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ORODISPERSIBLE LIQUISOLID COMPACTS

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Abstract

Orodispersible liquisolid compacts (ODLSCs) are an advanced drug delivery system developed by combining the principles of liquisolid technology and orodispersible tablets (ODTs). This innovative approach enhances the dissolution rate and bioavailability of poorly water-soluble drugs while providing rapid disintegration in the oral cavity without the need for water. In a liquisolid system, the drug is dispersed in a non-volatile liquid vehicle and converted into a dry, free-flowing, and compressible powder using suitable carrier and coating materials. The incorporation of superdisintegrants enables the formulation to disintegrate within seconds in the mouth, resulting in a faster onset of action. ODLSCs offer significant advantages for pediatric, geriatric, bedridden, and dysphagic patients who experience difficulty swallowing conventional tablets. Additionally, this system improves patient compliance and may partially bypass first-pass metabolism through pregastric absorption. Despite challenges such as limited drug-loading capacity and sensitivity to moisture, orodispersible liquisolid compacts represent a promising platform for enhancing the therapeutic efficacy of poorly soluble drugs. Their ease of administration, cost-effectiveness, and potential for industrial scalability make them an emerging trend in modern pharmaceutics.

Introduction

Orodispersible liquid solid compacts are a novel drug delivery system that combines the benefits of the liqui solid technique with orodispersible tablets to create a fast-dissolving tablet from liquid medications. This approach addresses the slow dissolution rate of poorly water-soluble drugs by converting liquid drugs into a powder form that disintegrates rapidly in the mouth without water, improving patient compliance and allowing for faster action.

The liquid solid technique is a method used in pharmaceutical development to enhance the solubility, dissolution rate, and bioavailability of poorly water-soluble drugs. Also known as "powdered solution technology," it converts liquid medications, including drug solutions or suspensions in a non-volatile solvent, into a solid, free-flowing, and compressible powder [1].

History

complementary concepts: the liqui solid technique for converting liquids into solid powders, and the orodispersible tablet (ODT) technology. The liquid solid concept, which began with "powdered solutions" in the early 20th century, evolved into the modern liqui solid technique in the late 20th century to enhance the dissolution of poorly soluble drugs by using a combination of carrier and coating powders to create a flowable The history of orodispersible liquid-solid compacts is rooted in the development of two separate but, compressible powder from a liquid medication. Separately, ODTs emerged as a patient-friendly dosage form, with the first commercial product launching in the early 1990s, and their development has been further spurred by pediatric drug development regulations in the 2000s. The combination of these two fields, resulting in orodispersible liqui solid compacts, aims to create a rapidly dissolving solid dosage form for drugs that are

difficult to dissolve, combining the benefits of both technologies [2].

Early roots: "Powdered solutions

- The earliest precursor was the "powdered solutions" technique, which focused on converting a drug solution into a dry-looking powder by adsorbing it onto highly porous carriers like silica.
- These early preparations were not designed to be compressed into tablets and were studied as powders, not solid compacts.

Evolution to liquid solid technology

- Later, researchers added compression enhancers like microcrystalline cellulose to the "powdered solution" systems to make them compressible.
- This led to the modern liqui solid technique, which uses a two-part excipient system: a carrier that adsorbs the liquid drug, and a coating material (typically highly porous silica) to coat the surface and absorb any excess liquid.
- This process converts liquid medications into free-flowing, compressible powders that can be compressed into tablets.
- The liqui solid technique was developed specifically to enhance the dissolution and bioavailability of poorly water-soluble drugs [3].

The rise of orodispersible tablets (ODTs)

- The development of the Zydis technology by R.P. Scherer Corporation in 1986 marked a significant step for ODTs.
- The first commercial ODT, famotidine, was launched in Sweden in 1993.
- The FDA approved its first ODT, Claritin RediTabs, in 1996.
- The development of ODTs was further accelerated by the implementation of pediatric drug development regulations in the 2000s, which emphasized patient-friendly dosage forms.

The convergence: Orodispersible liqui solid compacts

- Orodispersible liqui solid compacts emerged as a combination of liqui solid and ODT technologies.
- This new approach leverages the liqui solid technique to create a solid dosage form for poorly soluble drugs and incorporates the characteristics of ODTs, such as rapid disintegration in the mouth, to address issues with swallowing.
- The goal is to create a product that is patient-friendly (especially for children and the elderly) and offers the benefits of both technologies: improved drug dissolution and an orodispersible form [4].

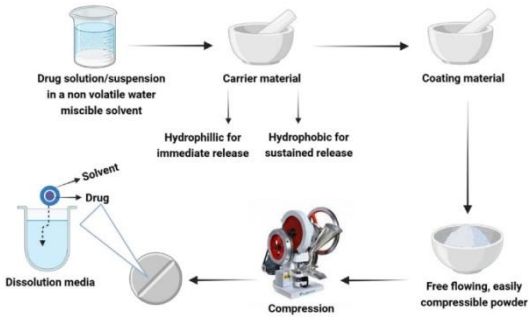

Figure 01: Liqui solid technology overview

Liqui solid system

According to Spireas, the liqui solid technology enables liquids to be readily transformed into free-flowing, readily compressible, and seemingly dry powders through an ordinary physical blending process using specific excipients known as the carrier and coating material. The liqui solid technique is a unique way to administer drugs orally. This method works well for immediate or sustained release formulations, highly permeable drugs (BCS Class II drugs), and poorly soluble or water-insoluble drugs without requiring any additional modifications, a liquid lipophilic drugs can be converted into a liqui solid system. On the other hand, to formulate a drug solution or drug suspension with the appropriate concentration, a solid water-insoluble drug needs to be dissolved or suspended in a suitable nonvolatile solvent system. The ideal liquid vehicles are inert, preferably water-miscible, organic solvent systems with a high boiling point and a relatively low viscosity, such as glycerin, propylene glycol, liquid polyethylene glycols, polysorbates, fixed oils, or propylene glycol. This is an unfamiliar "Powder Solution Technology" which utilizes coating materials, liquid drugs, drug suspensions incorporated with appropriate carriers, and absorption and adsorption efficiency to formulate a powder that is compressible, dry-looking, free-flowing, and non-adherent.Liqui solid formulations yield rapid release rates, which can be effectively applied to water-insoluble solid drugs, liquid lipophilic drugs, or water-insoluble solid drugs dissolved in nonvolatile solvents. The resulting liquid drug can be easily compressed, flow freely, and appear dry and non-adherent. Given that the medication is in liquid form, it is either molecularly dispersed or solubilized. Liqui solid tablets of water-insoluble medicines exhibit an enhanced dissolution profile and greater bioavailability as a result of increased wetting and increased surface area for dissolution [5].

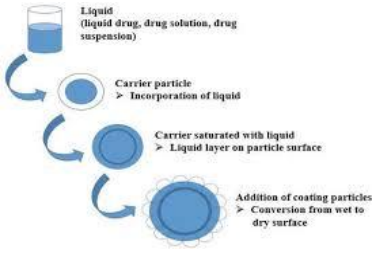

Figure 02: Liqui solid system

Classification of liqui solid systems

• Pharmaceutical powder solutions
• Pharmaceutical powder suspensions
• Pharmaceutical powder liquids

Powdered drug solutions and suspensions are created by converting liquid medications (such as clofibrate and liquid vitamins) or solid medications (such as gemfibrozil suspension in polysorbate 80) into liquid-solid systems. Prednisolone solution in propylene glycol and gemfibrozil suspension in polysorbate 80 are examples of the former [6].

According to the formulation technique used

• Liqui solid Microsystems
• Liqui solid Compacts

Components of Liqui solid Compact Formulation

- Nonvolatile solvent
- Disintegrant
- Drug candidate
- Carrier material
- Coating material

Non combustible Solvent

Non-volatile solvents must be inert, have a high boiling point, preferably dissolve in water, be non-extremely viscous organic solvent systems, and be drug-compatible. In the liqui solid formulation, the non-volatile solvent acts as a binding agent. Some examples include glycerine, polysorbate 80, propylene glycol, and polyethylene glycol 200 and 400 [7].

Disintegrant

Superdisintigrants accelerate drug release, increase water solubility, and improve wettability of liquid-solid granules. The most commonly used superdisintigrants are crosspovidone and sodium starch glycolate.

Disintegrants are pharmaceutical excipients that cause tablets and other solid oral dosage forms to break apart into smaller fragments when they come into contact with water or another aqueous environment. This process, called disintegration, is crucial because it increases the surface area of the active drug, which allows it to dissolve more rapidly and be absorbed into the body more effectively.

Drug candidate

The liquidsolid approach has been successfully used to treat low-dose BCS class II and IV medicines that are poorly water soluble and dissolve slowly. Chlorpheniramine, water-soluble vitamins, fish oil, and hydrocortisone are just a few examples, as are carbamazepine, famotidine, piroxicam, indomethacin, hydrocortisone, naproxen, and prednisolone

A drug candidate for an orodispersible formulation, whether a tablet (ODT) or a film (ODF), is selected based on specific physicochemical and pharmacokinetic properties that ensure rapid disintegration, proper absorption, and patient compliance. This innovative dosage form is especially beneficial for pediatric, geriatric, and mentally impaired patients who have difficulty swallowing conventional

Carrier material

The carrier material must be porous and have a high absorption capacity to aid in liquid absorption. Because the carrier and coating materials can only hold a certain amount of liquid while maintaining proper flow and compression properties, increasing the moisture content of the carrier reduces the flowability of the powder [8].

Characteristics of carrier materials

- **Porous nature:** The carrier must have a porous structure to hold the liquid medication within its pores.
- **High absorption capacity:** It needs to absorb a significant amount of liquid to prevent liquid squeezing out during compression.
- **Flowability and compressibility:** After absorbing the liquid, the mixture must still be a powder that can be easily compressed into tablets.
- **Molecular dispersion:** The carrier helps to keep the drug in a molecular state of subdivision, which can improve its dissolution rate [9].

Materials for Coatings

The coating substance should contain tiny, extremely adsorptive particles that help to cover the wet carrier particles and create the appearance of dry powder by adsorbing any excess liquid. Coating material is required to keep the surface covered and the powder flowability intact.

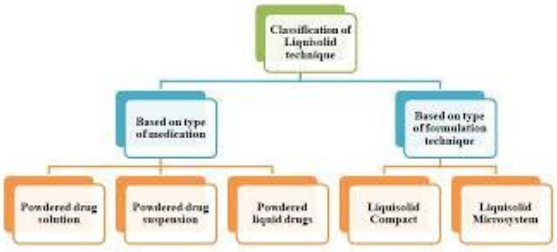

Figure 03: Classification of liqui solid system

Application of mathematical model for designing efavirenz liqui solid formulations

Spireas and Bolton have introduced a mathematical model for producing liqui solid compacts with acceptable flowability and compactibility. This model is based on the hypothesis that powder material can only accommodate a specific amount of liquid medicament (co-solvent + drug) in the inner matrix while preserving acceptable flowability and compatibility. Once the proportion of liquid exceeds the certain limit, the flow property and compactibility of

the powder material starts to decline. This maximum amount of liquid which a powder material can retain while maintaining acceptable flowability and compatibility is known as flowable liquid-retention potential (Φ – number) and compressible liquid-retention potential (Ψ – number) respectively. The acceptable compactibility means the ability of powder material to produce cylindrical compacts of adequate crushing strengths (approximate 5–6 kg/cm2) and acceptable friability without presenting any "liquid-squeezing - out" phenomena during compression. Once the inside matrix is saturated with liquid medication, the extra liquid will start to deposit as a layer on the surface of powder material. This extra layer of liquid is adsorbed by adding another powder excipients known as "coating material" that finally leaves the total powder material free-flowing, non-adherent and compressible. "Excipient Ratio" (R) is defined as the ratio of carrier and coating material required to make powder with acceptable flowability and compressibility [10].

R=Q/q
where Q = amount of carrier material and q = amount of coating material.

Determination of flowable liquid-retention potential (Φ – value)

The liquid medicament was gradually added to the fix quantity powder material (10 gm) and this resulted admixture was placed at one end of the polished metal plate. The metal plate was gradually uplifted from one side while keeping the other side on the ground. The angle formed between plate and ground was considered as the angle of slide (Elkordy et al., 2013). The angle of slide value of around 33 represents the optimal flowable property of powder excipient with respect to the particular liquid vehicle used.

Determination of compressible liquid-retention potential (Ψ – value)

The liquid medicament was added gradually to 1 gm powder material for making uniform admixture. The admixture was compressed with specific hardness in the rotary tablet machine to make a tablet. In this investigation, the crushing strength value between 5 and 7 Kgf was considered as an acceptable one. During compression, it was also observed that there was no leakage of liquid medicament from the powder admixture

Formulation design and preparation of liqui solid system

Liquid vehicle

Liquid vehicle used in liqui solid systems should be orally safe, inert, not highly viscous, and preferably water-miscible nonvolatile organic solvents, such as propylene glycol, glycerin, PEG 200 and 400, polysorbate 20 and 80, etc . The solubility of drug in nonvolatile solvent has an important effect on tablet weight and dissolution profile. Higher drug solubility in the solvent leads to lower quantities of carrier and coating material, and thus lower tablet weight can be achieved. On the other hand, the higher the drug solubility in the solvent, the greater FM value (the fraction of molecularly dispersed drug) will be, which confers an enhancement of the dissolution rate . The selection of liquid vehicle mainly depends on the aim of study. Namely, a liquid vehicle with high ability to solubilize drug will be selected in the case of dissolution enhancement. While if the aim is to prolong drug release, liquid vehicle with the lowest capacity for solubilizing drug may be chosen . 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

Moreover, it is claimed that liquid vehicle can act as a binder in a low concentration, which contributes to the compactness of liqui solid tablets. The reason may lie on the presence of hydroxyl groups in the molecular structure of liquid vehicle which leads to hydrogen bonding between solvents and other excipients in liqui solid formulations [11].

Carriers

Carriers should possess porous surface and high liquid absorption capacity. As carriers allow an incorporation of large amount of liquid medication into the liqui solid structure, the properties of carriers, such as (SSA) and liquid absorption capacity, are of great importance in designing the formulation of liqui solid system. The liquid adsorption capacity mainly depends on the SSA value. Additionally, it is also influenced by the type of coating material and the physicochemical properties of the liquid vehicle, such as polarity, viscosity, and chemical structure

Function of the carrier

- **Absorption:** The carrier absorbs the liquid medicament (drug dissolved in a non-volatile solvent).
- **Disintegration:** It retains the drug's dissolution while maintaining flowability and compressibility for compacting.
- **Drug delivery:** By providing a large surface area, the carrier can enhance drug dissolution, especially for poorly soluble drugs.
- Characteristics of a suitable carrier
- **Spongy nature:** It should have a porous internal structure to hold a significant amount of liquid.
- **High surface area:** A larger surface area leads to a higher capacity for liquid absorption and better drug dispersion.
- **Good flow and compressibility:** Theresulting powder must be able to flow freely and be compressible into a stable tablet [12].

- **Compatibility:** It should be physically and chemically compatible with the drug and other excipients in the formulation.

Coating materials

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 by adsorbing any excess liquid . It was proved that the replacement of Aerosil® 200 by Neusilin® US2 as a coating material in liqui solid system considerably increased the liquid adsorption capacity and reduced tablet weight . Since Neusilin® can be either a carrier or a coating material, its usage will greatly simplify the preparation procedure of liqui solid formulations.

Types of coating materials

- **Colloidal Silica:** Grades like Aerosil® 200 are frequently used. They have a high adsorptive capacity, meaning they can efficiently absorb excess liquid, creating a dry-looking powder.
- **Neusilin®:** This can be used as both a carrier and a coating material, simplifying the formulation process. It has a high liquid adsorption capacity and has been shown to reduce tablet weight compared to other coating materials.
- **Syloid 244FP:** Another grade of silica that is effective as a coating material for liquisolid compacts.
- **Magnesium Aluminometasilicates:** These are also used as coating materials in liquisolid systems.

Function of the coating material

- **Adsorption of excess liquid:** The primary function is to adsorb any liquid that the carrier material cannot absorb, preventing the powder from becoming sticky.
- **Improved flowability:** By creating an apparently dry powder, the coating material improves the flow properties of the mixture, which is essential for consistent tablet compression.
- **Enhanced tabletability:** The fine, highly adsorptive particles cover the wet carrier particles, contributing to the overall compressibility of the powder mix.
- **Solubility enhancement:** The porous nature of many coating materials, like mesoporous silica, can facilitate drug dissolution by allowing the dissolution medium to enter and carry the drug out.

Additives

The disintegration of solid dosage forms obviously influences drug release. Therefore, disintegrants are usually included in liqui solid tablets to allow a fast disintegration. Some commonly used disintegrants in liqui solid system include sodium starch glycolate, croscarmellose sodium, and low substituted hydroxypropyl cellulose . Polyvinylpyrrolidone (PVP) is another promising additive, which has the potential to incorporate high amount of drug into liqui solid systems, and thus reduce the tablet weights. Besides, due to the crystal growth inhibition effect of PVP, liqui solid tablets containing PVP show an improvement of dissolution rate . There is another additive in liqui solid systems – HPMC, which usually acts as a release retarding agent to extend drug release

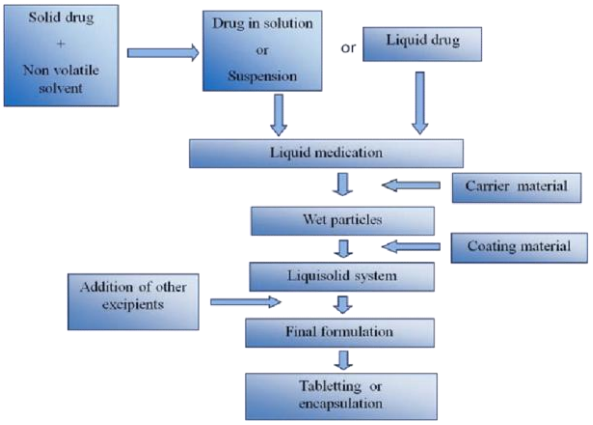

Figure 04: Formulation of liqui solid tablets

Advantages of liqui solid system

1. Enhances solubility of poorly water-soluble drugs.
2. Increases dissolution rate and drug release.
3. Improves oral bioavailability, especially for BCS Class II drugs.
4. Simple and easy manufacturing process.
5. Cost-effective technique-no complex equipment needed.
6. Provides good flow properties of the final powder.
7. Offers excellent compressibility-suitable for tablet production.
8. Prevents drug recrystallization by keeping it in a solubilized state.
9. Can be used for both immediate and sustained-release formulations.
10. improves wetting properties of hydrophobic drugs.
11. Enhances content uniformity.
12. Helps mask the bitter taste of drugs.
13. Suitable for liquid, oily, or low-dose drugs.
14. Can improve patient compliance due to better performance [13].

Disadvantages of liqui solid system

1. Not suitable for drugs requiring high dose (large tablet size results).
2. Limited drug loading capacity due to saturation of carrier materials.
3. Moisture sensitivity may affect flow and stability.
4. Drug-excipient interaction may occur because drug remains in a liquid state.
5. Requires large amounts of carrier and coating materials.

6. Poor compatibility with hygroscopic or unstable liquids.
7. Flowability problems may still occur if not optimized properly.
8. Difficulty in achieving sustained release for some drugs.
9. May show stability issues during long-term storage.
10. Scale-up challenges for industrial manufacturing if formulation not optimized.
11. Risk of drug precipitation if improper liquid vehicle is selected.
12. Limited to lipophilic drugs only (mainly BCS Class II drugs) [14].

Applications of liqui solid system

1. Psychiatric patients: Non-compliant, uncooperative, or mentally challenged patients are a key target group for ODTs, which can reduce the physical and psychological stress of taking medication.
2. Patients with motion sickness: When water is unavailable, such as during travel, orodispersible tablets are a convenient option for rapidly treating conditions like nausea and vomiting.
3. Antidepressants and anxiolytics: These are available in ODT form for ease of administration and rapid action in conditions where a quick response is required.
4. There is no risk of suffocation due to physical obstruction when swallowed, thus offers improved safety.
5. No need of water
6. Good chemical stability as conventional oral solid dosage form.
7. Decreased first pass metabolism
8. More rapid drug absorption from the pre-gastric area, i.e., mouth, pharynx, esophagus which may produce rapid onset of action.
9. Central Nervous system (CNS) Disorders: Rapid onset of action for drugs treating CNS such as migraines and epilepsy.
10. Emergency use: For certain conditions requiring a rapid onset of action, such as an asthma attack, ODTs can be designed for faster absorption [15].

Conclusion

Orodispersible liqui solid compacts represent an innovative drug delivery approach combining liqui solid technology and orodispersible systems to improve the solubility, dissolution rate, and bioavailability of poorly water-soluble drugs. By transforming liquid medications into compressible, flowable powders, these compacts enhance drug dissolution through increased surface area, improved wettability, and sometimes pre-gastric absorption via the oral mucosa, leading to rapid onset of action. They are particularly beneficial for pediatric and geriatric patients due to ease of administration without water.The technique uses carriers and coating materials to convert liquid drug formulations into solid powders that disintegrate quickly in the mouth, enhancing patient compliance and therapeutic efficacy. Optimizing formulation parameters ensures good flow, compressibility, and stability. The orodispersible nature allows fast disintegration and absorption, potentially reducing the required dose and enhancing bioavailability even further.In summary, orodispersible liqui solid compacts provide a promising strategy for enhancing the delivery of lipophilic, poorly soluble drugs by combining rapid dissolution, improved bioavailability, and patient-friendly dosage forms. Their development is supported by advanced formulation techniques and characterization methods to ensure efficacy, stability, and patient compliance.

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Not Declared

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contribution

All contribute equally

Financial Support

None

Ethical Considerations and Informed Consent

Not Applicable

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