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ORODISPERSIBLE LIQUISOLID COMPACTS – A NOVEL APPROACH TO ENHANCE SOLUBILITY AND BIOAVAILABILITY: A REVIEW

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Abstract:
A liquisolid system has the ability to improve the dissolution properties of poorly water-soluble drugs. Liquisolid compacts are flowing and compactable powdered forms of liquid medications. The design of liquisolid systems are mainly intended for enhancement of solubility, dissolution rate and bioavailability of poorly water-soluble and highly lipophilic drugs. Improvement in bioavailability may be due to increased surface area, increased aqueous solubility and increased the wettability of the drug. Orodispersible tablets may give rapid onset of action by rapid absorption through pre-gastric absorption of drug from mouth, pharynx and oesophagus as saliva passes down and beneficial to reduce dose. By combining Liquisolid technique and Orodispersible DDS, may enhance solubility, dissolution rate by means of Liquisolid technique and can achieve rapid onset of action with lower dose of drug by using Orodispersible DDS and hence may increase patient compliance. The current review mainly focuses on theory and applicability of liquisolid compact technique towards solubility or bioavailability enhancement. Different carriers, Non-Volatile Solvents, coating materials, Disintegrant and Methods employed are elucidated.

KEYWORDS: *liquisolid systems, lipophilic drugs, dissolution, bioavailability, sustained release systems, novel technique*

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INTRODUCTION

In order for a drug to be absorbed into the systemic circulation following oral administration, the drug must be dissolved in the gastric fluids. For hydrophobic drugs, the dissolution process acts as the rate-controlling step and which determines the rate and degree of absorption. Bioavailability of poorly water soluble drugs is limited by their solubility and dissolution rate.[1]

Therapeutic efficiency of a drug is dependent on the bioavailability and eventually upon the solubility and absorption of drug molecules [2,3]. The solubility is an important parameter to achieve the required concentration of drug in the systemic circulation and hence to attain the biological activity of the drug in the body. As a matter of fact, more than one-third of the drugs listed in the U.S. Pharmacopoeia fall into the poorly water-soluble or water-insoluble categories.[4]

The solubility issues can affect the oral delivery of the new drugs and also the delivery of many existing drugs. The drugs with poor solubility exhibit many in vitro formulation related difficulties, such as restricted choices of delivery of drug and highly c omplex dissolution testing with inadequate correlation to the in vivo absorption[5] . These types of issues with in vivo and in vitro characteristics and the problems in attaining expected and reproducible in vivo/in vitro correlations (IVIVC) are often due to solubility issues with many newly synthesized compounds Hence, it is essential to improve the solubility of such drugs by applying different solubility enhancement techniques [6].

Drugs with poor aqueous solubility are still an ongoing challenge in the successful formulation of therapeutic products due to their low oral bioavailability. In the 1990s; the biopharmaceutical classification system (BCS) was introduced to characterize various drugs according to their solubility and permeability. It reports that over70%of drugs and active entities are poorly water-soluble compounds (BCS II or BCS IV) due to the considerable involvement of high through put screening and combinatorial chemistry. These active pharmaceutical ingredients (APIs) often suffer from formulation challenges because of limited dissolution and low permeability. Accordingly; applicable formulation techniques are highly aspired to improve the apparent solubility or dissolution of poorly soluble drugs and thus enable them become bioavailable.[7]

LIQUISOLID SYSTEM

The liquisolid technology is described by Spireas as liquid may be transformed into a free-flowing, readily compressible, and apparently dry powder by simple physical blending with selected excipients named the carrier and coating material. The liquisolid technique is a novel approach for delivery of drugs through the oral route. This technique is suitable for poorly soluble or water insoluble drugs, highly permeable drugs (BCS Class II drugs) and also for immediate or sustained release formulations.

A liquid lipophilic drug can be converted into liquisolid system without being further modified. On the other hand, if a solid water-insoluble drug is formulated, it should be initially dissolved or suspended in suitable nonvolatile solvent system to produce drug solution or drug suspension of desired concentration. Inert, preferably water-miscible organic solvent systems with high boiling point and a not highly viscous organic solvent system such as propylene glycol, liquid polyethylene glycols, polysorbates, fixed oils, or glycerin are best suitable as liquid vehicles[8].

It is a novel "Powder Solution Technology" that involves absorption and adsorption efficiencies, making use of liquid medications, drug suspensions admixed with suitable carriers, coating materials and formulated into free flowing, dry looking, and non-adherent and compressible powder forms. Improvement in bioavailability may be due to increased surface area, increased aqueous solubility and increased the wettability of the drug. Liquisolid technique also has the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release systems. Overall, liquisolid technique is a most promising and novel technique for enhancing the dissolution and bioavailability of poorly water soluble drugs and sustaining drug release from tablet matrix. The liquisolid compacts are regarded as acceptably flowing and compressible powdered forms of a liquid medication. The latter include liquid lipophilic drugs or solid water-insoluble drugs dissolved in suitable water miscible non-volatile solvents [9].

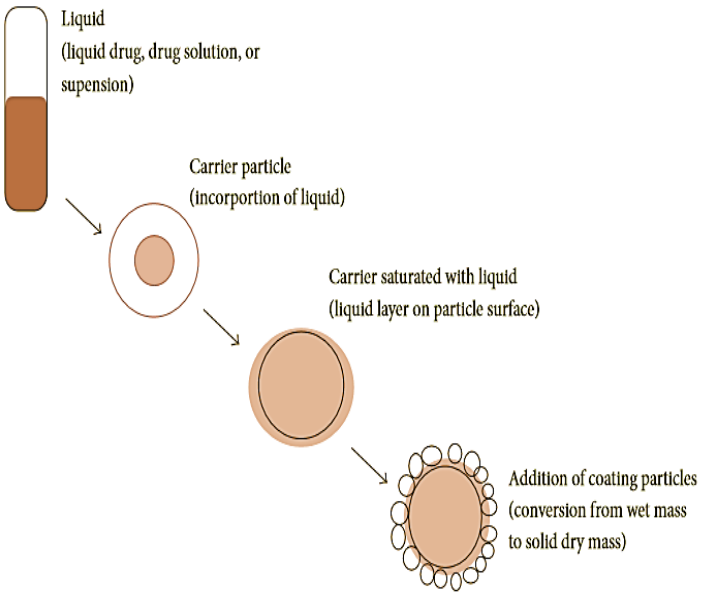

Fig 1. Schematic representation of liquisolid systems

Fig 1. Schematic representation of Liquisolid system [12].

The liquisolid compacts are prepared by simple admixture of liquid medications with carrier and coating materials. Initially, the liquid medication is dispersed into the porous carrier having high absorption properties. As the carrier got saturated with the liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles. In the liquisolid system, the drug is held within the powder substrate in solution or in a solubilized, almost molecularly dispersed state. Therefore, due to their significantly increased wetting properties and surface area of drug available for dissolution, liquisolid compacts of water-insoluble drugs are expected to enhance the drug release characteristics and consequently to improve oral bioavailability [10].

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 (Lf)
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.[11]

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 (Lf):
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.
Lf = 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: Lf = Ø + Ø (1/R) eq….. (3)

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

Lf = (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 Lf 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[12].

MECHANISMS OF ENHANCEMENT OF SOLUBILITY AND BIOAVAILABILITY

A. Increased effective surface area:

If the drug within the liquisolid system is completely dissolved in the liquid vehicle, it is located in the powder substrate still in a solubilized and molecularly dispersed state. Therefore, the surface area of drug available for release is much greater than that of drug particles within directly compressed tablets. Accordingly, with increasing drug content exceeding the solubility limit and thus, increasing fraction of undissolved drug in the liquid vehicle the release rate decreases. With various drugs it could be shown that the release rates are directly proportional to the fraction of the molecularly dispersed drug (FM) in the liquid formulation.

FM is defined by Spireas as the ratio between the drug's solubility (Sd) in the given liquid vehicle and the actual drug concentration (Cd) in this vehicle carried by each system.

Therefore, FM = Sd/ Cd

In addition it is thought that the adsorption and absorption of molecularly dispersed drug onto the surface and interior of the carrier particles impart increased effective surface area available for the mass transfer during the drug dissolution process.

Fig 2. Increased Drug Surface Area [9].

B. Increased aqueous solubility:

It is expected that the solubility of the drug might be increased with liquisolid systems. In fact, the relatively small amount of liquid vehicle in a liquisolid compact is not sufficient to increase the overall solubility of the drug in the aqueous medium. However, in the micro-environment of the solid/liquid interface between an individual primary liquisolid particle and the release medium, it is possible that the amount of liquid vehicle diffusing out of a single liquisolid particle together with the drug molecules might be sufficient to increase the aqueous solubility of the drug if the liquid vehicle can act as a cosolvent.

C. Improved wetting properties:

Due to the fact that the liquid vehicle can either act as surface active agent or has a low surface tension, wetting of the primary liquisolid particles is improved. Wettability of these systems can be demonstrated by contact angles and water rising times. Also the adsorption of the drug on the carrier particles increases the effective surface area, improving the contact of drug and wettability [13].

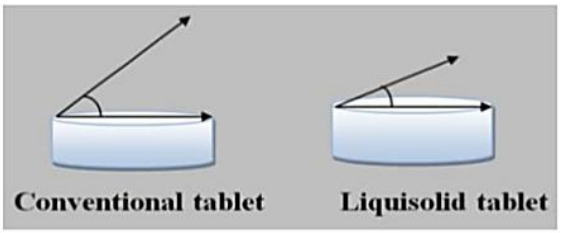

Fig 3. Contact angle of conventional and liquisolid tablet

ADVANTAGES

Liquisolid tablets have many advantages. These include:

- Liquisolid systems are low cost formulations than soft gelatin capsules.
- Drug release can be modified using suitable formulation ingredients.
- Drug can be molecularly dispersed in the formulation.
- Capability of industrial production is also possible.
- Enhanced bioavailability can be obtained as compared to conventional tablets.
- Several slightly and very slightly water soluble and practically water-insoluble liquid and solid drugs can be formulated into liquisolid systems [14].
- Even though the drug is in a tablet or capsule form, it is held in a solubilized liquid state, which contributes to increased drug wetting properties, thereby enhancing drug dissolution.
- Rapid release liquisolid tablets or capsules of water insoluble drugs exhibit enhanced Invitro and in-vivo drug release when compared to their commercial counter parts, including soft gelatin capsules preparation.
- Sustained release liquisolid tablets or capsules of water insoluble drugs exhibit constant dissolution rates (zero-order release) comparable only to expensive commercial preparations that combine osmotic pump technology and laser-drilled tablets.
- Better availability of an orally administered water insoluble drug.
- Production of liquisolid systems is similar to that of conventional tablets.
- Can be used for formulation of liquid oily drugs.
- Can be used in controlled drug delivery [15].

LIMITATIONS

- Liquisolid systems require high solubility of drug in nonvolatile solvents.
- Acceptable compression properties may not be achieved since during compression liquid drug may be squeezed out of the liquisolid tablet resulting in tablets of unsatisfactory hardness [16].

APPLICATIONS

Liquisolid compact technology is a powerful tool to improve bioavailability of water insoluble drugs. Several water insoluble drugs on dissolving in different non-volatile solvents have been formulated into liquisolid compacts.

- Different drugs can be incorporated into liquisolid compacts.
- Rapid release rates.
- Used for water insoluble solid drugs or liquid lipophilic drugs.
- Sustained release of drugs
- Solubility and dissolution improvement.
- Flowability and compressibility.
- Designing of controlled release tablets.
- Bioavailability enhancement.
- Application in probiotics.
- Improvement of drug photo stability [17].

ORODISPERSIBLE TABLETS

For the past one decade, there has been an enhanced demand for more patient-friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing annually. Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency and the production of more cost-effective dosage forms.[18]

For most therapeutic agents used to produce systemic effects, the oral route still represents the preferred way of administration, owing to its several advantages and high patient compliance compared to many other routes[19]. Tablets and hard gelatin capsules constitute a major portion of drug delivery systems that are currently available. However, many patient groups such as the elderly, children and patients who are mentally retarded, uncooperative, nauseated or on reduced liquid-intake/diets have difficulties swallowing these dosage forms. Those who are traveling or have little access to water are similarly affected[20].

To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage form known as "Orally Disintegrating Tablets (ODT)" which disintegrate rapidly in saliva, usually in a matter of seconds, without the need of water. Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms[21].

Although chewable tablets have been on the market for some time, they are not the same as the new ODTs. Patients for whom chewing is difficult or painful can use these new tablets easily. ODTs can be used easily in children who have lost their primary teeth but do not have full use of their permanent teeth[22].Recent market studies indicate that more than half of the patient population prefers ODTs to other dosage forms [23] and most consumers would ask their doctors for ODTs (70%), purchase ODTs (70%) or prefer ODTs to regular tablets or liquids (>80%) [24].
ODTs have been developed for numerous indications ranging from migraines (for which rapid onset of action is important) to mental illness (for which patient compliance is important for treating chronic indications such as depression and schizophrenia)[25].

Description of orally disintegrating (OD) dosage forms All fast disintegrating tablets approved by United States Food and Drug Administration (US FDA) are classified as "ODTs". European Pharmacopoeia adopted the term "orodispersible tablets" for tablets that dispersed or disintegrate in less than 3 min in the mouth before swallowing. Such a tablet disintegrates into smaller granules or gel like structure, allowing easily swallowing by patients. As per recent US FDA guideline on ODT, disintegration time of ODT should have an in vitro disintegration time of approximate 30 s or less, when based on United States Pharmacopoeia (USP) disintegration test method or alternative[26]. ODTs are different from conventional sublingual tablets, buccal tablets and lozenges, which require more than a minute to dissolve in oral cavity.

Drug selection criteria for orodispersible tablets:

- Able to saturate the oral mucosa.
- At least moderately non-ionized at oral cavity pH.
- Have the ability to diffuse and partition into the epithelium of upper GIT.
- Small to moderate molecular weight.
- Low dose drugs mostly less than 50 mg.
- Should have good stability in saliva and water.
- Drugs with lower bio availability are good candidates for ODT.
- Frequent dosing drugs are unsuitable for ODT [27].

ADVANTAGES

- Administration to the patients who cannot swallow, such as the elderly, stroke victims, bedridden patients, patients affected by renal failure and patients who refuse to swallow such as paediatric, geriatric and psychiatric patients.
- Rapid drug therapy.
- Increased bioavailability/rapid absorption through pregastric absorption of drugs from mouth, pharynx and esophagus as saliva passes down.
- Better patient compliance for disabled, bedridden patients, travellers and busy people, who do not always have access to water.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in paediatric patients.
- The risk of chocking during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety [28,29].

LIMITATIONS FOR ORODISPERSIBLE TABLETS

Drugs with relatively larger doses are difficult to formulate into ODTs. example. antibiotics like ciprofloxacin with adult dose tablet containing about 500 mg of the drug

- Palatability - ODTs are intended to be dissolved in mouth. Most of the drugs have bitter taste.
- ODT requires special packaging for proper stabilization and safety of stable product [30,31].

MATERIALS AND METHODS

COMPONENTS OF LIQUISOLID SYSTEMS: The major formulation components of liquisolid compacts are:

Carrier Material:

These are compression-enhancing, relatively large, preferably porous particles possessing a sufficient absorption property which contributes in liquid absorption. Example: various grades of cellulose, starch, lactose, sorbitol, Avicel PH 102 and 200, Eudragit RL and RS, amorphous cellulose.

Coating Material:

These are flow-enhancing, very fine (10 nm to 5,000 nm in diameter), highly adsorptive coating particles (example:silica of various grades like Cab-O-Sil M5, Aerosil 200, Syloid 244FP.) contributes in covering the wet carrier particles and displaying a dry-looking powder by adsorbing any excess liquid.

Non-Volatile Solvents:

Inert, high boiling point, preferably water-miscible and not highly viscous organic solvent systems. Various non-volatile solvents used for the formulation of liquisolid systems include Polyethylene glycol 200 and 400, glycerin, polysorbate 80 and propylene glycol, polysorbates, glycerin, N, N- dimethylacetamide, fixed oils.

Disintegrant:

Superdisintegrants increases the rate of drug release, water solubility and wettability of liquisolid granules. Mostly Superdisintegrants like sodium starch glycolate and Crosspovidone and croscarmellose sodium are used [32].

Other additives:

The disintegration of solid dosage forms noticeably influences drug release, Sodium starch glycolate is most commonly used disintegrant in the formulation of liquisolid tablets. Polyvinylpyrrolidone (PVP) is another promising additive, which has the potential to incorporate a high amount of drug into liquisolid systems and minimizes the overall tablet weight. There is another additive used in liquisolid systems– HPMC, which usually acts as a release retarding agent to sustain drug release from liquisolid compact [33].

METHODS

1. Direct compression:

A) Liquid drug can be converted into a dry liquisolid system without being further chemically modified. If liquisolid system of a solid water-insoluble drug is to be formulated, it should be initially dissolved or suspended in a suitable non-volatile solvent system to produce a drug solution or drug suspension of desired concentration.

Next, a certain amount of the prepared drug solution or suspension or a liquid drug itself is incorporated into a specific quantity of carrier material which should be preferably of a porous nature and possessing sufficient absorption properties.

The resulting wet mixture is then converted into a dry, non adherent, free-flowing and readily compressible powder by the simple addition and mixing of a calculated amount of coating material Excipients possessing fine and highly adsorptive particles are suitable for this step. Before compression or encapsulation, various adjuvants like lubricants and super-disintegrants added to final liquisolid system to produce orodispersible liquisolid compacts [34].

The promising flowable liquisolid powders were compressed following the direct compression method to prepare liquisolid tablets, the liquisolid powders were mixed with lactose (filler) and croscarmellose sodium (superdisintegrant) for 10 minutes in a glass mortar. Following, the mixtures were lubricated with sodium stearyl fumarate for another 3 min. Finally, 100 mg of each mixture was fed manually into the die of a single punch tablet press machine fitted with flat faced punches to produce liquisolid tablets [35].

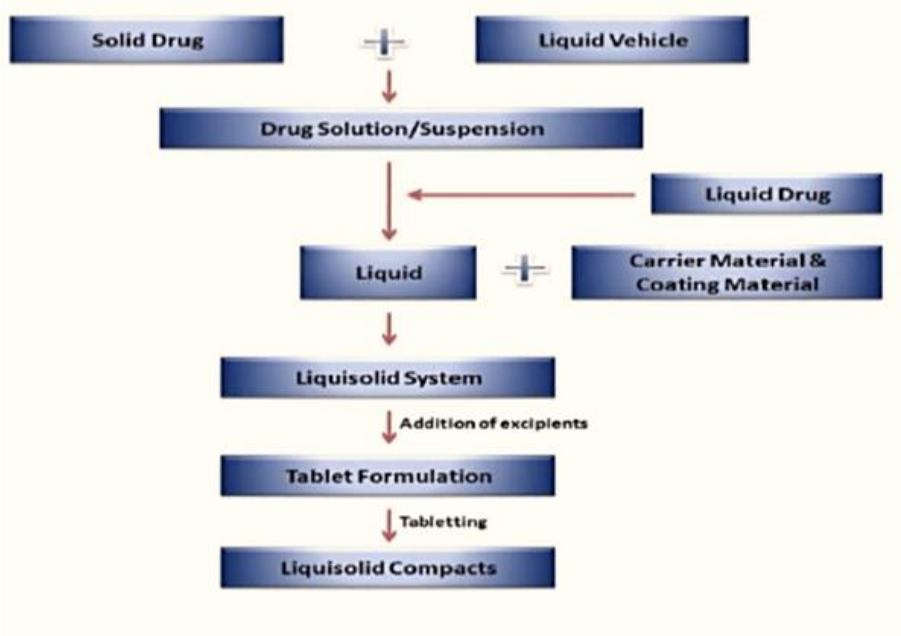

Fig 4.Steps involved in the preparation of liquisolid system

B) Preparation of orodispersible liquisolid compacts of drug were prepared by dispersing the drug in dissolution enhancing agent PEG 600. Microcrystalline cellulose was added as carrier and silica as coating material. Superdisintegrants in different concentration were used. Superdisintegrants was added both 50% intra and 50% extra granularly. Powder damp mass was passed through sieve no.80 to obtain granules and granules were dried at 45 ˚C for period of 12 hrs. Magnesium stearate and lactose were mixed with granules as a glidant and lubricant respectively finally granules were compressed using manual Tableting machine at constant compression force to obtain tables of uniform dimensions [36].

2. Preparation of granules from liquisolid compact:

Drug was dispersed in a nonvolatile vehicle (propylene glycol-PEG 400).Then a binary mixture of carrier coating materials (microcrystalline cellulose and dibasic calcium phosphate as the carrier powder and HPMC as the coating material at a ratio) was added to the mixture containing the drug and propylene glycol under continuous mixing in a mortar. Finally, disintegrants was mixed with the prepared mixture for a period of 5 minutes. The obtained liquisolid system was then compressed using die and flat punches. The obtained liquisolid compact was then beaked and passed through sieve no # 20 to obtain uniform sized granules from liquisolid compact [37].

3. Preparation of granules by compression technique:

Prepare the slug of Physical powder mixtures of different polymers and drug: Slugs were prepared by compression of the resulting physical mixtures on a Press with 30 second dwell time. Round, flat-faced punches with 13-mm diameter were used. A compression force of 1 tone was utilized for all slugs. The resulting slugs were milled in mortar and pastel then passed through sieve no # 20 so as to form uniform compacted granules containing drug and polymers. Prepared the physical mixture of the all compacted formulation by simply mixing the drug and polymer in the mortar and pastel without compaction [38]

.

CONCLUSION:

The Liquisolid system is a technique for formulation of water insoluble drugs to enhance their aqueous solubility, absorption as well as dissolution rate which leading to enhancement of bioavailability of drugs as compared to conventional directly compressed tablets. At the same time sustaining the drug release from dosage forms helps in a better and proper utilization of the drug. Both of these applications are major requisites for enhancement of drug bioavailability. Orodispersible tablets may give rapid onset of action by rapid absorption through pre-gastric absorption of drug from mouth, pharynx and esophagus as saliva passes down and beneficial to reduce dose. By combining Liquisolid technique and Orodispersible DDS, may enhance solubility,

dissolution rate by means of Liquisolid technique and can achieve rapid onset of action with lower dose of drug by using Orodispersible DDS and hence may increase patient compliance. liquisolid technology is one of the most promising approaches. It is found to be a multipotential and promising technology for dosage form development, because of the process simplicity, low economic inputs during production and possible industrial feasibility due to the good Flow and compaction characteristics of liquisolid formulations. Thus liquisolid technology shall be used to improve the release rate of poorly water soluble drugs that will make the dosage form will be cost effective.

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