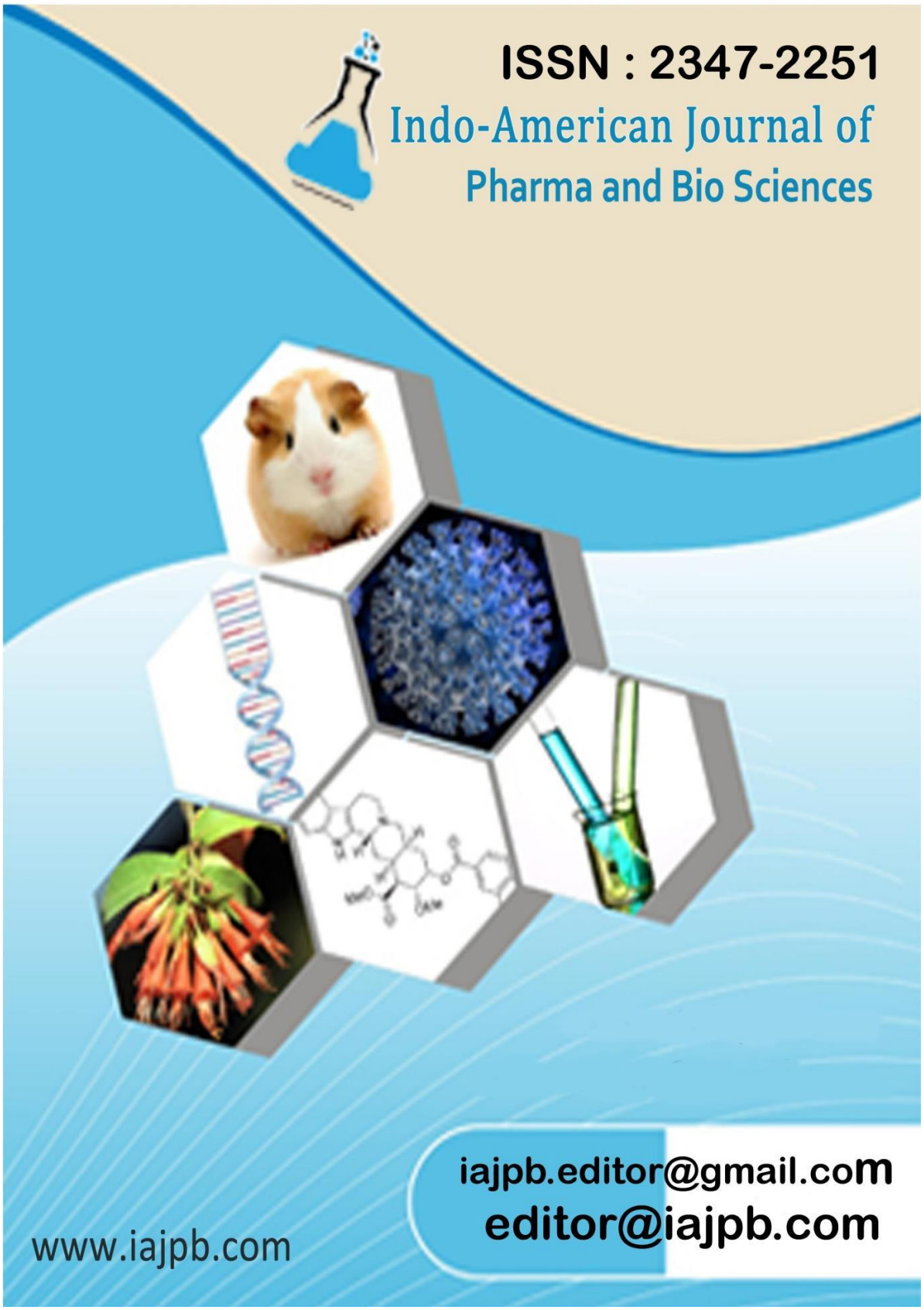
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FORMULATION AND EVALUTION OFORLISTAT LIQUISOLID TABLETS

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ABSTRACT

Orlistat is an almost insoluble anti-obesity drug; this study aimed to apply the liquisolid technology to increase its solubility. Orlistat was dissolved in Polyethylene Glycol, and then different liquisolid tablets were made by using Avicel PH 102 as the carrier, Aerosil 200 as the coating material, and Sodium starch glycolate as the disintegration agent. The formulations included dissolving agents such polyvinyl pyrrolidine, hydroxypropyl methylcellulose, and hydroxypropyl guar. Calculations were made using the liquid load factor for the liquid vehicle to determine the optimum quantities of carrier and coating materials required to create suitable flowing and compactable powder admixtures feasible for tablet formation. The resulting liquisolid tablets were analysed after compression for properties such as weight variation, hardness, friability, drug content, and in-vitro dissolving tests. The medicine and excipients were not identified to have any chemically significant interactions in the FT-IR analysis. The drug's transformation from crystalline to amorphous form in liquisolid tablets was confirmed by differential scanning calorimetry. Orlistat pills in liquid form exhibited greater wetting qualities and a larger surface area accessible for disintegration, allowing them to release more medication than directly broken tablets. This research shows that liquisolid technology has the potential to increase the water solubility of medications that are just slightly soluble in water.

Aerosil 200, Avicel PH 102, Orlistat, in-vitro dissolution, liquisolid pills, and anti-obesity are some keywords to bear in mind.

INTRODUCTION

According to medical professionals, being overweight or obese is harmful to one's health and may shorten one's life expectancy. If a person's body mass index (BMI) is between 25 and 30 kg/m2, they are considered overweight (per-obesity), and if it's 30 or more, they are considered obese. One's body mass index is determined by dividing their weight in kilogrammes by the square of their height in meters or feet and inches.

Metric: BMI = kilograms / meters^2

US customary and imperial: BMI=lb 703/in^2

where lb is the subject's weight in pounds and in is the subject's height in inches.

Numerous nations, both industrialized and developing, face a serious health crisis due to the prevalence of childhood and adolescent obesity. The startling doubling of its incidence over the previous two decades has led the World Health Organization (WHO) to name obesity as one of the world's top 10 health concerns. Males lose

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an average of 7.1 years off their lives and females 5.8 years due to obesity-related causes. After the United States and China, India is third in the global ranking of countries with the greatest prevalence of obesity and overweight persons (11% of adolescents and 20% of all adults are obese or overweight).Worldwide, a massive

obesity epidemic has emerged. The United States is not alone in seeing a rise in the prevalence of overweight and obesity; this pandemic can be seen across the industrialized globe. There has been no safe haven from

this pandemic for countries with weaker medical systems. As standards of living have risen, more people are overweight or obese, shifting the balance away from the underweight. Overweight or obese people are estimated to number 1.5 billion globally. Studies have shown that obesity is much more harmful than smoking or drinking. Diabetes, high blood pressure, and cancer are just a few of the many deadly illnesses and ailments linked to obesity. Overweight and obesity are the fifth greatest cause of mortality in the world. The American Medical Association (AMA) officially classified obesity as a disease in June 2013.Increased physical activity and caloric restriction are now recommended for the treatment of obesity. If symptoms do not improve with behavioral therapy, physicians may suggest medication. Several medications originally licenced to treat obesity have been taken off the market due to an excessive number of reports of harmful side effects. The increased risk of mental illness and non-fatal myocardial infarction or stroke led to the revocation of licences for amphetamine, rimonabant, and sibutramine. Orlistat is the primary option for treating obesity due to its efficacy in controlling diabetes and its minimal cardiovascular side effects. 4

EFFECTS AND COMPLICATIONS OF OBESITY

Asthma has been linked to high cholesterol and atherosclerosis (the buildup of fat in the arteries).
Diabetes, high blood pressure, and excess body fat are all components of the metabolic syndrome.As a breathing condition, sleep apnea may be dangerous since it causes patients to stop breathing repeatedly while they sleep.Symptoms of osteoarthritis often include joint pain and stiffness.
In the absence of alcohol use, a condition known as nonalcoholic fatty liver disease may develop.
Disorders of the cardiovascular system and the endocrine system, such as high blood pressure and swings in blood sugar.Terrible levels of HDL cholesterol and triglycerides.What Factors Influence Your Body Fat Percentage, and How to Determine Them

Table No: 01 BMI CLASSIFICATION

BMI	WHO Classification	Popular description
< 18.5	underweight	Thin
18.5–24.9	normal weight	'Healthy', 'normal', 'acceptable'
25.0–29.9	Grade-I overweight	Overweight
30.0–39.9	Grade-II overweight	Obesity
≥ 40.0	Grade-III overweight	Morbid obesity

FACTORS INFLUENCING OBESITY

In the past, it was believed that being overweight was due to nothing more nefarious than consuming more calories than one burnt. However, studies have shown that genetic, physiological, and behavioral variables all interact in complex ways and may contribute to obesity. Food, including protein, carbohydrates, and fat, is our primary source of energy. These extra calories are deposited as triglycerides in the body's adipose tissue (body fat). Overeating on a regular basis without corresponding increases in energy expenditure has been linked to obesity and weight gain. Thermic impact of food, BMR, and thermic effect of physical activity (including both activity-related thermogenesis, or voluntary exercise, and non-activity-related exercise thermogenesis, or all other activity not connected to "sports-like" exercise), all contribute to total energy expenditure. Twenty percent of the variation in daily energy expenditure is attributable to minor, incidental activities. (7) The word "obesity" is used to refer to a collection of disorders with similar symptoms but different causes. An individual's weight is determined by a combination of physiological mediators of energy intake and expenditure, genetic, environmental, and psychological variables. While it is true that genetic variations have a role, technological progress may also be blamed for the dramatic increase in obesity rates by influencing people's lifestyles and eating patterns.

Fig No: 01 FACTORS INFLUENCING OBESITY

CAUSES AND ASSOCIATIONS OF OBESITY

Table No: 02 CAUSES AND ASSOCIATIONS OF OBESITY

Environmentalcauses	Excess calorie intakePhysical Inactivity	Major determinants ofobesity
Genetic causes	Monogenic (rare)	Leptin deficiency/ resistance
		Melanocortin 4 receptor mutation
	Chromosomal Rearrangements (rare)	Prader-Willi Syndrome
		Lawrence-Moon-Biedl Syndrome
	Polygenic (common)	A large number of human genes show variations in DNA sequences that might contribute to obesity.
Secondary causes	Cushing syndrome	
	Hypothyroidism	
	Hypothalamic lesions	
	Polycystic variant syndrome	
	Medications: E.g. Steroids	

METHODS TO ENHANCE THE SOLUBILITY

Solubility may be improved in a number of ways, including by physical alteration, chemical modification, and others. (13)

Table No: 03 METHODS TO ENHANCE THE SOLUBILITY

Physical Modification				
Particle size reduction	**Modification of the crystal habit**	**Drug dispersion in carriers**	**Complexation**	**Solubilisation by surfactants**
1. Micronization 2. Nanosuspension Homogenization Wet milling 3. Sono-crystallization Supercritical fluidprocess Spray drying	polymorphs Pseudo Polymorphs	1. Eutec tic mixtures Hot plate method Solvent evaporation method Hot- melt extrusion Melting-solvent method	Use of complexing agents Inorganic Coordination Chelates Metal-olefin Inclusion Molecular complexes	Microemulsions Self-microemulsifying drug delivery systems
Chemical Modification				
a. Soluble prodrugs	b. Salt formation			
Other Techniques				
a. Co-crystallisation	b. Cosolvency	c. Hydrotrophy	d. Solubilizing agents	e. Nanotechnology approaches

LIQUISOLID TECHNIQUE:

When Spireas16 realised that a liquid might be converted into a freely flowing, highly compressible, and superficially dry powder by combining it with a carrier and coating material of choice, he introduced the liquisolid technique. A liquid component, such as the drug itself or a suspension or solution of the drug in an appropriate non-volatile liquid vehicle, may also be included into the porous carrier material. Polyethylene glycols, propylene glycols, and glycerin are all good choices due to their low reactivity and high boiling points. Submerging a carrier causes the coating particles to swiftly soak up the liquid, leaving just a thin film of liquid on the surface of the carrier. 17

Powdered versions of liquid pharmaceuticals, known as "liquisolid compacts," are just as effective as the original drugs while being more convenient to use. Liquid medicine is a pharmaceutical product that has been dissolved in a liquid vehicle that is safe for human consumption, and does not contain lipophilic (oily) drugs or water-insoluble solid pharmaceuticals. Combining a liquid drug with certain powder excipients, known as the "carrier and coating components," turns it into a dry-looking, nonadherent, free-flowing, and readily compressible powder. 18

COMPONENTS OF LIQUISOLID COMPACT FORMULATION

Examples of liquid pharmaceuticals include lipophilic liquid medicines, as well as suspensions or solutions of solid water-insoluble substances in a suitable non-volatile solvent system. By dissolving liquid lipophilic medicines, drug suspensions, or solutions of water-insoluble solid pharmaceuticals in suitable non-volatile solvent systems, and then drying the resulting mixture, one obtains a powder admixture that is dry, non-adherent, free-flowing, and easily compressible; this is known as a "liquisolid system" (19).

Liquisolid compact mainly includes,

Non volatile solvent

Disintegrant

Carrier materials

Coating materials

CLASSIFICATION OF LIQUISOLID SYSTEM

There are three distinct categories of liquisolid systems that may be defined by the liquid medicine they deliver:

Powdered drug solutions

Powdered drug suspensions

Powdered liquid drugs

Both of the earlier kinds may be made by concentrating pharmaceutical liquids, whereas both of the latter types are the direct result of concentrating pharmaceutical liquids. This is because the medicine was formulated in a liquid vehicle that did not evaporate during processing, resulting in a more even distribution of the drug throughout the finished product.Liquisolid systems may be broken down into two groups, depending on the formulation method used.
Changing from a liquid to a solid state

Liquisolid microsystems

An additive, like Polyvinylpyrrolidone (PVP), is added to the liquid medication before it is combined with the carrier and coating materials to create an acceptably flowing admixture for encapsulation in the new concept of liquisolid microsystems. This method is identical to the preparation of liquisolid compacts.

PREPARATION OF LIQUISOLID TABLETS

The medication is mixed with the non-volatile solvent in a certain ratio, and the combination is then heated to facilitate drug breakdown. After adding the carrier and coating ingredients to the medication solution, the mixture is thoroughly combined. Spireas et al. define the mixing process as having three separate stages (21)
First, the powder and liquid medicine are thoroughly combined at a mixing rate of approximately one rotation per second for about a minute. Next, you'll want to give the mortar a uniform coating of the liquid/powder admixture and let it sit for about five minutes so the powder can soak up the medicinal solution from the inside out. Next, using an aluminium spatula, scrape the powder from the mortar surfaces and mix it with the disintegrant for another 30 seconds. Because of this, liquisolid pill compositions are one step closer to reality.

A single punch tablet press machine is used to compact the resultant liquid-to-solid formulation.

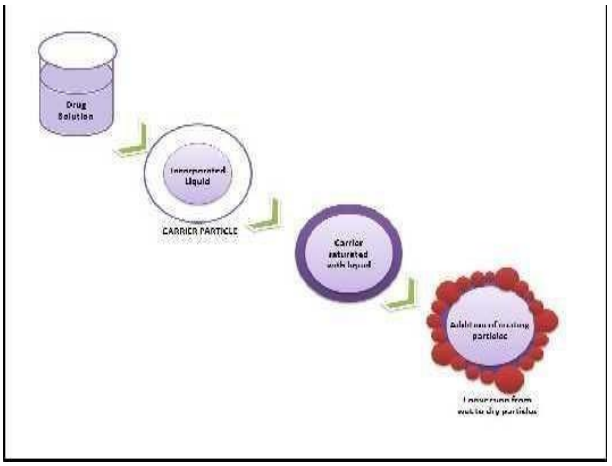
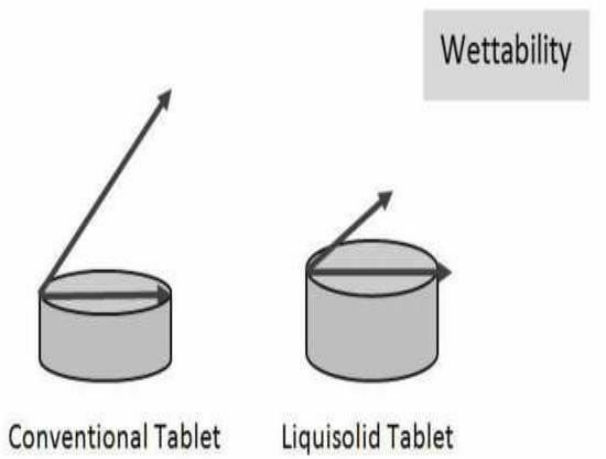


Fig No: 02 SCHEMATIC REPRESENTATION OF LIQUISOLID SYSTEMS

MECHANISM OF SOLUBILITY ENHANCEMENT BY LIQUISOLID TECHNIQUE

Several arguments have been made for why the liquisolid approach could be useful for improving medication delivery. Liquisolid systems, in which the medication has been fully dissolved in the liquid vehicle while remaining solubilized and molecularly disseminated in the powder substrate, are one of the three main hypothesised processes. Therefore, a lot more drug surface area is accessible for release, as compared to drug particles inside directly broken tablets.
The liquisolid system may be used to boost drug release in a second way, by boosting the drug's solubility in water (Cs). The little quantity of liquid vehicle in a liquisolid compact is insufficient for increasing a drug's solubility in an aqueous dissolving solution. If the liquid vehicle acts as a co-solvent, the microenvironment at the solid/liquid interface between the main particle and the release medium might be conducive to increasing the drug's water solubility.
The main particles are more extensively wetted when the liquid carrier contains a surface active agent or has a low surface tension. Using contact angle and water-rise time measurements, we can see that these materials are indeed wettable. Wetting medication particles with a nonvolatile solvent in liquisolid technology reduces the interfacial tension between the dissolving liquid and the tablet's surface, facilitating faster and more complete drug dissolution. Liquisolid compacts' reduced contact angle compared to that of standard tablets is evidence of their better wettability. (24)



LIQUISOLID COMPACTS

ADVANTAGES OF LIQUISOLID TECHNIQUE

Drugs with varying degrees of water solubility, as well as those that are completely insoluble in water, may all benefit from administration through liquid drug delivery systems. Many drugs that aren't water soluble and are typically taken orally may have increased bioavailability when administered intravenously. These strategies are far less expensive than the production of soft gelatin capsules.By maintaining the drug's solubilized liquid condition during tablet or encapsulated dosage form production, the drug's dissolving profile and wetting properties are improved.
Since more of the drug's surface area will be exposed to the solvent, absorption will be increased.The liquisolid method might be used to give medicines that arrive in a powdered liquid form.

Rapid or slow administration is possible with these liquisolid solutions.
capsules or tablets that release their contents slowly over time, often loaded with a liquid that isn't water-soluble.Preserve the uniformity of solubility rates (zero order release).Dosage accuracy may be enhanced by incorporating these technologies into the pharmaceutical industry.On a molecular scale, the medicine might be dispersed throughout the formulation.A medication's release rate may be managed by the formulation's components.The capacity to manufacture on an industrial scale is also achievable.Absorption rates may be higher with this method of delivery than with the more conventional oral tablets, according to certain studies.Differentiating dosage forms may be accomplished in part by colouring the liquid carrier.
We plan on comparing the product to other formulations, such as solid dispersions, in an effort to lessen the overall quantity of fillers used.
Nano- and micro-focused processes should be avoided.

DISADVANTAGES OF LIQUISOLID TECHNIQUE

It calls for the use of excipients with high specific surface areas and high adsorption capacities. More carrier may be added to the powder to improve its flowability, but this makes the tablets heavier than one gramme and more challenging to swallow.
Do not use in the production of soluble pharmaceuticals in doses more than 100 milligrammes.
Because the liquid medicine within liquisolid tablets may seep out during compression, the tablets may not be hard enough or have good enough compression qualities.
For present, it is unclear whether this technique can be used commercially to efficiently insert tiny amounts of viscous liquid solutions onto massive quantities of carrier material.

OBJECTIVES

Formulation and evaluation of orlistat liquisolid tablets

OBJECTIVES OF THE PRESENT STUDY:

Because orlistat, an anti-obesity medicine, is only slightly soluble in water, the liquisolid technique was developed to hasten its dissolution.For the purpose of this research, liquisolid tablets containing Orlistat will be created by dissolving the medication in a variety of nonvolatile solvents.The purpose of this research is to evaluate the solubility of Orlistat in a variety of non-polar solvents.
The goal of this research is to increase knowledge about the liquisolid process prior to compression.The purpose of this study is to test the resilience of liquisolid pills.
The finished liquisolid capsules will be put through in vitro drug release testing. The goal of this research is to better understand how excipients modify the release profile of pharmaceuticals in liquisolid systems.
The study's primary objective was to evaluate the release patterns of liquisolid pills against those of conventionally broken tablets.
The new formulation's stability depends on the results of tests conducted in accordance with ICH standards.

REVIEW OF LITERATURE

In order to improve valsartan's solubility, Chellaa N, Shastria N, and Tadikondab R R developed a liquisolid compact. Propylene glycol served as the solvent, Avicel PH 102 served as the carrier, and Aerosil 200 served as the coating material in the manufacturing of the liquid-solid compact. Dissolution tests were conducted at several pH levels on both the liquisolid formulation and the commercially available product. In comparison to the pure drug, which released just 4.02 percent of the active component after 15 minutes, the commercial version generated 13.58 percent. There was a 29.47% increase in release after just 15 minutes when liquisolid compacts were broken apart. It was shown that at acidic pH values, the dissolving rate was much faster than with the commercially available product. To decrease the amount of time it takes for a famotidine pill to dissolve, researchers Fahmay R H and Kaseem MA have looked at liquisolid formulations. In an attempt to improve

famotidine's solubility, liquid systems were devised, and tablets formulated using these systems were evaluated in vitro for their performance across a variety of criteria. While liquisolidification progressed, DSC and XRD data indicated that famotidine crystallinity decreased. In comparison to both regular tablets and physically crushed tablets, the dissolving rates of all liquisolid tablet formulations tested were much greater. Hydrocortisone liquisolid tablets were developed by Spireas, Sadu, and Grover, and their in vitro release profiles were analysed (28). (28). The in vitro release patterns of a corticosteroid with intermediate water solubility were investigated under varying dissolution circumstances after directly compressed tablets were manufactured. More consistent in vitro medication dissolving rates were observed when liquid-solid tablets were used rather than plain tablets. (29)

Researchers led by Javadzadeh Y. examined the possibility that liquisolid compacts might enhance the rate at which the body absorbs the painkiller piroxicam. This study compared the solubility of piroxicam in simulated gastric fluid (SGF, pH 1.2) to that in simulated intestinal fluid (SIF, pH 7.2). The drug release rates from liquidsolid compacts, a relatively new type of medication administration, were shown to be much higher than those from traditional tablets in a recent research. (30)

Javadzadeh Y and Navimipour J B developed and evaluated carbamazepine liquisolid compacts including additions of PVP, HPMC, and PEG 35000. Examining the coating material to carrier ratio, PVP concentration, and carrier type led to insights on the dissolving rates of liquisolid compacts. The combination of PVP as an adjuvant and MCC as a carrier has been proven to improve carbamazepine absorption. (31)

MATERIALS

Table No: 04 LIST OF CHEMICALS AND EXCIPIENTS

SL No.	Materials	Manufacturer or Supplier
1.	Orlistat	Hetero Drugds Hyderabad
2.	Microcrystalline cellulose (Avicel pH 102)	S.D Fine Chemicals Pune
3.	Silicon dioxide	S.D Fine Chemicals Pune
4.	Lactose Monohydrate	S.D Fine Chemicals Pune
5.	Sodium starch glycolate	S.D Fine Chemicals Pune
6.	Magnesium stearate	S.D Fine Chemicals Pune
7.	Polyethylene glycol 200, 400, Tween 80, Propylene glycol	S.D Fine Chemicals Pune
8.	Polyvinyl pyrrolidone	S.D Fine Chemicals Pune
9.	Hydroxy Propyl Methyl Cellulose	S.D Fine Chemicals Pune
10.	Hydroxy Propyl guar	S.D Fine Chemicals Pune
11.	Methanol	Spectro Chem PVT LTD.

Table No: 05 LIST OF INSTRUMENTS USED

Sl No.	Instruments	Manufacturer or Supplier
1.	Digital weighing balance	Shimadzu, Acculab
2.	UV visible spectrophotometer	UV-1800, Shimadzu UV spectrophotometer.
3.	Tablet compression machine	Rimek RSB-4 minipress.
4.	Hardness tester	Pfizer hardness tester.
5.	pH meter	Eutech instruments
6.	Roche friabilator	Electrolab tablet friability tester.
7.	Tablet disintegration tester	Labindia
8.	Dissolution test apparatus	Electrolab TDT-06T dissolution tester.
9.	FTIR	IRAffinity-1S FT-IR, Shimadzu.
10.	DSC	DSC-60 Plus, Shimadzu.
11.	Programmable environmental test chamber	Remi instruments

DRUG PROFILE:

ORLISTAT:

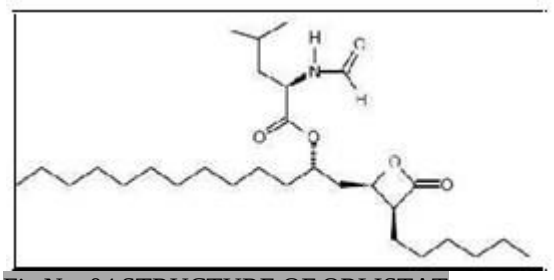


Fig No: 04 STRUCTURE OF ORLISTAT

Molecular formula: $C_{29}H_{53}NO_5$

Molecular weight: 495.735

IUPAC name: (2S)-1-[(2S,3S)-3-Hexyl-4-oxo-2-oxetanyl]-2-tridecanyl N-formyl-L-leucinate
Characteristics:

State: SolidOdour: None
Melting point: 45-50^0 C

Solubility: Freely soluble in chloroform, very soluble in methanol and poorly solublein water.

Description:

Orlistat is the saturated derivative of lipstatin, a powerful natural inhibitor of pancreatic lipases that was first discovered from Streptomyces toxytricini. Because of its ease of use and consistency, orlistat was chosen as a potential anti-obesity medicine instead of lipstatin.
Taking a Closer Look at the Obesity Debate

: fully grasp the device's operation, you'll need to

Orlistat blocks the action of a group of enzymes in the small intestine called lipases, preventing the breakdown of triglycerides and the absorption of fat. Decreasing lipase activity may decrease the absorption of free fatty acids from dietary lipids.

POLYMER REVIEW:

MICROCRYSTALLINE CELLULOSE (MCC)

Structures for Naming References This is in addition to the USP and JP Names Applications of Microcrystalline Cellulose It is the European version of microcrystalline cellulose.Crystalline cellulose goes under many different brand names, including Avicel PH 101,102, Cellets, Celex, cellulose gel, hellulosum microcristallinum, Celphere, Ceolus KG, and E460. Other manufacturers include Emcocel, Ethispheres, Fibrocel, and MCC Sanaq.
Cellulose's spatial organisation into discrete units.

Empirical Formula and Molecular Weight: $(C_6H_{10}O_5)_n$ (36 000), n=220.

The following are examples of ingredients like diluents, disintegrants, and suspending agents that go into making tablets and capsules.
Powdered microcrystalline cellulose has no discernible flavour or odour and appears transparent. It is an unaltered form of cellulose that has undergone partial depolymerization.

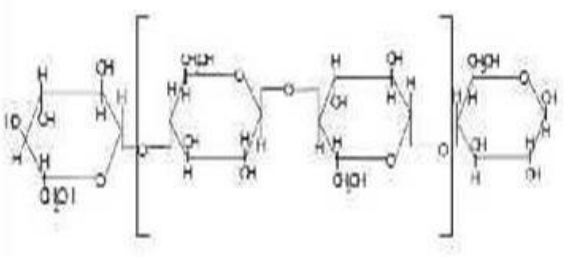


Fig No: 05 STRUCTURAL FORMULA FOR MCC

Typical Properties:

When compared to Emcocel 90M's 34.40 degrees, Ceolus KG's repose angle is much larger at 490 degrees. Bulk The tap density is just 0.478 g/cm3, but the real density is between 1.512 and 1.668 g/cm3.
Temperatures between 260 and 270 degrees Celsius are suitable for melting chars.
Regularly, it contains around 5% water by weight. Water availability may, however, vary considerably across regions. Hygroscopicity describes the swelling and shrinking of microcrystalline cellulose in reaction to moisture.
It may be dissolved in a diluted sodium hydroxide solution, but not in water. When mixed with water, it produces a white, opaque gel or dispersion. It doesn't dissolve in acids like lemon juice or orange juice, and it also doesn't dissolve in water or most organic solvents.

Microcrystalline cellulose has several applications in the pharmaceutical business. It is most often used as a binder/diluent in oral tablet and capsule formulations, for which wet granulation and direct-compression techniques are used. Microcrystalline cellulose serves as a disintegrant, lubricant, and binder in the tableting process.
Microcrystalline cellulose is fragile and hygroscopic, thus it has to be handled and stored carefully. The bulk material should be kept in a sealed container in a cold, dry area.Strong oxidising agents have an adverse effect on microcrystalline cellulose.

SOLVENT DESCRIPTION POLYETHYLENE GLYCOL:

Common Measurement System: Macrogols (or BP) Some macrogols in the Japanese language are shown below: 400, 1500, 4000. Prefix Uniformity Across Systems Progress in Notation:
The terms "Carbowax sentry," "Lipoxol," "Lutrol E," "polyethylene glycol," and "pluriol" are all equivalent.

This substance's chemical name is "-Hydroxy—hydroxypoly" (oxy-1, 2-ethanediyl)

Empirical formula: $HOCH_2 (CH_2OCH_2) mCH_2OH$ (Where m represents the average number of oxyethylene groups.)
Molecular weight: PEG 200 = 190-210

PEG 400 = 380-420

Structural formula:

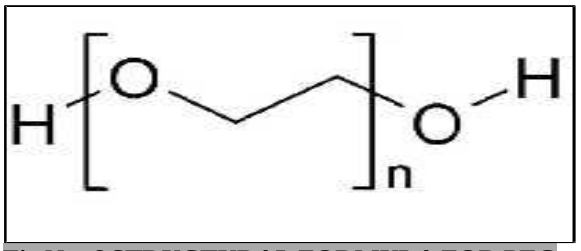


Fig No: 6 STRUCTURAL FORMULA FOR PEG

Used as a plasticizer, solvent, and base for suppositories as well as a lubricant for tablets and capsules.
There isn't much variation in density from 1.11 to 1.14 g/cm3.
Liquid PEGs have the potential to absorb huge quantities of moisture from their environment because to their high hygroscopicity. The ability to absorb moisture decreases as the molecular weight of a substance grows.
PEGs are miscible with a wide variety of liquids, including acetone, alcohols, benzene, glycerin, and glycols, to name a few. Because to its chemical stability in air and solution, it may be stored indefinitely without any additional handling. Polyethylene glycols are very resistant to both microbial development and oxidation. Polyethylene glycols should be kept in a cool, dark place with the lid well covered to prevent the chemical from deteriorating.
When one of polyethylene glycol's terminal hydroxyl groups is esterified or etherified, incompatible reactions occur. Due to the existence of peroxide impurities and secondary products formed by autoxidation, oxidising activity may be present in all classes.
To safeguard your safety, they will often be labelled as nonirritant and nontoxic. Negative reactions to polyethylene have been reported, with the lowest molecular weight glycols exhibiting the greatest toxicity.

PROPYLENE GLYCOL

You may find the chemical known as "Propylene Glycol" under a number of brand names. There are a number of names for 1,2-dihydroxypropane. Some of them are methyl ethylene glycol, methyl glycol, propane-1,2-diol, and propylenglycol.
Trade Jargon: 1,2-Propanediol

Empirical Formula and Molecular Weight: $C_3H_8O_2$ (76.09)

Structural Formula:

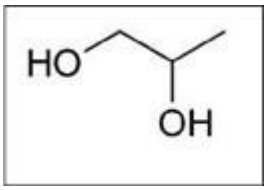


Fig No: 7 STRUCTURAL FORMULA FOR PROPYLENE GLYCOL

It's possible for an antimicrobial cosolvent to also serve as a preservative, disinfectant, humectant, plasticizer, solvent, stabilising agent, and be miscible in water.
Like glycerin, the taste of propylene glycol is sweet and somewhat acidic, while the liquid itself is clear, colourless, thick, and essentially odourless.

Typical Properties

Auto ignition temperature: 371 ^{0}C

Boiling point: 188 ^{0}C

Density: 1.038g/cm^3 at 20 ^{0}C

Flammability: Upper limit, 12.6% v/v in air; lower limit, 2.6% v/v in air.

Flash point: 99 ^{0}C (open cup)

Heat of combustion: 1803.3 kJ/mol (431.0 kcal/mol)
Heat of vaporization: 705.4 J/g (168.6 cal/g) at b.p.
Melting point: 59 ^{0}C

Refractive index: nD20 = 1.4324

Fixed oils and light mineral oils are not soluble in ether, however certain essential oils are (1 part ether to 6 parts acetone, chloroform, 95% ethanol, glycerin, or water).
Stability and Storage Conditions: Propylene glycol forms byproducts such propionaldehyde, lactic acid, pyruvic acid, and acetic acid during oxidation when heated and exposed to oxygen, but is stable when maintained at ambient temperature and away from air. Mixing propylene glycol with ethanol (95%) or glycerin (5%), or even water, helps preserve its chemical stability; watery solutions can be sterilised using an autoclave.
To provide just one example, the use of propylene glycol with oxidising chemicals like potassium permanganate is not recommended.

POLYSORBATE 80

Synonyms: Atlas E; Armotan PMO 20; Capmul POE-O; Cremophor PS 80; Crillet 4; Crillet 50; Drewmulse POE-SMO Protasorb O-20; Ritabate 80.
Chemical Names: Polyoxyethylene 20 sorbitan monooleate

Empirical Formula and Molecular Weight: $C_{64}H_{124}O_{26}$ (1310)

Structural formula:

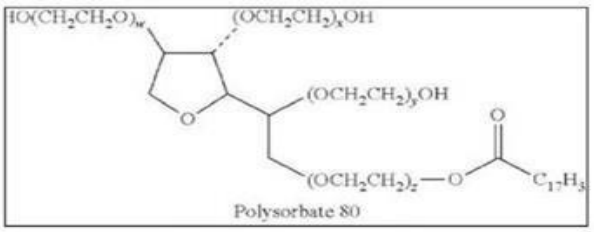


Fig No: 8 STRUCTURAL FORMULA FOR POLYSORBATE 80

Agents like dispersing agents, emulsifying agents, nonionic surfactants, solubilizing agents, suspending agents, wetting agents, and wetting agents are used to accomplish certain tasks.
Polysorbates emit an unique odour and taste warm and somewhat bitter; the exact colour intensity of the goods may vary from batch to batch and manufacturer to manufacturer.

Pharmacopoeial Specifications Typical Properties:
Acid value: 2

Acidity/alkalinity pH = 6.0–8.0 for a 5% w/v aqueous solution.

Flash point: 149 ^{0}C

HLB value: 15.0

Hydroxyl value: 65-80

Moisture content: 3.0 %

Saponification value: **45-55**

Solubility: soluble in ethanol, insoluble in mineral oil and water.

Specific gravity: 1.08 g/ml

Stability and Storage Conditions:
Even though polysorbates do not react with electrolytes or mild acids or bases, they will nevertheless undergo saponification if they come into prolonged contact with such acids or bases. After being stored for a long time, peroxides may form. Polysorbates must be kept in a cold, dry, dark place, ideally away of direct sunlight.
There may be a change in colour or even precipitation if you mix substances that aren't compatible, such as phenols, tannins, tars, and tar-like compounds. It has been shown that combining paraben preservatives with polysorbates lowers their antibacterial effectiveness.

METHANOL

Molecular weight: 32.04 g/mol

Methanol is the simplest type of alcohol; it is a colourless, flammable, and highly volatile liquid with a smell similar to but somewhat sweeter than ethanol's (drinking alcohol). This polar liquid has several applications at room temperature, including antifreeze, solvent, fuel, and denaturant for ethanol.

Density: 791.80 kg/m^3 **Melting point:** 98 ^{0}C **Boiling point:** 65 ^{0}
Solubility in water: 2.7g/100mL (20°C)

Refractive index: 1.328

Structural formu

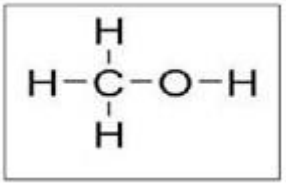


Fig No: 9 STRUCTURAL FORMULA FOR METHANOL

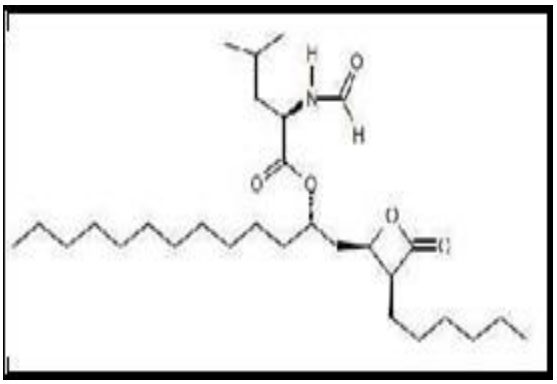
Denatured alcohol, sometimes called methylated spirit, is produced when ethanol and methanol are mixed. Ethylene glycol is used as an antifreeze in pipelines and windscreen washer fluid, among other places. Typical applications include removing paint and laminating paper.
The Fabrication of Rubber Goods and Printing Equipment. The health risks associated with methanol are well-documented, and it is one of the most poisonous chemicals studied by scientists. Pure methanol may degrade into formic acid and cause blindness even if just 10 mL is taken. The median lethal dosage is about 100 mL, while as little as 30 mL has been shown to be deadly. The harmful effects of a poison may not show up for a few hours, but by that point it is typically too late to use the available antidotes to avoid irreparable damage.Always use fireproof glass containers for storage, since this will prevent the chemical from reacting with air and setting fire.

METHODOLOGY

PREFORMULATION STUDIES

Drug characteristics:

Orlistat:



Molecular formula: $C_{29}H_{53}NO_5$

Molecular weight: 495.735

IUPAC name: (2S)-1-[(2S,3S)-3-Hexyl-4-oxo-2-oxetanyl]-2-tridecanyl N-formyl-L-leucinate

Characteristics:

State: Solid

Odour: None

Melting point: 43-50^0 C

Two of the most effective solvents are chloroform and methanol, whereas water is the least effective.

Using infrared absorption spectrophotometry, we were able to positively identify the medicine by comparing the sample spectra to a reference spectrum of Orlistat. The infrared spectra of several orlistat samples were compared with a reference spectrum. If you put it in an airtight container and keep it in the fridge, you can preserve it for months.

Analysis at its Highest Level The orlistat was dissolved in methanol to create a stock solution (100g/ml). It took a lot of work to dilute the original solution down to 40 g/ml, the concentration of this solution. ShimadzuUV1800 UV- Visible spectrophotometer covering 200-400 nm was used to analyse the product. It was observed that 202 nm was the optimal wavelength for detecting the drug's absorbance in methanol.

FORMULATION OF ORLISTAT TABLETS BY DIRECT COMPRESSION

We used direct compression to create the Orlistat capsules. The magnesium stearate and talc were added after the components had been measured and well combined. Powder properties such as bulk density, tapped density, angle of repose, compressibility index, and hausner's ratio were measured after it was prepared. Following the evaluation of the powder mixture, tablets were pressed.

Table No: 06 FORMULATION OF ORLISTAT TABLETS

Ingredients	Quantity/ Tablet (mg)
Orlistat	60
Microcrystalline cellulose	135
Lactose monohydrate	50
Aerosil	15
Sodium starch glycolate	10
Magnesium stearate	10

Table No: 7 FORMULATION TABLE OF LIQUISOLID COMPACTS OFORLISTAT

Liquisolid System Code	Carrier: Coating(R)	Liquid Load Factor (Lf)	Non-Volatile Solvent (mg)	Active Ingredient(mg)	Weight Of Liquid Medication (mg)	Carrier (mg)	Coating (mg)	Disintegrant(mg)
LS-1	10.66	0.625	40	60	100	160	15	10
LS-2	12	0.694	40	60	100	144	12	10
LS-3	15	0.66	40	60	100	150	10	10
LS-4	16.5	0.6	40	60	100	165	10	10
LS-5	21.25	0.58	40	60	100	170	8	10
LS-6	26	0.64	40	60	100	156	6	10
LS-7	13	0.76	40	60	100	130	10	10
LS-8	13	0.76	40	60	100	130	10	10
LS-9	13	0.76	40	60	100	130	10	10

EVALUATION OF PRE-COMPRESSION PARAMETERS

BULK DENSITY (Db)

Powder density is determined by dividing the total mass by the total volume of the powder. The capacity of the cylinder was then recorded after the powder was measured by weight. This substance's worth is expressed in terms of grammes per millilitre (68)

$$D_b = \frac{M}{V_b}$$

Where, M= is the mass of powder.

Vb= is the bulk volume of the powder.

TAPPED DENSITY (Dt)

The density of a powder is its mass per unit volume after extraction. After tapping, the powder was dispersed uniformly, allowing for precise volumetric measurements. This quantity is expressed as a mass in grammes per millilitre using the following formula:

$$D_t = \frac{M}{V_t}$$

Where, M = is the mass of powder.

V_t = is the tapped volume of the powder.

ANGLE OF REPOSE (θ)

Scientists utilise the angle of repose to calculate the frictional forces present in a powder (). This is the kind of angle that may be made by the surface of a freely moving pile of powder on a flat surface.

$$Tan\ \theta = h/r$$

Where, θ = Angle of repose

You are to measure the powder mound's height (h) and diameter (d) in metres (r).

A funnel attached to a vertical platform was used to receive the granular material. The formula was used to

the data collected by measuring the height and radius of a powder mound to get the angle of repose.

POST COMPRESSION PARAMETERS GENERAL APPEARANCE
by the use of sight.
HARDNESS
A Pfizer hardness tester was used to determine the average tablet hardness. Measurements are made in kilogrammes per centimetre squared (kg/cm2).

THICKNESS:
The tablets' thickness was measured using a screw gauge, and the results were given in millimetres.

WAVEY IN THE FEMALE SENSE (F)
To find just how readily the pill would shatter, we utilised the Roche friabilator. This value is presented in the form of a percentage (%). Ten pills were taken from the Winitial scale and placed into the Friabilator. For the whole four minutes, the friabilator never went beyond 25 RPM. We reweighed the pills just to be sure (Wfinal). Finally, the fragility rating was arrived at by,

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} X\ 100$$

DISINTEGRATION TIME
Using a Disintegration apparatus and 0.1N HCl as the disintegration medium kept at 370C, the time required for the core tablet to dissolve was calculated. After dismantling all six tablets, a time was recorded.
WEIGHT CHANGE
The recommended daily intake of the tablets has been changed. To obtain an average, we weighed 20 pills. We then measured and weighed each pill separately. The following method was used to determine the standard deviation and percentage of variation in pill weight from the mean:

$$\%\ Deviation = \frac{Individua\ l\ weight - Average\ weigh\ t}{Individual\ weight} X\ 100$$

If there are less than two tablets that deviate from the mean by more than the standard deviation, then the tablets are of appropriate quality.

RESULTS

UV SPECTRUM OF ORLISTAT:MODE: Spectrum
STARTING WAVELENGTH: 200 nm

ENDING WAVELENGTH: 400 nm

SAMPLE: Orlistat

The maximum absorbance of Orlistat in methanol was measured to be 202 nm in this publication, which represents the first stage in the study process. The regression coefficient found to be 0.9962 is statistically significant. The %CDR was calculated using a slope of 0.0055.

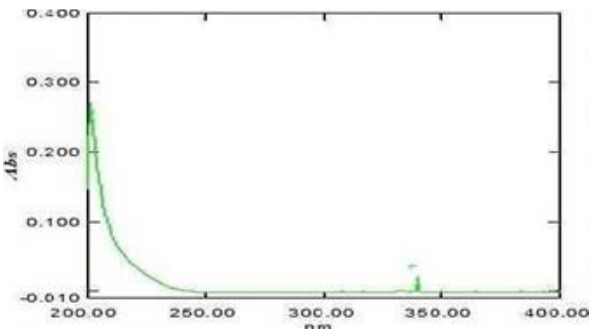


Fig No: 10 UV SPECTRA OF ORLISTAT

Table No: 8 CALIBRATION CURVE DATA FOR ORLISTAT IN METHANOL

SL No.	Vol of SS1 (ml)	Vol made upto (ml)	Conc. (µg/m)	Absorbance @ 202nm			AVG abs	SD
				Trial 1	Trial 2	Trial 3		
1	1	10	10	0.133	0.141	0.135	0.136	0.00416
2	2	10	20	0.169	0.165	0.166	0.166	0.00208
3	3	10	30	0.219	0.222	0.22	0.220	0.00152
4	4	10	40	0.27	0.273	0.271	0.271	0.00152
5	5	10	50	0.312	0.325	0.322	0.319	0.00680
6	6	10	60	0.395	0.39	0.391	0.392	0.00264
7	7	10	70	0.448	0.452	0.45	0.45	0.002
8	8	10	80	0.498	0.501	0.499	0.499	0.00152
9	9	10	90	0.556	0.558	0.557	0.557	0.001
10	10	10	100	0.617	0.62	0.623	0.62	0.003

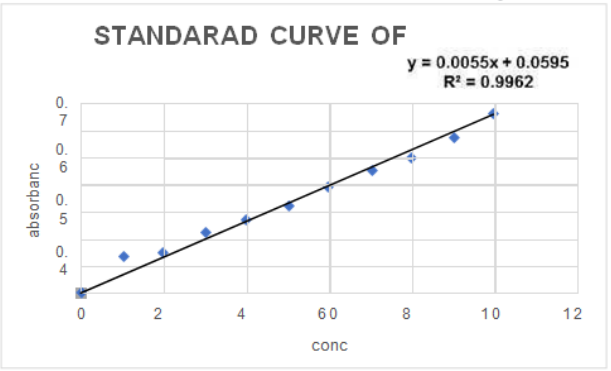


Fig No: 11 CALIBRATION CURVE FOR ORLISTAT

COMPATIBILITY STUDIES:

FOURIER TRANSFORM INFRARED SPECTROSCOPY:

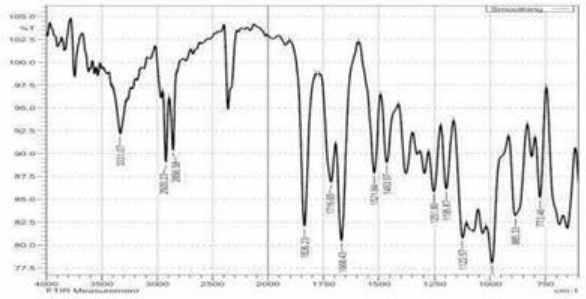


Fig No: 12 FT-IR SPECTRA OF ORLISTAT

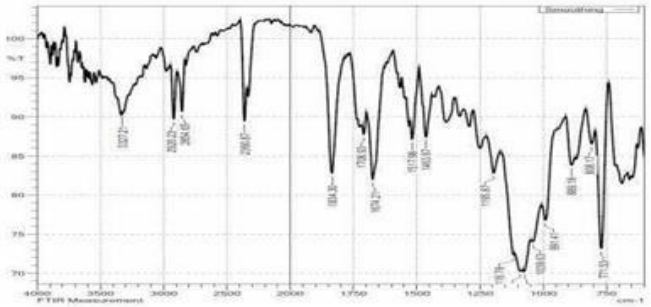


Fig No: 13 FT-IR SPECTRA OF THE OPTIMIZED FORMULATION

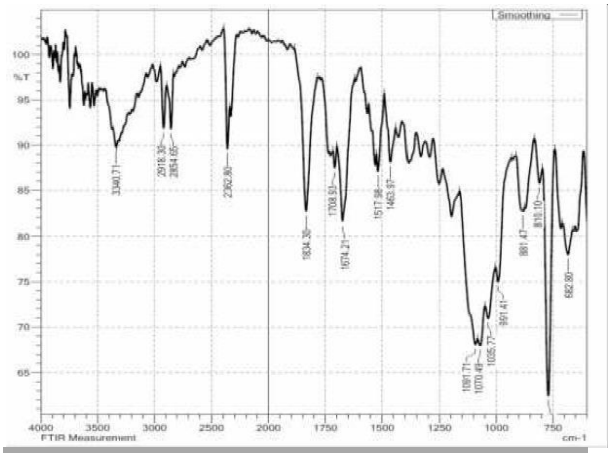


Fig No: 14 FT-IR SPECTRA OF DIRECTLY COMPRESSED TABLETS

Table No: 9 COMPARISON OF FT-IR SPECTRA OF PURE DRUG WITH **OPTIMIZED FORMULATION**

Functional groups	Characteristic peaks in cm^{-1}	
	Orlistat	Optimised formulation
C=0 Stretching	1716.65	1708.93
C-H Stretching in CH_2	2920.23	2920.23
N-H Stretching	3331.07	3327.21
C-H Deforming	885.33	889.18
C=C Aromatic stretching	1521.84	1517.98
C-N Stretching	1195.87	1195.87

DIFFERENTIAL SCANNING CALORIMETRY:

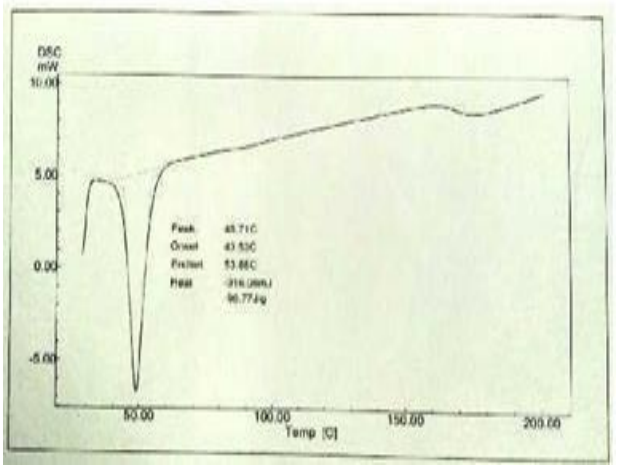


Fig No: 15 DSC SPECTRA OF ORLISTAT

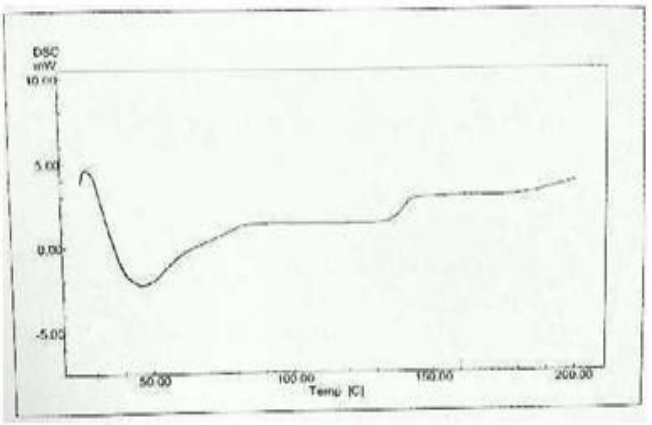


Fig No: 16 DSC SPECTRA OF THE OPTIMIZED FORMULATION

SOLUBILITY STUDIES:

Table No: 10 SOLUBILITY OF ORLISTAT IN VARIOUS NON-VOLATILE SOLVENTS

SL. No	Solvent	Solubility (mg/ml)
1	Propylene glycol	57.72
2	PEG 200	50.9
3	PEG 400	48.62
4	Tween 80	53.18

PRE-COMPRESSION PARAMETERS

Table No: 11 PRE-COMPRESSION PARAMETERS

Liquisolid formulationcode	Bulk density(g/ml)	Tapped density(g/ml)	Carr's index(%)	Hausner'sratio	Angle ofrepose
LS-1	0.454±0.01	0.526±0.02	13.68	1.15	30.4±0.03
LS-2	0.444±0.04	0.526±0.02	15.58	1.18	32.4±0.64
LS-3	0.454±0.01	0.555±0.01	18.19	1.22	27.82±0.78
LS-4	0.465±0.05	0.555±0.03	16.21	1.19	33.69±1.05
LS-5	0.454±0.04	0.540±0.04	15.92	1.18	31.21±1.2
LS-6	0.465±0.04	0.526±0.02	11.59	1.13	29.05±1.6
LS-7	0.476±0.02	0.571±0.05	16.63	1.19	32.4±0.66
LS-8	0.465±0.02	0.526±0.06	11.59	1.13	30.57±0.13
LS-9	0.465±0.08	0.555±0.05	16.21	1.19	31.21±0.69
DCT	0.454	0.540	15.92	1.18	32.15

POST-COMPRESSION PARAMETERS

Table No: 12 POST-COMPRESSION PARAMETERS

Formulation Code	Thickness (mm)	Hardness (Kg/cm²)	Friability (%)	% Drug Content	DT (secs)	Weight Variation(%)
LS-1	4.20±0.06	4.1±0.1	0.40	94.7±0.2	276	-0.92 to +0.77
LS-2	4.04±0.02	3.9±0.1	0.61	95.09±0.1	250	-0.86 to +0.95
LS-3	4.20±0.05	3.7±0.1	0.60	93.1±0.3	245	-0.71 to +1.0
LS-4	4.46±0.03	4.3±0.11	0.38	96.5±0.2	288	-0.67 to +0.67
LS-5	4.47±0.036	4.3±0.15	0.32	95.8±0.1	275	-0.79 to +0.34
LS-6	4.04±0.025	3.7±0.15	0.62	94.9±0.15	242	-0.89 to +0.17
LS-7	4.11±0.02	4.1±0.36	0.50	97.0±0.3	276	-0.65 to +0.71
LS-8	4.27±0.015	4.1±0.25	0.49	96.7±0.25	270	-0.79 to +0.92
LS-9	**4.05±0.005**	**3.9±0.2**	**0.48**	**98.1**±0.15	**255**	**-0.83 to +0.88**
DCT	4.14±0.011	4.5±0.34	0.32	98.5±0.3	295	-0.75 to +1.02

Fig No: 17 GRAPHICAL REPRESENTATION OF THICKNESS

Fig No: 18 GRAPHICAL REPRESENTATION OF HARDNESS

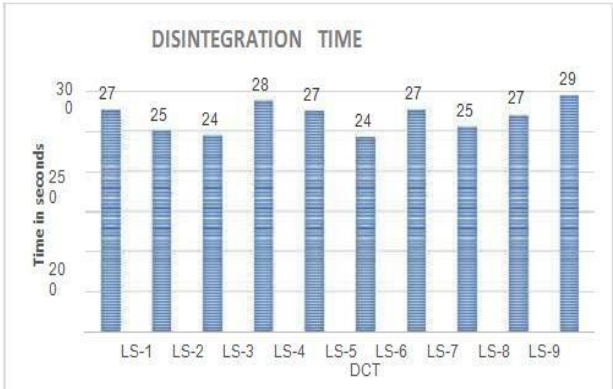


Fig No: 19 GRAPHICAL REPRESENTATION OF FRIABILITY

Fig No: 20 GRAPHICAL REPRESENTATION OF % DRUG CONTENT

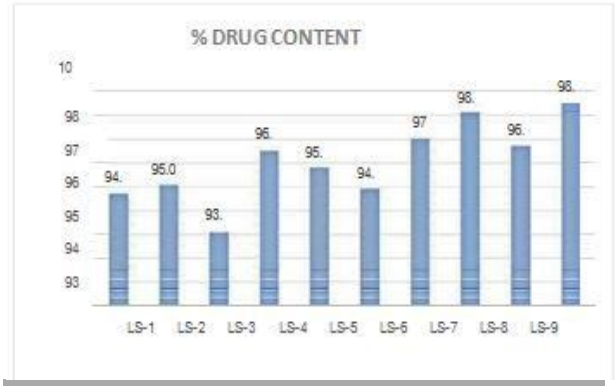


Fig No: 21 GRAPHICAL REPRESENTATION OF DISINTEGRATION TIME

***IN-VITRO* DISSOLUTION STUDIES**
Apparatus - USP Type II (Paddle type).
Dissolution medium - 900 ml of 0.1N HCl
Temperature - 37±0.5°c
RPM - 50
Volume withdrawn - 5 ml
Time interval - 10, 20, 30, 40, 50 and 60 minutes interval
λmax - 202 nm
Beer's range - 10-100 µg/ml

Table No: 13 *IN-VITRO* DRUG RELEASE PROFILE OF LS-1

Time	Abs	Conc µg/ml	Amt 10ml	Amt 900ml	CLA	CDR	%CDR
0	0	0	0	0	0	0	0
10	0.052	9.45	0.094	17.01	0	17.01	29.95
20	0.094	17.09	0.170	30.76	0.094	30.85	54.30
30	0.124	22.54	0.225	40.58	0.265	40.84	71.88
40	0.136	24.72	0.247	44.50	0.490	45	79.19
50	0.151	27.45	0.274	49.41	0.738	50.15	88.27
60	0.154	28	0.28	50.4	1.012	51.41	90.48

DISCUSSION

Powder solution technique and liquid-solid method both mean the same thing. As a result, the medication is now more soluble in water. The goal of this study was to develop a liquisolid tablet formulation of Orlistat, a medication that dissolves poorly in water.
By mixing the liquid medicine with certain powder excipients, the innovative formulation approach of liquisolid turned liquid drugs like solutions or suspensions of Orlistat in nonvolatile liquid vehicles into freely flowing and compressible powders. In order to create liquisolid tablet formulations, the right ratio of powder to liquid components had to be identified, and this was achieved by use of a novel mathematical model, which allowed for the creation of admixtures that were both flowable and compressible. Many different formulas were created and tested to determine the best effective one.

UV SPECTRUM OF ORLISTAT:

Determination of λmax:

Orlistat (40 mg/ml) in methanol, scanned between 200 and 400 nm. This medication was quite consistent, with an absorbance maximum (max) at 202 nm. Fig No: 15 Orlistat in methanol, with a typical calibration curve. Calibration data for orlistat at a wavelength of 202 nm may be found in TableNo.15.
Calibration curve for methanol (shown in Fig. 16) has a regression value of 0.9962 and a slope of 0.0055. When the concentration was varied from 10 to 100 g/ml, a linear correlation was seen.

DESIGN AND CHARACTERIZATION OF LIQUISOLID TABLETS

COMPATIBILITY STUDIES:

With the use of Fourier transform infrared spectroscopy, we analysed the drug polymer's compatibility with the excipients to see whether Orlistat interacted with them. The FT-IR spectra of the formulations and the pure drug have been compared, and the findings are reported in Table No. 16. Tablets produced from pure Orlistat showed no chemical interaction with excipients since the drug's characteristic absorption peaks were still present. FT-IR spectra are visually shown in Figures 17, 18, and 19.
Analysis Using Differential Scanning Calorimetry
Figure 20 of the DSC thermograms shows that the melting endothermic peak for crystalline orlistat occurs at a temperature of 48.710C. Although a more obvious melting endothermic peak was not seen in the DSC scan of the formulation, the melting endotherm of the liquisolid tablet (LS-8) containing orlistat was found to be 450 °C (Fig No: 21). No negative drug-excipient interactions were discovered in these investigations.

CONCLUSION

Due of its low water solubility, this study devised

liquisolid tablets to improve medication administration. Avicel PH 102 was employed as the tablet's carrier, and Aerosil was used as the coating component, to generate the Orlistat Liquisolid capsules. The IR values had not altered much, as measured by FT-IR spectroscopy. The lack of any data suggesting a chemical interaction between the medicine and the excipients lends credence to this theory. Each formulation was examined beforehand to determine its optimal parameters, such as the Carr's index, Hausner's ratio, and the Angle of repose. The outcomes were really close to ideal in every respect. Hardness, friability, weight fluctuation, thickness measurement, disintegration time, and drug content were all found to be within acceptable ranges after compression.

The DSC results support the idea that the crystalline form of the drug was transformed to an amorphous form during formulation, which helps with solubilization and boosts the dissolving rate.The LS-9 formulation with Propylene glycol and HPMC as adjuvant was shown to be the most effective based on both pre- and post-compression assessment criteria.

The study's results showed that the drug release is controlled by non-fickian diffusion, with first-order kinetics providing the best match. The resulting liquisolid formulations were shown to be chemically and physically stable for 30 days after production.

According to the results, the liquisolid approach might be used to hasten the breakdown of medications that are difficult to dissolve in water.There is evidence that liquid-solid orlistat pills have a higher rate of breakdown, leading to greater bioavailability.

SUMMARY

Although orlistat's water solubility is low, the liquisolid technique has the potential to significantly increase the drug's bioavailability. Orlistat liquid compacts significantly outperformed directly compressed tablets in terms of in-vitro release qualities, perhaps as a result of the drug's increased wetness and the compact's increased surface area for disintegration. This innovative formulation strategy has the potential to improve oral bioavailability.

As a result of combining Avicel PH102 as the carrier, Colloidal silica(Aerosil) as the coating material, and Propylene glycol as the liquid vehicle of choice, an effective liquisolid compact of orlistat was produced. A solution was prepared from polyvinylpyrrolidone (PVP), hydrochloric acid (HCPG), and hydroxypropyl methyl cellulose (HPMC). After 60 minutes, medication release profiles from liquid-solid tablets with propylene glycol as the non-volatile solvent and HPMC as an addition were the most favourable. In the end, LS-9 was chosen as the best compression formula after careful consideration of a number of pre- and post-compression assessment criteria.DSC and FTIR results showed a decrease in crystallinity and chemical interaction. After 30 days, the liquisolids were determined to be chemically and physically stable.

Drugs that are insoluble in water may have their solubility and bioavailability increased by using the liquisolid approach. The formulation's use of a nonvolatile solvent improves the wettability of the drug and guarantees the molecules are evenly dispersed throughout the solution, even if the drug is insoluble in water. Bigger drug particles and stronger wetting qualities are thought to be the cause of the quicker dissolving time and enhanced bioavailability of liquid tablets.

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