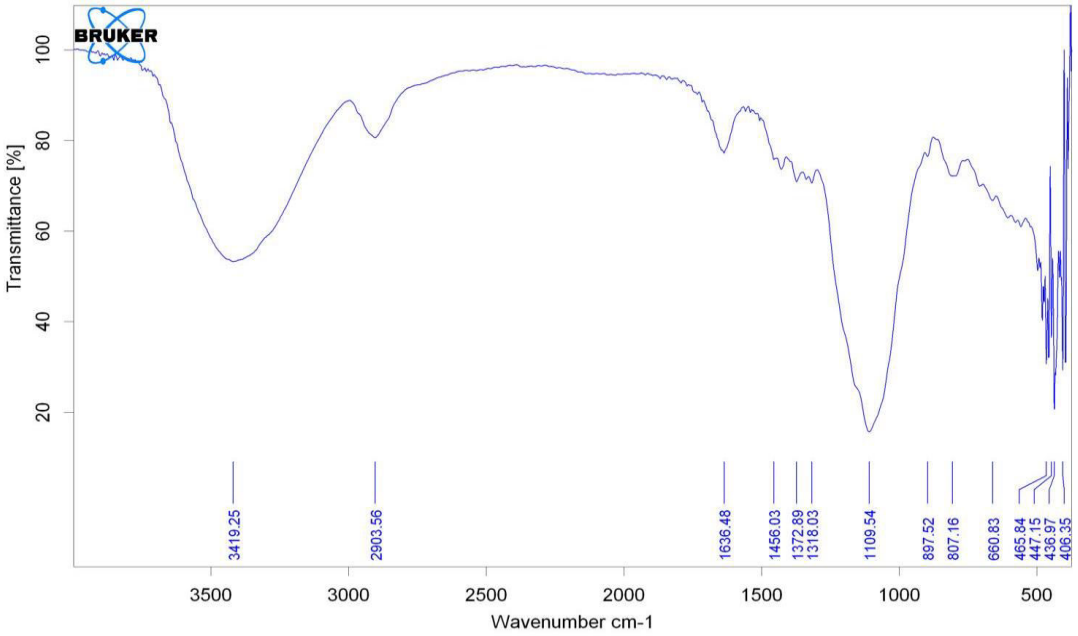


TABLE NO 8: Preformulation Studies

Formulations	Angle of repose	Bulk density(gm/ml)	Tapped density(gm/ml)	Carr's index (%)	Hausner's ratio
F1	28 ± 0.21	0.22 ± 0.02	0.25 ± 0.05	12.53 ± 0.12	1.13 ± 0.11
F2	**30 ± 0.20**	**0.25 ± 0.03**	**0.27 ± 0.01**	**7.40 ± 0.29**	**1.08 ± 0.23**
F3	29 ± 0.25	0.22 ± 0.05	0.25 ± 0.01	12.53 ± 0.19	1.13 ± 0.25
F4	28 ± 0.12	0.23 ± 0.01	0.26 ± 0.03	12.69 ± 0.17	1.13 ± 0.12
F5	27 ± 0.16	0.22 ± 0.07	0.26 ± 0.07	16.34 ± 0.21	1.18 ± 0.16
F6	28 ± 0.30	0.23 ± 0.09	0.25 ± 0.04	8.00 ± 0.15	1.08 ± 0.12
F7	32 ± 0.20	0.25 ± 0.01	0.28 ± 0.01	10.74 ± 0.32	1.12 ± 0.20
F8	30 ± 0.39	0.22 ± 0.03	0.27 ± 0.04	18.51 ± 0.24	1.22 ± 0.24
F9	28 ± 0.45	0.20 ± 0.04	0.26 ± 0.02	23.07 ± 0.31	1.30 ± 0.11

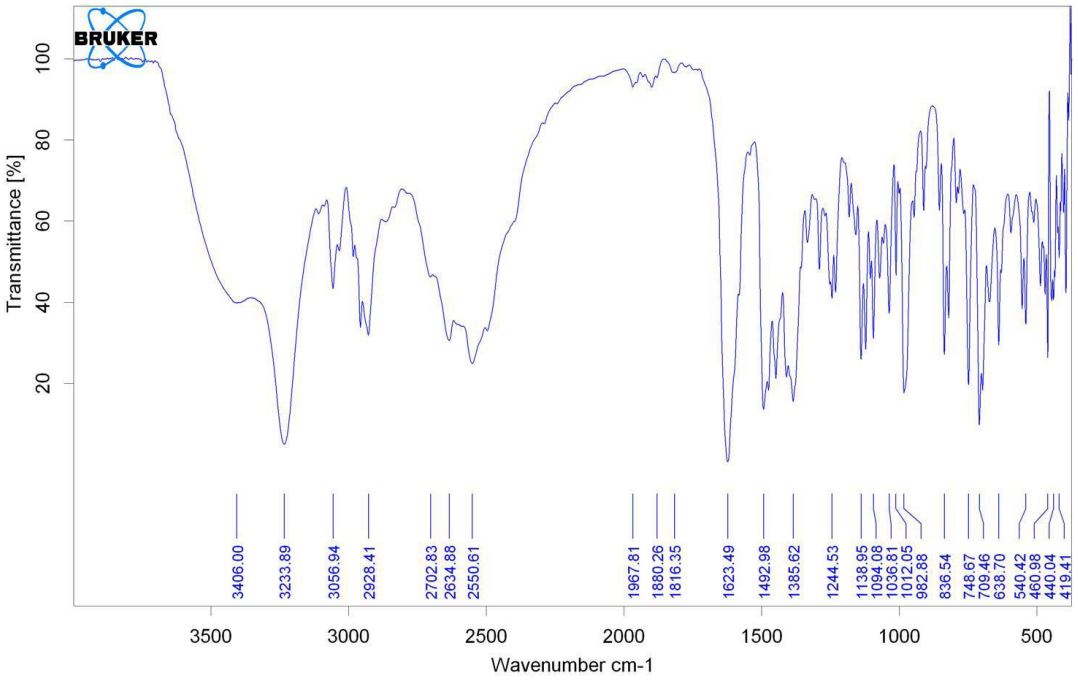
FT-IR STUDIES OF PHYSICAL MIXTURE WITH DRUG



C:\Program Files\OPUS_65\MEAS\LOPERAMIDE.0	LOPERAMIDE	Instrument type and / or accessory	17/06/2014

Page 1/1

FT-IR STUDIES OF PURE DRUG: LOPERAMIDE



C:\Program Files\OPUS_65\MEAS\LOPERAMIDE PURE DRUG.0	LOPERAMIDE PURE DRUG	17/06/2014

Page 1/1

FT-IR SPECTRA OF OPTIMIZED FORMULA: (F2)

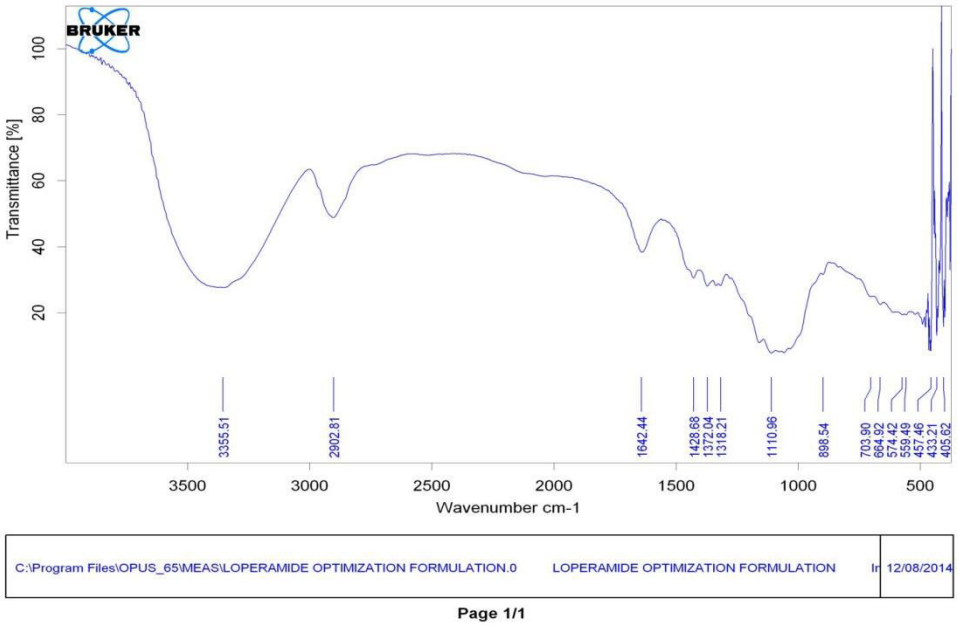


TABLE NO 9: Evaluation Parameters:

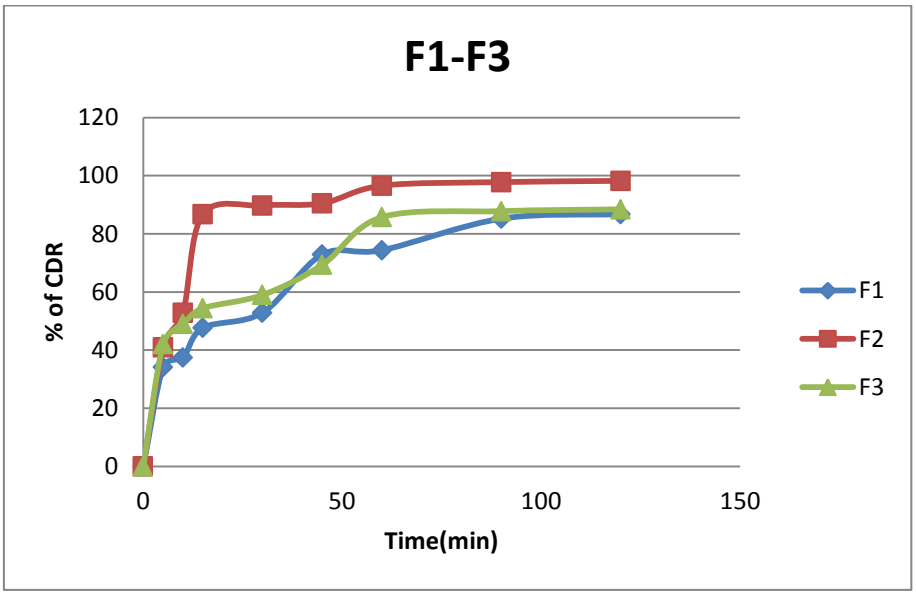
Formulations	Weight Variation	Hardness kg/cm2	Disintegration time (min)	Friability%	% of Drug content (%w/w)
F1	323 ± 3.0	4.5 ± 0.02	3	0.79	96.5
F2	**292 ± 2.5**	**3.0 ± 0.05**	**4**	**0.65**	**98.2**
F3	302 ± 3.11	3.0 ± 0.01	4	0.53	92.9
F4	327 ± 4.7	4.0 ± 0.03	3	0.56	94.00
F5	263 ± 2.14	4.5 ± 0.04	3	0.77	95.9
F6	243 ± 3.23	3.5 ± 0.03	5	0.71	97.43
F7	315 ± 7.43	3.0 ± 0.01	4	0.39	92.24
F8	333 ± 3.56	3.0 ± 0.01	4	0.48	90.09
F9	302 ± 1.98	3.5 ± 0.03	3	0.82	94.89

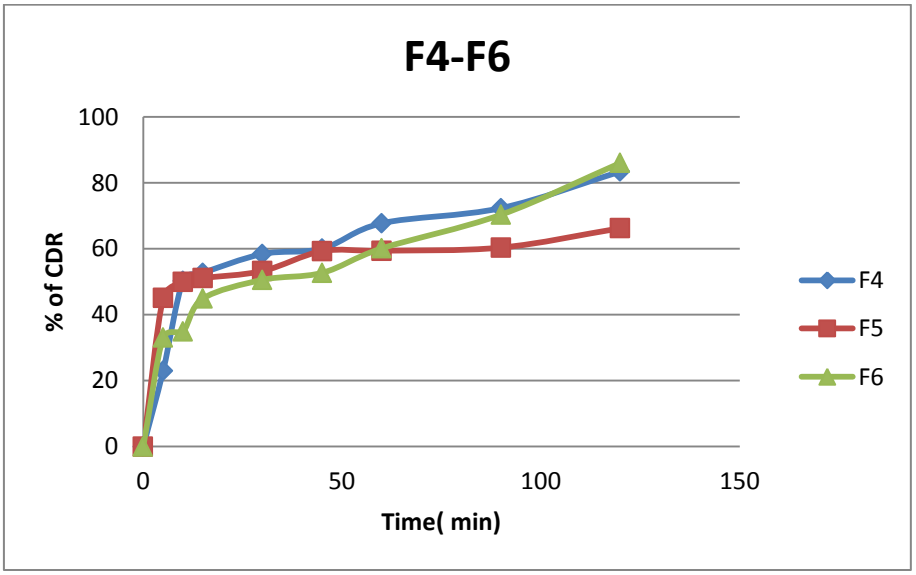
TABLE NO 10 :Invitro% Drug Release Profile Data Of Loperamide Liquisolid Compacts

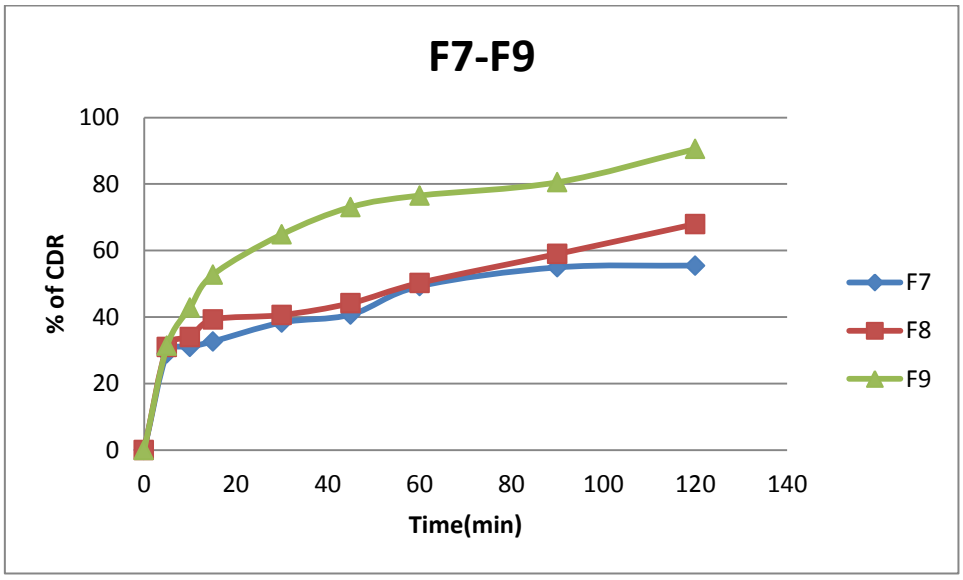
Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	34.50±0.9	**40.98±1.0**	42.06±1.09	23.00± 0.9	45.06 ± 0.9	33.02 ± 1.20	29.07± 0.8	30.96 ±0.08	24.43 ± 0.8
10	37.44±1.2	**52.89±1.0**	49.0±1.04	50.10± 0.7	49.92 ± 1.4	34.93 ± 1.12	31.01 ± 0.9	33.98 ± 0.6	30.67 ± 0.9
15	47.66±0.8	**86.81±1.0**	54.40±1.20	52.66± 0.9	51.09 ± 1.3	44.88 ± 1.05	32.65 ± 0.9	39.25 ±1.01	49.05 ± 0.9
30	52.90± 0.8	**89.76± 0.9**	58.99±1.15	58.50± 1.1	53.22±1.21	50.56 ± 1.04	38.36±1.24	40.61 ±1.04	53.01± 0.7
45	72.89±1.10	**90.50±1.0**	69.35±1.6	60.01± 0.9	59.24±1.02	52.68 ± 1.09	40.74±1.02	44.17 ± 0.9	58.90±1.00
60	74.38±0.7	**96.57± 1.1**	85.76±0.9	67.71± 0.5	59.38 ± 1.3	60.09 ± 1.10	49.27±1.10	50.26 ± 0.8	61.96±1.03
90	85.23±0.4	**97.8± 1.00**	87.81±1.12	72.30± 0.3	60.33 ± 0.7	67.8 ± 1.03	54.93±1.42	50.37 ±1.12	69.87 ± 0.9
120	86.79±1.3	**98.27± 0.9**	88.44±0.9	83.4 ± 0.9	66.22 ± 0.9	70.31 ± 1.32	55.48 ± 1.3	51.52 ±1.01	72.08 ± 0.9

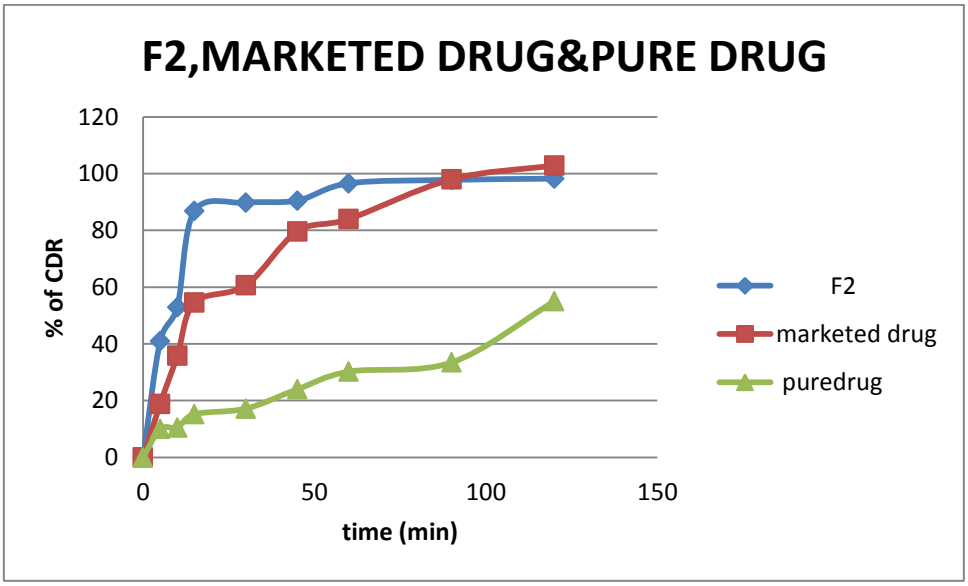
TABLE NO 11: Optimized Formula Compared With the Pure Drug And Marketed Product

Time (min)	Optimized Formula F2	Marketed drug	Pure drug (loperamide)
0	**0**	0	0
5	**40.98**	18.8	9.99
10	**52.89**	35.83	10.5
15	**86.81**	54.57	15.21
30	**89.76**	60.64	17.18
45	**90.5**	79.66	23.98
60	**96.57**	84	30.2
90	**97.8**	98	33.45
120	**98.21**	102.89	55.01

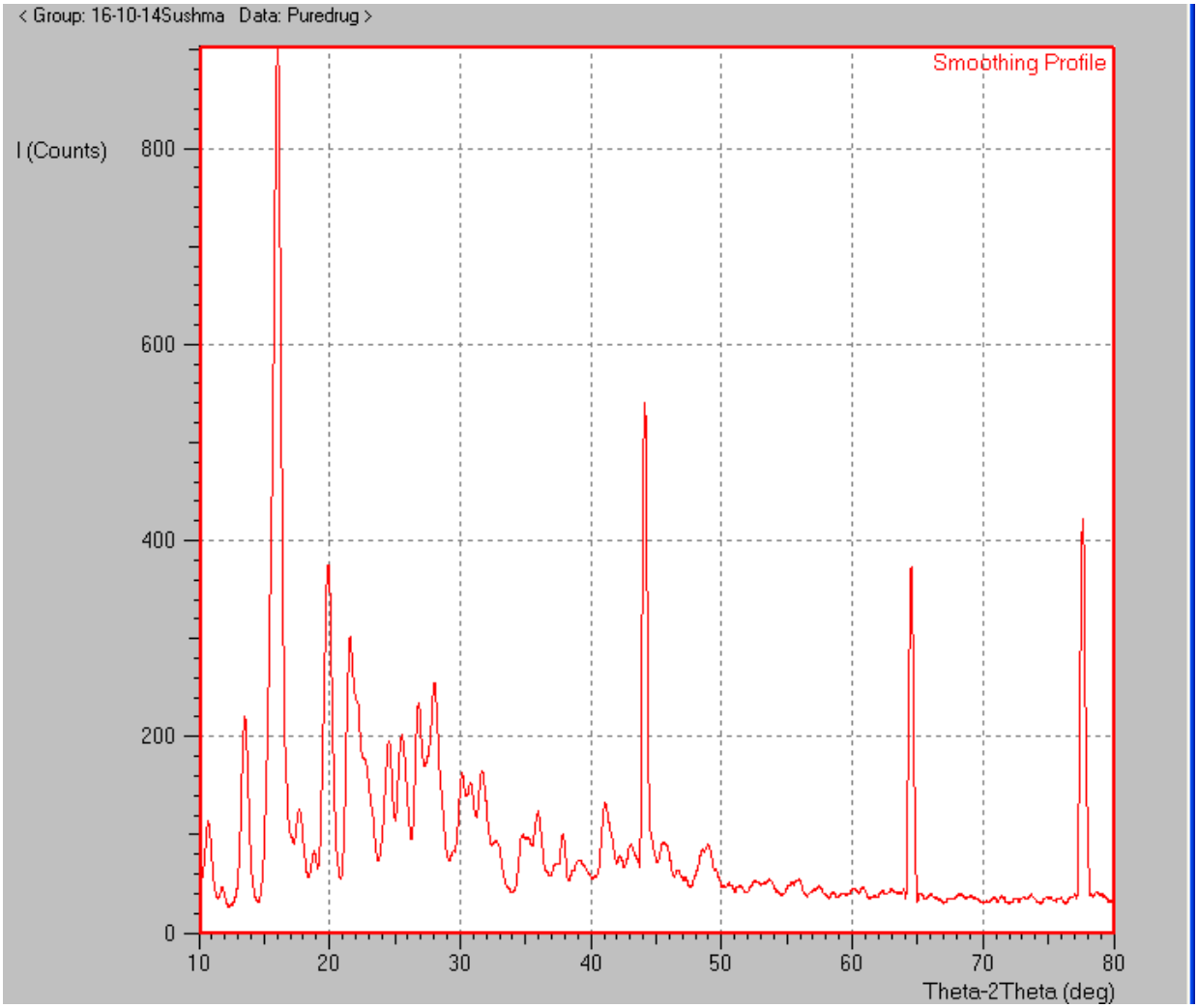

F1-F3
120
100
80
60
40
20
0
% of CDR
0
50
100
150
Time(min)
F1
F2
F3


F4-F6
100
80
60
40
20
0
% of CDR
0
50
100
150
Time(min)
F4
F5
F6

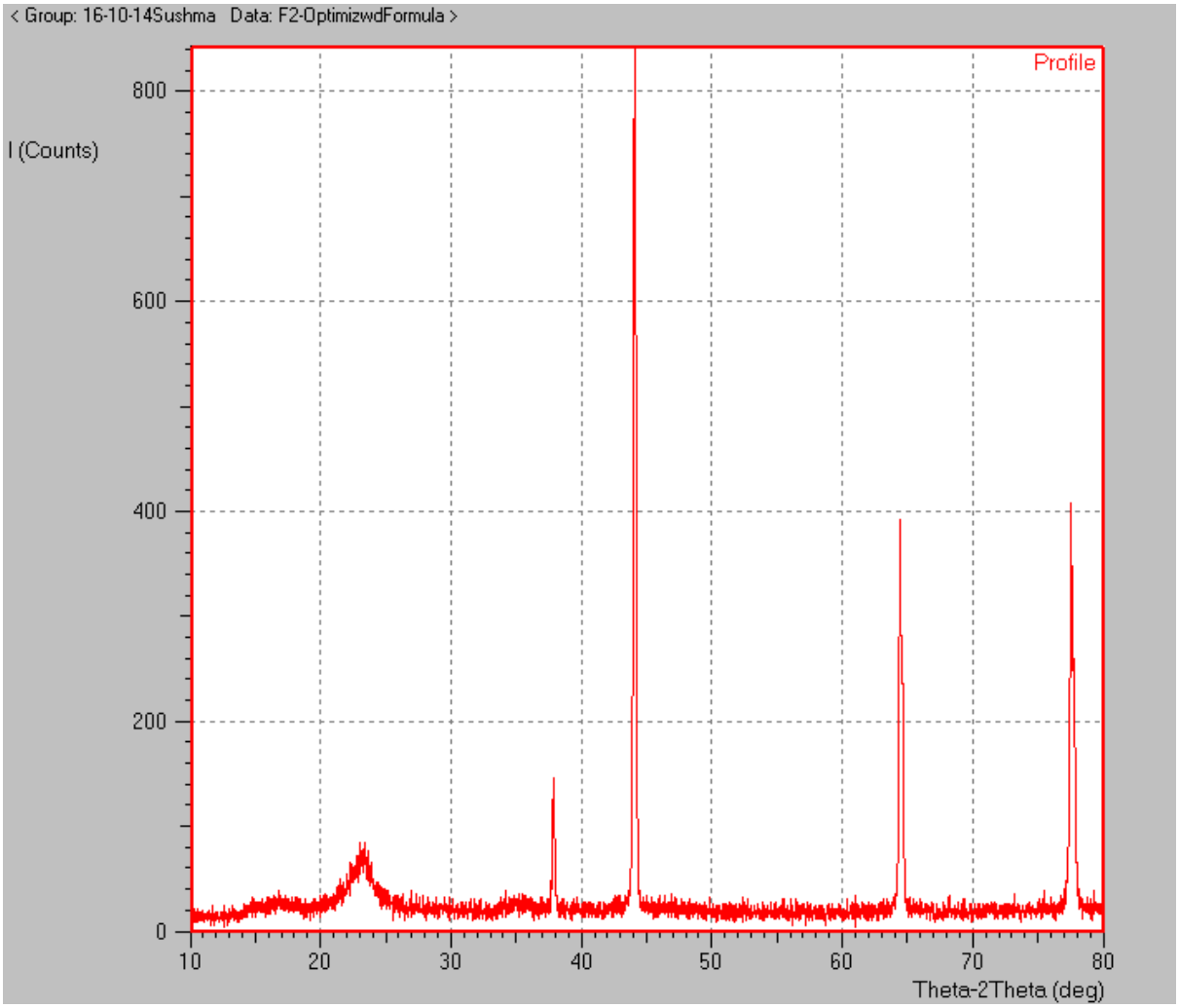

F7-F9
100
80
60
40
20
0
% of CDR
0
20
40
60
80
100
120
140
Time(min)
F7
F8
F9


F2,MARKETED DRUG&PURE DRUG
120
100
80
60
40
20
0
% of CDR
0
50
100
150
time (min)
F2
marketed drug
puredrug

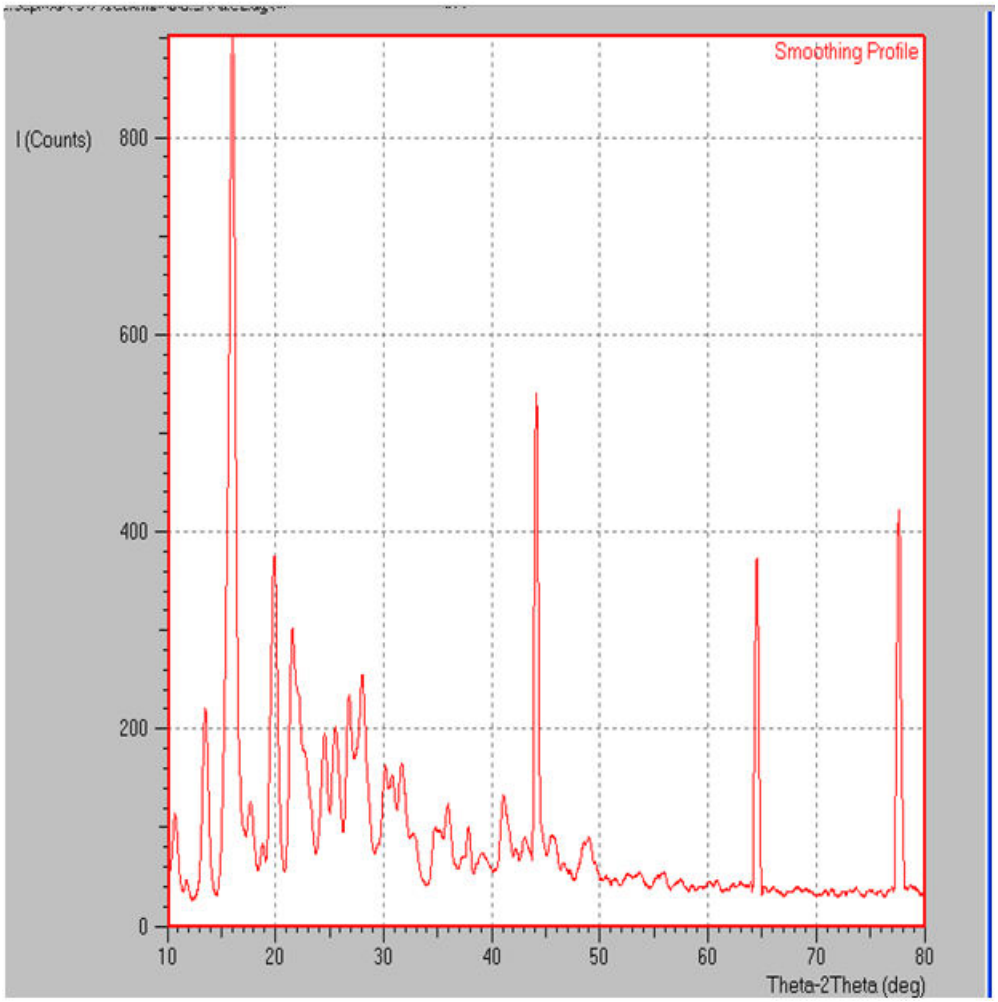
POWDER ANALYSIS: (XRD) X-Ray Diffraction :Pure drug:



Optimized formula F2:



Physical mixture,



STABILTY STUDIES:

TABLE NO 13: Temperature 40 ± 2^{0}C & Relative Humidity 75±5%.

S.No	Time Intervals	Drug Content %
1	Initial	99.2
2	1month	98.90
3	2 Months	98.07
4	3 Months	97.84

6.0. DISCUSSION:

6.1. Calibration Curve Of Loperamide:

The calibration curve of Loperamide was obtained in the range of 0.2 to 1.8 µg at wavelength of 214 nm. It has shown good linearity with a regression coefficient of 0.999. (R2 value)

6.2.Solubity Studies:

The solubility of loperamide in hydrochloric acid, methanol ,water, tweens & spans, Polyethylene glycol 300, 400, 600, and Propylene glycol were studied by preparing saturated solutions of the drug in these solvents and analysing their drug content spectrophotometrically. At 214 nm for their drug content. The results were extrapolated to determine the percent mg/ml of loperamide in its saturated solution with the solvents under investigation.

Among all these vehicles loperamide was highly soluble in propylene glycol

149.65mg/ml.

6.3. Evaluation Parameters For Immediate Release Tablets of Loperamide

6.3.1. Pre Compression Parameters:

The values for Angle of Repose were found to be in the range of 28 °-32 °, Bulk Densities and Tapped Densities of various formulations were found to be in the range of 0.20 ± 0.006 to 0.25 ± 0.007 (g/cc) and 0.25 ± 0.006 to 0.28 ± 0.005 (g/cc) respectively.

Carr's Index of the prepared blends falls in the range of 7.4% to 23.07%. from the result it was concluded that the powder blends had good to fair flow properties and these can be used for tablet manufacture.

6.3.2. Post Compression Parameters:

Hardness:

Hardness of the three tablets of each batch was checked by using Monsanto hardness tester.

The results showed that the hardness of the tablets was in the range of 3.0 to 4.5 Kg/cm2.

Weight variation Test:

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet.

Friability:

Tablets of each batch were evaluated for percentage friability and the data's were shown in above. The average friability of all the formulations lies in the range of 0.39 % to 0.82% which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

In Vitro Disitegration Time:

Tablets of each batch were evaluated for *In vitro* Disintegration Time

The Results Showed That The Disintegration Time Of prepared Tablets Were In The Range Of 3 Mins To 5 Mins.

In Vitro Dissolution Studies:

Finally, Tablets were evaluated for *In Vitro* dissolution studies in simulated gastric fluid and the results were shown in table no: 11

Formulation F1 showed 86.79% of drug release with 4% SSG, Aerosil 15.5 mg, Formulation F2 showed 98.27% of drug release with the 4% SSG Aerosil 20 mg, F3 which contain 4% SSG, 10mg of Aerosil showed 88.44% of drug release, Formulation F4 showed 83.40% of drug release with 4% SSG & Aerosil 40 mg, Formulation F5 showed 66.22% of drug release with 4% SSG & Aerosil 20 mg, Formulation F6 showed 70.31% of drug release with the 4% SSG& Aerosil 25 mg, Formulation F7 showed 55.48% of drug release with the 4% SSG& Aerosil 24 mg, Formulation F8 showed 51.52% of drug release with the 4% SSG & Aerosil 12.5 mg and finally F9 showed 72.08% of drug release with the 4% SSG & Aerosil 15 mg, This result exhibit direct relationship between concentration of propyleneglycol and concentration of Aerosil. Among various formulations the tablets of batch F2 prepared with 2% Propylene glycol and 20 mg Aerosil showed within 15 minutes 85% of drug will be released.

6.4. POWDER X-RAY DIFRACTION:

Powder Analysis of loperamide, physical mixture and liquisolid formulation were studied using X-ray diffractometer .

6.5. Stability studies:

Stability studies were carried out for the selected formulation F2 and the results were shown in table no: 12. The result showed that there was no significant difference in the drug content, disintegration time, hardness and friability at various sampling intervals. The In-vitro dissolution profiles were super impossible which confirms the stability of the product.

The study conducted on formulation and evaluation of liquisolid compacts of loperamide for the Effective management of Anti-diarrheal with the following conclusion:

The tablets were prepared by compression of loperamide immediate release.

The FT- IR study conducted using combination of drugs and excipients concluded that the drug and polymers where compatible.

The pre compression parameters of the powder blends used for preparation of loperamide liquisolid compacts were in acceptable range of pharmacopeial specification with excellent flow and good compressibility.

Loperamide liquisolid compacts was formulated as immediate release tablets using sodium starch glycolate as disintegrants in increased concentration by direct compression method. The loperamide tablets are evaluated for post compression parameters suggested that hardness, thickness, weight variation and friability were in acceptable limit with good handling properties. All the loperamide immediate release formulations where rapidly disintegrates in less than 5min. All the formulated loper amide liquisolid compacts showed drug content of more than 92%.

CONCLUSION AND SUMMARY

7.0. CONCLUSION

The Following conclusions were drawn from the Liqisolid compacts studies:

The solubility studies of Loperamide in presence of Propylene Glycol was high when compared with PEG and Tweens & spans.

The liquisolid technique was found to be a promising approach for improving the dissolution of poorly soluble drugs like lopermide.

The Dissolution of loperamide was significantly increased in liquisolid formulation compared to the marketed product. The IR spectra indicate there was no interaction between the drug and excipients.

The increased dissolution rate may be due to increased wetting and increased surface area of the particles.

From the XRD, FT-IR, Drug content & *In Vitro* dissolution studies of loperamide liquisolid compacts it was concluded that the formulation F2 is the best formulation.

The following conclusions were drawn from the Liquisolid compacts formulated to tablets:

The powder blend was subjected to various physical characteristics such as bulk density, tapped density, Hausner's ratio, compressibility index. The powder was compressed and the core tablets were evaluated for weight variation, hardness, disintegration time, drug content, dissolution studies, powder analysis like XRD, FT-IR studies & stability studies is concluded the best formulation is F2.

7.1.0. SUMMARY

The major problem in oral drug formulations is low and enteric bioavailability, which mainly results from poor aqueous solubility. Liquisolid compacts is the techniques are the most attractive processes to improve solubility of poorly soluble drugs .

Loperamide hydrochloride an oral Anti-diarreheal agent used for the treatment of diarrheal.

Loperamide is a Piperidine derivative. Loperamide is an opioid-receptor agonist and acts on the μ-opioid receptors in the myenteric plexus of the large intestine.

- Slows intestinal motility and affects water and electrolyte movement through the bowel.Inhibits peristaltic activity by a direct effect on circular and longitudinal muscles of the intestinal wall.
- Prolongs the transit time of intestinal contents; reduces fecal volume, increases fecal viscosity and bulk density, and diminishes loss of fluid and electrolytes.
- Inhibits peristalsis of intestinal wall musculature and intestinal co ntents. Also reduces fecal volume, increases fecal bulk, andminimi zes fluid and electrolyte loss.

Here the solubility of Loperamide is enhanced by liquisolid compacts with propylene glycol as liquid medication. Then the formed liquisolid compact is characterized and evaluated by FT-IR , drug content and

In Vitro dissolution studies.

Among the various liquisolid compacts were prepared, the formulation F2 i.e., the liquisolid compacts of Loperamide with PG 2% shows faster dissolution rate.

The prepared tablets of LOPERAMIDE were evaluated for precompession parameters like angle of repose, bulk density, tapped density, carr's index and post compression parameters like hardness,

friability, weight variation, drug content, *In Vitro* disintegration time and *In Vitro* dissolution studies.

Accelerated stability studies was carried out for selected formulations F2 which showed no significant difference in the drug content, disintegration time , hardness, friability and *In vitro* dissolution studies which confirm the stability of product.

REFERENCES

1. S. Erturk, S. E. Aktas. An HPLC method for the determination of Atorvastatin and its impurities in bulk drug and tablets. J. Pharm. Biomed. Ana. 2003, 33: 1017-1023.

2. Charman SA, Charman WN. Oral modified release delivery systems, In: Rathbone MJ. Hadgraftb J, Roberts MS. Modified Release Drug Delivery Technology, New York, 2003, pp.1-9.

3. Darwish AM, El-Kamel Ah. Dissolution enhancement of glibenclamide using liquisolid tablet technology, Acta Pharm. 2001, 51: 173-181.

4. Rasenack N, Muller BW. Dissolution rate enhancement by in situ micronization of poorly water-soluble drugs. Pharm Res. 2002; 19: 1894-1900.

5. Modi A, Tayade P. Enhancement of Dissolution Profile by Solid Dispersion (Kneading) Technique. AAPS Pharm Sci Tech. 2006; 7(3): 2-17.

6. Kulkarni G.T, Gowthamarajan K, Suresh B. stability testing of pharmaceutical product: an overview Indian J Phar Edu 2004; 38(4): 194-202.

7. Colombo P., Bettini Release., Catellani P.L. Drug volume fraction profile in the gel phase and drug release kinetics in hydroxypropyl methyl cellulose matrices containing a soluable drug, European Journal of Pharmaceutical Sciences. 2002; 86: 323 – 32.

8. Ajit KS, Nagesh H, Aloorkar, MS, Jayashree B, Gaja. Liquisolid Systems: A review. Int J PhamaSci Nano 2010; 3:795-802.

9. Grimm W. Extension of the international conference on harmonization tripartite guideline for stability testing of new drug substances and products to countries of climatic zones III and IV. Drug Dev Ind Pharm 1998; 24:313-25.

10. Spire as S, Bolton M. Liquisolid Systems and Methods of Preparing Same. U.S Patent 5,968,550, 1999.

11. David JH (2002). Lipid-Based Systems for Oral Drug Delivery. Enhancing the Bioavailability of Poorly Water Soluble Drugs. In forma Healthcare. USA.

12. Hecq, JJ (2006). Development, characterization and evaluation of crystalline nanoparticles for enhancing the solubility, the dissolution rate and the oral bioavailability of poorly water-soluble drugs. Open thesis. 11(17).

13. Javadzadeh Y, Jafari- Navipour B, Nokhodchi A (2007).Liquisolid technique for dissolution rate enhancement of high dose water-insoluble drug carbamazepine.

14. InternationalJournalofPharmaceutics.341(12):2634http://dx.doi.org/10.1016/j.ijpharm.2007.03.034PMid:17498898

15. Spire as S, Sadu S, Grover R (1998). In vitro release evaluation of hydrocortisone liquisolid tablets. Journal of Pharmaceutical Sciences. 87(7): 867-872.http://dx.doi.org/10.1021/js970346g PMid:

9649356Spireas S, Bolton SM (1999). Liquisolid systems and methods of preparing same. Google Patents. Patent number: 5800834

16. Spire as S, Sadu S (1998). Enhancement of prednisolone dissolution properties using liquisolid compacts.

17. International Journal of Pharmaceutics. 166(2): 177-188.http://dx.doi.org/10.1016/S0378-5173(98)00046-5Sugawara M, Kadomura S, He X, Takekuma Y, Kohri N,Miyazaki K (2005). The use of an in vitro dissolution and absorption system to evaluate oral absorption of two weak bases in pH-independent controlled-release formulations. European Journal of PharmaceuticalSciences.26(1): 1-8.http://dx.doi.org/10.1016/j.ejps.2005.02.017PMid:15961297Aleti SR, Rangaraju D, Kant A, Shankraiah MM,Venkatesh JS, Rao RN, Nagesh C (2011). Solubility and Dissolution Enhancement of Cefixime Using Natural Polymer by Solid Dispersion Technique. International Journal of Research in Pharmacy and Chemistry. 1(2):283-288.

18. Vidyadhara S, Babu JR, Sasidhar RLC, Ramu A, Prasad SS, Tejasree M (2011). Formulation and evaluation of glimepiride solid dispersions and their tablet formulations for enhanced bioavailability. International Journal of Advances in Pharmaceutical sciences. 2(1).Yalkowsky S, Rubino JT (1985). Solubilisation by cosolventsI: Organic solutes in propylene glycol-water mixtures. Journal of pharmaceutical sciences. 74(4):416421.http://dx.doi.org/10.1002/jps.2600740410PMid:3999002

19. Youn YS, Jung JY, Oh SH, Yoo SD, Lee KC (2006).Improved intestinal delivery of salmon calcitonin by Lys18-amine specific PEGlytion: Stability, permeability, pharmacokinetic behaviour and in vivo hypocalcaemia efficacy. J Control Release. 114:334342.http://dx.doi.org/10.1016/j.jconrel.2006.06.007 PMid: 16884808

20. Killinger JM, Weintraub HS, Fuller BL. Human pharmacokinetics and comparative bioavailability of L operamide hydrochloride *Clin Pharmacology*. 1979; 19:211-8. [IDIS 105319] [Pub Med 438356]

21. McNeil Consumer. Imodium A-D (Loperamide hydrochloride) caplets and oral solution prescribing information. In: Sifton DW, ed. Physicians' desk reference. 55th ed. Montvale, NJ: Medical Economics Company Inc; 2001:1817-8.

22. Food and Drug Administration. Loperamide marketed over-the-counter. *FDA Drug Bull*. 1988; 18:2.

23. Lewis JH. Summary of the 31st meeting of the Food and Drug Administration gastrointestinal drugs advisory committee. December 8-9, 1986: loperamide as an OTC anti-diarrheal. *Am J Gastroenterology*. 1987; 82:443-4.

24. US Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA) Prevention of Opportunistic Infections Working Group. 2001 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons with human immunodeficiency virus. From HIV/AIDS Treatment Information Services (ATIS) website

25. Wolfe MS. Protection of travelers. *Clin Infect Dis*. 1997; 25:177-86. [IDIS 392200] [Pub Med 9332506]

26. Centers for Disease Control and Prevention. Health information for international travel, 2003–2004. Atlanta, GA: US Department of Health and Human Services; 2003:184-91,226-7,233. Updates available from CDC website ().

27. Anon Advice for travellers . *Med Lett Treat Guid*. 2004; 2:33-40.

a. AHFS Drug Information 2003. McEvoy, GK, ed. Loperamide Hydrochloride. Bethesda, MD: American Society of Health-System Pharmacists; 2003:2740-2.

b. McNeil Consumer. Imodium Advanced (Loperamide hydrochloride and simethicone) caplets and chewable tablets prescribing information. In: PDR.net [database online]. Montvale, NJ: Thomson Healthcare; 2004.

c. McNeil Consumer. Imodium A-D (Loperamide hydrochloride) liquid and caplets prescribing information. In: PDR.net [database online]. Montvale, NJ: Thomson Healthcare; 2004.

d. Teva Pharmaceuticals. Loperamide hydrochloride capsules prescribing information. Sellersville, PA; 1998 Jul.