LIQUISOLID TECHNIQUE: A NOVEL APPROACH FOR DOSAGE FORM DESIGN

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Received: 25 Mar 2017, Revised and Accepted: 17 Apr 2017

ABSTRACT

The liquisolid technique is a novel approach for delivery of drugs through the oral route. This technique is suitable for poorly soluble or water insoluble drugs, highly permeable drugs (BCS Class II drugs) and also for immediate or sustained release formulations. It is a novel “Powder Solution Technology” that involves absorption and adsorption efficiencies, making use of liquid medications, drug suspensions admixed with suitable carriers, coating materials and formulated into free flowing, dry looking, non-adherent and compressible powder forms. The design of liquisolid systems are mainly intended for enhancement of solubility, dissolution rate and bioavailability of poorly water-soluble and highly lipophilic drugs. Improvement in bioavailability may be due to increased surface area, increased aqueous solubility and increased the wettability of the drug. Liquisolid technique also has the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release systems. Overall, liquisolid technique is a most promising and novel technique for enhancing the dissolution and bioavailability of poorly water soluble drugs and sustaining drug release from tablet matrices. The current review mainly focuses on theory and applicability of liquisolid compact technique towards solubility or bioavailability enhancement. Different carriers, solvents and coating materials employed are elucidated. Literature reports on the applicability of liquisolid compact techniques over a wide range of pharmaceutical formulations are also explicated.

Keywords: Lipophilic, Bioavailability, Wettability, Carrier, Sustaining

INTRODUCTION

Out of the numerous challenges in the design of pharmaceutical dosage forms, the most important is the solubility enhancement of poorly water-soluble drugs and improvement of bioavailability [1]. In recent years, the number of drug candidate has increased. However, most of these drugs are highly lipophilic and poorly water-soluble about 40% of the newly developed drugs and nearly 60% of the synthesised chemical entities suffer from solubility issues [2, 3].

Table 1: Descriptive terms for solubility according to Indian pharmacopoeia [4]

| S. No. | Descriptive terms          | Parts of solvent required to dissolve one part of solute (ml) |
|--------|---------------------------|--------------------------------------------------------------|
| 1      | Very soluble              | Less than 1                                                 |
| 2      | Freely soluble            | More than 1 but less than 10                                 |
| 3      | Soluble                   | More than 10 but less than 30                                |
| 4      | Sparingly soluble         | More than 30 but less than 100                               |
| 5      | Slightly soluble          | More than 100 but less than 1000                             |
| 6      | Very slightly soluble     | More than 1000 but less than 10,000                          |
| 7      | Insoluble                 | More than 10,000                                            |

Those belonging to the BCS class II and IV, dissolve poorly, slowly, and irregularly and hence possess serious delivery challenges like the incomplete release of drug from the dosage form, poor bioavailability of drug and high inter-patient variability [5].

Table 2: Biopharmaceutical classification system [5]

| S. No. | BCS class | Solubility | Permeability | Examples                      |
|--------|-----------|------------|--------------|-------------------------------|
| 1      | I         | High       | High         | Metoprolol, Diltiazem, Verapamil, Propranolol, Nifedipine, Ketoprofen, Naproxen, Nifedipine, Ketoprofen, Naproxen, |
| 2      | II        | Low        | High         | Danazol, Taxol, Furosemide.    |
| 3      | III       | High       | Low          | Atenolol, Carprofen Ranitidine, Acyclovir, Taxol, Furosemide. |
| 4      | IV        | Low        | Low          | Taxol, Furosemide.             |

Techniques for solubility enhancement

Many approaches have been developed for enhancement of solubility of poorly water-soluble and lipophilic drugs. Micronization technique is the most commonly used approach to improve drug solubility of poorly soluble drugs due to an increase in surface area. Other approaches, such as inclusion complexes, microencapsulation, and preparation of self-nanomulsions and solid lipid nanoparticles have also been studied for dissolution enhancement of poorly water-soluble drugs [2].

Liquisolid compact technique

The liquisolid technique is a novel and most promising technique for improving the dissolution rate of poorly water-soluble drugs. In this technique with the use of carrier and coating materials the liquid form of drug converted into dry looking, non-adherent, free flowing, and directly compressible powder. In liquisolid system, the liquid portion is a drug suspension, liquid drug, or drug solution made in suitable non-volatile liquid vehicles [6, 7].

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*Powdered drug solution, suspension, the liquid drug is produced from the conversion of drug solutions or drug suspensions, and formulation of liquid drugs into liquisolid systems.

**Theory of liquisolid system [2, 9-11]**

For the production of liquisolid systems amounts of powder excipients required is calculated by using a mathematical approach developed by Spiroas. This approach is depends on the flowable (φ-value) and compressible (φ-number) liquid retention potential introducing constants for each powder/liquid combination.

The φ-number of a powder is defined as the maximum amount of non-volatile liquid the powder can retain inside its bulk while maintaining acceptable compatibility resulting in compacts of sufficient hardness during compression. It can be measured as the maximum crushing strength of one-gram tablet compacted at sufficiently high compression forces.

The φ-value of a powder is defined as the maximum amount of a given non-volatile liquid that can be retained inside its bulk while maintaining an acceptable flowability.
The liquid load factor that ensures acceptable flowability ($\varphi_L$) can be determined by:

$$\varphi_L = \varphi + \varphi' (1/R)$$

Where, $\varphi$ and $\varphi'$ are the $\varphi$-values of the carrier and coating material, respectively.

Depending on the excipient ratio (R) of the powder substrate an acceptably flowing and compressible liquisolid system can be obtained only if a maximum liquid load on the carrier material is not exceeded.

$$R = Q/q$$

$R$ represents the ratio between the weights of the carrier ($Q$) and the coating ($q$) material present in the formulation.

By using the following equation we can measure the quantities of carriers ($Q_0$) and coating ($q_0$) materials are required to convert liquid formulation ($W$) into acceptably flowing and directly compressible powder.

$$Q_0 = W/L_0$$

$$q_0 = Q_0/R$$

### Table 3: $\varphi$-values and $\varphi'$-values of different carrier and coating materials [12]

| S. No. | Powder excipients          | $\varphi$ value | $\varphi'$ value | $\varphi$ value | $\varphi'$ value |
|--------|-----------------------------|-----------------|------------------|-----------------|-----------------|
| 1      | Avicel PH102                | 0.16            | 0.005            | 0.224           | 0.242           |
| 2      | Avicel PH200                | 0.26            | 0.02             | 0.209           | 0.232           |
| 3      | Cab-O-Sil M5 with Avicel PH 102 | 3.31         | 3.26             | 0.560           | 0.653           |
| 4      | Cab-O-Sil M5 with Avicel PH 200 | 2.56         | 2.44             | 0.712           | 0.717           |

### Enhanced drug release mechanism from liquisolid systems

Three main mechanisms are involved for enhancement of drug release from liquisolid systems are as follows

**Increased drug surface area**

In liquisolid system the surface area of drug available for drug release is much greater than that of drug particles within directly compressed tablets because the drug present in the liquisolid system is completely dissolved in the liquid vehicle and present in the powder substrate still in a solubilized, molecularly dispersed state [9].

Consequently, with increasing drug content, the solubility limit also increases and thus, increasing the fraction of undissolved drug in the liquid vehicle and thus, the release rate decreases. In the liquid solid formulation, the release rate of the drug is directly proportional to the fraction of the molecularly dispersed drug (FM). Spireas defined FM as the ratio of the drug solubility ($S_d$) and the actual drug concentration ($C_d$) in the liquid vehicle [13].

$$FM = \frac{S_d}{C_d}$$

Where $FM = 1$ $S_d \geq C_d$

**Increased aqueous solubility of the drug**

The solubility of the drug may be increased with liquisolid system. In fact, the small amount of the liquid vehicle in a liquisolid compact is not sufficient to increase the overall solubility of the drug in the aqueous dissolution medium. If the small amount of liquid vehicle acts as a co-solvent in liquisolid system less amount of vehicle is sufficient to increase the aqueous solubility of the poorly water soluble drug [14].

**Increased wettability**

The non-volatile solvent present in the liquisolid system provides wetting of drug particles by decreasing interfacial tension between tablet surface and dissolution medium so the contact angle of liquisolid system is lower when compared to the conventional formulation thus improved wettability [13].

### Requirements for preparation of liquisolid systems

**Drug candidates [15]**

Drug substance with solubilities below 0.1 mg/ml face significant solubilization obstacles, and often even compounds with solubilities below 10 mg/ml present difficulties related to solubilization during formulation.

**Table 4: Drugs used in liquisolid systems [15]**

| S. No. | Name of the drug  | Use       |
|--------|-------------------|-----------|
| 1      | Griseofulvin      | Anti-fungal |
| 2      | Lovastatin        | Hypertriglyceridemia |
| 3      | Felodipine        | Anti-hypertension |
| 4      | Budesonide        | Anti-asthmatic |
| 5      | Aceclofenac       | NSAIDs    |
| 6      | Carbamazepine     | Anti-epileptic |
| 7      | Nevirapine        | Anti-viral |
| 8      | Praziquantel      | Anti-helmed |
| 9      | Trimethoprim      | Anti-biotic |
| 10     | Clofibrate        | Anti-hyperlipidemic |
Non-volatile solvent

Non-volatile solvents used in the liquisolid systems should be safe, water-miscible, inert, not highly viscous. The carriers and coating materials required to prepare the liquisolid system decreases with increase in the solubility of the drug in a non-volatile solvent [16].

Carrier materials

Carriers used in liquisolid systems should have a porous surface and high liquid absorption capacity. Specific surface area and liquid absorption capacity are the most important properties of carriers and these carriers incorporate large amount liquid in its structure [2, 16].

Table 5: Various non-volatile solvents used in liquisolid system [6]

| S. No. | Non-volatile solvent               | HLB value |
|-------|-----------------------------------|-----------|
| 1     | Propylene glycol                  | 2.5       |
| 2     | Polyethylene glycol 200 monostearate | 8         |
| 3     | Polyethylene glycol 400 monostearate | 11.5      |
| 4     | Polysorbate 80                    | 15        |
| 5     | Capryol® 90                       | 5         |

Table 6: various types of carrier materials used in liquisolid system [2, 6]

| S. No. | Carrier material      | Specific surface area (m²/g) |
|-------|-----------------------|-------------------------------|
| 1     | Micro-crystalline cellulose | 1.18                         |
| 2     | Lactose               | 0.35                          |
| 3     | Sorbitol              | 0.37                          |
| 4     | Starch                | 0.6                           |
| 5     | Fujicalin®            | 40                            |
| 6     | Neusilin®             | 300                           |

Table 7: Various types of coating materials used in liquisolid system [6]

| S. No. | Coating material | Composition                          | Specific surface area (m²/g) |
|-------|------------------|-------------------------------------|-----------------------------|
| 1     | Cab-O-Sil® M5-P  | Untreated fumed silica              | 220                         |
| 2     | Syloid®          | Amorphous silicon dioxide           | 312                         |
| 3     | Aerosil® 200     | Hydrophilic fumed silica            | 200                         |
| 4     | Neusilin®        | Amorphous aluminomagnesium metasilicate | 44-250                   |

Other additives

The disintegration of solid dosage forms noticeably influences drug release. Sodium starch glycolate is most commonly used disintegrant in the formulation of liquisolid tablets [1]. Polyvinylpyrrolidone (PVP) is another promising additive, which has the potential to incorporate a high amount of drug into liquisolid systems and minimizes the overall tablet weight.

There is another additive used in liquisolid systems—HPMC, which usually acts as a release retarding agent to sustain drug release from liquisolid tablet [8].

Advantages of liquisolid systems [11, 15, 17]

1. Liquisolid technique has the potential to formulate liquisolid tablets or capsules with pH-independent drug release profiles.
2. Enhanced bioavailability can be obtained in liquisolid technique.
3. Though the drug is in a tableted dosage form it is held in a solubilized liquid state, which increases drug wetting properties, drug dissolution rate and bioavailability.
4. Industrial production of liquisolid tablets or capsules is possible.
5. Water insoluble drugs exhibit enhanced in vivo and in-vitro drug release profiles in the liquisolid system.
6. For the formulation of the liquisolid system, less excipients are required when compared to conventional formulations.
7. Increased surface area of drug exposed to dissolution medium.
8. By using hydrophobic carriers like Eudragit® RL and RS formulation of sustained release liquisolid tablets are possible.
9. Production cost is low when compared to soft gelatin capsules.
10. Liquisolid approach omits the process approaches like nanonisation, micronization techniques.

Disadvantages of liquisolid systems [18-20]

1. Liquisolid systems require high solubility of drug in non-volatile solvents.
2. High levels of carrier material and coating materials should be required in order to achieve acceptable flowability and compactibility for liquisolid powder formulation.
3. Liquisolid system is the problematic formulation of a high dose of poorly water soluble drugs (e.g., carbamazepine, budesonide).

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**Applications of liquisolid systems [21-25]**
1. Drug photostability in solid dosage forms is improved by liquisolid technique.
2. The rapid and prolonged release of drugs is obtained in liquisolid formulations.
3. The liquisolid technique is most efficiently used for water-insoluble solid drugs or liquid lipophilic drugs.
4. Liquisolid technique minimizes effect of pH variation on drug release.

**Procedure for designing of liquisolid formulation**

```
  Solid drug + Non volatile solvent → Drug in solution or Suspension or Liquid drug → Liquid medication
                           ↓                                      ↓
                           Wet particles                          Carrier material
                           ↓                          Liquid suspension
                           →                           Liquisolid system
                           ↓                                      ↓
                          Final formulation                          Final formulation
                          ↓                                      ↓
                          Tabletting or encapsulation

Fig. 7: General preparation procedure of liquisolid formulation [2]
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Padmapreetha J et al. (2016) had formulated liquisolid compact to enhance the dissolution rate of leflunomide by using kolliphor EL, avicel PH 102, aerosol, and sodium starch glycolate as a non-volatile solvent, carrier, coating material and super disintegrant respectively. The results showed that during the first 10 min (Q<sub>10</sub>) the optimized formulation released 73.39% of its content compared to 18.94% of the conventional formulation. In conclusion, leflunomide dissolution rate can be enhancing to a greater extent by liquisolid technique [27].

Mowafaq MG et al. (2015) had prepared liquisolid compact for solubility enhancement of tenoxicam using tween 80 as a non-volatile liquid, avicel PH102 as a carrier, and aerosil 200 as a coating material. Liquisolid formulations containing various drug concentrations in liquid medication ranging from 10% to 35% w/w were prepared. Liquisolid formulations showed greater drug release rates than conventional and marketed tablets due to increasing surface area of the drug and wetting properties [28].

Hitesh J et al. (2014) had compared liquisolid and inclusion complexation techniques for dissolution rate enhancement of valsartan. This study was designed for screening of suitable non-volatile liquid solvent for the preparation of liquisolid compact such as tween 80, polyethylene glycol 400 and propylene glycol by using the mathematical equation. The study was also aimed for enhancement of dissolution rate and comparison of liquisolid technique with inclusion complex of β-cyclodextrin. The liquisolid formulation showed highest dissolution rate compared with directly compressed tablet, pure drug, and formulation prepared by complexation technique [29].

Yesubabu B et al. (2014) had formulated fast disintegrating tablets of lamotrigine using different super disintegrating agents such as crospovidone, sodium starch glycolate. Various batches of liquisolid tablets were prepared. Formulations consisting of sodium starch glycolate were found to be fulfilling all the parameters satisfactorily
when compared with crospovidone. In-vitro, drug release studies showed that within 30 min almost 90% of the drug was released from all the formulations confirming enhancement of drug dissolution by liquisolid technique [30].

All N et al. (2008) had designed sustained release liquisolid compact of propranolol hydrochloride by dispersing the drug in polysorbate 80 as the non-volatile solvent. A binary mixture of Eudragit RL or RS were used as the carrier. Silica was added to the liquid medium as the coating material with continuous mixing in a mortar. Then the final mixture was compressed using the tablet punching machine.

The effect of drug concentration, loading factor, thermal treating and aging on drug release profiles of propranolol HCl from liquisolid compacts was investigated at two different pH values such as 1.2 and 6.8. In conclusion, propranolol HCl tablets prepared by liquisolid system showed greater retardation properties than conventional matrix tablets [31].

Table 8: Literature reports on formulations of liquisolid compact

| S. No. | Drug                  | Non-volatile solvent | Carrier material | Coating material   | Ref. No. |
|-------|-----------------------|----------------------|-----------------|--------------------|----------|
| 1     | Budesonide            | PEG 400              | Avicel PH 102   | Aerosil 200        | 19       |
| 2     | Carvediol             | PEG 400              | Avicel PH 101   | Aerosil 200        | 32       |
| 3     | Candesartan cilexetil | TWEEN 80             | Avicel PH 102   | Aerosil 200        | 33       |
| 4     | Elavirenz             | Propylene glycol     | Avicel PH 102   | Aerosil 200        | 34       |
| 5     | Felodipine            | PEG 400              | Avicel PH 102   | Aerosil 200        | 35       |
| 6     | Glidazide             | Acrysol EL 135       | Avicel PH 102   | Aerosil 200        | 36       |
| 7     | Glyburide             | PEG 400              | Avicel PH 102   | Aerosil 200        | 37       |
| 8     | Hydrochlorothiazide   | PEG 400+Water+TWEEN 60 | Microcrystalline cellulose | Colloidal silica dioxide | 38       |
| 9     | Ibufrofen             | PEG 400              | Avicel PH 101   | Aerosil 200        | 39       |
| 10    | Indomethacin          | Glycerin             | Micro crystalline cellulose | Silica | 40       |
| 11    | Naproxen              | PEG 400, 200, 600, PG, Glycerin, TWEEN 80, Cremophor EL and Poloxamer 181 | Microcrystalline cellulose and Dicalcium phosphate | Colloidal silica | 12       |
| 12    | Nateglinide           | PEG 400              | Avicel PH 102   | Aerosil 200        | 41       |
| 13    | Nifedipine            | PEG 400, PG and TWEEN 80 | Avicel PH 102 | Silica gel powder | 42       |
| 14    | Olmesartan medoxomil  | Acrysol EL 135       | Avicel PH102, Fujicillin and Neusilin | Aerosil | 43       |
| 15    | Trimetazidine dihydrochloride | TWEEN 80            | Avicel PH 102   | Aerosil 200        | 44       |
| 16    | Tramadol hydrochloride | Propylene glycol     | Avicel PH 102   | Aerosil 200        | 45       |

CONCLUSION
Enhancement of the solubility and dissolution rate of poorly water-soluble drugs is still a major challenge for pharmaceutical scientists. At the same time sustaining the drug release from dosage forms helps in a better and proper utilization of the drug. Both of these applications are major requisites for enhancement of drug bioavailability. Finally, from this review, it can be concluded that, among the various techniques involved for the drug bioavailability enhancement, liquisolid technology is one of the most promising approaches. It is found to be a multipotent and promising technology for dosage form development, because of the process simplicity, low economic inputs during production and possible industrial feasibility due to the good flow and compaction characteristics of liquisolid formulations.

ACKNOWLEDGMENT
The authors are expressing sincere thanks to the principal and management of Institute of Pharmacy and Technology, Salipur, Cuttack, Odisha and M. R. College of Pharmacy, Vizianagaram, A. P. for supporting the work.

CONFLICTS OF INTERESTS
Declare None

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How to cite this article
• Satyajit Panda, R Varaprasad, K Priyanka, Ranjit P Swain. Liquisolid technique: a novel approach for dosage form design. Int J Appl Pharm 2017;9(3):8-14.