LIQUISOLID TECHNIQUE: AN APPROACH FOR ENHANCEMENT OF DISSOLUTION

Nitin Biradar[1], Gopinath E[2], Ganesh N S[3], Vineeth Chandy[4]

PG Student, Pharmaceutics, T John college of pharmacy, Karnataka, India

Assistant professor, Pharmaceutics, T John college of pharmacy, Karnataka, India

Head of the department, Pharmaceutics, T John college of pharmacy, Karnataka, India

Principal, Pharmaceutics, T John college of pharmacy, Karnataka, India

ABSTRACT

The liquisolid system is a novel delivery system for drugs via the oral route. Increasing the solubility of low-aqueous-soluble drugs and lipophilic drugs can be accomplished with this technique. The medication could be in a solid dosage form that is held in solution inside the powder substrate, or it could be in a solubilized, virtually molecularly disseminated condition. As a result, their wetting qualities and drug surface area available for dissolution are greatly increased. It is expected that liquisolids containing water-insoluble substances would enhance the drug release properties and ultimately increase the bioavailability. The liquisolid tablets are prepared by dissolving the drug in a non-volatile solvent with suitable carrier and coating materials. A Liquisolid system is formed by mixing these components and subjected to a direct compression process for tableting. Liquisolid systems can be obtained with a sustained release by using hydrophobic carriers (e.g., Eudragit RL and RS) instead of hydrophilic carriers. This review's major focus is on the liquisolid technique that has been successfully used to enhance in vitro drug release of low aqueous soluble drugs.

Keywords: *Liquisolid system, Nonvolatile solvent, Carrier material, Coating material, Dissolution enhancement.*

INTRODUCTION:

Drug delivery via oral is still considered the best method due to its convenience, patient compliance, and low production cost. A drug must be dissolved in gastric fluids in order to absorb in the systemic circulation. Active pharmaceutical ingredients present in solid dosage forms must undergo dissolution to allow absorption from the gastrointestinal tract. The dissolution process is the rate-controlling step for lipophilic drugs and shows the incomplete absorption in the gastrointestinal tract of animals and humans. It is estimated that 40% of all newly developed drugs are insoluble in water or poorly soluble[1,2].

Drugs which are having low aqueous solubility (BCS Class 2 and 4) are a major obstacle in the development of pharmaceutical dosage forms. Various formulation techniques have been developed, to improve the solubility of poorly soluble substances [3]. Like the conversion of crystalline to amorphous state[4], particle size reduction co-grinding[5], micronization[6], liquisolid technique[7], solid dispersions[8], Inclusion complex[9], and Self-emulsifying drug delivery system (SEDDS)[10].

Liquisolid compact converts liquid medications into compact and flowable powders. The term “liquid medication” refers to liquid lipophilic (oily) drugs, as well as solutions or suspensions of poorly water-soluble drugs in non-volatile liquid systems that are water miscible[11]. This liquid medication, that is, drug dissolved or dispersed in a non-volatile solvent is converted into a dry, nonadherent, free flowing, and compressible powder blend by mixing with selected carriers, and coating materials[12].

CONCEPT OF LIQUISOLID TECHNIQUE

Drugs dissolved in the liquid vehicle can absorb and adsorb into carrier materials with porous surfaces (When the drug dissolved in the liquid vehicle are incorporated into a carrier material with a porous surface both absorption and adsorption take place), the liquid initially absorbed in the internal structure of particles after saturation of this process, there is liquid adsorption onto both the internal and external surfaces of the porous carrier particles. The coating material is having high adsorptive properties and a large surface area, providing the liquisolid system with desirable flow characteristics[13]. In liquisolids, the drug is already in solution in a liquid vehicle but is also carried by powder particles (microcrystalline cellulose and silica) at the same time. Thus, liquisolid compacts of water-insoluble substances exhibit significantly enhanced wetting characteristics and surface area of drug available for dissolution, they may result in enhanced drug release characteristics and, consequently, better oral absorption.[14]

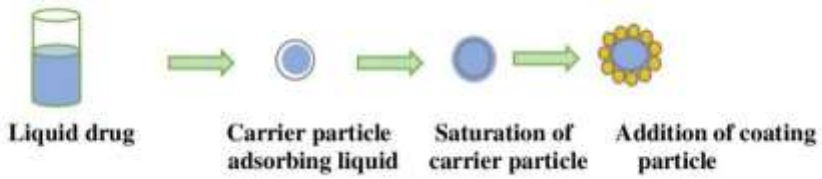

Fig. 1- Schematic representation of liquisolid system formation.

MECHANISM OF SOLUBILITY ENHANCEMENT BY LIQUISOLID SYSTEM

1. Increased aqueous solubility of the drug
2. Improved wetting properties
3. Increased drug surface area for dissolution

Increased aqueous solubility of the drug:

The enhancement of drug release, in a liquisolid system the solubility of the drug and saturation solubility of the drug could be increased in dissolution medium (Cs). It is not sufficient to increase the drug's overall general solubility within an aqueous dissolution medium by the amount of non-volatile liquid vehicle in a system if the liquid vehicle act as a co-solvent between the solid-liquid interface of an individual particle and the release in a medium of liquisolid system, the amount of liquid vehicle released from a liquisolid particle with the drug molecules can be sufficient to extend its solubility in water

Improved wetting properties:

The liquid vehicle (e.g.: polysorbate 80) acts as a wetting agent, it increases the wetting property or surface-active agent (it reduces the surface tension) of liquisolid particles. Wettability is evaluated by measuring contact angles and rising times of water.

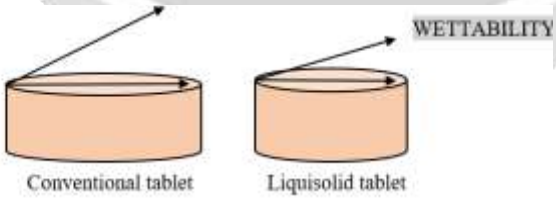

Fig.2: Comparison of wettability between the convention and liquisolid tablet

Increased drug surface area for dissolution:

Liquisolid systems dissolve drugs in liquid vehicles, Solubilized, and the molecularly dispersed drug is positioned in the powder substrate. Therefore, the liquisolid system drug particles have a greater surface area than the drug particles of directly compressed tablets. The rate of release of a drug decrease when its solubility limits are exceeded, and a greater fraction of the drug remains undissolved in a liquid vehicle[15].

Optimization of liquisolid formulations with enhanced drug release

Liquisolid Technique has been successfully used for drugs with low water solubility and low doses. The Liquisolid Technique has limitations in the formulation of high-dose, poorly water-soluble drugs. A higher dose of the drug requires a higher amount of liquid for the desired release profile. Therefore, to obtain a liquisolid system with acceptable flowability and compatibility high levels of coating and carrier materials are used which results in increase in tablet sizes which leads to difficulty in swallowing. To overcome this problem liquisolid technique has several formulation parameters that can be optimized[16].

Sl.No	Formulation parameters	Optimization	Effect
1.	Liquid vehicle	Drugs solubilized well in vehicles	Increased fraction of the molecularly dispersed drug ($F_{M)}$
2.	Carrier and coating material	High specific surface area	Increased liquid load factor (L_f)
3.	Addition of excipient	PVP, super disintegrant	Inhibition of precipitation Fast disintegration
4.	Excipient ratio (R)	High R- value	Inhibition of precipitation

Table-1: Optimization parameters of liquisolid formulation

General preparation procedures of liquisolid tablets

- The drug substance was initially dispersed in a nonvolatile solvent system it is termed liquid medication with a Drug: vehicle ratio.
- Then a mixture of carriers or excipients is added to the above liquid medication with continuous mixing in a mortar. The amount of carrier and excipient is sufficient to maintain acceptable flow and compression properties.
- Add a super disintegrant, such as sodium starch glycolate and other additives to the above binary mixture. The ingredients are mixed for 10 to 20 minutes in a mortar.
- After the final mixture was mixed, it was compressed using a manual tableting machine to achieve tablet varying hardness.
- Characterize the final liquisolid granules for their solubility, dissolution, flowability, compressibility, and other physical characteristics[17].

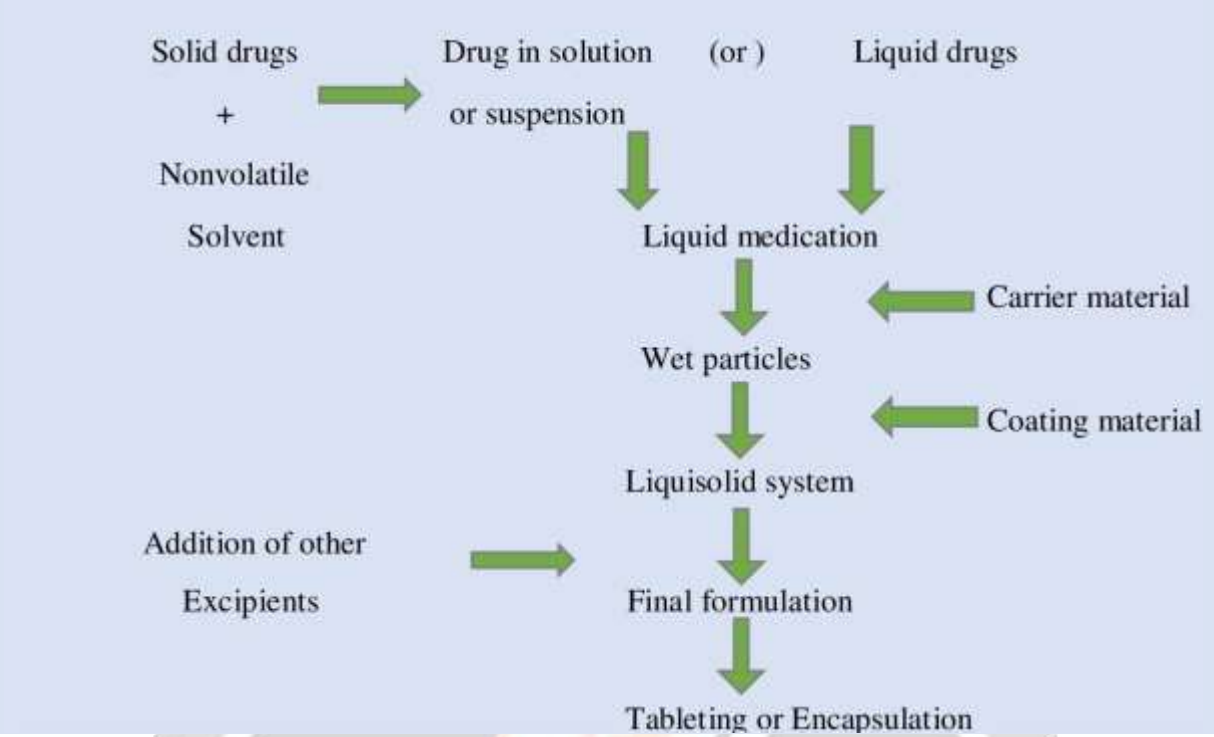

Fig-3: Schematic representation of Liquisolid technique

THEORY OF LIQUISOLID SYSTEM

To get good flow properties and compressibility of liquisolid systems, *Spirea*s et al developed a mathematical model for the design model of liquisolid tablets. The requirements for this are a suitable drug candidate, non-volatile solvent, carrier, and coating materials. The amount of carrier and coating materials used for liquisolid compacts and the flowable liquid retention values (Φ-value) and the liquid loading factors (Lf) depend on it.

According to new theories, for good flow and compression property certain amount of liquid remain in the carrier(Q) and coating(q) powder materials. Depending on the excipients ratio (R) or the carrier: the coating powder system used

R= Q/q------ (1)

Where,

R= excipient ratio

Q= weights of carrier

q=weight of coating material

Calculation of Liquid loading factors (Lf)

It is a ratio of the weight of the liquid medication (*W*) and weight of the carrier material (*Q*) in the system which could be possessed by an acceptably flowing and compressible liquisolid system

Lf = W/Q------ (2)

where,

Lf= liquid loading factor

W= liquid medication (drug +non-volatile liquid)

Q=weight of carrier

The powder excipient ratios(R) and liquid load factor (Lf) relate in the formulation as
Lf=Φ +Φ (1/R) ------(3)

where,

Φ= Liquid retention potentials of powder excipient (constant)

While determining the weight of liquid medication(W) and liquid load factor (Lf), The above equations (1) and (2) could be used to calculate the appropriate quantities needed to make liquisolid compacts with the acceptable flow and compressibility properties [18,19].

COMPONENTS OF LIQUISOLID COMPACTS FORMULATION

1. Drug candidates
2. Non-volatile liquid
3. Carrier material
4. Disintegrants
5. Coating material

1. DRUG CANDIDATES

Drug candidates should be poorly aqueous soluble and belongs to BCS II and BCS IV[2]. Lower the molecular weight (less then 100mg). e.g., Carbamazepine, Griseofulvin, digitoxin, hydrocortisone, spironolactone, prednisolone, and hydrochlorothiazide[20].

2. NON-VOLATILE LIQUID

- Inert
- High boiling point
- Preferably water miscible
- Less viscous solvent system

  e.g., propylene glycol, liquid polyethylene glycols, polysorbates, PEG 200 and 400[21],

3. CARRIER MATERIAL

- Porous material
- Sufficient absorption properties
- In their interiors, fibers are closely matted

  e.g., Microcrystalline, amorphous cellulose, starch, MCC (Avicel PH102), Eudragit RL, and RS.

4. DISINTEGRANTS

Super disintegrate increases the solubility, wettability, and rate of drug release in liquisolid granules. e.g., sodium starch glycolate and crosspovidone[22]

5. COATING MATERIAL

The coating material covers wet carrier particles and displays dry powder by adsorbing excess liquid. To cover the surface and maintain powder flowability, a coating material is needed. e.g., Silicon dioxide, Aerosol[23].

Component	Examples
Non-volatile liquids	Polyethylene glycol (PEG), Propylene glycol (PG), Glycerine, and fixed oils.
Carrier materials	Microcrystalline cellulose PH 101AND 200, Methylcellulose, Eudragit RL, HPMC, Guar gum, Ethylcellulose.

Coating materials	Aerosil 200, colloidal silicon dioxide, Titanium dioxide.
Disintegrants	Sodium starch Glycolate, cross polyvinyl pyrrolidine, Croscarmellose sodium.
Glidant	Talc
Lubricant	Magnesium stearate
Release retardant material	Eugragit RS, Hydroxy Propyl Methylcellulose k100M, K15M, K4M.

Table-2: Some of the materials used in the liquisolid system

CLASSIFICATION

A. Classification based on type of liquid medication
   1. "Powder drug solution"
   2. "Powder drug suspensions"
   3. "Powdered liquid drug"

The first two groups may exit from the conversion of drug solutions (e.g. prednisolone solution in propylene glycol) or drug suspensions (e.g. gemfibrozol suspension in polysorbate 80), and the liquid drugs (e.g. valproic acid, clofibrate,) formulation into liquisolid systems.

B. Based on the formulation technique used
   1. Liquisolid compacts
   2. Liquisolid microsystems

Liquisolid compacts: The Liquisolid system describes the immediate sustained-release tablets or capsules.

Liquisolid Microsystems: The term "liquisolid systems" is usually used in conjunction with an additive to create capsules with a unit size that is significantly smaller than that of a liquisolid compact[24].

ADVANTAGES OF LIQUISOLID SYSTEMS

- A Liquisolid system is a low-cost formulation compared to Gelatin capsules
- Suitable formulation ingredients can be used to modify drug release
- A more effective bioavailability can be achieved than with conventional tablets
- Industrial production capability is also possible
- In the formulation, the drug can be molecularly dispersed
- The production of such tablets is like that of conventional tablets
- A simple method of preparation
- Drugs that are poorly soluble or insoluble can be made more soluble by altering the rate of dissolution

LIMITATIONS

- It is not applicable to high-dose insoluble drugs (>100 mg)
- It requires such excipients which are having high surface area and adsorption properties
- Sometimes liquid drugs can be squeezed out of tablets during compression, leading to improper hardness[25]

EVALUATION OF LIQUISOLID SYSTEM

I. Pre Compression studies

1. Determination of Solubility of the drug in different nonvolatile solvents
2. Determination of the flow properties
   - Angle of repose
   - Carr's index
   - Hauser's ratio
3. Scanning electron microscopy (SEM)

4. X-ray powder diffraction (XRPD)
5. Differential scanning calorimetry (DSC)
6. Wetting properties
7. Fourier Transform Infrared spectroscopy (FTIR)

II. Post compression studies

1. Weight variation
2. Hardness
3. Content uniformity
4. Disintegration time
5. Friability
6. In-vitro dissolution studies and Effect of dissolution volume on the drug release rate

These should be in the official limits prescribed by official pharmacopeia

Determination of Solubility of the drug in different nonvolatile solvents:

Various non-volatile solvent systems, including polyethylene glycol (PEG) 200, PEG 400, PEG 600, and propylene glycol (PG), Tween (20,80) Span (20, 80), DMSO were used to study the solubility of the drug to select the best nonvolatile solvent system. Accurately one mg of drug dissolved in one ml of different solvents shake vigorously for 5min check the solubility by observing visually or Uv-spectroscopy. Select the solvent which is completely soluble[26].

Determination of the flow properties

Angle of repose

The angle of repose of the powder can be determined by the fixed funnel method to estimate the flow property of the powder. The funnel was raised to the height needed so that the tip of the funnel was just touching the apex of the heap of the powder which is placed on graph paper on a horizontal surface. Accurately weighed quantity of powder drug pass through the funnel to form a cone shape file on graph paper. The height of the file(h) from the horizontal plane and diameter(d) of the cone is noted from this calculation of the radius(r). The angle of repose is calculated by using the following formula[27].

$\tan\theta = h/r \qquad \theta = \tan^{-1}(h/r)$

Here ɵ is the angle of repose, h = is the height of the cone, r = is the radius of the cone

Compressibility index: Bulk density and tapped density values are required to evaluate Carr's index. Bulk density can be determined by placing a fixed quantity of powder in a graduated cylinder and the occupied volume measured. Bulk density is calculated by using the formula

$D_b = M/V_b$

Here D_b = bulk density, M = mass of the powder, V_b = bulk volume

Tapped density can be determined by placing the weighed quantity of powder in the graduated cylinder by 100 taps and the occupied volume measured. It can be calculated by using the formula

$D_t = M/V_t$

Here D_t = tapped density, M = mass of the powder, V_t = tapped volume

The compressibility index is determined from bulk and tapped densities. It is more flowable when a material is less compressible and measures the inter-particulate interaction. The more interparticular interaction gives a greater difference between the bulk and tapped densities will be observed which affects the compressibility index which can be calculated by using the formula [28].

$$CI\ (\%) = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100$$

Fourier Transform Infrared spectroscopy: Chemical interactions between the excipients and the drug in the fo=mulation can be determined by FTIR studies. The presence of drug peaks in the formulation and the absence of extra peaks suggest no chemical interactions[29].

Scanning electron microscopy: To Analyze the morphology of raw materials and drug-carrier systems is achieved by using scanning electron microscopy (SEM).

Differential Scanning calorimetry: It is used to determine the interaction between excipients used in the liquisolid formulation. DSC thermograms in which there is no characteristic peak for the drug indicate that the drug is in solution form in liquisolid formulations, and no characteristic peak can be seen, so the drug is molecularly dispersed in the system. The DSC method is used to analyze the thermal properties of the untreated drug and prepared samples[30].

X-ray powder diffraction: The polymorphic change of a drug may affect its dissolution rate and its bioavailability in the body. X-ray diffractogram of a liquisolid shows the absence of constructive reflection (specific sharp peak), which indicates the drug has almost entirely changed from crystal form to amorphous or solubilization in a liquid vehicle, adsorbed in carrier and coating material.

Wetting Properties: The liquid medium act as a surface-active agent and it enhances the wetting properties of the main molecules of liquisolid. The wettability of these systems can be demonstrated by contact angles and water rising times. As a result, the drug's adsorption on the carrier particles increases the effective surface area for better drug contact[31].

Post compression studies

Weight variation: The weight variation of liquisolid compact tablets is determined by taking twenty tablets and their individual weight and average weight of it by digital weighing balance. For determining the uniformity of drug content, the weight variation test could be used. The calculation for percentage deviation of weight variation by using a formula

$$\% \text{ Deviation} = \frac{\text{individual weight} - \text{Average weight} \times 100}{\text{Average weight}}$$

Tablet hardness: A tablet's hardness is defined as the amount of force required to break it across its diameter. Hardness, in the form of storage, transformation, and handling before use, determines how resistant the tablet is to chipping and breakage. Using Monsanto's hardness tester, the hardness of 6 tablets was determined, and an average was calculated and presented with a standard deviation[32].

Friability: It is a method to determine the mechanical strength of tablets. Roche friability was used to determine the friability, calculated by using the formula.

$$\% \text{ Friability} = \frac{W_1 - W_2 \times 100}{W_1}$$

Where, W_1 = initial weight of 20 tablets, W_2 = Wight of the 20 tablets after testing

Content uniformity: Initially 10 tablets were weighed and powdered, 5mg of the equivalent weight of drug added with 10ml of methanol and made up to the 100ml of volume with pH 6.8 phosphate buffer by using the volumetric flask(100ml). The filtered solution was analyzed spectrophotometrically by UV-spectrophotometer[33].

Disintegration Time: The liquisolid tablet's disintegration time was measured by disintegration test apparatus with distilled water (37± 2^{o}C) and a disk. Six tablets from each formulation were tested for the disintegration time calculations[34].

In-vitro dissolution studies: Tablet dissolution apparatus USP Type II was used to measure dissolution rates of all formulations. To perform the dissolution studies, 900 ml of phosphate buffer (pH 6.5) was used as a solution medium, at 50 rpm and at a temperature of 37 ± 0.5 ^{o}C. sample withdrawn at time intervals 5,10,15,20,25,30, and 45min and filtered through Whatman filter paper and diluted as per need with phosphate buffer pH 6.5. throughout the study, the sink conditions were maintained. By using the UV-vis spectrophotometer the samples were analyzed at λ_{max} [36]. Various mathematical models were used to determine correlation coefficient (r2) and release kinetics using the released drug data, including Zero order, First order, Higuchi, Korsmeyer-Peppas, Hixon-Crowell, Weibull, and Peppas-Sahlin models[36].

In vivo evaluation of liquisolid tablets: Various pharmacokinetic parameters were estimated on various animals, such as rabbits, beagle dogs, and mice to confirm the improved oral bioavailability. Results reveal that liquisolid tablets have a much higher absolute bioavailability than marketed tablets.[37]

Application Of Liquisolid Techniques:

- Solubility and dissolution improvement
- Bioavailability improvement
- Flowability and compressibility
- Designing of sustain release tablet

Solubility and dissolution improvement: The liquisolid tablets were formulated as to overcome the limited solubility of the pharmaceuticals. The preparation method of liquisolid tablets as well as the effect of various formulation and processing variables on the preparation and release properties of the tablets were studied by a number of scientists. For low-dose water insoluble drugs, this technique is the most prominent method of preparation. High-dose water insoluble drugs such as liquisolid tablets are one of the limitations of the liquisolid technique[2].

Dissolution enhancement was not significant with a low level of hydrophilic carrier or coating materials in a drug dose of more than 50 mg. But adding materials like polyvinylpyrrolidone (PVP) it is possible to produce dry powder formulations containing liquid with a high concentration of drug while added to the liquid medication.

Bioavailability improvement: In a liquisolid system the drug is dispersed as a solid form in a powder solution system, In a powder substrate, it is either held in solution or in a solubilized, almost molecularly dispersed state. Therefore, the increased surface and wetting properties of the drug alter the rate of dissolution. As a result, liquid-solid compacts of insoluble substances are likely to exhibit enhanced drug release properties, and consequently, improved bioavailability.

Flowability and compressibility: A liquidsolid compact has acceptable flowability and compressibility. These are prepared using selected powder excipients such as carrier and coating materials by a simple blending method. The high levels of carriers and coating materials are added to the liquisolid powder formulation to achieve acceptable flowability and compatibility and the weight of each tablet will exceed 1 gm, which is very difficult to swallow. As result, it is impossible to formulate liquisolid tablets of high-dose drugs with tablets less than one gm.

Therefore, compression enhancers like microcrystalline cellulose, etc are added to the system, the drug exists in a molecular state of subdivision and the systems were free flowing, nonadherent, dry-looking powders. The compression of these later systems caused a 'Liquid Squeezing Out' phenomenon.

Designing of sustain release tablet: It is beneficial to develop sustained release oral dosage forms to improve patient compliance, efficacy, safety, and efficacy. Controlled release dosage forms will maintain therapeutic levels of the drug in the blood throughout the dosage period. Several techniques exist for preparing sustained release formulations, among which control of drug dissolution is a good procedure due to its simplicity and low cost. Several methods have been developed to achieve this aim.

To change the dissolution rate of drugs, a new and promising liquisolid method is developed. Hydrophobic carriers such as Eudragit's RL and RS can be used as an alternative to hydrophilic carriers to achieve sustained release in liquisolid systems, it is claimed. As a result, it can be suggested that this method may be optimized to reduce drug dissolution rates and thereby produce sustained-release formulations [38].

CONCLUSION

In conclusion, liquisolid compacts are formulations, referred to as a conversion of solid state to a liquid state, drug suspensions, or drug solution in non-volatile solvents into dry, nonadherent, free-flowing, and compressible powder mixtures by blending the suspension or solution with selected carriers and coating agents. Dissolution is enhanced due to an increase in the wetting properties and surface area of drug particles, the formed liquisolid tablets showed a significantly greater degree of absorption than the conventional tablets. By using hydrophobic carriers in liquisolid systems instead of hydrophilic carriers, it is also possible to design sustained release systems.

REFERENCES

1) Raj A, Sreerekha S. A review on liquisolid technology. Innoriginal: Int J Sci 2015 Dec; 2(6):4-8.
2) Walke PS, Pawar AY, Sonawane DD, Bhamber RS. Liquisolid: a novel technique to enhance solubility and dissolution rate of BCS class II pharmaceuticals. J Pharm Res 2011 Nov;4(11):4011-4014.

3) Javadzadeh Y, Siahi-Shadbad MR, Barzegar-Jalali M, Nokhodchi A. Enhancement of dissolution rate of piroxicam using liquisolid compacts. Il Farmaco 2005 Apr 1;60(4):361-5.
4) Murdande SB, Pikal MJ, Shanker RM, Bogner RH. Solubility advantage of amorphous pharmaceuticals: A thermodynamic analysis. J Pharm Sci 2010 Mar 1;99(3):1254-64.
5) Kürti L, Kukovecz Á, Kozma G, Ambrus R, Deli MA, Szabó-Révész P. Study of the parameters influencing the co-grinding process for the production of meloxicam nanoparticles. Powder technology 2011 Sep 15;212(1):210-17.
6) Rasenack N, Müller BW. Dissolution rate enhancement by in situ micronization of poorly water-soluble drugs. Pharm res 2002 Dec;19(12):1894-900.
7) Burra S, Galipelly SK. Enhancement of solubility and dissolution rate of Frusemide through liquisolid technique. Scholars Research Library 2010;2(6):321-28.
8) Betageri GV, Makarla KR. Enhancement of dissolution of glyburide by solid dispersion and lyophilization techniques. Int J Pharm1995 Dec 29;126(1-2):155-60.
9) Chen M, Diao G, Zhang E. Study of inclusion complex of β-cyclodextrin and nitrobenzene. Chemosphere 2006 Apr 1;63(3):522-29.
10) Balakrishnan P, Lee BJ, Oh DH, Kim JO, Hong MJ, Jee JP, Kim JA, Yoo BK, Woo JS, Yong CS, Choi HG. Enhanced oral bioavailability of dexibuprofen by a novel solid self-emulsifying drug delivery system (SEDDS). Eur J Pharm Biopharm 2009 Aug 1;72(3):539-45.
11) Gavhane KS, Sayyad FJ. Liquisolid compact a review. IJPBR May 2013;4(2):26-31.
12) Savkare AD, Bhavsar MR, Gholap VD, Kukkar PM. Liquisolid technique: a review. Int J Pharma Sci Res 2017 Jul 1;8(7):2768-75.
13) Kadam SV, Shinkar DM, Saudagar RB. Review on solubility enhancement techniques. IJPBS 2013;3(3):462-75.
14) Rokade M, Khandagale P, Phadtare DI. Liquisolid compact techniques: a review. Int J Curr Pharm Res 2018;10(4):1-5.
15) Sreenath. C, Ganesh n.s, Kumar V, Chandy V. Liquisolid technique for dissolution enhancement: an overview. IRJPBS 2021 Mar 11; 5(7): 33-44.
16) Thakur N, Khokra SL, Sharma D, Thakur NS, Purohit R, Arya V. A review on pharmaceutical application of liquisolid technique. Am J Pharmtech Res 2011;1(3):1-18.
17) Lu M, Xing H, Jiang J, Chen X, Yang T, Wang D, Ding P. Liquisolid technique and its applications in pharmaceutics. Asian J pharm sci 2017 Mar 1;12(2):115-23.
18) Hentzschel CM, Alnaief M, Smirnova I, Sakmann A, Leopold CS. Enhancement of griseofulvin release from liquisolid compacts. Eur J Pharm Biopharm 2012 Jan 1;80(1):130-35.
19) Siju VV, Sonwala M. Review on Development of Liquisolid Compact Using Experimental Design. Int. J. Pharm. Sci Rev Res March - April 2017;43(1): 173-177.
20) Karmarkar AB, Gonjari ID, Hosman AH, Dhabal PN, Bhis SB. Liquisolid tablets: a novel approach for drug delivery. Int J Health Res 2009;2(1): 45-50.
21) Javadzadeh Y, Jafari-Navimipour B, Nokhodchi A. Liquisolid technique for dissolution rate enhancement of a high dose water-insoluble drug (carbamazepine). Int J Pharm2007 Aug 16;341(1-2):26-34.
22) Venkateswarlu K, Preethi JK, Chandrasekhar KB. Enhancement of loperamide dissolution rate by liquisolid compact technique. Adv Pharm Bull 2016 Sep;6(3):385-390.
23) Hamsanandini J, Parthiban S, Vikneswari A, Tamiz MT. Dissolution enhancement techniques of poorly soluble drugs by liquisolid compacts. Int J Res Pharm Nano Sci 2014;3(4):298-304.
24) Burra S, Yamsani M, Vobalaboina V. The Liquisolid technique: an overview. BJPS 2011 Sep; 47:475-82.
25) Chandel P, Kumari R, Kapoor A. Liquisolid technique: an approach for enhancement of solubility. J Drug Deliv Ther 2013 Jul 13;3(4):131-7.
26) Nokhodchi A, Javadzadeh Y, Siahi-Shadbad MR, Barzegar-Jalali M. The effect of type and concentration of vehicles on the dissolution rate of a poorly soluble drug (indomethacin) from liquisolid compacts. J Pharm Pharm Sci 2005;8(1):18-25.
27) Chella N, Narra N, Rama Rao T. Preparation and characterization of liquisolid compacts for improved dissolution of telmisartan. J Drug Deliv 2014;2014:1-10.
28) Manish G, Mohammed H, Rama R, Maimuna A. Preparation and evaluation of nilvadipne liquisolid compacts. Int J Pharm Pharm Sci 2014;6(7):1-8.
29) Kulkarni AS, Aloorkar NH, Mane MS, Gaja JB. Liquisolid systems: a review. IJRPNS 2010 Apr;3(1):795-802.
30) Gubbi SR, Jarag R. Formulation and characterization of atorvastatin calcium liquisolid compacts. Asian J Pharm Sci 2010;5(2):50-60.
31) Kapure VJ, Pande VV, Deshmukh PK. Dissolution enhancement of rosuvastatin calcium by liquisolid compact technique. J Pharm2013;2013:1-9.

32) Tiong N, Elkordy AA. Effects of liquisolid formulations on dissolution of naproxen. Eur J Pharm Biopharm 2009 Nov 1;73(3):373-84.
33) Butreddy A, Dudhipala N. Enhancement of solubility and dissolution rate of trandolapril sustained release matrix tablets by liquisolid compact approach. Asian J Pharm Oct-Dec 2015;9(4):1-8.
34) Depika G, Ganpati M, Nandendla NN. A Comprehensive Review on Liquisolid Tablets. Int J Pharm Sci Rev Res. , March - April 2021; , 67(1):195-201.
35) Sayyad FJ, Tulsankar SL, Kolap UB. Design and development of liquisolid compact of candesartan cilexetil to enhance dissolution. J Pharm Res 2013 May 1;7(5):381-88.
36) Jhaveri M, Nair AB, Shah J, Jacob S, Patel V, Mehta T. Improvement of oral bioavailability of carvedilol by liquisolid compact: optimization and pharmacokinetic study. Drug Deliv Trans Res 2020 Aug;10(4):975-85.
37) Kaur M, Bala R, Arora S. Liquisolid technology: a review. Int J Adv Pharm Sci 2013;4(1):1-15.s
38) Yadav VB, Yadav AV. Liquisolid granulation technique for tablet manufacturing, an overview. J Pharm Res 2009 Apr;2(4):670-74.