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LIQUISOLID COMPACTS: A COMPREHENSIVE REVIEW

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ABSTRACT

Solubility is the main Criteria for dissolution and bio availability. Most of the Drug entities are lipophilic in nature and are poorly water soluble. There are several techniques which are used to increase the solubility of water insoluble drugs. Some of the techniques are Nanonization, Complex formation using Cyclodextron, self-emulsifying systems, use of surfactants, use of salt forms, solid dispersion, Micronization etc. Liquisolid compact is one such novel technique used to formulate the poorly water-soluble drugs by using appropriate non-volatile solvents, carrier material, coating material, and disintegrant into free-flowing compressible powder. These free-flowing powders are subjected to compression for tablet or filled in capsules. Liquid solid compacts are also known as "Powder solution technology". The advantages of liquid solid compacts and their wide applications makes it a promising technology.

KEYWORDS: Liquisolid compacts, carrier material, coating material, non-volatile solvents, bioavailability, dissolution.

INTRODUCTION

Solubility is one of the main criteria to be considered before deciding a dosage form of an active compound.[1] It is an important aspect to get the desired concentrations of drug in the blood for the therapeutic response. Bio availability is another essential determinant of drug for its pharmacological effect. This in turn depends on the solubility of a particular drug in the Gastro-Intestinal system.[2] As most of the drugs are lipophilic and are poorly water soluble, it is a challenge to increase their Solubility and Dissolution rate.[3] Which ultimately improves absorption and bioavailability of the drug.[4] The rate determining step for the absorption of drug is dissolution rate.[1] Recent studies found that nearly 40 percent of the newly developed drugs and about 60 percent of the new drug candidates exhibits low water solubility.[5,6] Many wonderful drugs cannot reach the public mainly because of this problem.

The Bioavailability of the drugs belonging to Biopharmaceutics classification system [BCS] class II is majorly affected by their poor water solubility and their dissolution rate.[7,8] There are many ways to enhance the dissolution rate of such drugs. Methods like Nanonization, Complex formation using Cyclodextron, self-emulsifying systems, use of surfactants, use of salt forms, solid dispersion, Micronization[9,10] etc. (Out of all of these mentioned methods, liquid solid compact technology is the best method to increase the bioavailability of BCS class II drugs.[11,12]

Liquid solid compacts are also known as "Powder solution technology". It is a process by which a solution or suspension of a water insoluble solid drugs in non-volatile vehicles are converted into a non-sticky, dry looking, free flowing, non-adherent and readily compressible powder. This technique was introduced by Spireas et al.[13] It is prepared by addition of some excipients such as carriers and coating materials. Carriers used must show the great absorption when added to liquid. The most commonly used carrier is CMC. The various grades of cellulose, lactose, starch, etc. can also be used as carriers.[14,15] And the coating material used to cover the surface, to provide flowability, to provide content uniformity to the tablet formulation. Silica powder with very fine particle size can be used as coating material.[16] In liquid solid compacts the drug is held in a solubilized liquid state and it advances drug wetting properties which consequently contributes to enhancement in drug dissolution profile and enhanced aqueous solubility.[17]

THEORIES: There is a mathematical approach to calculate the required amounts of excipients for liquid solid compact formulation. This approach is based on flowable [Φ-value] and also on compressible [Ψ -value] Liquid retention potential introducing constant for each and every liquid powder blend. The Flowability can also be calculated by the rate of powder flow or by Means of using Angle of repose. The Φ-value defines the maximum quantity of liquid that can be retained per unit

quantity of powder to maintain acceptable Flowability. The Ψ-value defines the maximum quantity of liquid that will retain per unit quantity of powder to maintain an acceptable compressible liquid or powder mixture with the ability to give compacts of satisfactory hardness without any leaks from liquid solid mass during compression.[14,15,18]

The excipient Ratio [R] Or carrier coating material ratio can be represented as.

$$R=Q/q \text{ --------} 1$$

Here R = Quantitative relationship between the weights of carrier material (Q) and coating material (q)
For a successful formulation R should be selected carefully.

An acceptable flow and compressibility of liquid solid system depends upon the [R] of the powder and can be only obtained. When the maximum load of liquid on the carrier is not exceeded. The maximum load of liquid on the carrier material is termed as Liquid load factor (Lf) and [w/w] is defined as the ratio of weights of liquid medication (W) and the carrier material (Q)

$$Lf = W/Q \text{ -------} 2$$

The [Lf] that ensures required flow ability can be determined by

$$Lf = \Phi + \varphi/R \text{-----} 3$$

Here Φ and φ are Φ values of carrier material and coating material.

Similarly, the liquid load factor for the production liquid solid system with the required compressibility (ΨLf) is determined by

$$\Psi Lf = \Psi + \psi/R \text{-----} 4$$

Where Ψ and ψ are Ψ numbers of carrier material and coating material.

So, therefore the optimal liquid loading factor (L0) which produces a liquid solid system with required flowability and compressibility is equivalent to either **ΦLf** or **ΨLf**, whichever has a lower value.

As the **Φ, Ψ, φ**, and **ψ** values are the constants for each and every powder–liquid combination for a given excipients ratio (R), the optimal liquid loading factor (L0) can be calculated in accordance to (3) or (4). Then, in accordance to various drug concentrations, different quantities of liquid medication (W) have to be used. Thus, based on the calculation of L0 and W, the suitable quantities of carrier (Qo) and coating material (qo) can be calculated in accordance to the Equations (1) and (2), respectively.[19,20,21]

MATERIALS AND METHODS

The major formulation components for liquid-solid preparation include: -

Drugs

According to BSC classification, class II and IV drugs have less solubility and dissolution rate. Therefore, such drugs are incorporated as candidates for the liquid-solid technique.

Examples: Chlorpheniramine, digoxin, piroxicam, ibuprofen, carbamazepine, etoposide, water-insoluble vitamins, fish oil, clofibrate, indomethacin, etc.[7]

Carrier material

Carriers preferred to have large-sized, coarser, porous particles, compression-enhancing ability, and high liquid absorption capacity, which should be spongy and granular to maintain flowability.[18] As a large amount of liquid medicament is embodied in carriers, it is desired to have two crucial characteristics such as SSA value and liquid absorption capacity that aid in designing a liquid-solid formulation.[22] Example: Microcrystalline cellulose (MCC PH 101) is most commonly used as a carrier as it has exhibited better flowability, dissolution, and compressibility profiles in the case of piroxicam liquid-solid tablets. SSA value has a direct influence on the liquid absorption capacity of the carrier.[23,24]
Carriers with low SSA values have limited applications.

Table 1: A few examples of low SSA values are given below.[23]

Compound	SSA (m^2/g)
Lactose	0.35 m^2/g
Sorbitol	0.37 m^2/g
Starch	0.6 m^2/g

Table 2: Recently developed new carriers possess high SSA values with increased liquid absorption capacity which includes.[25]

Carrier	SSA	LAC (Liquid Absorption Capacity)
Fujicalin	40 m^2/g	1.2 mL/g
Neusilin	300 m^2/g	3.4 mL/g

Other promising carriers are ordered mesoporous silicate used in carbamazepine preparation which shown increased drug loading capacity as well as formed reservoirs for liquid medication. This carrier has a larger surface area (up to 1500 m^2/g) and larger porous volume making it the carrier of choice in designing liquid solid formulations.[26,27]

Coating materials

These are used to cover the carrier particles that have been wet by absorbing liquid in an excess amount and help in presenting dry-looking, non-adherent, free-flowing powder. Coating materials are flow-enhancing, very fine [10nm - 5000nm in diameter], and highly assimilative coating particles. Example: Silica grades like cab-O-sil, Aerosol® 200, calcium silicate, etc, Neusilin® is preferred as a coating material due to its high liquid absorption ability and contributes to formulating tablets of reduced weight. Usage of Neusilin® eases the preparation of the liquid-solid

formulation as it can be used either as a carrier or a coating material.[22,28]

Liquid Vehicle

Non-volatile organic solvents are preferred as liquid vehicles in the liquid-solid systems of drugs. Along with this, it should be orally safe, inert, water-miscible, high boiling point and it should not be extremely viscous in nature. It should possess good solubilization power and it can act as a binder in low concentration leading to the compactness of tablets. Based on the type of formulation like a fast or delayed release, it may be hydrophilic or lipophilic in nature.[29]

Example: PEG200 and 400, polysorbate 20 and 80, liquid paraffin, glycerine, fixed oil, propylene glycol, etc are the best suited as non-volatile organic solvents.

Super disintegrant

Explotab, pumogel, Sodium Starch Glycolate (SSG), and Cross povidone are the most commonly used disintegrants. Super disintegrants help in increasing wettability, solubility, and rate of release on drug particles within a limited period of time. These agents help in the breakdown of particles into smaller-sized particles.[30]

Additives

Polyvinyl Pyrrolidone (PVP) can incorporate a large amount of the drug into a liquid-solid system due to which usage of PVP can reduce the tablet weight. It inhibits the crystal growth rate effect of tablets and contributes to a better dissolution rate profile.[19]

The addition of HPMC in the formulation acts as a drug release delaying agent and thus helps in the extended release of drugs.[29]

Lubricant

Magnesium stearate is most widely used as a lubricant in liquid-solid tablet formulation.[30]

Required equipment

UV spectrophotometer, tablet hardness tester, thickness tester, disintegration tester, dissolution apparatus, single punch tablet press, water bath, electric balance, etc.

METHOD OF PREPARATION

General procedure for liquid-solid tablet preparation involves accurately weighing pure drug and dissolving it in a suitable non-volatile solvent of the required amount to form a molecular dispersion.[31] Saturated solutions of drugs in non-volatile solvents are prepared by adding the excess drug to vehicles and shaking them under steady vibration for a specific period of time, then filtered and analysed spectrophotometrically. Solid and Liquid drugs both can be used for liquid-solid compact preparation.

Initially, dissolve the pre-weighed solid drug into the Non-volatile solvent by agitating the mixture. If required, subject it to heat to form a drug solution or drug suspension of the desired concentration.[31]

The liquid drug is added to the drug solution or drug suspension which is then incorporated into a calculated amount of carrier material which is preferably porous in nature, closely matted fibres are present in its interior surface (e.g., cellulose). And blended at a mixing rate of one rotation / sec for one minute to get a homogenous mixture of liquid medication and carrier. The internal structure absorbs the liquid initially. After the saturation, liquid absorption occurs into the external and internal structures of the carrier particles in ratios from 50:1 to 5:1 on a trial-and-error basis.[32]

Finally, the coating material is added and adsorptive particles such as silicon dioxide are added and mixed to convert the wet mixture to a free-flowing, dry-looking, non-adherent, easily compressible powder. Mixing is an essential step because it ensures even distribution of liquid medication in powder and allows absorption of drug solution. This formulation is compressed by a single punch tablet press machine but before compression, additives such as lubricant, disintegrant, polymers, binders, etc. in calculated concentration are added and mixed to produce liquid solid compacts either in tablet or capsule dosage form.[33,34,35]

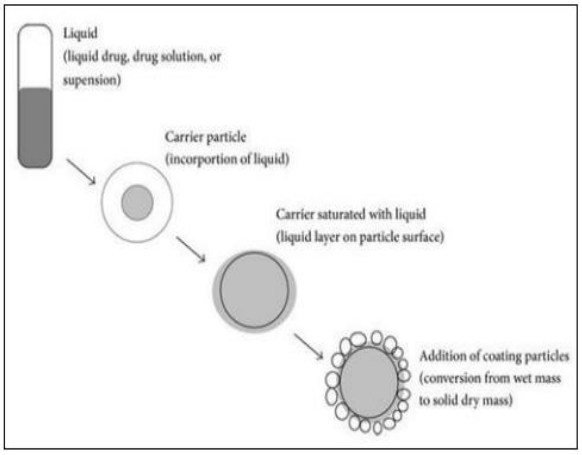

Fig 1: Schematic diagram of steps involved in Liquisolid compacts.

Classification of the liquid-solid system

- ❖ Based on the kind of liquid medication used it is categorized into 3 sub-groups.

1. Fine drug solution - e.g.: (Prelone resolution in propylene glycol)
2. Fine drug suspension - e.g.: (medication suspension in polysorbate 80)
3. Fine liquid medicine - e.g.: (Clofibrate, liquid vitamins, etc)

- ❖ Based on the formulation technique used, it is categorized into 2 types

1. Liquid Solid Compacts
2. Liquid solid microsystems

Liquid solid compact is a method to provide tablets and capsules whereas liquid solid microsystems employ a similar method in combination with additives. Eg: PVP in liquid medication is added into carrier and coating materials to enhance the flowability and compressibility for encapsulation.[36]

MECHANISMS

Several mechanisms of enhanced drug release have been proposed for liquisolid systems. The three main mechanisms include an increased face area of drug available for release, an increased arid solubility of the drug, and bettered wettability of the drug patches. Conformation of a complex between the drug and excipients or any changes in crystallinity of the drug could be ruled out using DSC and XRPD measures.[32]

A) Increased drug surface area

Still, molecularly dispersed state, if the drug within the liquisolid system is completely dissolved in the liquid vehicle it's located in the cream substrate still in a solubilized. therefore, the face area of drug available for release is important lower than that of drug patches within directly compressed tablets.[32]

B) Increased aqueous solubility of the drug[29]

In addition to the first medium of drug release enhancement it's anticipated that Cs, the solubility of the drug, might show increase with liquisolid systems. In fact, the fairly small amount of liquid vehicle in a liquisolid compact is not sufficient to increase the overall solubility of the drug in the arid dissolution medium. Still, at the solid/ liquid interface between an individual liquisolid primary flyspeck and the release medium it's possible that in this medium the amount of liquid vehicle diffusing out of a single liquisolid flyspeck together with the drug molecules might be sufficient to increase the arid solubility of the drug if the liquid vehicle acts as a cosolvent.

C) Bettered wetting properties

Due to the fact that the liquid vehicle can either act as face active agent or has a low face pressure, wetting of the liquisolid primary patches is bettered. Wettability of these systems has been demonstrated by measuring contact angles and water rising times.

EVALUATION

Pre-compression studies of liquisolid compacts

❖ **Angle of repose**[37,38,39]

This is the maximum angle possible between the face of a pile of powder and the horizontal plane. Weigh 10gm of powder was allowed to flow by funnel from 4 cm of height from the base. The height of pile and borderline of the base was measured and calculate the angle of repose by the following the formula -

$$\text{Tan } \theta = h/r$$

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

Where = Angle of repose,
h = Height of the heap
r = Radius of the heap.

Table 3: Angle of repose.

Flow property	Angle of repose (degrees)
Excellent	25 – 30
Good	31 – 35
Fair-aid not needed	36 – 40
Passable – may hang up	41 – 45
Poor – must agitate, vibrate	46 – 55
Very poor	56 – 65
Very, very poor	>66

❖ **Bulk Density**[37]

Accurate amount of Powder, which was preliminarily passed through sieve #40 (USP) and precisely poured into a graduated cylinder. Also, after pouring the greasepaint into the graduated cylinder, the greasepaint bed was made in variant without disturbing. Also, the volume was measured directly from the scale marks on the cylinder as ml. The volume measured was called as the bulk volume.

Bulk Density is calculated by following formula-

Bulk density = Weight of powder / Bulk volume

❖ **Tapped Density**[37]

After measuring the bulk volume, the same measuring cylinder was set into Tapped Density apparatus. It was set to 300 taps drop/minute and operated for 500 gates. Volume was noted as (Va) and again tapped for 750times and volume was noted as (Va). Continue tapping for 750 times and note volume as (vb).

If the difference between VA and Vb not lower than 2% also Vb is to consider as final tapped volume.

The tapped density is calculated by the following formula-

Tapped density = Weight of powder / Tapped Volume

❖ **Carr's index** (compressibility indicator)[39]

The simplest way for measurement of free flow of powder is Carr's Index.

The following formula is used -

Carr's indicator = Tapped density - Bulk density / Tapped density X 100

Table 4: Carr's Compressibility index.

Flow property	C.I (%)
Excellent	≤10
Good	11 – 15
Fair	16 – 20
Passable	21 – 25
Poor	26 – 31
Very poor	32 – 37
Very, Very Poor	>38

❖ **Hauser's rate**[40]

Hauser's rate is an important character to determine the flux property of cream and grains. This can be calculated by the following formula-

Hauser's ratio = Tapped density/ Bulk density

Table 5: Hauser's ratio.

Flow property	Hausner ratio
Excellent	1.00 – 1.11
Good	1.12 – 1.18
Fair-aid not needed	1.12 – 1.18
Passable – may hang up	1.26 – 1.34
Poor – must agitate, vibrate	1.35 – 1.45
Very poor	1.46 – 1.59
Very, very poor	>1.60

Post- compression of liquisolid compacts[41,42,43]

❖ **Weight variation:** It is measured by selecting 20 tablets randomly and weighed individually to check whether the tablet falls in the given pharmacopeial criteria or not.

❖ **Thickness:** The Thickness of the tablet was measured by using venier Caliper. Expressed in mm. ± 5% variation is allowed

❖ **Hardness:** Hardness it's a measure of the mechanical strength of a tablet using a hardness tester (Monsanto hardness tester). The force applied to the edge of the tablet is increased by moving the screw knob gradually forward until the tablet breaks. Reading is expressed in kg/cm.

❖ **Friability:** It was determined using Roche friabilator, the chance loss in tablet weight ahead and after 100 revolutions of tablets was calculated and taken as a measure for friability.

▪ $F= (W_{initial})-(W_{final})/(W_{initial}) \times 100$

❖ **Uniformity of Drug Content:** To determine the Drug content. Triturate the tablets and take the avg weight of powder and add it into a 100ml of suitable buffer and continue stirring for 30min. And check the absorbance spectrophotometrically.

❖ **Disintegration time:** 6 Tablets were taken randomly and subjected in the USP Disintegration apparatus. Note down the down taken for each tablet to disintegrate completely

❖ **In vitro dissolution studies**: It is determined using USP dissolution testing apparatus Type 2 (Paddle). 900ml of suitable buffer at temperature 37±0.5^{o}C is used.

ADVANTAGES[44,45,46]

1. By using suitable ingredients in the formulation such as release retarding agents like HMPC and hydrophobic carriers like Eudragit® RL and RS, it is possible to alter the release rate of the drug.
2. Excipients used in the formulation are cost-effective/economical and readily available.
3. Manufacturing process of liquid systems is similar to that of a conventional tablet.
4. pH-independent drug release profiles can be achieved in this technique.
5. In a liquid-solid system, a large number of water-insoluble, slightly water-soluble, and very slightly water-soluble drugs can be formulated.
6. Better bio-availability and enhanced dissolution profiles can be observed.
7. Liquid-sold technique is suitable for large-scale production due to its good flow properties and compressibility of solid-liquid powder.
8. Only liquid drugs can also be formulated.
9. When compound to other conventional dosage forms such as soft gelatin capsules, it exhibits enhanced invitro-in vivo drug release.
10. It can be used in controlled drug delivery systems.

DISADVANTAGES[44,47,48]

1. Large amounts of carrier material and coating materials are used in the formulation which increases the tablet weight above one gram, therefore patient compliance is decreased.
2. Formulation of the high-dose lipophilic drug, the liquid-solid tablet is the limitation.
3. Mathematical calculation must be applied to dissolve the required amount of pure drug into a suitable solvent.
4. To increase the drug release rate, ingredients with better absorption rates can be added.
5. Acceptable compression may not be achieved as a liquid drug may be squeezed out from a tablet resulting in inadequate hardness.

APPLICATIONS[49,50]

- Enhancement of solubility and dissolution rate in drugs belonging to Class II and Class IV
- Formulation of sustained release tablets by using hydrophobic carriers like Propranolol Hydrochloride, Tramadol Hydrochloride etc.
- Applicable in probiotics.
- Formulation of controlled release systems
- This technique is widely employed for liquid lipophilic drugs / oily drugs.

CONCLUSION

Most of the drugs have limitation of solubility which in turn influences the bioavailability. The liquid solid technique can be an effective way for enhancing the dissolution profiles and bio availability of water insoluble solid and liquid drugs (example indomethacin) into a rapid release tablet by using non-volatile solvents which causes increase in the wetting property and the surface area of drug particles available for the dissolution. Use of liquid solid technique is not only to enhance dissolution of water insoluble drugs but also a great and wonderful method to formulate sustained release zero order release pattern tablets by using the appropriate biodegradable polymers in suitable excipient ratios. Addition of disintegrants along with carrier materials and coating materials enhances the drug release from liquid solid compact. Thus, coating material carrier material and disintegrants selection should be appropriate as displays a major rule. The advantages of

liquid solid compacts and their wide applications makes them a promising technology.

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