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REVIW ARTICLE

LIQUISOLID TECHNIQUE: AN APPROACH FOR ENHANCEMENT OF SOLUBILITY

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ABSTRACT:

Liquisolid technique is also known as powder solution technology. It is the technique which deals with the solubility enhancement of poorly soluble drugs. As these days there are many drugs in the market with poor solubility which leads to poor dissolution and bioavailability, so solubility is becoming rate limiting factor in the development of new drugs. To overcome this problem there are many techniques but liquisolid technique is most promising technique which is discussed in this article. Liquisolid is mainly composed of drug, non volatile solvent, carrier material, coating material, and disintegrant. In liquisolid technique carrier and coating material which should be in the ratio of 20:1 is mixed into the non volatile solvent and then disintegrant is added and final material is compressed into tablets. Hence, the liquisolid technology allows the transformation of liquid systems into solid drug delivery systems. Both immediate and sustained release of drug can also be achieved with the help of liquisolid technique. For sustained release of drug hydrophilic polymer like Hydroxy Propyl Methyl Cellulose can be the best option. The purpose of this article is to describe about the liquisolid technique like basics, classification, preformulation studies, characterisation, precompression studies, formulation of tablet, postcompression studies, advantages, disadvantages, applications.

Keywords: Liquisolid, bioavailability, dissolution, sustained release.

INTRODUCTION:

With the discovery of new drug molecules today low solubility is the main hurdle to be overcome. There are many techniques like solid dispersions, inclusion complexes with β-cyclodextrins, micronization, eutectic mixtures and spray-drying which can overcome this problem but among all liquisolid technique is most easy and cost effective technique. In liquisolid technique even though the drug is in a solid dosage form, it is held within the powder substrate in solution or, in a solubilised almost molecularly dispersed state, which contributes to the enhanced drug dissolution properties.[1]

Definitions

Liquid medication:

Liquid medication includes liquid lipophilic drugs and drug suspensions or solutions of solid water insoluble drugs in suitable non-volatile solvent systems.[2]

Liquisolid 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.[3]

Non-volatile solvent:

Non-volatile solvent may be hydrophilic or lipophillic in nature depending upon the type of formulation like immediate release or sustained release. Non solvent should be inert, high boiling point, water miscible.[4]

Carrier material:

Carrier material refers to a preferably porous material possessing sufficient absorption properties, such as microcrystalline and amorphous cellulose, which contributes in liquid absorption.[4]

Coating material:

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. Furthermore replacement of commonly used carrier and coating materials like Avicel and Aerosil respectively with Fujicalin and Neusilin led to considerably higher liquid adsorption capacity because of large specific surface area and good flow property.[4,5]

Disintegrant:

5 % of disintegrant is used in formulation, mainly Sodium Starch glycolate is used as disintegrant.

Basics of Liquisolid System

Spireas *et al* developed a mathematical approach for formulation of liquisolid compact.[6] This approach is mainly to calculate required amount of carrier and coating material in liquisolid technique. As a powder can retain only limited amount of liquid while maintaining acceptable flow and compression properties, this approach is based on the flowable (Φ-value) and compressible (Ψ-number) liquid retention potential.[6]

Flowable liquid retention potential (ϕ-value) is defined as the maximum weight of liquid that can be retained per unit weight of powder material in order to produce an acceptably flowing liquid/powder admixture.

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Compressible liquid retention potential (ψ-value) is defined as the maximum weight of liquid that can be retained per unit weight of the powder material in order to produce an acceptably compressible liquid or powder admixture.[7]

The excipient ratio (R) or the carrier: coating material ratio is represented as follows:

$$R = Q / q \quad \ldots\ldots \text{ (equation. 1)}$$

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. This liquid/carrier ratio is termed "liquid load factor (Lf) [w/w] and is defined as the weight ratio of the liquid formulation (W) and the carrier material (Q) in the system:

$$Lf=W/Q \quad \ldots\ldots\ldots \text{ (equation. 2)}$$

The liquid load factor that ensures acceptable flow ability ($^{\Phi}L_f$) can be determined by:

$$^{\Phi}L_f = \phi + \phi. (1/R) \ldots\ldots\ldots \text{ (equation. 3)}$$

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 ($^{\Psi}L_f$) can be determined by:

$$^{\Psi}L_f = \psi + \psi. (1/R) \ldots\ldots \text{ (equation. 4)}$$

Where Ψ and ψ are the Ψ-numbers of the carrier and coating material respectively. Therefore, the optimum liquid load factor (L_0) required to obtain acceptably flowing and compressible liquisolid systems is equal to either $^{\Phi}L_f$ or $^{\Psi}L_f$, whichever represents the lower value.[7]

Classification of liquisolid systems

Based on the type of liquid medication contained therein, liquisolid systems may be classified into three sub-groups.

1) Powdered drug solutions
2) Powdered drug suspensions
3) Powdered liquid drugs

Powdered drug solutions and suspensions may be produced from the conversion of drug solutions or drug suspensions into liquisolid systems and powdered liquid drugs are produced from the formulation of liquid drugs into liquisolid systems.

Simultaneously, based on the formulation technique used, liquisolid systems may be classified into two categories namely,

1) Liquisolid compacts
2) Liquisolid microsystems

The term "liquisolid compacts" refers to immediate or sustained release tablets or capsules prepared and combined with the inclusion of appropriate adjuvants required for tabletting or encapsulation, such as lubricants, and for rapid or sustained release action, such as disintegrants or binders.

The term "liquisolid Microsystems" refers to capsules prepared by combining the drug with

carrier and coating materials with inclusion of an additive e.g., PVP in the liquid medication wherein the resulting unit size may be as much as five times that of liquisolid compacts.[5]

Main components of liquisolid technique are represented in table no 1.

Table 1: Components of Liquisolid Technique

Drug Candidates	Hydrochlorothiazide, Digitoxin, Prednisolone Hydrocortisone, Spironolactone, Digoxin etc.
Non Volatile Liquids	Poly Ethylene Glycol 200, Poly Ethylene Glycol 300, Poly Ethylene Glycol 400, Glycerine, Propylene Glycol, fixed oils.
Carrier Materials	Microcrystalline Cellulose PH 101, Microcrystalline Cellulose PH 200, Lactose, Methyl Cellulose, Ethyl Cellulose, Starch1500, Ethocel, Eudragit RL, Eudragit RS 12, Hydroxy Propyl Methyl Cellulose K4M, Hydroxy Propyl Methyl Cellulose K100M, Xanthum Gum, Guargum.
Coating Materials	Aerosil 200, Silica (Cab-O-Sil M5), Syloid 244FP, and Colloidal Silicon Dioxide.
Disintegrants	Sodium Starch Glycolate (Explotab, Primogel), Croscarmellose Sodium, Cross Polyvinyl Pyrrolidine, Pregelatized Starch.
Glidant	Talc
Lubricant	Magnesium Stearate
Release retardant material	Eudragit RS, RL, Hydroxy Propyl Methyl Cellulose K100M, K15M, K4M.

Pre-formulation Studies

1) **Solubility studies:** Solubility studies are carried out to select the best non volatile solvent for dissolving or suspending the drug in non - volatile solvent. Solubility studies are carried by preparing saturated solutions of drug in non-volatile solvent. Saturated solutions are prepared by adding excess of drug to vehicles and shaking them on shaker for 24 hour under constant vibration. Then the solutions are filtered diluted suitably and analyzed spectrophotometrically at a particular wavelength.[7] The review of the solubility of different drugs in various non volatile solvent is shown in table no 2.

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Table 2: Review of the Solubility of Drugs in Various Non Volatile Solvent

Drug	Non-volatile solvent	Solubility(mg/ml)
Carbamazepine[8]	Propylene Glycol	40.896
	Poly Ethylene Glycol 200	87.668
	Poly Ethylene Glycol 400	71.820
	Glycerin	7.789
	Polysorbate 80	45.831
Famotidine[9]	Propylene Glycol	9.5693
	Polyethylene Glycol-600	6.149
Etoricoxib[10]	Propylene Glycol	44.95
	Poly Ethylene Glycol 200	62.16
	Poly Ethylene Glycol 400	65.08
	Tween 20	34.42
	Tween 80	36.80
Nimesulide[11]	Propylene Glycol	2.760
	Poly Ethylene Glycol 400	63.5
Glibenclamide[12]	Propylene Glycol	3
	Poly Ethylene Glycol 300	12
	Polyethylene Glycol 400	15
Propranolol Hydrochloride[13]	Propylene Glycol	10.29
	Poly Ethylene Glycol 200	7.98
	Poly Ethylene Glycol 400	7.97
	Glycerin	3.91
	Polysorbate	1.33

2) **Determination of angle of slide**: To determine angle of slide required amount of carrier is weighed and placed at one end of a metal plate with a polished surface. The end is gradually raised till the plate becomes angular to the horizontal at which powder is about to slide. This angle is known as angle of slide. It was used as a measure of the flow properties of powders. Angle of 33° is regarded as optimum.[5]

3) **Determination of flowable liquid retention potential:** The flowable liquid-retention potential (Φ value) of a powder material describes its ability to retain a specific amount of liquid while maintaining good flow properties. The Φ value is defined as the maximum weight of liquid, (W_{liquid}) that can be retained per unit weight of the sorbent (W_{solid}), yielding a mixture with acceptable flowability,

$$W_{liquid}/W_{Solid}$$

As the flowable liquid-retention potential of the carrier material is approached, the liquid is held entirely in the interior of the particles. This maintains the surface of carrier material relatively dry, thus yielding powders with acceptable flow properties. When the Φ value is exceeded, the interior of particles become saturated, resulting in the formation of a liquid layer on the available surface of carrier particles.[5]

Calculation of liquid load factor (L_f): It is defined as the ratio of weight of liquid medication (W) to weight of carrier material (Q). Different concentrations of non volatile solvents are taken and the drug is dissolved and the carrier coating material is added and blended.

$$L_f=W/Q$$

W=ratio of weight of liquid medication

Q= weight of carrier material

The liquid load factor that ensures acceptable flowability (L_f), and can be measured by:

$$L_f= (1/R)$$ [14]

4) **Liquisolid compressibility test**: It was developed to determine Ψ values and involves steps such as preparing carrier coating material admixture systems, preparing several uniform liquid/powder admixtures to tablets, determining average hardness, measuring of average liquid content of crushed tablets, as well as determining plasticity, sponge index and Ψ value and L_f.[14]

Preparation of Liquisolid Tablets

A calculated quantity of drug should be dispersed in the non volatile solvent system (Polysorbate 80, Poly Ethylene Glycol-200) termed as liquid vehicle with different drug: vehicle ratio. Then resulting hot medication should be incorporated into carrier and coating material under continuous mixing in a mortar. Mixing process is to be carried out in three steps which is shown in fig. no. 1.

Step1. System is blended at an appropriate mixing rate of one rotation per second for approximately one minute in order to evenly distribute liquid medication in the powder.

Step 2: The liquid / powder admixture is evenly spread as a uniform layer on the surface of a mortar and left standing for approximately 5 minute to allow dug solution to be absorbed in the interior of powder particle.

Step 3: Powder is scraped off the motor surface by mean of aluminium spatula and then blended with disintegrant like Sodium Starch Glycolate and other remaining additives are added according to their application and mixed for a period of 10 to 20 minute in a mortar.

The final mixture should be compressed using the manual tabletting machine to achieve tablet hardness.[15]

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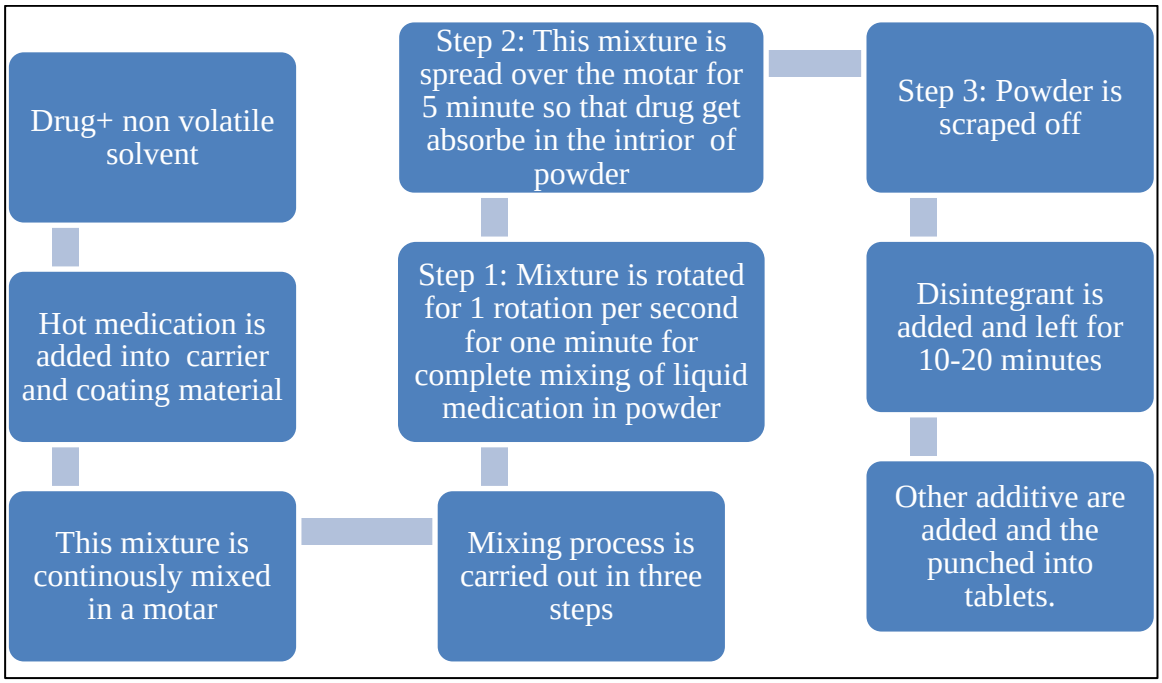

Figure 1: Steps of Liquisolid Technique

Characterisation:

1) Differential scanning calorimetry (DSC): Is a thermoanalytical technique in which the difference in the amount of heat required to increase the temperature of a sample and reference is measured as a function of temperature. Both the sample and reference are maintained at nearly the same temperature throughout the experiment. It is used to know the possible interactions between drug and excipients used in the formulation. If the characteristic peak for the drug is absent in the DSC thermogram, there is an indication that the drug is in the form of solution in liquisolid formulation and hence it is molecularly dispersed within the system. Thermal properties of the untreated drug and prepared samples are analyzed by DSC. About 5 mg of sample is heated in a hermetically sealed aluminium pans. Heat runs for each sample were set from 30°C to 350°C at a heating rate of 10°C/ min, using nitrogen atmosphere of flow rate 100ml/ minute.[16]

2) Fourier transform infra-red spectroscopy (FTIR): It is a technique which is used to obtain an infrared spectrum of absorption, emission and Raman scattering of a solid, liquid or gas. FTIR spectrometer simultaneously collects spectral data in a wide spectral range. FTIR spectrum of the drug and the prepared samples were subjected to IR spectrophotometer under identical conditions by Potassium Bromide pellet technique. Spectrum is collected over a region of 4000-400 cm^{-1}.[16]

3) X ray diffraction (XRD): A primary use of the technique is the identification and characterization of compounds based on their diffraction pattern. For the characterization of crystalline state, (XRD) patterns are determined for physical mixture of drug and excipients used in formulation and for the prepared liquisolid compacts. Absence of constructive specific peaks of the drug in the liquisolid compacts in X-ray diffractogram specify that drug has almost entirely converted from crystalline to amorphous or solubilised form. Such lack of crystallinity in the liquisolid system was understood to be as a result of drug solubilization in the liquid vehicle i.e., the drug has formed a solid solution within the carrier matrix. This solubilization of drug in the liquisolid compacts it may contribute to the consequent improvement in the apparent solubility and enhancement of dissolution rate of the drug.[14]

Precompression Studies of Liquisolid Preparation

1) Angle of repose: Angle of repose can be measured by fixed funnel method. The frictional forces in loose powder or granules can be measurement by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. Thus, r being the radius of the base of the conical pile.[17] This is shown in table no 3.

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

Table 3: Angle of Repose[17]

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

2) Bulk density: Bulk density refers to the measure used to describe a packing of particles or granules. Bulk density is defined as the mass of powder divided by the bulk volume and is expressed in grams per milliliter (g/mL) although the international unit is kilogram per cubic meter (1 g/mL = 1000 kg/m^3) because the measurements are

made using cylinders. It may also be expressed in grams per cubic centimetre (g/cm^3). The equation for determining bulk density (ρ_b) is [17]

$$\rho_b = M / V_b$$

where ρ_b = Bulk density

M = Mass of sample in g

V_b = Total volume of packing

3) Tapped density: Tapped density can be defined as mass of blend in the measuring cylinder divided by its tapped volume.[17]

$$\rho_t = M / V_t$$

Where ρ_t = Tapped density

M = Mass of blend in g

V_t = Tapped volume of blend in cm^3

4) Carr's index: The compressibility index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities and is calculated using the following formulas and is shown in table no. 4:

$$\text{Carr's Index} = \rho_t - \rho_b/\rho_t * 100$$

ρ_b = bulk density

ρ_t = tapped density.[17]

Table 4: Carr's Index[17]

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

5) Hausner's ratio: A flow property of powder mixure can be determined by Hausner's ratio. It is calculated by following formula and is shown in table no. 5

Hausner's ratio = Tapped density/ Bulk density

A Hausner ratio greater than 1.25 is considered of poor flow ability[18]

Table 5: Hausner Ratio[18]

Flow property	Hausner ratio
Excellent	1.00 – 1.11
Good	1.12 – 1.18
Fair	1.19 – 1.25
Passable	1.26 – 1.34
Poor	1.35 – 1.45
Very poor	1.46 – 1.59
Very, very poor	>1.60

Post Compression Evaluations

1) **Hardness:** Monsanto hardness tester can be used for the determination of the hardness. The tablet to be tested was held between a fixed and moving jaw and reading of the indicator adjusted to zero. The force applied to the edge of the tablet is gradually increased by moving the screw knob forward until the tablet breaks. Reading is noted down and is expressed in kg/cm.[19]
2) **Thickness:** The crown to crown thickness of tablets is measured by Vernier Caliper. It is expressed in mm. the thickness variation allowed are ± 5% of the size of the tablet.[19]
3) **Weight variation:** 20 tablets are selected randomly from the lot and weighed individually to check for weight variation.[19] Pharmacopoeial limits are shown in table no 6.

Table 6 Pharmacopoeial Limits of Weight Variation[19]

Limit	IP/BP	USP
10%	80 mg or less	130mg or less
7.5%	More than 80mg or Less than 250mg	130mg to 324mg
5%	250mg or more	More than 324mg

4) **Uniformity of Drug content:**
5) The drug content can be determined by triturating sufficient amount of tablets and powder equivalent to average weight was added in 100 ml of suitable buffer solution. Followed by stirring for 30 min. Dilute suitably and the absorbance of resultant solution was measured spectrophotometrically.[19]
6) **In-vitro drug release studies:** The release rate of drug from tablets can be determined using USP dissolution testing apparatus 2 (paddle method). The dissolution test performed using 900 ml of suitable buffer solution at 37±0.5ºC.[19]

7) **Friability:** The friability of the tablet can determined using Roche Friabilator. It is expressed percentage (%). 10 tablets were initially weighed ($W_{initial}$) and transferred into the friabilator. The friabilator was operated at 25 rpm for 4 minutes. The tablets were weighed again (W_{final}). And the % friability was calculated as.

$$F = (W_{initial})-(W_{final})/(W_{initial}) \times 100$$[19]

Advantages[20]

1) Improved bioavailability of orally administered water insoluble or poorly soluble drugs.
2) Industrially applicable.
3) Useful for the formulation of oily drugs/liquid drugs.
4) Drug release can be modified using different carriers and additives like PVP, PEG 60000, Hydroxy Propyl Methyl Cellulose and Eudragit etc.
5) A number of poorly soluble drugs can be formulated in to the system.
6) Production cost is low compared to that of preparation of soft gelatin capsules.

7) Method of preparation is very simple and it is similar to that of conventional tablets preparation.
8) Drug can be dispersed molecularly in the formulation.
9) Enhance the bioavailability when compared to that of conventional tablets.
10) It does not involve the operations like micronization, nanonization of particles.
11) This system is specifically for the powdered liquid medications.

Disadvantages/Limitations[20]

1) High solubility of drug in the non-volatile liquid drugs for the improvement of dissolution rate and bioavailability.
2) It requires excipients of high adsorption properties and high specific surface area.
3) It is not applicable to high dose insoluble drugs (>100 mg).
4) During compression sometimes liquid drug may be squeezed out of the tablet result in improper hardness.

Applications[20]

1) Enhancement of solubility and dissolution rate in drugs like Indomethacin, Famotidine, Furosemide, Naproxen, Prednisolone, Bromhexine Hydrochloride, Carbamazapine, Rofecoxib, Piroxicam etc.
2) Enhancement of bioavailability of drugs like Atorvastatin Calcium, Hydrochlorthiazide, Repaglinide, Famotidine etc.
3) Formulation of sustained release tablets by the use of hydrophobic carriers like Propanolol Hydrochloride, Tramadol Hydrochloride, and Theophylline etc.
4) It is also applicable in probiotics.
5) Controlled release formulations are also prepared by the use of different carriers that may show the zero order release similar to osmotic pumps.
6) This technique is widely employed for liquid lipophilic drugs / oily drugs.

Liquisolid Technique in the Formulation of Sustained Release Tablets

Development of sustained release oral dosage form is beneficial for optimal therapy in terms of efficacy, safety and patient compliance. Several methods have been developed to this end or to achieve this aim. It is suggested that liquisolid technique has the potential to be optimised for the reduction of drug dissolution rate and there by production of sustained release system.[21] Sustained release dosage forms are designed to release the drug at a predetermined rate by maintaining a constant drug release for specific period of time with minimum side effects in terms of efficacy, safety and patient compliance. Ideally, controlled release formulations will provide therapeutic concentration of the drug in the blood which is maintained throughout the dosing interval. Liquisolid technique is a new approach to alter the dissolution properties of the drug by using hydrophobic carriers instead of hydrophilic carriers.[3] The presence of non-volatile solvent reduces the glass transition temperature (Tg) of polymer and imparts flexibility. Therefore, reduction of Tg of the polymer might be the reason for the release prolongation of liquisolid tablets. In the temperature above the Tg, a better coalescence of the polymer particle occurs that form a fine network and a matrix with lower porosity an higher tortusity. In this way, the drug is surrounded by the polymer network, resulting in the restricted leaching of the drug thus sustained the release of drug from the liquisolid matrix.[21] Review of the drug molecules with sustained release liquisolid compact is shown in table no 7.

Table 7 Review of the Drug Molecules with Sustained Release Liquisolid Compact

Drug	Polymer Used In Sustained Release Formulation
Tramadol Hydrochloride[22]	Hydroxy Propyl Methyl Cellulose K4M
Propranolol Hydrochloride[23]	Hydroxy Propyl Methyl Cellulose (4000 mPa·s)
Metoprolo Succinate[24]	Hydroxy Propyl Methyl Cellulose K15M
Theophylline[25]	Hydroxy Propyl Methyl Cellulose (4000 mPa·s)

CONCLUSION:

Nowadays, new chemical entities often possess a high molecular weight and a high lipophilicity, especially poorly soluble drugs. Poor bioavailability is solely caused by low water solubility. One of the techniques to increase solubility is liquisolid technique which is discussed above. As highest drug release rates are observed with liquisolid technique, liquisolid compacts may be optimized by selection of proper non volatile solvent, carrier and coating materials.

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