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Liquisolid Compacts - A Novel for Retarding the Drug Release

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ABSTRACT

Liquisolid technique is a novel concept for delivery of drugs through oral route. This approach of delivering drugs is suitable mostly for lipophilic drugs and poorly or water insoluble drugs. With this approach sustained release formulation of hydrophilic drugs or freely water soluble drug can also be prepared. Release enhancement of poorly soluble drugs is achieved by choosing nonvolatile solvent with maximum drug solubility, Unlike this, in retardation of drug release nonvolatile solvent with lowest drug solubility is chosen. It was found from the study that if nonvolatile solvent alone is not sufficient for prolonging the drug release then various release retarding agent is used. The release retarding or sustained release agent used, may be of natural or synthetic origin.

Keywords: Liquisolid, Carrier, Coating material, sustain release liquisolid compact

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INTRODUCTION

Sustained release dosage form is mainly designed for maintaining therapeutic blood or tissue levels of the drug for extended period of time with minimized local or systemic adverse effects. Economy and greater patient compliance are other advantages ¹. To reduce frequent administration of dosage form and to improve patient compliance, a sustained-release formulation is desirable.

The drugs which are freely water soluble require selection of release retarding excipients to achieve a constant sustain release rate of the drug. Various approaches have been used by researchers to sustain drug release in the form of tablets ^{2,3,4}.

liquisolid compacts is one of the most promising and new technique which promotes dissolution rate of water insoluble drugs¹.The term liquisolid compact refers to immediate release or sustained release tablets or capsules, combined with the inclusion of appropriate adjuvant required for tableting or encapsulating^{5,6,7}.

The liquisolid technique as described by Spireas⁸ 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.^{8,9} In case of water soluble drugs, the sustained release can be obtained ¹⁰.

Advantages of Sustained Release dosage form:¹¹

1. Decreased local and systemic side effects:
 - Reduced gastrointestinal irritation.
2. Better drug utilization:
 - Minimum drug accumulation on chronic dosing.
3. Improved efficiency in the treatment:
 - More uniform blood concentration.
 - Reduction in fluctuation in drug level and hence more uniform pharmacological response.
4. Improved patient compliance:
 - Less frequent dosing.
 - Reduced night-time dosing.
5. Economy

Although the initial unit cost of sustained release products is usually greater than that of the conventional dosage form because of the special nature of these products, the average cost of treatment over an extended time period may be less.

Disadvantages¹¹

1. Dose dumping:

- Dose dumping may occur with faulty formulations.

2. Need for additional patient education:

- Patients may need substantial additional information as to the proper use of sustained release products e.g. “Do not crush or chew the dosage unit. Tablet residue may appear in the stools”. In some instances, patients must be started on an immediate release product and then switched over to the sustained release products.

3. Possible reduction in systemic availability:

- Reduced systemic availability has been shown for some sustained release formulations of Theophylline, Procainamide and Vitamin combinations.

Concepts of liquisolid compact with reference to sustain release dosage form.

As for water insoluble drug, in liquisolid systems the drug is already in solution in liquid vehicle, while at the same time, it is carried by the powder particles (microcrystalline cellulose and silica). Thus, due to significantly increased wetting properties and surface area of drug available for dissolution, liquisolid compacts of water-insoluble substances may be expected to display enhanced drug release characteristics and consequently, improved oral bioavailability. the same way for water soluble drug, the use of appropriate nonvolatile solvents with least drug solubility is selected to retard the drug release. From the further study it has been noted that only nonvolatile solvent alone is not sufficient to sustaining the drug release so with that various release retarding agents are used, which may be of natural or synthetic origin (such as various grades of HPMC and various natural gums etc).

Classification of liquisolid systems

A. Based on the type of liquid medication contained therein, liquisolid systems may be classified into three subgroups

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

The first two may be produced from the conversion of drug solutions or (e.g. prednisolone solution in propylene glycol¹⁵ drug suspensions (e.g. gemfibrozil suspension in polysorbate 80¹², and the latter from the formulation of liquid drugs (e.g. clofibrate, liquid vitamins, etc.) into liquisolid systems.

B. Based on the formulation technique used, liquisolid systems may be classified into two categories

1. Liquisolid compacts
2. Liquisolid Microsystems

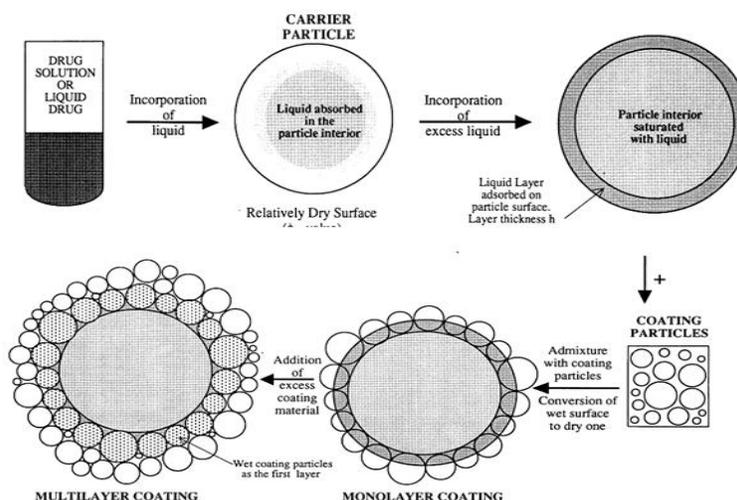


Figure-1: Mechanism represents formulation of liquisolid system

Components of Liquisolid Compact

Liquisolid compact mainly includes

1. Non volatile solvent
2. Disintegrant (for enhancing drug release)
3. Sustain release agent (For retarding the drug release)
4. Drug candidate
5. Carrier material
6. Coating material

Non volatile Solvent

Non volatile Solvent should be Inert, high boiling point, preferably water-miscible and not highly viscous organic solvent systems and compatible with having ability to solubilise the drug. The non volatile solvent acts as a binding agent in the liquisolid formulation¹³. Various non-volatile solvents used for the formulation of liquisolid systems include Polyethylene glycol 200 and 400, glycerin, polysorbate 80 and propylene glycol.

Disintegrant

Superdisintegrants increases the rate of drug release, water solubility and wettability of liquisolid granules. Mostly superdisintegrants like sodium starch glycolate and croscopolone are used¹⁴.

Sustain release agent

To achieve the sustained drug release over a long period of time through liquisolid technique, the sustained release agents are used to retarding the drug dissolution over the desired period of time. The time taken by the formulation for complete drug release can be modified by altering the strength of sustained release agent in appropriate formulation. Mostly Various grades of HPMC polymer, natural gums (like guar gum, xanthine gum etc) have been reported to be used as sustained release agent.

Drug candidates

This technique was successfully applied for low dose BCS class II and class IV drugs which are poorly water soluble and have slow dissolution rate ¹⁵. Examples of drug candidates include carbamazepine, famotidine¹⁶, piroxicam¹⁷, indomethacin¹⁸, hydrocortisone¹⁹, naproxen²⁰ and prednisolone¹⁵, digoxin, digitoxin, prednisolone, hydrocortisone, spironolactone, hydrochlorothiazide, polythiazide, and other liquid medications such as chlorpheniramine, water insoluble vitamins, fish oil etc ^{22,23}.

Carrier Materials

Carrier material should be porous material possessing sufficient absorption properties which contributes in liquid absorption. The carrier and coating materials can retain only certain amounts of liquid and at the same time maintain acceptable flow and compression properties hence, increasing moisture content of carrier's results in decreased powder flowability ¹⁵.

These include various grades of microcrystalline cellulose such as avicel PH 102 and avicel PH200^{22,23}, lactose, eudragit R1 and eudragit RS12 (to sustain drug delivery) etc.

Coating Materials

Coating material should be a material possessing fine and highly adsorptive particles which contributes in covering the wet carrier particles and displaying a dry-looking powder by adsorbing any excess liquid. Coating material is required to cover the surface and so maintain the powder flowability³⁴. Coating material includes silica (Cab-O-Sil) M520,²² Aerosil 200 ¹⁶, Syloid, 244FP ²² etc.

Liquisolid formulations for sustained drug release

Numerous methods have been described to produce sustained release formulations, among which the liquisolid technology is a quite new and promising technology resulting in a sustained release pattern with zero order kinetics ²⁴. So far, only few drugs have been formulated as liquisolid systems with prolonged drug release. In Table 1 the formulations of these drugs with the respective liquid vehicle, carrier and coating material as well as the additional retarding agent (matrix forming material) are listed.

Table-1: Formulations of liquisolid systems with sustained drug release (abbreviations are listed at the end of the table)

Drug	Liquid vehicle	Carrier & coating material	Additional retardant agent	Ref.
Nifedipine	PEG 400	MCC & Colloidal Silica	HPMC(15 mPa·s)	43,44
Propranolol HCl	Polysorbate 80	Eudragit [®] RS or RL & C.Silica	HPMC*(4000 mPa·s)	25,26
Theophylline	Polysorbate 80	Eudragit [®] RS/ RL & C.Silica	HPMC*(4000 mPa·s)	27
Tramadol HCl	PG	MCC & Colloidal Silica	HPMC(4000 mPa·s)	45

* only some batches

Mechanisms of sustained drug release from liquisolid systems

With X-ray crystallography and DSC measurements it could be confirmed, that sustained drug release from these liquisolid compacts is not caused by a change in crystallinity or by complex formation of the drug during the manufacturing process of the sustained release liquisolid formulations^{25,26}. Liquisolid formulations with sustained drug release may contain hydrophobic carriers such as Eudragit[®] RL or RS instead of hydrophilic carriers, the latter being used for fast release liquisolid formulations^{26,27}. Hydrophobic carriers may lead to poor wetting properties of the compacts resulting in slow disintegration and thus, prolonged drug release.

Furthermore, the liquid vehicle may affect drug release. A comparison of drug release from conventional matrix tablets (direct compression) and liquisolid compacts, both containing Eudragit[®] RS or RL as matrix forming material, showed that the retardation effect of liquisolid compacts with polysorbate 80 as liquid vehicle is much more pronounced than that of conventional matrix tablets^{26,27}. This confirms the important role of the liquid vehicle in sustaining drug release from liquisolid matrix systems. It was shown that the liquid vehicle polysorbate 80 may act as a plasticizer and thus, decreases the glass transition temperature of the polymer Eudragit[®] RS.

Accordingly, with liquisolid compacts the coalescence of the polymer particles occurs at lower temperatures than with conventional matrix tablets. This more pronounced coalescence of polymer particles of liquisolid compacts leads to a matrix with lower porosity and higher tortuosity. Consequently, the drug is surrounded by a fine network of the hydrophobic polymer resulting in a sustained release of the drug. Moreover, it has been shown that the addition of hydroxypropyl methylcellulose (HPMC) increases the retardation effect of liquisolid compacts^{28,29}. HPMC is commonly used for the preparation of hydrophilic matrix systems. Depending on its molecular weight the polymer either swells in contact with water or forms a hydrated matrix layer through which the drug has to diffuse or erodes resulting in a zero order drug release

kinetic. In the case of HPMC it was also found that a stronger retardation effect was observed with liquisolid compacts as compared to directly compressed tablets (conventional formulation).

Optimization of liquisolid formulations with sustained drug release

In contrast to liquisolid compacts with immediate drug release liquisolid sustained release formulations may be optimized by selection of low R -values, suspensions with a high percentage of undissolved drug and by avoidance of disintegrants.

If the R -value is low, which means that the applied amount of silica is high, the liquisolid compacts are overloaded with liquid formulation due to a high liquid load factor. In such cases oversaturation might occur resulting in local precipitation of the drug and thus, decreased release rates. Moreover, the higher the percentages of undissolved drug in the liquid formulation the slower the release rate. This is especially important for poorly soluble drugs, as the dissolution rate of these drugs is low. In addition, as drug release from a tablet is dependent on the disintegration of the tablet and the subsequent dissolution of the drug, the absence of disintegrants, which prevents disintegration, will slow down drug release. Furthermore, it was shown with liquisolid compacts that the higher the HPMC concentration and the higher the amount of Eudragit[®] RS / RL, respectively, the more pronounced the decrease in drug release³⁰

Technologies for the retardation of drug release

There are several retardation principles for oral sustained release dosage forms including inert insoluble matrices, hydrophilic colloid matrices, membrane-controlled drug delivery systems, ion exchange resins, and osmotic systems^{31,32}.

In a matrix tablet the drug is dispersed in either an insoluble or a soluble carrier which forms the matrix^{33,34}. Carrier materials for insoluble matrices are water insoluble polymers, fats, and waxes. From insoluble matrices the drug is released as soon as a solvent enters the matrix and dissolves the particles. The addition of channeling agents increases drug release by leaving tortuous capillaries after leaching^{35,36}.

The empty matrix (ghost matrix) is excreted with the feces. Carrier materials for hydrophilic colloid matrices are water swellable or erodible polymers such as hydroxypropyl methylcellulose of different molecular weight³⁷. In contact with water the polymer either swells and forms a hydrated matrix layer through which the drug has to diffuse or erodes resulting in a zero order drug release kinetic³⁸. Matrix formulations are widely used due to their simple manufacturing process, a high maximum possible drug load, low production costs, and low risk of dose dumping.

Oral dosage forms coated with water insoluble film forming polymers show membrane-controlled drug diffusion. Hydration of the coating film increases the permeability of the film and facilitates diffusion of the drug. Typical polymers used include ethylcellulose and polymethacrylates, e.g. Eudragit[®] RS, RL and NE grades³⁹. To modify the release characteristics of the film water soluble substances may be added as pore forming agents increasing the release rate⁴⁰. However, manufacture of coated dosage forms requires special equipment, the process is time-consuming, and dose dumping may occur with single-unit systems as a result of film failure or damage.

Cationic or anionic drugs may be bound to an ion exchange resin due to its ionic structure⁴¹. Drug release from these complexes depends on the pH and electrolyte concentration in the gastrointestinal tract. Release is faster in the acidic environment of the stomach than in the luminal contents of the small intestine⁴². Of course, this mechanism of sustained drug release can only be adopted to ionic drugs.

CONCLUSION:

The liquisolid compact technique can be effectively used to prepare sustained release dosage form of water-soluble or hydrophilic drugs. Modification of formulation by use of certain agents cause sustained release of drugs from the liquisolid compacts. This technique is a promising alternative for formulation of solid water-soluble and hydrophilic drugs. The retarded rate of drug dissolution from liquisolid tablets is probably due to use of insoluble polymers, fats and waxes as carrier materials. The advantages of sustained-release formulation are that they can often be taken less frequently than instant formulations of the same drug, and that they keep steadier levels of the drug in the bloodstream.

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