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Liquisolid Technology in Drug Delivery: Mechanistic Insights, Formulation Approaches, And Future Perspectives

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Abstract: Poor aqueous solubility remains one of the most significant challenges in modern drug development, particularly for orally administered drugs. A large proportion of newly discovered drug candidates exhibit low water solubility, which often results in poor dissolution rate and limited oral bioavailability. Various formulation strategies have been explored to overcome this limitation, including solid dispersions, micronization, lipid-based formulations, and inclusion complexes. Among these approaches, liquisolid technology has emerged as a promising and versatile technique for improving the dissolution behavior of poorly water-soluble drugs. Liquisolid systems are formulated by converting a liquid medication— comprising a drug dissolved or suspended in a nonvolatile solvent—into a dry, free-flowing, and compressible powder using suitable carrier and coating materials. This transformation allows the drug to remain in a solubilized or molecularly dispersed state within the powder matrix, which significantly enhances wetting properties and increases the effective surface area available for dissolution. Consequently, liquisolid formulations often exhibit improved dissolution profiles and enhanced oral bioavailability compared with conventional solid dosage forms. The design of liquisolid systems is supported by a mathematical model based on the flowable liquid retention potential (Φ-value) and liquid load factor (Lf), which allows the prediction of the maximum amount of liquid that can be incorporated into a powder system while maintaining acceptable flow and compressibility properties. This theoretical framework has enabled the rational development of liquisolid formulations and facilitated their application across a wide range of poorly soluble drugs. In addition to dissolution enhancement, liquisolid technology has also been investigated for sustained-release formulations, bioavailability enhancement, and industrial drug delivery applications. Recent research has further expanded the scope of this technique through the development of liquisolid pellets, liquisolid microsystems, and nanotechnology-based liquisolid systems. Despite these advantages, challenges such as high excipient load, scale-up limitations, and stability considerations remain important factors influencing the practical implementation of this technology. This review provides a comprehensive overview of liquisolid technology, including its mechanistic principles, formulation strategies, evaluation methods, and pharmaceutical applications. Furthermore, recent advances, regulatory considerations, and future perspectives of liquisolid drug delivery systems are critically discussed to highlight the potential of this technology in overcoming solubility-related challenges in pharmaceutical development.

KEYWORDS

Liquisolid systems, Powdered solution technology, Dissolution enhancement, Non-volatile solvents, Poorly soluble drugs, Bioavailability enhancement

INTRODUCTION

Background of Solubility Challenges in Drug Delivery

Oral administration is the most desirable route of drug administration in terms of convenience, economy and compliance (1–3). But many orally administered drugs have limited therapeutic activity due to low aqueous solubility, which directly influences the dissolution rate and subsequent absorption of drugs in the gastrointestinal tract (4,5). According to the reports, approximately 70% of synthesized chemical entities and 40% of newly developed medications have solubility problems (6,7).

The Biopharmaceutics Classification System (BCS) is a scientific classification system for medications based on intestinal permeability and water solubility.(8,9) After lead optimization, it is discovered that the majority of new drugs fall into BCS class 2 or 4 (10). Drugs belonging to BCS Class II and Class IV typically exhibit poor aqueous solubility, which often becomes the rate-limiting step in drug absorption following oral administration (11)

Drug substances are classified into high/low soluble and permeable classes (12,13) as follow,

Table 1: Biopharmaceutical classification system (BCS) classification of drugs

Class	Solubility	Permeability	Examples
Class 1	High	High	Paracetamol, Verapamil, Chloroquine, Diltiazem, Metoprolol, propranolol(14–16)
Class 2	Low	High	Carbamazepine, Phenytoin, ketoconazole, Glibenclamide (14,16)
Class 3	High	Low	Acyclovir, Atenolol, Metformin, Ranitidine, Cimetidine(14,16)
Class 4	Low	Low	Taxol, Ritonavir, Furosemide, Cefuroxime, Saquinavir(14,16)

Numerous formulation techniques, such as cocrystallization (17,18),micronization (19), nanocrystalization (20), Cryogenic techniques(21), prodrug(22), cyclodextrin inclusion (23,24), hydrotropy(25), Eutectic mixtures(26), micelle solubilization (27), solid dispersion (28), and encapsulation in nanoparticles (29), lipid based drug delivery systems including self-emulsifying drug delivery systems, self-micro emulsifying drug delivery systems (SMEDDS)(30), self-nanoemulsifying drug delivery systems (SNEDDS)(31), liposomes(32), have been investigated to address the poor aqueous solubility of drugs.

Although these approaches have demonstrated certain advantages, they may also present limitations such as physical instability, high-end technologies, manufacturing complexity, or limited scalability (33–35). Therefore,

alternative formulation technologies capable of improving drug dissolution while maintaining formulation stability and ease of manufacturing are highly desirable.

Need for Liquisolid Technology

Liquisolid technique is one of the promising techniques for improving drug dissolution (36). According to the spireas, the liquisolid method is a novel idea that uses simple blend and appropriate additives to transform the liquid into a free flow that is easily compacted and perhaps as a dry powder(37).

“"Liquisolid technology" or "powder solution technology" is a process of transforming a liquid drug (containing of a medication dissolved or dispersed in a non-volatile solvent) into a dry, free-flowing, compressible powder by combining it with a suitable carrier and coating materials(38).

The capacity of liquisolid systems to improve the bioavailability of weakly water-soluble medications by providing the drug in a molecularly dispersed state inside the formulation, which increases the effective surface area accessible for dissolution, is one of its main benefits. As a result, enhanced drug release profiles and wetting characteristics can be attained.(6) Liquisolid systems provide a comparatively simple and affordable alternate for intricate methods like micronization, nanonization, or soft gelatin capsule formulations. It is appropriate technique for high-performance systems in terms of dissolution and bioavailability and large-scale industrial applications because the manufacturing process is similar to traditional tablet manufacture (35,39) Because of these benefits, liquisolid technology has attracted considerable attention as an effective strategy for improving the oral bioavailability of poorly soluble drugs.

Scope and Objective of the Review

The objective of this review is to give a thorough overview of liquisolid technology in drug delivery, with an emphasis on its mechanistic principles, formulation components, preparation methods, characterization techniques, theoretical underpinnings of liquisolid systems, including powdered solution technology, and the mathematical model employed to determine formulation parameters like the liquid load factor (Lf) and flowable liquid retention potential (Φ-value).
The review also covers the benefits, drawbacks, and pharmaceutical uses of liquisolid systems in improving the bioavailability and dissolving of poorly soluble medications. This review attempts to offer important insights into the potential of liquisolid technology as an effective technique for resolving solubility-related issues in pharmaceutical development by covering recent research and emerging trends.

HISTORICAL DEVELOPMENT OF LIQUISOLID TECHNIQUE

Early Concepts

Liquisolid compacts are historically evolved from "powdered solutions," an earlier method that involved primarily adsorbing the liquid onto silicas with large specific surfaces to turn a medication solution in a non-volatile solvent into a dry-looking, nonadherent powder(40). The idea of transforming liquid pharmaceuticals into dry, non-adherent, free-flowing, and compressible powder systems originated from the need to improve the dissolution rate and bioavailability of poorly water-soluble drugs. Early pharmaceutical research showed that liquid medications or drug solutions could be adsorbed onto porous carrier materials and then changed into solid dosage forms while maintaining acceptable flow and compression characteristics. This method improved drug wettability and increased the effective surface area available for dissolution, resulting in better drug release from solid dosage forms(37,41) .

Contribution to Liquisolid Systems

The volume of liquid that can be incorporated into a powder without compromising its flowability is called the flowable liquid retention potential (Φ-value), and was first described by Spireas. In order to generate liquisolid formulations with ideal flow and compression characteristics, a mathematical model was created based on this principle to calculate the proper amounts of carrier and coating ingredients needed(37,41).

Subsequent research by various investigators validated this model and demonstrated that liquisolid systems significantly enhance the dissolution rate of poorly water-soluble drugs due to improved wetting properties, increased drug surface area, and molecular dispersion of the drug in the liquid vehicle(42,43).

Evolution of Modern Liquisolid Systems

Liquisolid systems have evolved significantly beyond conventional liquisolid compacts, due to the requirement to address restrictions such as high excipient load, poor flowability at high liquid content, and scaling issues. Modern improvements have provided novel modifications, such as liquisolid pellets(44,45), Liquiground technique(46), and nanostructured liquisolid formulations(47), which provide increased drug loading capacity, flow characteristics, and dissolving performance.

Bianca et al. (2016) applied liquisolid technology to pellets using felodipine as a model drug and demonstrated its feasibility for enhancing dissolution performance. Their study showed that incorporating drug solutions into porous carriers allowed for improved wettability and dissolution compared to conventional pellets, highlighting the potential of liquisolid systems as an alternative approach for poorly soluble drugs(48).

Lam et al.,2019 formulated naproxen liqui-pellet, they showed improved flowability, rapid disintegration, and nearly complete drug release within 20 minutes, concluding that liqui-pellets are a scalable and effective approach for enhancing bioavailability of poorly soluble drugs(49).

Nazem et al.,2023 combined liquisolid technology with co-grinding to improve celecoxib dissolution. Using PEG-200, ball milling, and excipients like PVP, Avicel, silica, and sodium starch glycolate, they achieved faster drug release than conventional liquisolid or direct compression tablets. Solid-state studies confirmed reduced crystallinity without chemical interaction, and stability tests showed no adverse effects. The authors concluded that the liquisolid–co-grinding approach is a promising strategy for enhancing bioavailability of poorly soluble drugs(50).

Kamel et. al.,2013 designed a nanostructured liquisolid self-emulsifying system (SSEDDS) for rutin to improve its poor solubility and bioavailability. They optimized a formulation with Triton, Acconon, and Labrafac, producing very fine droplets (~5 nm). Adsorption onto carriers like Neusilin yielded solid powders with good flow and rapid drug release, while solid-state studies confirmed rutin's amorphous transformation. The authors concluded that nanostructured liquisolid SSEDDS is a promising oral delivery strategy for lipophilic compounds such as rutin(47).

PRINCIPLE OF LIQUISOLID TECHNIQUE

Concept of Powdered Solution Technology

The drug substances in a liquid vehicle are absorbed and adsorbed when mixed with carrier material that has a porous structure on the surface and tightly matted structure inside, such as cellulose. That is, the liquid that was initially absorbed into the particles is trapped inside the particles' structure, and when the absorption process reaches its maximum, the liquid is adsorbed by the internal and external surface of the porous carrier particles (51). The desired flow characteristics of the liquisolid system are then provided by the coating material with qualities and a large high adsorptive specific surface area. Thus, results in enhanced wetting properties and increased surface area for drug dissolution. Increased solubility of liquisolid formulation consequently increase the bioavailability of the drug (52)

Mechanism of Drug Release Enhancement

Liquisolid technology converts liquid medicine into dry, non-adherent, free-flowing, and compressible powder combinations using appropriate carrier and coating materials, enhancing the dissolution rate and oral bioavailability of poorly water-soluble drugs. The presence of the drug in a solubilized or molecularly distributed state within the liquid vehicle, which promotes quick drug dissolution upon contact with gastrointestinal fluids, is primarily responsible for the enhanced drug release from liquisolid systems. Increased drug surface area, increased aqueous solubility and improved wettability of drugs are three main mechanisms of drug release enhancement (53)

1. Increased surface area
2. Increased aqueous solubility
3. Increased wettability

Increased surface area

The drug remains in the powder substrate in a solubilized, molecularly dispersed state after being dissolved or dispersed in a liquid medium. As a result, compared to drug particles inside directly compressed tablets, the surface area of drug available for release is significantly larger. Increased surface area leads to increased dissolution of the drug (54,55)

Figure 1: Increased surface area

Increased aqueous solubility

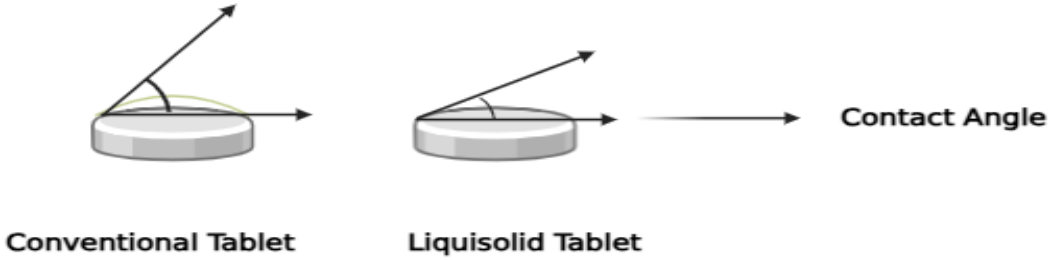
Drug solubility in water is increased when non-volatile solvents are used to the solid or liquid interface of a liquisolid particle and dissolution medium. This is because the non-volatile solvent acts as a co-solvent, allowing drug molecules and micro liquid carriers to emerge from liquisolid particles (37)

Figure 2: Increased aqueous solubility

Increased wettability

The liquid vehicle (non-volatile solvent) in the liquisolid system has a low surface tension or can function as a surface-active agent. Thereby, reduces the interfacial tension between the tablet surface and the dissolving liquid, which enhances the wetting of drug particles (56).

Figure 3: Increased wettability



Mathematical Model and Flowable Liquid Retention Potential (Φ-value)

Table 3. Flowable Liquid Retention Potential (Φ-value) of Common Carriers and Coating Materials with commonly used liquid vehicles

Material	Type	Φ-value	solvent	Reference
Avicel PH 102	Carrier material	0.16	Propylene Glycol	(57)
Avicel PH 102	Carrier material	0.005	PEG 400	(57)
Avicel 101	Carrier material	0.12	Propylene Glycol	(58)
Avicel 101	Carrier material	0.3265	Tween 80	(59)
Aerosil 200	Coating Material	1.5	PEG 400	(60)
Aerosil 200	Coating Material	0.04	Propylene Glycol	(58)
Neusilin US2	Carrier material	1	PEG 200	(61)
Neusilin US2	Carrier material	1.16	PEG 400	(61)
Neusilin US2	Carrier material	1.48	Propylene Glycol	(61)
Neusilin NS2N	Carrier material	0.54	Propylene Glycol	(58)
Fujicalin	Carrier Material	0.12	Propylene Glycol	(58)
Eudragit	Carrier Material	0.2364	Tween 80	(59)
Eudragit	Carrier Material	0.3184	PEG 400	(59)

Abbreviations: PEG 400- polyethylene glycol 400, PEG 200- polyethylene glycol 200, Φ- flowable liquid retention potential

COMPONENTS OF LIQUISOLID SYSTEMS

Drug Substance

Drugs used in liquisolid formulations are generally poorly water soluble and low dose drugs which are dissolved in non- volatile solvent to prepare drug solution or suspension. Drug must be in BCS class I and IV. Eg: Digoxin, Digitoxin, Prednisolone, Hydrocortisone, Carbamazepine, Aceclofenac etc.(62)

Liquid Vehicles

Liquid vehicles used in liquisolid technique are non-volatile, non-toxic, water miscible that are capable of dissolving poorly soluble drugs. Drug solubility plays vital role in liquisolid formulations, higher the solubility of drug in solvent, lower will be the carrier and coating material. Therefore, reduced formulation size and weight. E.g. propylene glycol, PEG 400, polysorbate 80, Labrasol, glycerin etc.(63)

Carrier Materials

Carriers are porous excipients with the capability to absorb and retain liqid medication within their internal structure. These are compression-enhancing, relatively large, preferably porous particles Example includes various grades of cellulose, sorbitol, Avicel PH 102 and 200, starch, Eudragit RL and RS, amorphous cellulose etc(64).

Coating Materials

Coating material is used to adsorb any excess liquid and to seal, coat the carrier particles and make dry-looking powder. These are very fine (10 nm to 5000 nm in diameter), highly adsorptive and flow enhancing material. E.g. Amorphous Silicon Dioxide (Aerosil 200, Cab-O-Sil® M5) is the most widely used as coating material (64,65)

Adjuvants

As per the requirements of formulation various excipients like binders, diluents, disintegrants, retardants can be added and mixed in the formulation. E.g. magnesium stearate, talc, maize starch etc.(66–68)

Table 4. Reported Liquisolid Formulations for Poorly Water-Soluble Drugs

Drug	BCS Class	Non-Volatile Solvent	Carrier	Coating Material	Main Outcome	Ref.
Famotidine	3	polyethylene glycol 400	Avicel PH 200	Aerosil 200	Showed higher drug dissolution rates than the conventional, directly compressed tables	[51, 69]
Fenofibrate	2	polyethylene glycol 600	Avicel PH 102	Aerosil 200	Dependant variables are more affected with amounts of PEG 600 and Aviel PH 102.	(69, 70)
Carbamazepine	2	polyethylene glycol 200	Avicel PH 102	Aerosil 200	Better dissolution rate in comparison with DC tablet and the dissolution rate reduced when the ratio of microcrystalline cellulose to silica	(71)

					was reduced from 10 to 5.	
Aceclofenac	2	Polyethylene glycol 400	Avicel PH 102	Aerosil 200	Showed significantly higher drug dissolution rate.	(60)
Hydrocortisone	2	Propylene Glycol	Avicel PH 200	Colloidal Silica	The hydrocortisone dissolving rates of liquisolid systems are directly proportional to the percentage of molecularly distributed drug in their liquid medication.	(72)
Ibuprofen	2	Cremophor RH 40, kolliphor p 188	microcrystalline cellulose	Aerosil 200	Significantly higher drug dissolution rates	(73)
Indomethacin	2	Propylene Glycol	microcrystalline cellulose	Colloidal Silica	Higher drug dissolution rates than those of conventionally made capsules	(74)
Indomethacin	2	polyethylene glycol 200	microcrystalline cellulose	HPMC	Liquisolid compacts technique can be a potential alternative for the formulation of water insoluble drugs	(75)
Bromhexine HCl	2	Propylene Glycol	Avicel PH 102	Aerosil 200	Liquisolid technique is a promising alternative for improvement of dissolution property	(36)
Furosemide	4	Synperonic® PE/L 81	Avicel PH 101	Colloidal Silica	At various pH levels, liquisolid compacts containing Synperonic® PE/L 81 showed a greater release rate.	(76)
Naproxen	2	Cremophor® EL	Avicel PH 102	Colloidal Silica	Cremophor EL-formulated liquisolid tablets with a 20%w/w drug concentration yielded a high dissolving profile and acceptable tablet characteristics.	(77)
Prednisolone	2	Propylene Glycol	Avicel PH 200	Colloidal Silica	Dissolution rate of prednisolone from	(78)

					the liquisolid compacts is independent of the dissolu-tion volume	
Piroxicam	2	Polysorbate 80	microcrystallin e cellulose	Colloidal Silica	Compared to conventionally manufactured (capsules and directly compressed tablets containing micronized piroxiam), Liquisolid compacts showed noticeably higher drug release rates.	(56)
Hydrochlorothiazide	4	polyethylene glycol 200	Avicel PH 101, Avicel PH 102, Magnesium carbonate	Aerosil	Absolute bioavailability of the drug from the liquisolid tablets was 15% higher than that from the commercial one.	(67, 79)
Theophylline	1	Polysorbate 80, PEG 200, PEG 600, Polysorbate 20, PG	Eudragit RL or RS	Silica	Liquisolid compacts has a potential to produce zero-order release kinetics for less water-soluble drugs	(80)
Repaglinide	2	Polysorbate 80	Avicel PH 101	Calcium Silicate	The bioavailability of repaglinide was improved significantly when administered orally as the liqiusolid compact preparation.	(81)
Deflazacort	2	Propylene Glycol	Avicel PH 102	Aerosil 200	Better alternate technique to improve dissolution	(82)
Methyclothiazide	2	Polyethylene glycol 400	microcrystallin e cellulose	Colloidal Silica	Liquisolid tablets displayed significantly enhanced dissolution profiles compared to those of marketed products.	(83)
Valsartan	2	Propylene Glycol	Avicel PH 102	Aerosil 200	Enhanced Dissolution was achieved	(84)

Ketoprofen	2	Polyethylene glycol 400	Avicel PH-101, Dicalcium Phosphate (DCP), Starch, and Lactose	Silica gel	Liquisolid formulations of ketoprofen exhibited higher percentage of drug release than marketed formulation	(85)

Abbreviations: PEG 600- polyethylene glycol 600, PEG 400- polyethylene glycol 400, PEG 200- polyethylene glycol 200, PG- Propylene Glycol, HPMC- hydroxy propyl methyl cellulose

TYPES OF LIQUISOLID SYSTEMS

On the basis of formulation techniques, liquisolid systems are mainly classified into two types (86,87).

Based on the type of liquid medication

1. **Powdered drug solution**

These are formed by conversion of drug solutions like prednisolone in propylene glycol, into liquisolid compact.

2. **Powdered drug suspension**

These involve converting drug suspensions, like gemfibrozil in Polysorbate 80, into liquisolid compact.

3. **Powdered liquid drug**

These include formulating liquid drugs, succlofibrate liquid vitamins, into liquisolid compact88).

Based on the formulation

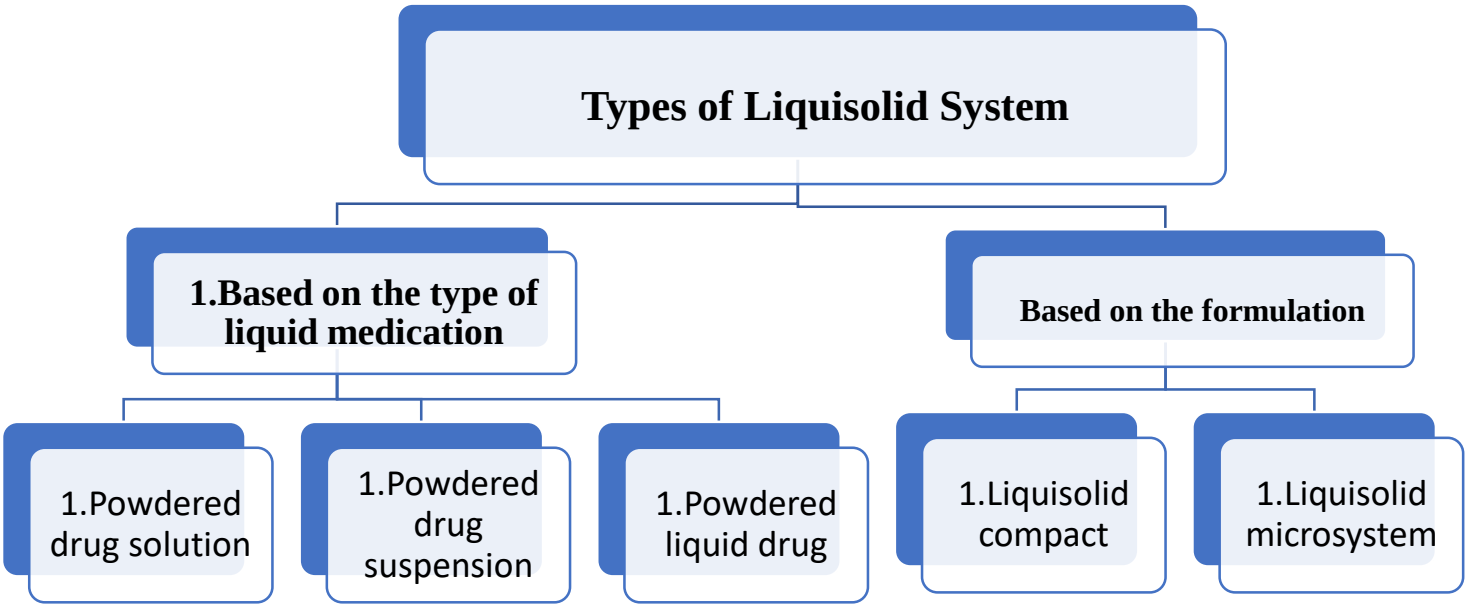
1. **Liquisolid compact**

These are prepared using the traditional method, producing tablets or capsules. The term “liquisolid compacts” refers to immediate or sustained release tablets or capsules.

2. **Liquisolid microsystem**

These are based on an innovative idea that uses a process similar to that of liquisolid compacts but adds a component to the liquid drug, like polyvinylpyrrolidone (PVP). In order to produce an appropriate flowing admixture for encapsulation, this additive is mixed with the carrier and coating materials(90).

Figure 4: Types of liquisolid system



FORMULATION METHODOLOGY

Liquisolid Mathematical model

Since a powder can only hold a certain amount of liquid while maintaining acceptable flow and compression properties, this technique is based on the flowable (Φ-value) and compressible (Ψ-number) liquid retention potential(51,91). These variables don't change for a specific powder/liquid (P/L) mixture(92,93).

Spireas et al. proposed mathematical methods for preparing the excipients and actives to create formulations with the necessary flow and compression characteristics (37,85).

Flowable liquid retention (Φ-value)

The maximum quantity of a particular non-volatile liquid that can be retained inside a powder's bulk (w/w) while still having a suitable flowability is represented by the Φ -value. The powder flow or the angle of repose can be used to calculate the flowability.

Compressible liquid retention (Ψ-value)

The maximum quantity of a particular non-volatile liquid that can be retained inside a powder's bulk (w/w) while still having a suitable compactability is represented by the Ψ-value. This allows for suitable hardness and friability, with no liquid squeezing out during compression.

The liquisolid flowability (LSF) test is a new method that may be used to assess the Φ value of powders. A novel technique called the liquisolid compressibility (LSC) test, which uses the "pactisity theories" to assess the compaction characteristics of liquid/powder admixtures, can be used to measure the Ψ number of powders(40,94). Pactisity is defined as maximum strength required to crush one gram of tablet, when compressed at high compression force.

CALCULATION OF LIQUID LOAD FACTOR

The Liquid Load Factor (Lf)

The Liquid Load Factor is the ratio of the liquid formulation to the amount of carrier material(78).

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

Where, W = Weight of the liquid formulation

Q = Weight of the Carrier

Excipient Ratio (R)

Excipient Ratio represents the ratio between the weights of the carrier (Q) and the coating (q) material present in the formulation(93).

$$R = \frac{Q}{q}$$

The liquid load factor that ensures acceptable flowability (Lf) can also be determined by:

$$Lf = \Phi + \varphi * (\frac{1}{R})$$

Where, Φ and φ are the Φ-values of the carrier and coating material, respectively.

In the same way, the liquid load factor (ΨLf) for producing liquisolid systems with adequate compactability can be determined by:

$$\Psi Lf = \Psi + \psi * (\frac{1}{R})$$

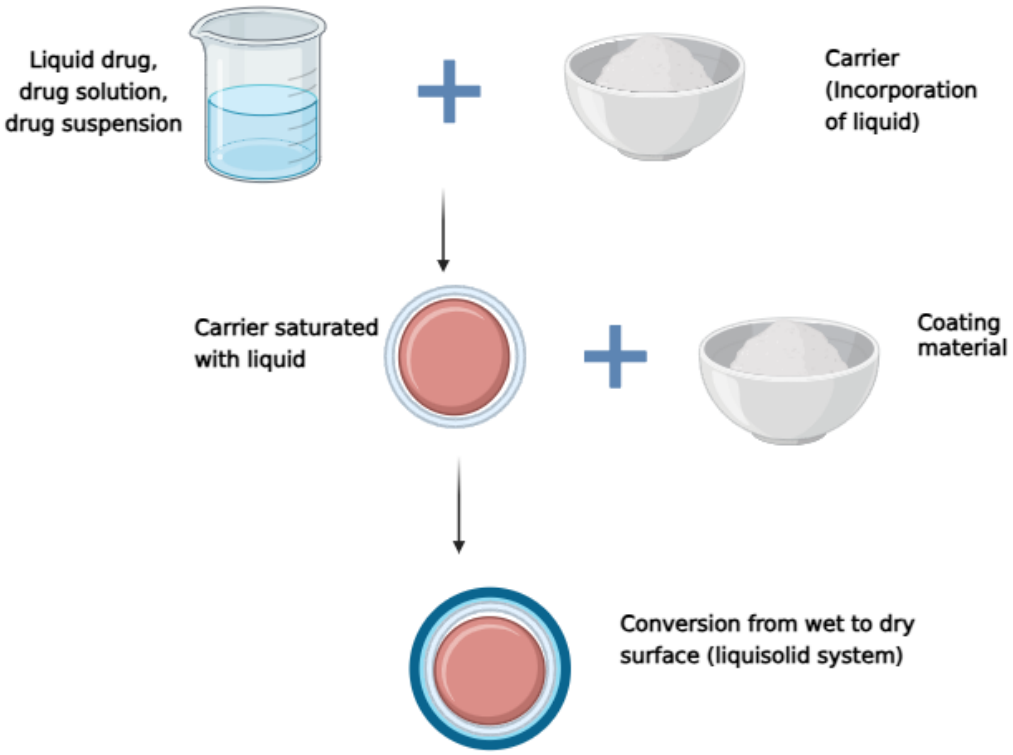
Where Ψ and ψ are the Ψ-numbers of the carrier and coating material, respectively(94).

PREPARATION PROCESS

The medication and non-volatile solvent are carefully weighed in a glass beaker before being heated to dissolve. The resultant heated medicine is mixed with determined amounts of carrier and coating components. Mixing process is done in 3 main stages(95,96)

1. For proper distribution of liquid medication in the powder, the system is mixed at a mixing rate of about one rotation per second for about one minute during the first stage.
2. For absorption of drug solution in the interior of the powder particle, the liquid/powder admixture is uniformly spread as a homogeneous coating over the surfaces of a mortar and allowed standing for about five minutes.
3. Using an aluminium spatula, the powder is scraped off the mortar surfaces in the third stage before being mixed with sodium starch glycolate for a further 30 seconds in a manner akin to the first. This provides the final liquisolid tablet composition(64,86).

Figure 5: Schematic representation of liquisolid preparation



EVALUATION AND CHARACTERIZATION

Pre-Compression Studies

Flow Properties

The formulation and industrial manufacturing of tablet dosage forms depend on the flow characteristic. It is necessary to calculate the angle of repose, Carr's index, Hausnar's ratio, tapped density, bulk density (97,98).

Angle of slide

The angle of slide is a measure used to assess the flow behaviour of liquisolid mixtures. The tested sample (10g) is placed at one end of a metal plate with a polished surface. This end was gradually elevated until the plate with the horizontal surface formed an angle that would allow the sample to move. The measurement was repeated three times, and the mean and standard deviation were computed. The slide angle of 33° is considered to be best for flow behaviour (99).

Angle of Repose

This is the maximum angle that can exist between a powder pile's surface and a horizontal plane. A funnel is used to let 10 grams of powder pour from 4 cm above the base. After measuring the pile's height and base's diameter, the angle of repose is calculated using the formula below (100).

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

$$\theta = \frac{1}{\tan} * \frac{\mathrm{h}}{\mathrm{r}}$$

where,

θ = angle of repose

h = height of the heap

r = radius of the heap

Table 5: Angle of Repose(101,102)

Flow Property	Angle of repose (degree)
Excellent	25-30
Good	31-35
Fair- aid not needed	36-40
Passable- may hang up	41-45
Poor- must agitate	46-55
Very poor	>56

Bulk density

Bulk density is calculated by pouring the mixture into a graduated cylinder, then bulk volume (V_b) and weight of powder is calculated (103).

$$Bulk\ density = \frac{Powder\ mass}{\text{Bulk volume (Vb)}}$$

Tapped density

The mass of the blend in the measuring cylinder divided by its tapped volume is known as the tapped density (104).

$$Tapped\ density\ (\rho t) = \frac{Powder\ mass}{Tapped\ volume(\mathrm{Vt})}$$

Carr's Index

Carr's index evaluates packing capacity and flow characteristics. Bulk (Db) and tapped density are used in its determination (105).

$$CI(\%) = \frac{tapped\ density - bulk\ density}{tapped\ density} * 100$$

Table 6: Carr's Index(106)

Flow character of powders	Carr index limit
Excellent	≤10
Good	11-15
Fair	16-20
Passable	21-25
Poor	>26

Hausner's Ratio

Hausner's ratio can be used to determine a powder mixture's flow characteristic. It is calculated using following formula (107),

$$Hausner's\ ratio = \frac{Bulk\ density}{tapped\ density}$$

Table 7: Hausner Ratio(108)

Flow character of powders	Hausner's ratio limit
Excellent	1.00-1.11
Good	1.12-1.18
Fair	1.19-1.25
Passable	1.26-1.34
Poor	1.35- 1.45
Very poor	1.46-1.59

POST-COMPRESSION STUDIES

Hardness

Primary micromeritic parameters, such as tablet thickness, diameter, weight, and hardness, are measured after liquisolid compact formulation. Vernier calipers are used to measure thickness and diameter, whereas the Monsanto hardness tester is used to detect hardness.

The force needed to break a tablet in a diametric compression force is known as tablet hardness. It is also known as tablet crushing strength. Hardness is quantified in kg/cm² (39,109).

Friability

Friability tests evaluate the impact of friction and shock, which can cause tablets to chip, cap, or break. Friabilator is utilized for this purpose. Compressed tablets should not lose more than 1% of their weight. The value is expressed as a percentage. Ten pills are weighed (Winitial) and placed in the Friabilator. The Friabilator is operated at 25 rpm for 4 minutes or up to 100 revolutions. Tablets were weighed again (Wfinal) (110).

$$F = \frac{\mathrm{W(initial)} - \mathrm{W(final)}}{\mathrm{W(initial)}} * 100$$

Dissolution Studies

Dissolution testing is used to assess the rate and range of drug tablet release. The tablets are put in a dissolution medium and the drug release is recorded over time using a dissolution instrument, such the USP apparatus. The pharmacopeial criteria specify the requirements that the tablet profile of dissolving must meet. The monograph for the formulation defines the medication and dissolving media used in the test.

The dissolution medium will be 900 ml of 6.8 pH phosphate buffer, kept at 37 ± 0.5°C. To keep the volume constant, 5 ml of the dissolution medium will be taken at regular intervals and replaced with an equal amount of new media. The collected samples will be diluted with phosphate buffer, filtered, and examined using a UV-visible spectrophotometer. The cumulative percentage of drugs released will be determined (111).

Disintegration studies

The disintegration test of liquisolid tablets is carried out using the USP disintegration apparatus. Six tablets are place individually in the basket rack assembly and operated at 900 ml of distilled water or suitable medium at 37°±2 °C. The average value of the time required for the tablets to disintegrate is reported (112,113).

Weight Variation

From each batch, twenty tablets were chosen at random and weighed separately. Three batches' average weight and standard deviation were determined. If no more than two of the individual tablet weights differ from the average weight by more than the permitted percentage deviation and none deviate by more than twice the percentage displayed, the weight variation test is passed (114).

Table 8: Pharmacopoeial Limits of Weight Variation(115)

Limit	IP/IB
10%	80 mg or less
7.5%	More than 80 mg or less than 250 mg
5%	250 mg or more

SOLID-STATE CHARACTERIZATION

DSC (Differential scanning calorimetry

DSC analysis is performed to investigate the thermal behaviour and compatibility of druf with excipients. Approximately 3-5 mg of the sample is placed in a sealed aluminium pan and heated from 25℃ to 300℃ at a heating rate of 10℃/min under nitrogen atmosphere. An empty aluminium pan is used as reference. The thermogram obtained is analysed for melting endotherm of drug (116,117).

XRD (X-ray diffraction)

X-ray diffraction is primarily used to identify and characterize substances using their diffraction patterns. XRD patterns are used to characterize the crystalline state of drug and excipient mixtures in formulations, as well as manufactured liquisolid compacts. The absence of constructive specific peaks in X-ray diffractograms indicates that the medication has transitioned from crystalline to amorphous/solubilized form. The absence of crystallinity in the liquisolid system was due to drug solubilization in the liquid vehicle, resulting in a solid solution within the carrier matrix (114).

FTIR

FTIR studies are used to determine the drug's compatibility with excipients. This method is used to obtain the infrared spectrum of a solid, liquid, or gas's absorption, emission, and Raman scattering. The drug's FTIR spectrum was obtained by subjecting the prepared samples to an IR spectrophotometer using the potassium bromide pellet technique. Spectrum is collected over a region of 4000-400 cm^{-1} (118).

SEM (Scanning electron microscopy)

The primary purpose of scanning electron microscopy is to identify the morphological properties of drug-carrier systems and raw materials. This study verifies if there are any crystals present, or else drug is present in completely solubilised form by absence of crystals of drug (119).

ADVANTAGES OF LIQUISOLID TECHNIQUE

- Liquisolid technique can provide a slow-release pattern with zero order release kinetics (80,120)
- Liquisolid technique offers simplicity, low-cost manufacturing and industrial scalability (121)
- It bypasses the process approaches such as nanonisation, micronization technique (6)
- This technique can offer pH-independent drug release (122)
- It is a better alternative to conventional coating approach for the improvement of drug photostability in solid dosage forms (123)
- Liquisolid technique has been widely used to improve the dissolution rate of low dose insoluble drugs.(124)
- The drug can be molecularly dispersed in the formulation (125)

LIMITATIONS AND CHALLENGES

- To prepare liquid-solid systems, the medication must be highly soluble in the liquid vehicle (63)
- One of the disadvantages of this approach is the formulation of a high dose poorly soluble drug (126)
- Weight of sustained release liquisolid tablets is generally higher than in conventional tablets (121)
- Drug’s solubility in non-volatile liquids affects its rate of dissolution and bioavailability (38)
- Failure to produce acceptable compression results in insufficient hardness (127)

APPLICATIONS OF LIQUISOLID SYSTEMS

Enhancement of Poorly Water-Soluble Drugs

Liquisolid technology is one of the most promising techniques to enhance the aqueous solubility of poorly water-soluble drugs. Several studies have demonstrated that liquisolid technique significantly enhances the dissolution rate of poorly water-soluble drugs. Khan et al. (2015) compared the effects of solid dispersion and liquisolid method on the enhancement of hydrochlorothiazide dissolution. This study showed that when hydrochlorothiazide was formulated as liquisolid compacts, its dissolution rate increased to 95%, however when it was prepared as a solid dispersion, its dissolution profile increased to just 88%(128). Kumar et al. (2015) formulated flurbiprofen liquisolid compact, the study demonstrated a marked improvement in disoolution rate compared to conventional tablets, indicating that the liquisolid technique effectively enhanced drug release due to wettability and increased surface exposure of the drug(129). Padmapreetha J et al. (2016) formulated leflunomide liquisolid compact by using

kolliphor EL, avicel PH 102, aerosol, and sodium starch glycolate as non-volatile solvents, carriers, coating materials, and super disintegrants to improve the dissolution rate.
The improved formulation released 73.39% of drug content in the first 10 minutes (Q10%), while the conventional formulation only released 18.94%(130). Similar improvements in dissolution rate using liquisolid technique have also been reported for several other poorly water-soluble drugs, including ketoprofen(131), Carvedilol(93), Rosuvastatin(132), Glibenclamide (46), Lercanidipine(133), Pioglitazone(134), Nifedipine(135).

Sustained Release Formulations

The liquisolid approach is a very new and promising method that offers zero order release kinetics and a slow-release pattern(120)(80). The original purpose of liquisolid systems was to enhance drugs solubility. It has recently been studied as a potential way to sustain release of drugs with appropriate carrier excipient selection. The idea behind liquisolid technology to extend drug release is that sustained release systems can be achieved by substituting hydrophobic carriers, such Eudragit RL and RS, with hydrophilic carriers. Hydrophobic carriers may lead to poor wetting properties of the compacts resulting in slow disintegration and thus, prolonged drug release. Hydrophilic HPMC polymer grades increase this technology's retardation impact(136). It is possible to maximize sustained drug release liquisolid formulations by avoiding disintegrants, choosing suspensions with a high percentage of undissolved drug, and choosing low R-values. A high liquid load factor causes the liquisolid compacts to be overloaded with liquid formulation if the R-value is low, indicating a high applied silica quantity. In such cases oversaturation might occur resulting in local precipitation of the drug and thus, decreased release rates(137).Various researchers have explored liquisolid technique for sustained release for drugs like diltiazem (138), trandolapril (139), lawsone(140), tramadol(141), atorvastatin (142), clopidogrel (143) , theophylline (80) , glibenclamide (46), trimetazidine dihydrochloride (68).

Bioavailability Enhancement

The liquisolid technique has been widely investigated as an effective approach for the oral bioavailability enhancement. Several studies have demonstrated the effectiveness of liquisolid technique in improving bioavailability of poorly water-soluble drugs by improving surface area for dissolution, wettability leading to better dissolution and ultimately enhanced bioavailability(144,145). El-Houssieny et al. studied the effect of repaglinide-containing liquisolid compacts on rabbit glucose tolerance. They demonstrated that administering repaglinide orally in the form of liquisolid compacts enhanced its bioavailability significantly when compared to commercially available tablets(81). Chen et al. reported that the absolute bioavailability of carbamazepine was raised by 82% when liquisolid tablets were tested in vivo compared to commercially available tablets(146). Jhaveri et al. reported that carvedilol liquisolid compacts exhibited rapid dissolution (>95% drug release within 30 min) and significantly improved systemic bioavailability compared with the conventional formulation ($p < 0.005$)(147). Other drugs formulated using liquisolid technique which showed enhanced bioavailability are risperidone(148), etodolac(149), ritonavir(150), nilvadipine(113), candesartan(151).

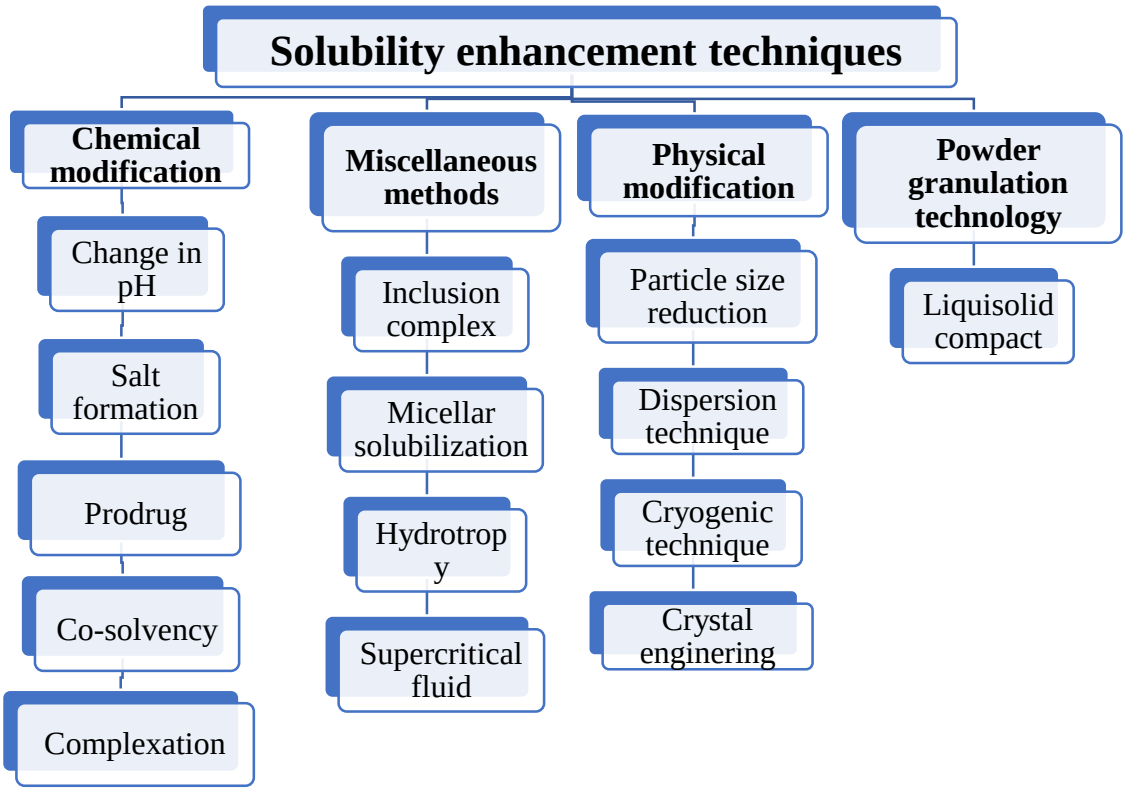
pH independence

Liquisolid technology has also been investigated as an effective strategy to minimize pH-dependent variations in drug release, thereby enhancing dissolution consistency across GIT. Weak acids and bases' solubility depend on both the pH of the surrounding environment and the compound's ionization constant (pKa). Therefore, the pH of gastrointestinal fluids has a significant impact on these medications' solubility and bioavailability(63). Hamadi et al. formulated loratadine liquisolid compacts to evaluate the influence of pH on drug release and reported that the liquisolid systems exhibited significantly higher release rates with reduced sensitivity to pH changes compared to conventional or marketed tablets(152). Badawy et al. prepared liquisolid tablets of mosapride citrate using biorelevant media to evaluate the effect of gastrointestinal pH variations and reported that the formulations exhibited rapid and consistent drug release under different simulated conditions. Furthermore, in vivo pharmacokinetic studies in human volunteers demonstrated a 121.20% enhancement in oral bioavailability compared to the commercial product, indicating the ability of liquisolid systems to minimize pH-dependent variability and improve drug absorption(153). Patel et al. developed a modified liquisolid compact formulation of

mifepristone and reported that the system exhibited 85–90% drug release within 90 minutes over a pH range of 1.2–7.4, indicating pH-independent dissolution behavior and improved drug absorption potential (154). Similarly, studies on telisartan(155), famotidine (51), propranolol (120) demonstrated that liquisolid formulations provided improved dissolution profiles across a wide pH range, indicating reduced reliance on acidic environments for drug release.

COMPARISON WITH OTHER SOLUBILITY ENHANCEMENT TECHNIQUES

Figure 6: Solubility enhancement techniques



Chemical modification

Change in pH

Changing the pH of the microenvironment to alter the ionization behavior is the most popular and straightforward method to improve the water's solubility behavior. The easiest and most effective way to make ionizable organic solutes more soluble in water is to change their pH. By changing the pH of the solution, the ionizable drug's solubility can rise exponentially under specific circumstances. Weakly basic medicines may become more soluble when the pH is lowered, while weakly acidic drugs may become more soluble when alkalizing excipients are added(156).

The main drawback of this approach is the potential of precipitation when the medication is less soluble at lower pH levels. The use of non-physiological pH levels may lead to tolerability issues and toxicity(157). In contrast liquisolid technique enhances drug solubility without altering physiological pH, thereby minimizing precipitation risks and improving tolerability.

Salt formation

APIs are often unstable and cannot be formed entirely. They are transformed into solid forms such as salts, co-crystals, solvates, hydrates, and polymorphs. Each offers unique physiochemical properties that enhance medication stability, bioavailability, purity, and manufacturability. For decades, salt production has been used to

improve the solubility of medication candidates with weak acids and bases. Salts develop when a chemical ionizes in solution. This approach is useful for parenteral, liquid, and solid dose forms. When an acidic or basic medicine is turned into salt, it becomes more soluble than the original drug(158).

The main drawback of this technique is that it is not feasible for neutral compounds, and it is challenging to form salts with very weak bases or acids to form salts (159). Liquisolid systems overcome these limitations by enhancing dissolution without requiring drug ionization, making them more versatile.

Prodrug

A prodrug is an inert or poorly active substance that contains the parent drug and is biotransformed in vivo by chemical or enzymatic cleavage, allowing the active molecule to be delivered at effective quantities(160,161). The prodrug method can improve aqueous solubility by adding polar moiety (phosphates and esters) or changing the active drug's crystal structure(162).

Key challenges in prodrug design include premature cleavage, pH-dependent hydrolysis, and chemical instability, especially in phosphate derivatives(163), whereas liquisolid systems enhance solubility without chemical modification, improving stability and reducing degradation risks.

Cosolvents

Cosolvents is a popular and efficient method for making a non-polar drug more soluble. Cosolvents can improve medication solubility by disturbing its crystal lattice structure and enhancing solubility inside the solvent. Common cosolvents are ethanol, propylene glycol, polyethylene glycols, and glycerin(164). The elixir, which is a sweetened, hydroalcoholic solution meant for oral use, is a typical example of a class of formulation that contains cosolvents. Another well-known example of a liquid dosage form including a cosolvent is tinctures, which typically contain much higher concentrations of alcohol(165).

The co-solvent technique can increase the drug's solubility and rate of dissolution, but its effectiveness is mostly constrained by toxicity effects, particularly at high concentrations. Furthermore, dilution may cause the medication to precipitate because of the co-solvent fraction's exponential reliance on the drug's solubility(162).

Complexation

Inclusion complex production is a highly effective strategy for increasing the aqueous solubility, dissolving rate, and bioavailability of medicines that are weakly water soluble. Inclusion complexes are generated by inserting a non-polar molecule or region into the cavity of another molecule or set of molecules (known as the host). The most commonly used host id cyclodextrin. Cyclodextrin (CD) are macrocyclic oligosaccharides consisting of a hydrophilic outer surface and a hydrophobic inner cavity where guest molecules having a lipophilic nature can be accommodated(166). As a result, the medications are enclosed in the cavity, improving their dissolution rates and aqueous solubility. The main drawbacks of this approach are the toxicity of cyclodextrin complexes at high concentrations, which restricts the dose level, and the creation of cyclodextrin complexes, which requires particular molecular characteristics that may not work for some substances. The use of cyclodextrins in the formulation of ionizable medications has a significant drawback(157).

Miscellaneous methods

Hydrotropy

Hydrotrophy is a solubilization process in which the addition of a substantial amount of second solute, the hydrotropic agent, increases the water solubility of the first solute(167). Hydrotropic agents are ionic organic salts made up of alkaline metal salts of different organic acids. Additives or salts that improve solubility in a given solvent are called to "salt in" the solute, whereas salts that decrease solubility "salt out" the solute. Several salts with large anions or cations that are particularly soluble in water cause the "salting in" of non-electrolytes known as "hydrotropic salts"; this process is known as "hydrotropism." Hydrotrophy refers to an increase in solubility in

water caused by the presence of a large quantity of chemicals. The hydrotropes are known to self-assemble in solution(168).

Hydrotropy enhances solubility but is associated with limitations such as possible drug–hydrotrope interactions, difficulty in complete removal of water, and toxicity concerns at higher hydrotrope concentrations. In contrast, liquisolid systems employ non-volatile solvents, minimizing stability issues and improving safety (169). In contrast, liquisolid systems utilize non-volatile solvents, reducing the risk of drug degradation and eliminating issues related to residual solvent presence, thus offering better stability and safety.

Inculsion complex

The primary purpose of cyclodextrins is to increase a drug's water solubility [9]. The cyclodextrin itself has a lipophilic chamber in the middle and an outside hydrophilic surface. They combine with water-insoluble lipophilic medications to generate hydrophilic inclusion complexes. Drug molecules bound to the inclusion complex and free molecules are in a dynamic equilibrium in aqueous solutions. Therefore, cyclodextrins improve a drug's solubility in water without altering its inherent capacity to pass through lipophilic membranes(170). Different methods to prepare the cyclodextrin inclusion complex are co-precipitation, Kneading. Super critical carbon dioxide, grinding, microwave irradiation, spray drying (171)

Cyclodextrin complexes may reduce drug permeability and bioavailability while increasing formulation bulk (170), whereas liquisolid systems enhance solubility without compromising permeability or increasing dosage form size.

Micellar solubilization

Micellar solubilization utilizes surfactants—widely employed as solubilizers, emulsifiers, and wetting agents—which above their critical micelle concentration (CMC) self-assemble into micelles that encapsulate hydrophobic drugs within their lipophilic core while the hydrophilic shell stabilizes them in aqueous media(172). However, this approach may suffer from dilution-induced micelle dissociation, Critical Micelle Concentration (CMC) dependence, Drug–surfactant interactions(173), whereas liquisolid system provide more stable solubilization.

Supercritical fluids

Supercritical fluids (SCFs) have the ability to dissolve non-volatile solvents, with the critical point of carbon dioxide, the most widely used supercritical fluid(174). Above its critical temperature (Tc) and pressure (Pc), a SCF exists as a single phase. Due to their intermediate characteristics between pure liquid and gas (i.e., liquid-like density, gas-like compressibility and viscosity, and higher diffusivity than liquids), SCFs are beneficial to product processing (21).

The use of SFT for most medications is limited due to the excessive pressure required, high maintenance costs, and the need for accessories/auxiliary equipment(174). However, liquisolid technique does not require high-end equipment and high maintenance costs.

Physical modification

Particle size reduction

Particle size reduction is a technique that enhances the pharmaceutical compounds' surface area, which enhances their bioavailability and dissolution rate. Traditional methods for reducing particle size include milling, high-pressure homogenization, and spray drying(175). some novel approaches are solid self-emulsifying drug delivery system, polymeric micells, freeze-dried liposomes, solid lipid nanoparticles(176).

High energy process, causes disruption in drug crystal lattice, Disordered/Amorphous regions are thermodynamically unstable and upon storage in hot and humid conditions these are susceptible to recrystallization are some of the major drawback of this technique(33).

Dispersion technique

Dispersion is a process that involves dispersing or embedding a chemical in another molecule or continuous phase to improve its dissolving rate(177). In recent years, there has been a lot of interest in Liquisolid systems as a potential substitute for the traditional dispersion methods for dissolving and bioavailability enhancement. Liquisolid systems exhibit the best dispersibility and physical stability among different dispersion systems because they are not constrained by the hydrophobic contact and Van der Waals attraction between drug particles(178).

Cryogenic technique

Cryogenic approaches have been developed to improve medication dissolution rates by producing amorphous drug particles with great porosity at extremely low temperatures. and the composition of the cryogenic liquid. Dry powder can be obtained via cryogenic processing using spray freeze drying, atmospheric freeze drying, vacuum freeze drying, or lyophilization(179,180).

One of the major drawbacks of cryogenic technique is high equipment cost, operational complexity, need for specialized cryogenic systems (liquid nitrogen handling) (181), whereas liquisolid technique offers cost-effectiveness and simplicity.

Crystal engineering

Crystal engineering involves controlling the crystallization conditions to produce drug crystals with desired properties like particle size, crystal habit, and polymorphic form. Polymorphism, where a drug can exist in different crystal forms, can significantly impact solubility and dissolution. The most thermodynamically stable polymorph is often preferred for reproducible bioavailability. Solvates and hydrates, where solvent molecules are incorporated into the crystal lattice, can also affect solubility and dissolution compared to the anhydrous form. Pharmaceutical cocrystals, formed by combining a drug with a cocrystal former, can enhance solubility and dissolution compared to the individual components. Novel crystallization techniques like supercritical fluid processing and melt sono-crystallization are being explored to produce drug crystals with improved properties(4,182). However, this approach has limitations including polymorphic instability, complex processing, and scale-up challenges. In contrast, the liquisolid technique provides a simpler and cost-effective alternative by maintaining the drug in a solubilized state.

Powder granulation technology

When a dissolved drug is introduced to a carrier material containing fibres and a porous surface, it undergoes both adsorption and absorption. The liquid penetrates the particles and is captured by their internal structure. Once saturated, the liquid is adsorbed on the porous carrier particles' internal and external surfaces. Blending a liquid medicine with appropriate powder excipients, such as a carrier or coating substance, can create a free-flowing, dry, non-adherent, compressible powder. Coating materials include cellulose (microcrystalline and amorphous) and silica particles (183). Liquisolid formulations are generally more cost-effective than other drug delivery systems, pH- independent release, improved dissolution(164).

CONCLUSION

Liquisolid technology offers a practical approach to improve the dissolution of poorly water-soluble drugs by presenting the drug in a solubilized or molecularly dispersed state. The technique works through improved wettability, increased surface area, and the use of non-volatile solvents, which together enhance drug release and bioavailability. The mathematical model based on Φ-value and liquid load factor provides a rational basis for formulation design. Beyond immediate release, liquisolid systems have also shown potential in sustained release and reducing pH-dependent variability. However, limitations such as high excipient requirement, challenges with high-dose drugs, and scale-up issues remain important considerations. Recent developments like liquisolid pellets and nanostructured systems indicate that these limitations can be addressed. Overall, liquisolid technology stands as a simple, cost-effective and adaptable strategy with significant potential in improving oral drug delivery.

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