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AN OVERVIEW OF LIQUISOLID TECHNOLOGY TO ENHANCE DRUG DISSOLUTION

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ABSTRACT

Dissolution of drug and its release from the dosage form have basic impact on bioavailability. The solubility of a medication determines its bioavailability. As new medications are developed, solubility becomes a significant concern for the pharmaceutical industries. About 40% of recently developed medications fit into the poor water soluble or water insoluble classifications. Generally speaking, weakly water-soluble medications have an aqueous solubility of less than 100 µg/ml. There are numerous ways to improve the solubility of poorly soluble medications, and one particularly effective method is the use of liquisolid compacts. A unique idea for a drug delivery system (NDDS) that can speed up the rate at which water-insoluble medications dissolve is the Liquisolid compact system. The basis of this liquisolid method is the dissolution of the insoluble drug in a non-volatile solvent, followed by the mixing of drug-loaded solutions with suitable carriers and coating materials to produce powders that flow and compress into acceptable levels. These free flowing powders are compressed to make tablets or filled in capsules.

KEYWORDS: Liquisolid technology, Bioavailability enhancement, Carrier material, Coating material.

INTRODUCTION

Liquisolid compacts are the historical descendant of "powdered solutions," an earlier method that was mostly employed to adsorb the liquid on silica surfaces of considerable size in order to convert a drug solution into a non-volatile solvent and a dry-looking, non-adherent powder. Nevertheless, in subsequent research on powdered solutions, these preparations were examined for their dissolution profiles while in a powder dispersed state. To improve the compressibility of the systems, compression enhancers including microcrystalline cellulose were used in such dispersions.[1]

The bioavailability of a medicine, which is reliant on the solubility of drug molecules, determines its therapeutic efficacy. Solubility is a crucial component of attain the required drug concentration in the systemic circulation to elicit a pharmacological effect. Due to their limited solubility in the contents of the gastrointestinal tract, medicines that are poorly soluble in water will naturally be released slowly. Often, the rate-determining stage in drug absorption is the dissolution rate. For medications that dissolve slowly in water, increasing the rate of dissolution is a hurdle. Pharmaceutical dosage forms rely heavily on dissolution, which is a crucial criterion for batch-to-batch quality control, bioequivalency assessment, and occasionally in vitro-in vivo drug release correlation. The oral route is still the most popular way to administer drugs since it is convenient, patient compliance is high, and the cost of producing medicine is low. A medication needs to dissolve in the stomach juices in order to be absorbed into the systemic circulation after oral delivery.[2]

Liquisolid system is a novel drug delivery system to enhance the dissolution of poorly water soluble drugs. The Liquisolid technique refers to the conversion of liquid medications into apparently dry, non-adherent, free flowing and compressible powder mixtures by blending the liquid medications with suitable excipients, which are generally termed as carriers and coating materials and it is described by Spireas, He outlined the process for encouraging liquisolid compact formation or dissolution. The liquid component is integrated into the porous carrier material and can take the form of a liquid drug, a drug suspension, or a drug solution in appropriate non-volatile liquid vehicles.

The characteristics of liquid vehicle include

- Orally safe
- Chemically Inert
- Not highly viscous
- Preferably water-miscible organic solvent systems with a high boiling point.
- Examples; glycerine, propylene glycol, or liquid polyethylene glycols

The thin coated particles quickly adsorb the liquid layer that forms on the particle surface after the carrier is saturated with the fine coated particles quickly absorb the liquid layer that has formed on the particle surface. Consequently, a powder that seems dry, flows freely, and is compressible is produced. Amorphous silicon dioxide, sometimes known as colloidal silica, is typically utilized as the coating material and microcrystalline cellulose as the carrier material.[3],[4]

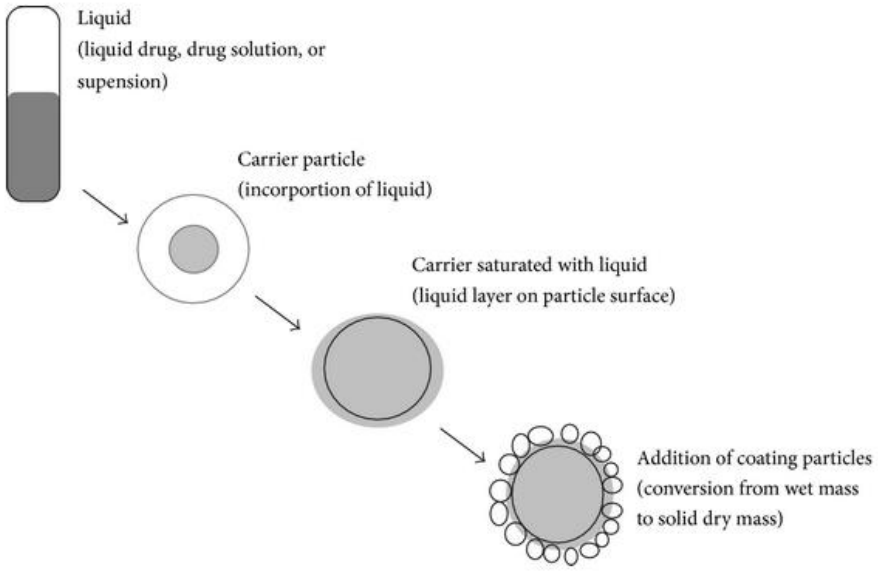


Fig. 1: Schematic representation of liquisolid system.

APPLICATIONS

- Enhancement of Solubility and Dissolution.
- An effective technique for increasing the bioavailability of water-insoluble medications is liquidsolid compact technology. A number of water-insoluble medications have been combined into liquisolid compacts by dissolving them in various non-volatile solvents.
- Several medications have been effectively combined into liquisolid compacts, according to literature.
- Liquisolid compositions yield rapid release rates.
- These work well for both liquid lipophilic medicines and solid medications that are insoluble in water.
- This approach has been used to generate sustained release of water soluble medicines, such as propranolol hydrochloride.
- Flowability and Compressibility;
- Design of Controlled Release Tablets.
- Improvement of Bioavailability.[5][6]

ADVANTAGES OF LIQUISOLID TECHNIQUE

- Liquisolid systems can be created from a large variety of Bio-Pharmaceutical Class II medications that have high permeability, are somewhat or very slightly soluble in water, and are practically insoluble as solids.
- It is possible to increase the bioavailability of a medicine that is water insoluble by administering it orally.
- This principle is primarily in charge of the enhanced dissolving profiles displayed by these preparations and regulates or administers the mechanism of drug delivery from liquisolid systems of powdered drug solutions.
- The medication is prepared as an encapsulated dosage form or tablet and is kept in a solubilized liquid state, which gives it enhanced or developed drug wetting characteristics and enhances its dissolving profiles.
- Compared to soft gelatin capsules, this method has lower production costs.
- This liquisolid method is intended just for liquid pills that are powdered.
- The dissolving solvent is exposed to a larger surface area of the medication.
- These Liquisolid systems can be formulated into dose forms with either sustained release or immediate release.
- Enhanced long-term release Water-insoluble medication liquidsolid tablets or capsules show constant rates of dissolving (Zero Order Release).[5][7]

DISADVANTAGES OF LIQUISOLID TECHNIQUE

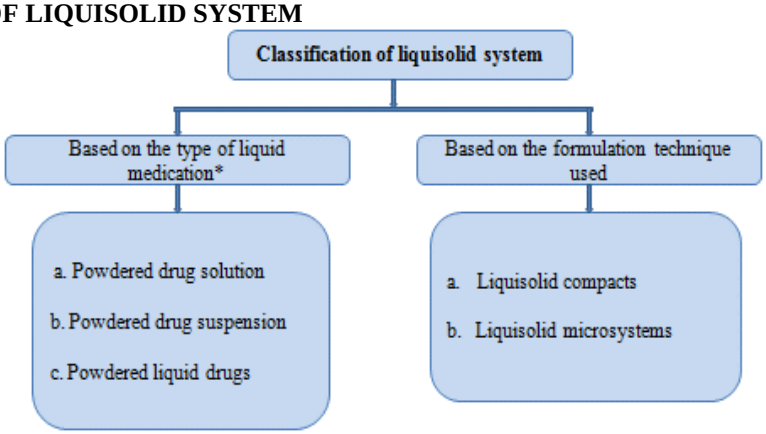
- This method is limited to medicines that are insoluble in water.
- The liquisolid tablet is one of the drawbacks of this method for the formulation of high dose insoluble medicines.
- High levels of coating and carrier ingredients should be added to the liquisolid powder formulation in order to produce appropriate compatibility and flowability. This will cause the tablets to weigh more than one gram, making them challenging to

swallow. Therefore, converting high dose tablets to liquisolid tablets with a tablet weight of less than 50 mg is not practical using standard tablet procedures. When there are low concentrations of the hydrophilic carrier—where the coating material has little bearing the dissolution profile is enhanced.[8][9]

LIMITATIONS

- Not applicable for formulation of high dose insoluble drugs.
- If more amount of carrier is added to produce free-flowing powder, the tablet weight increases to more than one gram which is difficult to swallow.
- 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.
- Introduction of this method on industrial scale and to overcome the problems of mixing small quantities of viscous liquid solutions onto large amounts of carrier material may not be feasible.
- Hydrotropy is suggested to be superior to other solubilization method, such as miscibility, micellar solubilization, cosolvency and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification.
- It only requires mixing the drug with the hydrotrope in water.
- It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.[5][6]

CLASSIFICATION OF LIQUISOLID SYSTEM



THE MAJOR FORMULATION COMPONENTS OF LIQUISOLID COMPACTS ARE

Carrier materials: Carrier materials should be sufficiently porous so that can enhance absorption properties and hence can absorb liquid sufficiently to enhance the solubility. *e.g.* Avicel PH 102 and 200, Eudragit RL and RS, starch, cellulose, lactose, sorbitol etc.

Disintegrant: Mainly superdisintegrants increases rate of drug release, its wettability and increases solubility of drug particles within short period of time. *e.g.* Sodium Starch Glycolate (SSG), Crosspovidone etc.

Coating material: Coating material should be with high adsorptive property so that when used for coating the carrier particles can absorb the excessive non volatile solvent layer over the carrier particles and can give dry solid appearance to the saturated carrier particles having liquid external layer of non volatile solvent. This can give dry, non adherent, free flowing powder particles.[1][8]

GENERAL PROCEDURE

Disperse the required quantity of solid drug in a suitable non volatile solvent having different drugs: solvent ratio and constantly stir to get homogeneous liquid. Add calculated amount of suitable carrier material with other excipient and mix with the initial mixture of drug and non volatile solvent, blend for 15 minutes. add suitable disintegrating agent to the prepared mixture. Incorporate suitable coating material which absorbs the layer of excess non volatile solvent over the carrier material, Due to this the liquid layer get converts into the solid layer and gives the dry, non adherent, free flowing powder particles. the steps involved in the preparation of liquisolid systems displays in fig.2. and the final mixture is then allowed to compress using tablet compression machine.[1]

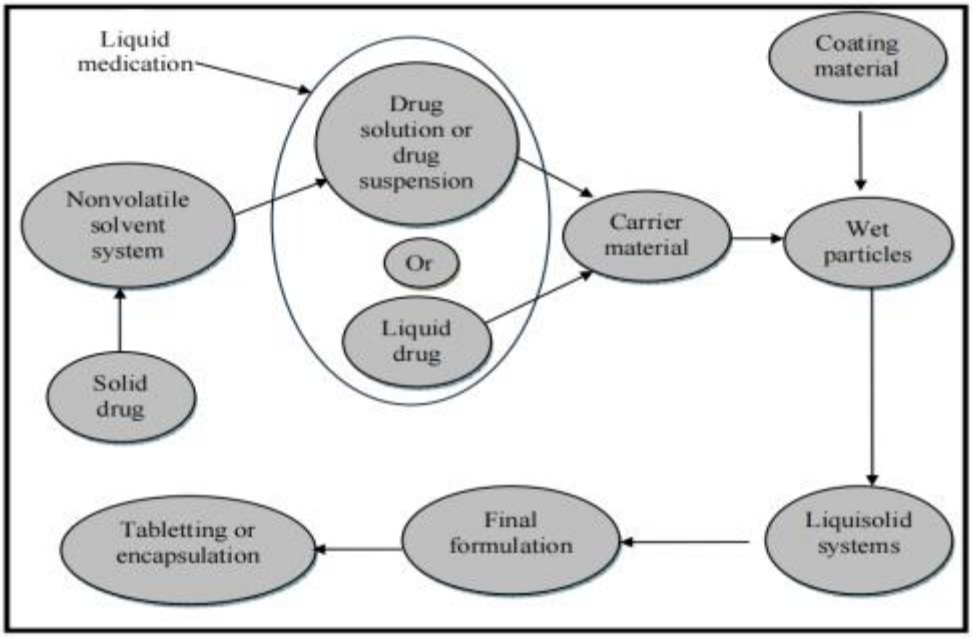


Fig. 2: Steps involved in the preparation of liquisolid systems.

MECHANISMS OF IMPROVEMENT OF DRUG RELEASE

Several mechanisms are developed to enhance the drug release. Three important mechanisms includes

1. An increase in effective drug surface area,
2. An increase in aqueous solubility
3. An improved wettability of drugs.

I. Enhancement of surface area: The medicine will dissolve more readily in a liquid medium when its effective surface area is increased.

II. Enhancement of aqueous solubility: It takes more than a very tiny amount of liquid vehicle to completely dissolve the entire amount of medication. However, it's feasible that a small amount of liquid vehicle will permeate from the total quantity at the solid-liquid interface between the particles and the dissolution medium along with the medication. If this happens, the small amount of liquid will be enough to boost the drug's water solubility.

III. Enhancement of wetting properties: Through its role as a surface active agent or its ability to lower surface tension, the liquid vehicle can improve the wettability of the liquidsolid primary particle. Water rising times and contact angles have been used to demonstrate the wettability of liquisolid systems.[2][10][11][12]

PREFORMULATION STUDIES

- **Solubility of drug:** The process involves making a saturated drug solution using different solvents. The extra medication is added to a non-solvent mixture to create this saturated solution. This solution is subjected to a specified period of shaking using a shaker before being filtered and examined under a UV spectrophotometer.[7]
- **Determination of angle of slide:** Powder flow characteristics are measured by angle of slide. Weighing the required quantity of carrier material and placing it at one end of a polished metal plate allows one to determine the angle of the slide. The end is lifted progressively until the plate is at an angle with respect to the horizontal, just before the powder slides. This angle is known as angle of slide. An angle of 33º is considered to be optimum.
- **Determination of flowable liquid retention potential(Φ value):** The term "flowable liquid-retention potential"(Φ-value) of a powder material describes its ability to retain a specific amount of liquid while maintaining good flow properties. The Φ-value is defined as the maximum weight of liquid that can be retained per unit weight of the powder material in order to produce an acceptably flowing liquid/powder mixture. The Φ values are calculated according to the following equation.

$$\phi value = \frac{weight\ of\ liquid}{weight\ of\ solid}$$

- **Calculation of liquid loading factor:** The medication is dissolved using various non-volatile solvent concentrations. This type of liquid medication is blended in with the carrier coating material mixture. The amounts of carrier and coating ingredients in each formulation are calculated using equation (2), which also determines the drug loading factors.

$$Lf = \frac{W}{Q}$$

W is weight of liquid medication
Q is weight of carrier material

- **Liquisolid compressibility test (LSC):** The liquid-solid compressibility test is used to calculate Φ values. It involves the following steps: creating admixture systems for carrier coating materials; creating multiple uniform liquid or powder admixtures; compressing each of these admixtures into tablets; evaluating average hardness; determining the average liquid content of crushed tablets; and determining plasticity, sponge index, Φ value, and LF.[7][8][13]

EVALUATION STUDIES

Micromeritic Properties of Powder

- **Bulk Density:** The mixture was poured into a graduated cylinder to determine the apparent bulk density, which was then used to determine the bulk density and tapped density using a bulk density apparatus. The powder's weight (M) and bulk volume (Vb) were calculated. The formula was utilized to determine the bulk density.

$$Bulk\ density = \frac{\text{weight of the powder}}{\text{Bulk volume}}$$

- **Tapped density:** In accordance with USP apparatus-11, the measuring cylinder carrying a known mass of powder blend was tapped a certain number of times. After tapping, the powder's lowest volume occupied was measured.

$$Tapped\ density = \frac{\text{weight of the powder}}{\text{tapped volume}}$$

- **Corr's index:** The formula for Corr's index is as follows: A powder with good flow characteristics has a value around 15%, and one with poor flowability is one with a value over 25%.

$$Corr's\ index = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100$$

- **Haussner's ratio**: It is an indirect index of ease of powder flow, it is calculated as follows. Haussner's ratio <1.25 indicates good flow property, where as >1.5 indicates poor flowability.

$$\text{Haussner's} = \frac{\text{tapped density}}{\text{bulk density}}$$

- **Angle of Repose:** The funnel method was used to determine the angle of repose. A vertically rising funnel was used to pour the mixture through until the highest cone height (h) was reached. After measuring the heap's radius (r), the angle of repose was computed as follows.[14][15][16]

$$\theta = \tan - 1\ \frac{h}{r}$$

Precompression studies

- **Powder systems**: Fourier Transform Infrared Spectroscopy, Differential Scanning Calorimetry, X-ray Diffraction, and Scanning Electron Microscope studies are to be carried out to verify the suitability of the chosen excipients. Before the powders are compressed into dosage forms like tablets and capsules, flowability experiments must also be conducted to determine the best formulas for compression.
- **Differential scanning calorimetry (DSC):** Any potential interactions between the excipients included in the formulation must be identified. This will also show whether the stability studies were successful. It is an indication that the medication is in the form of a solution in a liquisolid formulation and is therefore molecularly disseminated throughout the system if the characteristic peak for the drug is absent from the DSC thermo gram.
- **X-RAY powder diffractometry (XRPD):** X-ray diffraction (XRD) patterns are obtained for the manufactured liquisolid compacts and the physical mixture of drug and excipients utilized in formulation in order to characterize the crystalline state. The X-ray diffractogram's liquisolid compacts without constructing distinctive peaks for the drug indicate that the substance has nearly completely changed from its crystalline to an amorphous or soluble state. It was previously believed that the drug's solubilization in the liquid vehicle—that is, the drug's formation of a solid solution within the carrier matrix—was the cause of the liquisolid system's lack of crystallinity. The medication's amorphization or solubilization in liquisolid compacts may have improved the drug's apparent solubility and accelerated its rate of dissolution.
- **Fourier transformed infra red spectroscopy (FT-IR):** Using an FTIR-8400 spectrophotometer, the produced melt granules' FT-IR spectra are captured. Utilizing the potassium bromide (KBr) pellet method, background spectrum is collected in the same conditions. Every spectrum is produced by comparing a single average scan taken at a spectral resolution of 2 cm-2 with a background interfereogram in the 400–4000 cm-1 range. Software is used to evaluate spectra.
- **Scanning electron microscopy (SEM):** The presence or lack of the drug's crystal form or the excipients' crystal form in the formulation is revealed by scanning electron microscopy. If the SEM analysis reveals that the medication is no longer in its crystal form, it indicates that the drug has fully dissolved into the carrier system. Liquid-solid tablets are assessed for weight fluctuation, thickness, friability, and moisture content after they have been fully formulated.[17][18][19]

Post compression test

- **Estimation of drug content:** The liquisolid compacts are finely ground, and a suitable solvent is used to weigh and dilute 10 mg of the medication powder. A UV-Visible spectrophotometer is used to assess the drug content.
- **Hardness of tablet:** To ensure that the tablet can withstand hardness and strength during manufacture,

packing, and shipping, as well as when handled by the patient, it is crucial to consider the tablet's hardness and strength. The ideal range for tablet hardness is 5 to 10 kg/cm2.

- **Weight variation test:** The purpose of the weight variation test is to ensure that the manufactured pills weigh the same. Method: Weigh each of the twenty randomly chosen units one at a time, then determine the average weight. The pharmacopoeia specifies the maximum % deviation that any two individual weights can have from the average weight, and none can differ more than twice that amount.
- **Friability:** The issue known as "friability" occurs when a mechanical shock causes damage to the tablet's surface or reveals a damaged area. Utilizing the Roche friabilator, it is tested. The percentage of friability, as per B.P./I.P. =, should not exceed 0.8% - 1.0%. The U.S.P. states that the percentage of friability should not exceed 4%.
- ***In vitro* release:** *In vitro* release of liquisolid tablets is carried out by using USP II apparatus at 37 0C ± 2 0C. During this study many researchers observed that if there is low drug concentration in liquid formulation then there is rapid drug release from the formulation. If *In vitro* release rates for liquisolid tablets are higher than the absorption rate will also be higher which enhances drug bioavailability.
- ***In vivo* study:** This liquisolid technology is a promising tool for the enhancement of drug release of poorly soluble drugs. The absorption characteristics of Hydroclorothiazide liquisolid compacts in comparison with commercial tablets were studied in beagle dogs. Significant differences in the area under the plasma concentration time curve, the peak plasma concentration and the absolute bioavailability of the liquisolid and the commercial tablets were observed. However, for the mean residence time, the mean absorption time, and the rate of absorption no significant differences were found. The absolute bioavailability of the drug from liquisolid compacts was 15% higher than that from the commercial formulation.[8][19][20]

REVIEW OF LITERATURE

- **Mazen el Hammadi *et al* (2011) .,** Investigated the improve dissolution rate of the poorly soluble lorataine by formulating it as a liquisolid compact drug release rates produced by liquisolid compacts were significantly higher and less affected by pH variation compared with conventionally made (direct compression) and commercial (Clarityn) tablets. In conclusion, liquisolid compacts technique may be used as a tool to minimize the effects of pH variation on the dissolution rate of drugs with poor water solubility.[21]
- **Varaprasad Regu *et al* (2023).,** developed and evaluated liquisolid compact to improve the dissolution rate of the poorly soluble drug ibuprofen. Mathematical models were used to develop different liquisolid compacts. The calculated required quantities of microcrystalline (carrier), aerosil 200 (coating material), sodium starch glycolate (disintegrant) and cremophor RH 40, and kolliphor p 188 (non-volatile liquid vehicle) was used to produce acceptably flowable and compressible admixture. The liquisolid technique proved the success of improving the dissolution of a poorly soluble drug like ibuprofen.2023.559-571.[22]
- **Bhola Jaydip *et al* (2020).,** Investigated to improve the dissolution profile of Efavirenz by using a simple, scalable and cost-effective technique of liquisolid compact. The drug was dissolved in Trancutol-HP for preparing the liquid medicament which was subsequently mixed with carrier and coating material to make free-flowing and compressible powder.studies suggested that the high dissolution of the drug from the liquisolid compacts was possibly because of the drug either being in an amorphous state or being molecularly dispersed within the internal matrix of compacts.[23]
- **Suresh Bandari *et al* (2014).,** Investigated to enhance the solubility and dissolution rate of loratadine using solid dispersions (SDs) with Gelucire 50/13. SDs of loratadine using Gelucire 50/13 as carrier were prepared by the solvent evaporation method, it is evident that the solubility and dissolution rate of loratadine was enhanced by SDs with Gelucire 50/13.[24]
- **Kundawala AJ *et al* (2017).,** Investigated to enhance the solubility of a poorly soluble drug, Loratadine (LRD), using solid dispersion approach. Phase solubility study was performed using various concentration of βCyclodextrin, Poloxamer 407, PVP K30 and PEG 6000. Solid dispersions were prepared with above carriers in various ratios by kneading method, solvent evaporation method and fusion method.solid dispersion of Loratadine showed increased solubility that will further assist in oral dosage forms especially with faster dissolution properties.[25]

RECENTLY REPORTED LIQUISOLID FORMULATIONS

Table 1: List of recently reported liquisolid formulations.

S.No	Author name	Drug	Components	Report
1	Molaei MA *et al*, (2018)	ketoconazole	PEG400 MCC Silica	Ketoconazole liquisolid formulatios (F3,F2andF1) releases the more drug than direct compression (conventional) tablet.[26]
2	Argade p *et al*, (2019)	Candesartan Cilexetil	TranscutolHP Neusilin Aerosil	liquisolid tablets (T1 to T9) showed high drug dissolution than directly compressible tablet. Drug release of T2 and T3 were

				89.1% and 91.4%.[27]
3	Akbari J *et al*,(2015)	Spironolactone	Glycerin PEG400 Avicel pH 102 Aerosil	Dissolution rate of all PEG400 liquisolids was higher than Direct compression tablet.[28]
4	Al-Sarraf MA *et al*, (2014)	Telmisartan	Propyleneglycol Avicel PH102 Aerosil200	LS5 (R-value15) shows the more drug release 96.33% than direct compression tablet.[29]
5	Sharma G *et al*,(2012)	Valsartan	PEG200 Avicel PH102 Aerosil200	LSC2(using4%disintegrant) shows maximum drug release than LSC1 (5%disintegrant)direct compression tablets.[30]
6	Bhola Jaydeep *et al*, (2020)	Efavirenz	Transcutol HP Neusilin US2 Aerosil 200	The liquisolid formulations shows acceptable tableting properties such as flow property, compactibility, hardness, friability, content uniformity and disintegration time.[23]
7	Varaprasad Regu *et al*, (2023)	Ibuprofen	Cremophor RH MCC Aerosil200	The liquisolid formulation of ibuprofen shows more drug release than compressible tablet.[31]
8	Vinay AP *et al*,(2020)	curcumin	Propylene glycol Tween 80 Span 80 MCC Silicon dioxide	LST4 formulation was identified as ideal and better formulation due to curcumin solubility slightly higher in tween 80 compared to propylene glycol and span 80.[18]

FUTURE PROSPECTIVES

One of the main challenges to effective oral medication administration is poor bioavailability. Enhancing the oral bioavailability of medications that are poorly absorbed is a focus of much research. Prior to creating a delivery method, the cause of the low bioavailability must be understood. The encouraging outcomes seen when different delivery methods or strategies for increasing bioavailability are used appears promising. However, much more study is needed for the product's commercial development in order to overcome obstacles including scaling up, cost effectiveness, and formulation instability.

CONCLUSION

In conclusion, as the rate-determining stage in the absorption process is the inadequate dissolving of water-insoluble medications, it is well documented that this is the primary cause of their poor and unpredictable bioavailability. To improve the absorption characteristics of water-insoluble medications by increasing their disintegration, the liquisolid approach may be a viable substitute method. Liquisolid formulations are made to contain liquid drugs in powdered form; as a result, their drug delivery mechanisms resemble those of liquid-containing soft gelatin capsule preparations. Using non-volatile solvents, liquidsolid technology effectively increased the rate of dissolution and bioavailability of nearly water-insoluble pharmaceuticals. Through the use of suitable biodegradable polymers with the right excipient ratios, the approach also maintained the drug release qualities of the water soluble medicines. Water-insoluble medications become more wettable when nonvolatile solvents are used in the formulation, which also guarantees the drug's molecular dispersion. The increased wetting characteristics and surface area of drug particles that are available for dissolution are most likely the cause of the increased rate of drug dissolution from liquisolid tablets. When certain agents are added to a formulation, the result is a faster rate of disintegration than with traditional tablets, which leads to better release rates and increased bioavailability.

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