Research Article

Enhancement of Bioavailability of Poorly Water Soluble Drugs By Liquisolid Technique: A Review

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ABSTRACT

Dissolution rate of poorly water-soluble drugs is rate limiting step for its bioavailability so increases in bioavailability is the major challenging problem for drug development. **"**Powdered solution technology" or "Liquisolid technology", is a more recent technique which enhance the solubility of the poorly water-soluble drugs by improving wettability and surface area. In liquisolid technique, suspension and solution of solid drugs in non-volatile solvent systems and liquid drug convert into solid dosage form by using carriers and coating materials.

Keywords: poorly water-soluble drugs, Liquisolid compacts, carriers and coating materials.

INTRODUCTION

Solving solubility problems is a major challenge for the pharmaceutical industry with developments of new pharmaceutical products, since nearly half of the active substances being identified through the new paradigm in high throughput screening are either insoluble or poorly soluble in water[1]. At present 40% of the drugs in the development pipelines and approximately 60% of the drugs coming directly from synthesis are poorly soluble[2]. Therapeutic effectiveness of a drug depends upon the bioavailability which is dependent on the solubility and dissolution rate of drug molecules[3].

The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability[4].

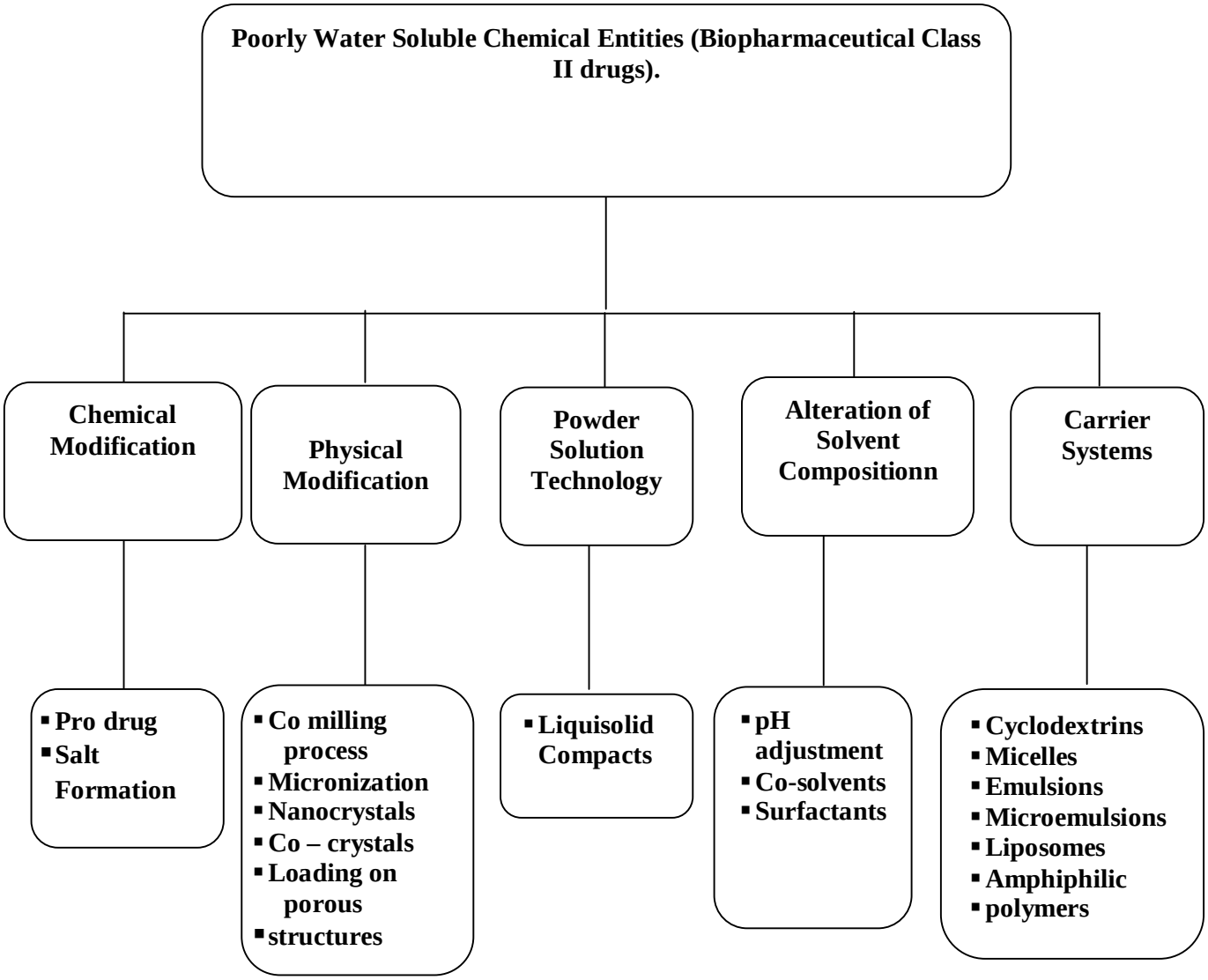
Table 1: Biopharmaceutical drug classification[4]

Class	Solubility	Permeability
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

Lipophilic molecules, especially those belonging to the biopharmaceutical classification system (BCS) class II and IV, dissolve slowly, poorly and irregularly, and hence pose serious delivery challenges, like incomplete release from the dosage form, poor bioavailability, increased food effect, and high inter-patient variability[3].

Various methods used to increase the solubility of poorly water soluble drugs which are given following chart-1[2,5].

Chart.1: Various Method for Increase the Solubility of Poor Water Soluble Drugs



Micronization

The particle size reduction technique enhance the solubility and dissolution rate of poorly water soluble drugs due to the enormous surface that is generated.

Solvent Deposition

In this method, the poorly aqueous soluble drug such as nifedipine is dissolved in an organic solvent like alcohol and deposited on a inert, hydrophilic, solid matrix such as starch or microcrystalline cellulose evaporation of solvent.

Use of soluble Prodrug

wherein the physico-chemical properties of the drug are improved by bio-reversible chemical alteration. The most common prodrug strategy involves the incorporation

of polar or ionizable moiety into the parent compound to improve aqueous solubility[6].

Solid dispersion

It involves dispersion of one or more active ingredients in an inert carrier or matrix at solid state. Melting (fusion) method, solvent evaporation method or melting evaporation methods can be employed for the preparation of the solid dispersions. The dissolution rate of the solid dispersion depends on the type of carriers used or the type of the matrix forming polymers used[7].

Liquisolid technique

The new developed technique by Spireas liquisolid system improves the dissolution properties of water insoluble or poorly soluble drugs[8].

The liquisolid technique is a novel concept where a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected carrier and coating material. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, is incorporated into the porous carrier material. Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles. Thus, an apparently dry, free flowing, and compressible powder is obtained. Microcrystalline cellulose is used as carrier material and amorphous silicon dioxide (colloidal silica) as coating material usually. Various excipients such as lubricants and disintegrants (immediate release) or matrix forming materials (sustained release) may be added to the liquisolid system to produce Liquisolid compacts[9].

Definitions

Liquid medication includes liquid lipophilic drugs and drug suspensions or solutions of solid water insoluble drugs in suitable non-volatile solvent systems.

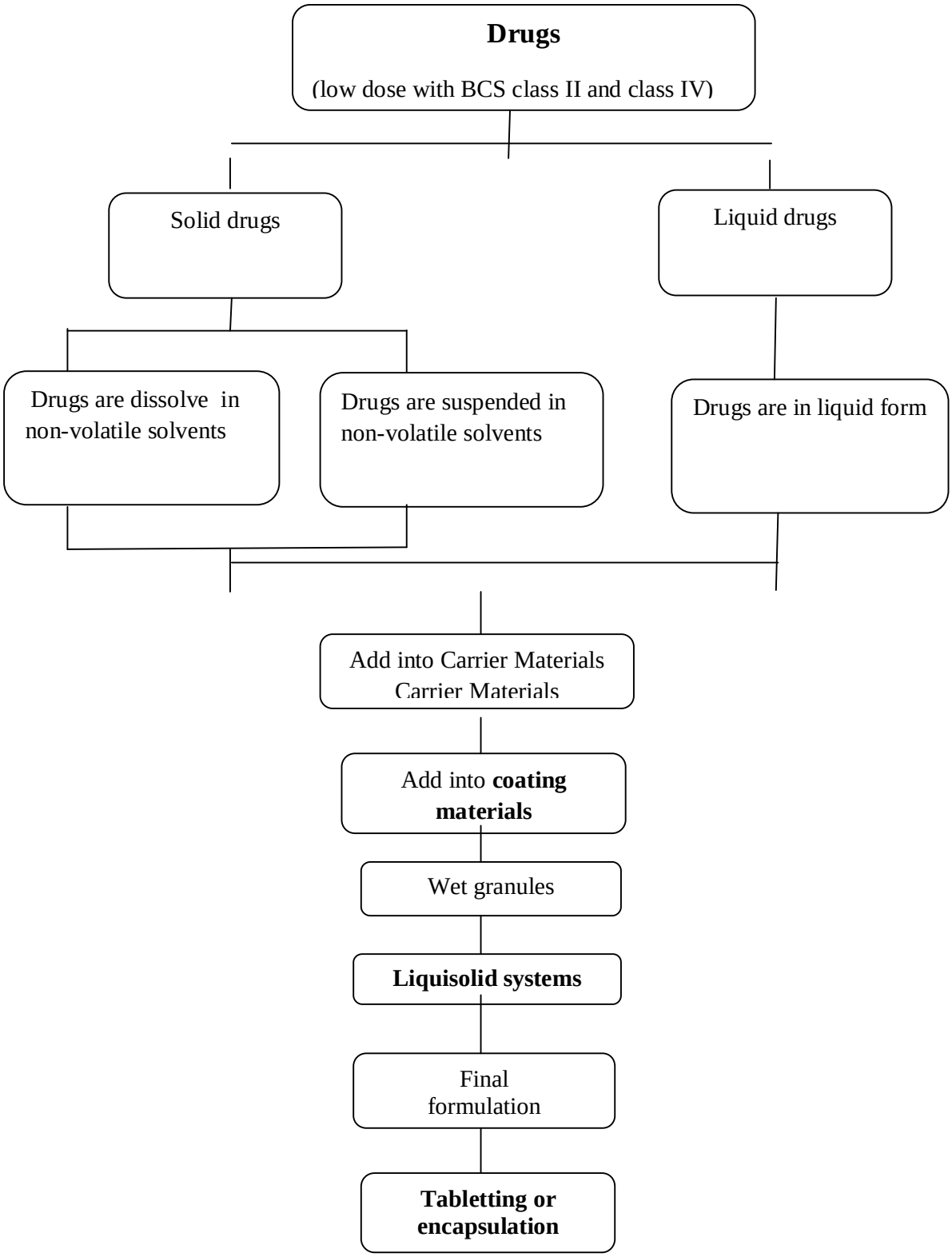
Liquisolid system refers to powdered forms of liquid medications formulated by converting liquid lipophilic drugs, or drug suspensions or solutions of water insoluble solid drugs in suitable non-volatile solvent systems, into dry, non-adherent, free-flowing and readily compressible powder admixtures by blending with selected carrier and coating materials.

Carrier material refers to a preferably porous material possessing sufficient absorption properties, such as microcrystalline and amorphous cellulose, which contributes in liquid absorption.

Coating material refers to a material possessing fine and highly adsorptive particles, such as various types of silica, which contributes in covering the wet carrier particles and displaying a dry looking powder by adsorbing any excess liquid[10].

METHOD OF PREPARATION[3,4]

Chart. 2: steps for method of preparation



Formulation

Components of Liquisolid Compact[1,2]

Liquisolid compact mainly includes

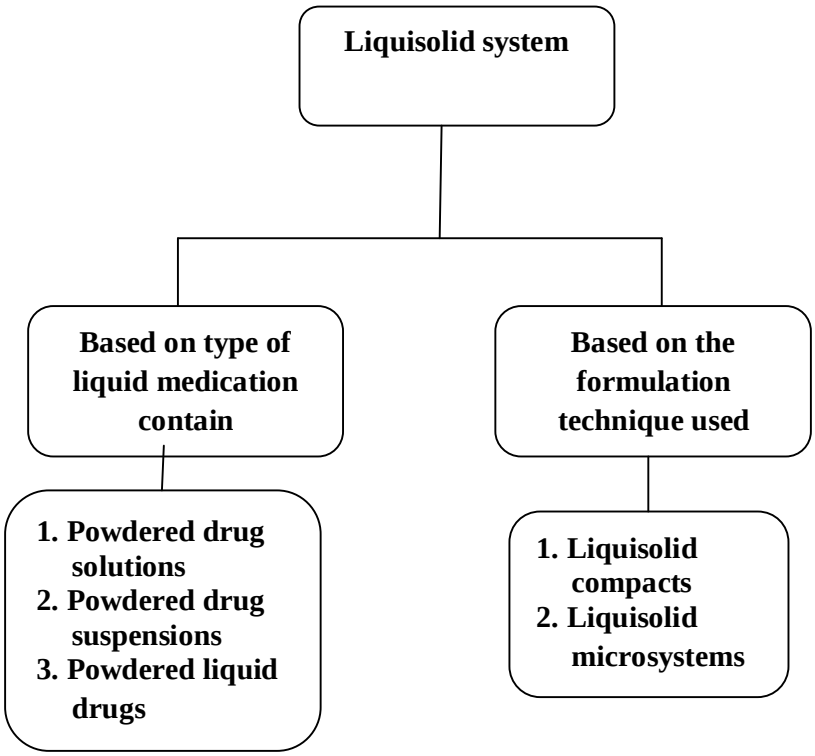
1. Non volatile solvent
2. Disintegrant
3. Drug candidate
4. Carrier material
5. Coating material

Table 2: Components and its characteristic of liquisolid techniques

Components	Drug candidates	Non volatile Solvent	Carrier Materials	Coating Materials
properties	low dose with BCS class II and class IV drugs	water-miscible ability to solubilise the drug. acts as a binding agent	Porous. Absorption properties	Fine. highly adsorptive particles
Examples	carbamazepine, famotidine, piroxicam, indomethacin, hydrocortisone, naproxen prednisolone, digoxin, digitoxin, prednisolone, hydrocortisone, spironolactone, hydrochlorothiazide, polythiazide, and other liquid medications such as chlorpheniramine, water insoluble vitamins, fish oil etc.	Polyethylene glycol 200 and 400, glycerin, polysorbate 80 and propylene glycol	grades of microcrystalline cellulose such as avicel PH 102 and avicel PH 200 20,35, lactose, eudragit Rl and eudragit RS12 (to sustain drug delivery) etc.	(Cab-O-Sil) M520,35 Aerosil 20030, Syloid, 244FP etc

Classification of Liquisolid System[11]

Chart. 3: For classification of liquisolid system



Theory of Liquisolid Systems

A powder can retain only limited amounts of liquid while maintaining acceptable flow and compression properties. To calculate the required amounts of powder excipients (carrier and coating materials) a mathematical approach for the formulation of liquisolid systems has been developed by Spireas[12,13]. This approach is based on the flowable (Φ-value) and compressible (Ψ-number) liquid retention potential introducing constants for each powder/liquid combination.

The Φ-value of a powder represents the maximum amount of a given non-volatile liquid that can be retained inside its bulk [w/w] while maintaining an acceptable flowability. The flowability may be determined from the powder flow or by measurement of the angle of repose.

The Ψ-number of a powder is defined as the maximum amount of liquid the powder can retain inside its bulk [w/w] while maintaining acceptable compactability resulting in compacts of sufficient hardness with no liquid leaking out during compression[14]. The compactability may be determined by the so-called "pactisity" which describes the maximum (plateau) crushing strength of a one-gram tablet compacted at sufficiently high compression forces. The terms "acceptable flow and compression properties" imply the desired and thus preselected flow and compaction properties which must be met by the final liquisolid formulation.

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 defined as the weight ratio of the liquid formulation (*W*) and the carrier material (*Q*) in the system:

Lf = W/Q------ (1)

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

R =Q/q------ (2)

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

Lf =Φ+ φ. (1/R) ----- (3)

Where Φ and φ are the Φ-values of the carrier and coating material, respectively. Similarly, the liquid load factor for production of liquisolid systems with acceptable compactability (Ψ*Lf)* can be determined by:

$^{\Psi}Lf$ = Ψ+ψ *(1/R) ------- (4)

Where Ψ and ψ are the Ψ-numbers of the carrier and coating material, respectively. In Table-2 examples of liquisolid formulation parameters of various powder excipients with commonly used liquid vehicles are listed.

Therefore, the optimum liquid load factor (Lo) required to obtain acceptably flowing and compressible liquisolid systems are equal to either *ΦLf* or Ψ*Lf,* whichever represents the lower value.

Table 3: Liquisolid formulation parameters of various powder excipients with commonly used liquid vehicles

Powder excipient or syste	Φ-value		Ψ-number	
	Propylene glycol	PEG 400	Propylene glycol	PEG 400
Avicel PH 102	0.16	0.005	0.224	0.242
Avicel PH 200	0.26	0.02	0.209	0.232
Cab-O-Sil M5 (silica)* With Avicel PH 102	3.31	3.26	0.560	0.653
Cab-O-Sil M5 (silica)* With Avicel PH 200	2.57	2.44	.712	0.717

*included as coating material in carrier/coating powder systems

As soon as the optimum liquid load factor is determined, the appropriate quantities of carrier (*Qo*) and coating (*qo*) material required to convert a given amount of liquid formulation (*W*) into an acceptably

flowing and compressible liquisolid system may be calculated as follows:

Q0 = W/Lo-----(5) **And q0 = Q0/R**-------(6)

The validity and applicability of the above mentioned principles have been tested and verified by producing liquisolid compacts possessing acceptable flow and compaction properties.

Advantages of Liquisolid Systems[2,3]

1. Number of water-insoluble solid drugs and liquid drugs can be formulated into liquisolid systems and give higher bioavailability of it.
2. Lower production cost than that of soft gelatin capsules as well as production is same like conventional tablets
3. Can be used for controlled drug delivery.
4. Exhibits enhanced in-vitro and in-vivo drug release as compared to commercial counterparts, including soft gelatin capsule preparations.

Limitations[2,5]

Not applicable for formulation of high dose insoluble drugs.

1. If more amount of carrier is added to produce free-flowing powder, the tablet weight increases to more than one gram which is difficult to swallow.
2. Acceptable compression properties may not be achieved since during compression liquid drug may be squeezed out of the liquisolid tablet resulting in tablets of unsatisfactory hardness.
3. Introduction of this method on industrial scale and to overcome the problems of mixing small quantities of viscous liquid solutions onto large amounts of carrier material may not be feasible.

Applications[3,9]

1. It gives rapid release and sustained release of drugs are obtained in liquisolid formulations.
2. Sustained release of drugs which are water soluble drugs such as propranolol hydrochloride has been obtained by the use of this technique.
3. Solubility and dissolution enhancement.
4. Designing of controlled release tablets.
5. Application in probiotics.

Review of Literature of Liquisolid Formulation

SR.NO	DRUG	CO-SOLVENT	CARRIER MATERIAL	COATING MATERIAL	RESULT
1	Carbamazepine[15]	PEG-200, PEG-400	MCC, Lactose	Silica	Improve the dissolution rate
2	Famotidine[16]	PG	MCC	Silica	Higher drug dissolution rates (DR) than the conventional, directly compressed tables. In addition, the selected optimal formula released 78.36% of its content during the first 10 min which is 39% higher than that of the directly compressed tablets.
3	Glimepiride[17]	PG	MCC	Silica	Improve the dissolution rate by decrease the crystallinity of the drug.
4	Hydrochlorthiazide[18]	PEG-200	Avicel PH101/102(MCC)	Aerosol	Improve the bioavailability
5	Indomethacin[19]	PEG-200, Glycerine	MCC	Silica	Enhanced oral bioavailability due to the increased wetting properties and the surface of drug available for dissolution.
6	Ketoprofen[20]	PEG-400	Avicel PH101(MCC)	Silica	Increase in oral bioavailability due to increased wetting and surface area available for dissolution.
7	Lansoprazole[21]	Polysorbate-80	Avicel PH102(MCC)	Silica	Increase the bioavailability due to increased wetting and surface area available for dissolution.

8	Naproxen[22]	Cremophor_-EL, Synperonic-PE/L61, PEG400	Avicel PH102(MCC)	Cab-o-sil M-5	Improve the dissolution profile.
9	Piroxicam[23]	Tween-80	MCC	Silica	40% enhanced dissolution than conventional tablets.
10	Propranolol[24]	Polysorbate -80	Eudragit RL or RS	Silica	Greater retardation properties.
11	Rofecoxib[25]	PEG 600	Avicel PH 101	Cab-O- Sil,	Improve the availability and in-vitro release.
12	Furosemide[26]	1,2,3-propanetriol, Caprol® PGE-860, PEG 400	MCC	Silica	Improve solubility
13	Griseofolvin[27]	PEG-300	Avicel PH200(MCC	Aerosil	High drug release rate.
14	Prednisolone[28]	Propylene glycol	Avicel PH101, Lactose	Cab-o-sil	Drug dissolution rate from liquisolid tablets was independent of the volume of dissolution medium

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