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A REVIEW ON LIQUISOLID FORMULATION.

Corresponding author Name: Shalini Shankar Rathod

Departmet of pharmaceutics

Konkan Gyanpeeth Rahul Dharkar College of Pharmacy and Research Institute,Karjat,Maharashtra

Author name: Dr. Bharat Tekade

Department of pharmaceutics, H K College of Pharmacy, Oshiwara, Jogeshwari, Mumbai, India

Author name: Swapnil Phalak

Department of pharmaceutics, Konkan Gyanpeeth Rahul Dharkar College of Pharmacy and Research Institute,Karjat,Maharashtra

ABSTRACT

Most of the newly developed drug candidates are lipophilic and poorly water-soluble. Enhancing the dissolution and bioavailability of these drugs is a major challenge for the pharmaceutical industry. Most of the newly invented molecules, around 90 % and 40 % of approved active pharmaceutical ingredients, showed poor solubility in water and ultimately low bioavailability The objective of this article is to present an overview of liquisolid technique and summarize the progress of its applications in pharamaceutics. These systems involve the conversion of a liquid drug or drug solution into a dry, free-flowing, and compressible powder by blending with selected carrier and coating materials.The excipient with very high surface area which usually covers the carrier surfaces containing liquid to improve Flowability of liquisolid powders is known as coating materials. The increased surface area, wettability, and improved dissolution profiles significantly enhance bioavailability. The in-vitro drug dissolution rates of Such preparations were compared to those of conventionally prepared directly compressed tablets using a USP-II apparatus. DSC and XRPD technique. Were used to ascertain any interaction and crystallinity changes of drug in LS compacts due to interaction between drug and other excipients.

Keywords: Liquisolid compacts, Rosuvastatin calcium, Solubility, Dissolution rate, Carrier, Coating material.

INTRODUCTION

The concept of liquisolid systems, developed by Spireas [1], stems from the need to overcome poor aqueous solubility, which limits drug absorption and bioavailability. By converting liquid drugs into free-flowing powders, this method enhances wetting properties and extends the surface area available for dissolution. The term ‘liquisolid systems’ (LS) is a powdered form of liquid drug formulated by converting liquid lipophilic Drug or drug suspension or solution of water-insoluble Solid drug in suitable non-volatile solvent systems, into Dry looking, nonadherent, free-flowing and readily Compressible powdered mixtures by blending with Selected carrier and coating materials. Various grades of Cellulose, starch, lactose, etc. are used as the carriers, Whereas very fine silica powder is used as the coating (or covering) material. The good flow and compression. Properties of LS may be attributed due to large surface Area of silica and fine particle size

of avicel. Hence LS Compacts containing water-insoluble drugs expected to display enhanced dissolution characteristics and Consequently improved oral bioavailability.[10]

Classification of Liquisolid Systems

A)Liquisolid systems can be categorized based on their physical nature and intended use:

- Powdered Drug Solutions: Solid formulations containing drug dissolved in a non-volatile solvent [3]
- Powdered Drug Suspensions: Suspensions of drug particles in a vehicle, suitable for drugs with limited solubility [1, 3].
- Powdered Liquid Drugs: Involve drugs that are inherently liquid at room temperature [1, 3].

B)Based on Release Profile:

- Immediate-Release Systems: Designed for rapid drug release and absorption [4, 5].
- Sustained-Release Systems: Utilize polymers to provide a prolonged effect [14].
- Orodispersible/Chewable Forms: Especially beneficial for pediatric or geriatric populations.

Advantages

- Enhanced Dissolution Rate: Due to increased surface area and solubilization [1].
- Improved Oral Bioavailability: Especially for BCS Class II drugs like rosuvastatin [5, 10].
- Versatility: Applicable to multiple dosage forms and drug types [4, 8].
- Simplicity: Uses conventional manufacturing equipment [7].
- Cost-Effectiveness: Requires fewer modifications than nanonization or solid dispersions [3, 4].
- Better Patient Compliance: Especially with orodispersible tablets [13].

Disadvantages

- Formulation Complexity: Requires precise calculation of liquid load factor (Lf) and carrier-coating ratios ® [1, 3].
- Solvent Compatibility Issues: Potential for drug-excipient incompatibility [4].
- High Excipients Requirement: Bulkier tablets due to high levels of carrier/coating materials [8].
- Stability Concerns: Especially with volatile components or long-term storage [14].
- Flowability Challenges: Particularly at high drug loading levels [3].

Components of Liquisolid Formulation

- Non-Volatile Liquid Vehicle: PEG 400, propylene glycol, glycerin, Tween 80 – aids in drug solubilization. The solubility of drug in nonvolatile solvent has an important effect on tablet weight and dissolution profile. Liquid vehicle with high ability to solubilize drug will be selected in the case of dissolution enhancement.In addition to the drug solubility in liquid vehicle,Several other physicochemical parameters such as the polarIty, lipophilicity, viscosity, and chemical structure also have Significant effects on drug release profiles [1, 12]

- Carrier Materials: Microcrystalline cellulose (Avicel PH 101), lactose monohydrate helps in liquid adsorption [5].Carriers should possess porous surface and high liquid absorption [1]It was observed that liquisolid formulations prepared from MCC PH 101 exhibited better flowability, compressibility, and dissolution profiles compared with those prepared from MCC PH102 and 200.In addition, aging has no significant effect on the hardness and Dissolution profiles of the prepared liquisolid tablets. Overall,MCC PH 101 is a suitable carrier to prepare liquisolid systems in terms of flowability, compressibility, and dissolution profile.[12]

- Coating Materials: Colloidal silicon dioxide (Aerosil 200), Neusilin, calcium silicate to enhances flow properties. Coating materials refer to very fine and highly adsorptive materials, such as Aerosil® 200, Neusilin®, and calcium silicate or Magnesium aluminometasilicates in a powder form.These materials play a contributory role in covering the wet carrier particles to form an apparently dry, non-adherent, and free flowing powder[6]
- Additional Excipients: Disintegrants (sodium starch glycolate), lubricants (magnesium stearate), glidants [5, 8].The disintegration of solid dosage forms obviously influences drug release.Therefore, disintegrants are usually included

in iquisolid tablets to allow a fast disintegration. Some commonly used disintegrants in liquisolid system include sodium Starch glycolate, croscarmellose sodium, and low substituted Hydroxypropyl cellulose.[6]

Theoretical Aspects

Determination of load factor and excipient ratio:

- Flowable Liquid Retention Potential (Φ-value): The flowable liquid retention potential value of carrier and coating material were reported earlier by spiread et al. It Indicates how much liquid a powder can hold while maintaining flowability [1].

  Lf= Φ+1/R
- Liquid Load Factor (Lf): Ratio of liquid drug to carrier material. Defined as: Lf = Φ_C + Φ_C(1/R) [1,9].

- Carrier to Coating Ratio ®: Usually optimized based on empirical studies [1,9]. These parameters determine the optimal formulation and are key in achieving a balance between compressibility and flow [3].

Preparations of Liquisolid Tablets

- Calculated amount of Drug is dissolved in a suitable non-volatile solvent(PEG 400) sonicated for completely solubilizing or evenly blending.
- The liquid medications were then incorporated into the calculated quantities of the carrier material (Q) and mixed thoroughly.
- The calculated amount of coating material is then added to convert the wet mass into dry, free-flowing powder.
- Lubricants and disintegrants are incorporated .
- The final blend is compressed using standard tablet machines.[12]

Preformulation Study

Preformulation studies assess physicochemical compatibility between the drug and excipients. FTIR, DSC, and XRD analyses confirm stability and predict potential interactions [4]. For rosuvastatin calcium, compatibility was evaluated using thermal and spectroscopic methods, affirming its stability with PEG 400 and Avicel . These studies determine parameters like drug solubility, hygroscopicity, and crystallinity[14].

X-ray diffraction (XRD):

It has been shown that polymorphic changes of the drug are important factors, which may affect the drug dissolution rate and bioavailability. It is therefore important to study the Polymorphic changes of the drug.the liquisolid system prepared were determined using X-ray diffractometer with a copper Target, at a voltage of 40 kV and current of 20MA. The rate of the scanning was 0.30°C /min.[11]

Differential scanning colorimetry:

Thermograms of the samples were recorded on a DSC-60 (Shimadzu,Japan). Samples (3–5 mg weighed to a precision of 0.005 mg) Were placed in aluminum pans and the lids were crimped using a Shimadzu crimper. Thermal behavior of the samples was Investigated under at scanning rate of 20 ◦C/min, covering a temperature range of 30–200 ◦C. The instrument was calibrated with an indium standard.

Pre-compression Evaluation

This stage evaluates powder properties before compression:

- The flow characteristics of the liquisolid blends were evaluated by determining the micromeritic properties such as Angle of repose, Carr's index and Hausner's ratio by the reported methods.[10]

- **Angle of repose**:This is the maximum angle possible between the surface of a pile of powder and the horizontal plane.10 gm of powder was allowed to flow by funnel from 4 cm of height from the base The height of pile and diameter of base was measured and calculate the angle of repose by following formula
  tan θ = h/r θ, tan-1 h/r
  Where, = angle of repose,H = Height of the heap,R = Radius of the heap[13].
- **Carr's Index** [Compressibility Index]It is one of the most important parameter to characteristic The nature of powders and granules. It can be calculated From the following equation
  Carr's index = Tapped density – Bulk density / Tapped Density X 100 [13].
- Hausner's Ratio :Hausner's ratio is an important character to determine the Flow property of powder and granules. This can be Calculated by the following [13]
  formula-Hausner's ratio = Tapped density / Bulk density

- Powder Uniformity: Ensures blend homogeneity .
- Moisture Content: Controlled to prevent degradation [10]. Research by Javadzadeh et al. [2], Vraníková [4], and others confirmed that liquisolid blends show acceptable flow characteristics when proper excipient ratios are used.

Post-compression Evaluation

- Hardness: Hardness was measured using Monsanto tablet hardness tester. It is expressed in kg/cm2.[10]
- Thickness: Thickness of tablet (mm) was measured by using vernier calipers[10]
- Dissolution Testing:using a dissolution test apparatus USP-II (ElectroLab). The dissolution study was carried out in 900ml of 0.1 N HCl as dissolution medium at 37°C ± 2°C at 50 rpm. The samples (5 ml) were withdrawn at 2 min intervals up to 30 min and 15 in interval from 30 to 60 min. The dissolution medium was then replaced by 5 ml of fresh dissolution fluid to Maintain sink condition. The withdrawn samples were Filtered and analyzed spectrophotometrically at 245 nm.
- Content Uniformity: Ensures dosage precision.[10]
- Studies confirmed mechanical integrity and reproducible drug release profiles [5].

Evaluation of Liquisolid Systems

- In Vitro Drug Release: Vitro Dissolution Studies. In vitro release of Rosuvastatin was determined using a standard paddle dissolution Apparatus (Sotax AT 7 Smart, Sotax, Switzerland) with a Paddle speed of 50 rpm in 500 mL of artificial gastric fluid (pH 1.2) at 37.0 ± 0.5∘C. Throughout the experiment, the withdrawn samples were analysed spectrophotometrically online at 242 nm at time intervals 5, 10, 15, 20, 25, and 30 min.Six randomly selected tablets of each formulation were tested;Results are presented as mean values and standard deviations.
- Stability Studies: Accelerated stability tests under ICH guidelines [10].
- Wettability and Powder Characterization: Contact angle, DSC, XRD, and FTIR [1,3].
- SEM Analysis: Surface morphology of prepared systems [8]. These tests establish system performance, safety, and robustness.

Applications

- Bioavailability Enhancement: For drugs with low water solubility [5, 10,].

- Modified Release Formulations: Sustained release formulations are designed to release the drug slowly at a predetermined rate for a certain period of time with High efficacy, high patient compliance, and minimum side effects. One of the main advantages of applying liquisolid technique in prolonging drug release is the possibility to attain a liquisolid system with zero order release kinetics.
- chewable and Orodispersible Tablets: For pediatric and geriatric patients.
- Delivery of Lipophilic Drugs: e.g., hydrocortisone and glibenclamide, Rosuvastatin calcium [9].
- Combination Therapies: Using multiple APIs Liquisolid technique as a tool to enhance drug dissolution The results suggested that a reduction of the particle size and crystallinity and an enhancement of the wettability were the main mechanisms for the enhanced disolution rate.

- Liquisolid technique as a tool to minimize the influence of pH variation on drug release. The solubility of weak acids and bases is dependent on the ionzation constant (pKa) of the compound and pH of the local environment. The results indicated that the dissolution rates of Liquisolid tablets were significantly higher and less affected by pH variation in comparison with the directly compressed tablets and marketed tablets (Clarityn®). The results suggested that Liquisolid technique is a promising tool to minimize the influence of pH variation on the dissolution rate of poorly water soluble drugs.

Conclusion

Liquisolid compact systems provide a simple yet effective strategy to improve the solubility and bioavailability of poorly water-soluble drugs. By integrating non-volatile solvents, carriers, and coating agents, these formulations ensure better drug release and therapeutic efficiency. Advances in preformulation, evaluation techniques, and diverse applications make liquisolid systems a promising tool in modern pharmaceutics. Future developments can focus on scaling up, regulatory standardization, and exploring newer excipients and APIs.

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