ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 13, Issue, 12 (A), pp. 2735-2742, December, 2022

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Research Article

REVIEW OF LIQUISOLID TECHNIQUE AND LIQUISOLID FORMULATION IN PHARMACEUTICS

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DOI: http://dx.doi.org/10.24327/ijrsr.2022.1312.0562

ARTICLE INFO

Article History:

Received 10th November, 2022
Received in revised form 25th November, 2022
Accepted 15th December, 2022
Published online 28th December, 2022

Keywords:

Liquisolid technique, bioavailability, dissolution, lipophilic.

ABSTRACT

The liquidsolid technique is a novel and advantageous method for modifying the dissolution rate of drugs that are insoluble in water. Due to insufficient dissolution rate of the drug, which is a controlling factor in oral bioavailability and one of the most exciting aspects of drug development, oral administration of poorly water soluble compounds frequently necessitates high doses in order to achieve therapeutic plasma concentrations. The vast majority of newly developed drug candidates are lipophilic and insoluble in water. Improving the dissolution and bioavailability of these drugs is a major task for the pharmaceutical industry. This article's goal is to provide an overview of the liquisolid technique and to summarise its progress in pharmaceutics applications. The primary benefits of this approach are its low cost, ease of processing, and high potential in industrial production.

INTRODUCTION

Dissolution is a critical pharmaceutical dosage form parameter that is used to ensure batch-to-batch consistency, bioequivalence assessment, and, on occasion, to correlate invitro and in-vivo drug release characteristics. Dissolution is still an important factor in drug absorption, especially for drugs that are insoluble in water. Poorly water soluble compounds' oral bioavailability is limited by insufficient dissolution rate.
Because of its convenience, high patient compliance, and low medicine production costs, the oral route of drug administration remains the preferred route of drug administration. A drug must be dissolved in gastric fluids after oral administration before it can be absorbed into the systemic circulation.

Liquisolid compacts are a novel and promising method for increasing the rate of dissolution of drugs that are insoluble in water. The term liquisolid compact refers to tablets or capsules that have been tableted or encapsulated with an appropriate adjuvant and are intended for immediate or sustained release. The "liquisolid systems" technique is used to create instant or sustained-release tablets or capsules.

Lubricants and other adjuvants required for tabletting or encapsulation are included, as are adjuvants required for rapid or sustained release action, such as disintegrants or binders. Powdered liquid medications that flow and compress well are known as liquidsolid compacts. Water-insoluble medications are transported in nonvolatile solvents as liquids.

With the addition of appropriate excipients, this liquid medication is transformed into a free-flowing powder. The carrier, coating material, disintegrants, lubricants, and glidants concentrations are optimised to produce a non-sticky, easily compressible blend. Because the drugs are completely solubilized in the appropriate solvents before being converted into free flowing mass, this technology increases the dissolution rate of poorly water soluble drugs.

Many of the aforementioned barriers can be overcome by the Liquisolid technique, a newly developed and advanced method for dissolution enhancement. This method for incorporating water-insoluble drugs into rapid release solid dosage forms was pioneered by Spireas *et al*.

The liquisolid system is designed to hold powdered liquid medications (liquid drugs, drug solutions, or suspensions) and deliver them similarly to soft gelatin capsules containing liquids. By combining liquid medications with appropriate excipients known as carriers and coating materials, the liquidsolid technique converts liquid medications into apparently dry, non-adherent, free flowing, and compressible powder mixtures. The liquid medication is first absorbed into the interior framework of the carrier. When the interior of the carrier is saturated with liquid medication, a liquid layer forms on the surfaces of the carrier particles, which is quickly absorbed by the fine coating materials.

As a result, a dry, free-flowing powder mixture that is compressible is formed. Watermiscible organic solvents with

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high boiling points, such as propylene glycol and polyethylene glycol (PEG) 400, are commonly used as liquid vehicles. Carriers are porous materials with a large specific surface area and a high liquid absorption capacity that absorb liquid medication. As carriers, various grades of cellulose, starch, and lactose can be used. As coating materials, only excipients with very fine particle size and high adsorptive properties, such as silica powder, can be used.

Despite being in a solid state within the liquisolid system, the drug is completely or partially molecularly dispersed. A liquisolid system may dissolve faster due to increased dissolution area, increased aqueous solubility, or improved wetting properties. In addition to improving dissolution, the liquisolid technique is being studied as a tool for drug release retardation, reducing the impact of pH variation on the dissolution profile, and improving drug photostability. Finally, liquidsolid systems do not have an inherent instability. The liquisolid technique and its applications in pharmaceutics are discussed in this article.

Time for Development

Historically, liquidsolid compacts are descended from 'powdered solutions,' an older technique based on converting a drug solution in a nonvolatile solvent into a dry-looking, nonadherent powder by primarily adsorbing the liquid onto silicas of large specific surfaces. However, because such preparations could not be compressed into tablets, their dissolution profiles were investigated while in powderdispersion form rather than as compressed entities.

Later studies on powdered solutions added compression enhancers to such dispersions, such as microcrystalline cellulose, to increase the compressibility of the systems. Large silicas were still used in these studies, and the products' flow and compression properties were never validated and standardised to industrial specifications and requirements.

When such modified powdered solutions were compressed into tablets, they displayed significant 'liquidsqueezingout' phenomena and undemanding tablets, making such systems unsuitable for industrial use.

Liquisolid compacts, on the other hand, are powdered forms of liquid medications that are sufficiently flowing and compressible to be used in industry. Furthermore, the term "liquid medication" includes drug suspensions, emulsions, and liquid oily drugs, as well as drug solutions such as powdered solutions. Unlike 'powdered solutions,' the term 'liquisolid compacts' is more general and can refer to four distinct formulation systems.

- Powdered medication suspensions
- Drug solutions in powder form
- Pharmaceutical emulsions in powder form
- Powdered liquid drugs

Furthermore, even in describing the original systems, the earlier term "powdered solutions" appears insufficient because it has not been proven that the drug remains in solution in the liquid vehicle after its deposition on the extremely large powder surfaces of silicas used. The new 'liquisolid' method can be used to convert liquid medications into tabletable or encapsulable powders (i.e., oily liquid drugs and solutions, suspensions, or emulsions of water-insoluble solid medications carried in nonvolatile liquid vehicles).

By combining such liquid medications with calculated amounts of a powder substrate containing certain excipients known as the carrier and coating powder materials, dry-looking, nonadherent, freeflowing, and easily compressible powders can be produced.

Theory

A powder can only hold a limited amount of liquid medication while remaining flowable and compressible. As a result, in order to achieve a liquisolid system with adequate flowable and compressible properties, a mathematical model is required. Liquids (drugs in liquid form, medication solutions, and drug suspensions) (drugs in liquid form, medication solutions, and drug suspensions) (Drug in liquid form, medication solution, drug suspension) Data-transporting particles A liquid-saturated carrier is mixed with a liquid. A liquid layer that forms on the surface of a particle. Addition of particle coating The mechanism of liquisolid system formation is the transition from a wet to a dry surface. The model is based on two basic powder properties: flowable liquid retention potential (value) and compressible liquid retention potential (val+e). The and values of a powder excipient represent the maximum amount of liquid vehicle that can be retained in the powder bulk without sacrificing flowability and compressibility.

The value is preferably determined by calculating the angle of slide of the prepared liquid-powder admixture. And the value can be measured using pactisity, which is defined as the maximum crushing power of a one-gram tablet compressed with sufficient compression force. A powder can only hold a certain amount of liquid while maintaining good flow and compression properties. Spireas devised a mathematical method for calculating the amounts of powder excipients required in the formulation of liquisolid systems. The flowable (-value) and compressible (-number) liquid retention potentials are used in this method, with constants introduced for each powder/liquid combination. The maximum amount of a given non-volatile liquid that can be retained within the bulk of a powder while maintaining acceptable flowability is defined as its -value.

The angle of repose or angle of slide can be used to determine the flowability of a powder. The -number of a powder is defined as the maximum amount of liquid it can retain within its bulk while maintaining acceptable compactability, resulting in compacts with sufficient hardness and no liquid leaking out during compression. It is the maximum crushing strength of a one-gram tablet compacted under high compression forces.
Various -values and carrier and coat material values The liquid load factor (L f) required to ensure acceptable flowability is calculated as follows:

$$L\,f = \Phi + \varphi.(1/R)$$

where and are the values of the carrier and coating material, respectively. Only by not exceeding a maximum liquid load on the carrier material, depending on the excipient ratio (R) of the powder substrate, can an acceptable flowing and compressible liquisolid system be obtained. R = Q/ q R represents the weight ratio of the carrier (Q) and coating (q) materials in the formulation. The quantities of carrier (Qo) and coating (qo) material required to convert a given amount of liquid formulation (W) into a flowable and compressible liquisolid system can be calculated after determining the optimal liquid load factor:

Q = W / L o as well as Q = Q o /R

In terms of efficacy, patient compliance, and safety, the development of sustained-release oral dose forms is advantageous for the most effective therapy. Because of its viability, drug dissolution control is one of the best and most effective approaches for developing prolonged release formulations. There are numerous approaches to creating sustained release formulations. A number of techniques have been developed to achieve this goal or purpose. It is proposed that liquisolid technology can be optimised for lowering drug dissolving rates and creating sustained release systems. In liquisolid systems, sustained release systems can be created by substituting hydrophobic carriers for hydrophilic ones, such as Eudragit RL and RS.

The longer release time is most likely due to the more effective encapsulation of drug particles by hydrophobic polymers. The presence of a nonvolatile solvent reduces the glass transition temperatures (Tg) of polymers, increasing their flexibility. As a result, the prolonged release of liquisolid tablets may be due to a decrease in the polymer's Tg. At temperatures above the glass transition, polymer particles coalesce more effectively, resulting in a fine network and matrix with lower porosity and greater tortuosity. Because the polymer network encircles and entangles the drug, leaching is limited and the drug's release from liquisolid matrices is sustained.

CLASSIFICATION OF LIQUISOLID SYSTEMS

This is determined by the liquid medication.

- 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.

According to the formulation technique used

- Liquisolid Microsystems
- Liquisolid Compacts

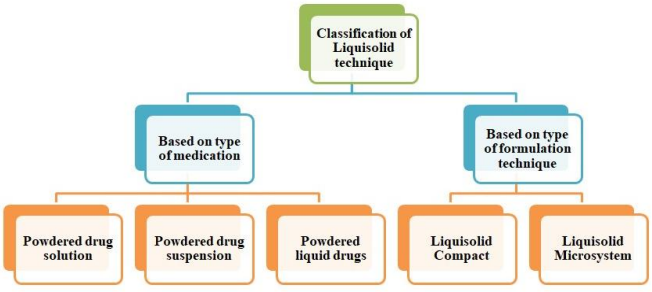


Chart Classification of Liquisolid Technique

Components of Liquisolid Compact Formulation

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

Noncombustible 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 liquisolid formulation, the non-volatile solvent acts as a binding agent. Some examples include glycerine, polysorbate 80, propylene glycol, and polyethylene glycol 200 and 400.

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.

Drug candidate

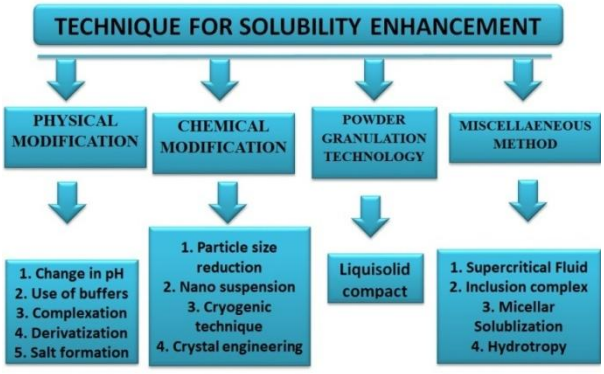
The liquidsolid approach has been successfully used to treat low-dose BCS class II and IV medicines that are poorly water soluble and dissolve slowly. Chlorpheniramine, water-soluble vitamins, fish oil, and hydrocortisone are just a few examples, as are carbamazepine, famotidine, piroxicam, indomethacin,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

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.

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.



The Advantages and Disadvantages of the liquisolid technique

Advantages

i. There are numerous advantages to using the liquisolid technique.
ii. Liquisolid systems can be used to produce pharmaceuticals that are barely water-soluble, barely water-soluble, or nearly water-insoluble, with improved dissolution and bioavailability.
iii. Sustained release formulations with zero order release patterns can be obtained by incorporating hydrophobic carriers or retarding agents into the liquisolid systems.

iv. This method could be used to create pH-independent drug release patterns in liquisolid tablets or capsules.
v. This method could be used to create drug release patterns in liquisolid tablets or capsules that are not pH dependent.
vi. The excipients used are inexpensive and widely available.
vii. The excipients used are inexpensive and widely available.

Disadvantage

The liquisolid technique has some disadvantages.

i. The technique can be used successfully for low doses of water-insoluble medications in liquisolid systems, but it cannot be used for high doses of water-insoluble medications. Due to the large volume of liquid vehicle required for these medications, significant amounts of carrier and coating material are required to produce liquisolid powder with adequate flow and compressibility. This may cause the tablet weight to exceed the limit, making swallowing difficult for patients.
ii. Numerous methods for overcoming the aforementioned difficulty have been reported. By increasing the viscosity of liquid pharmaceuticals with additives like PVP and PEG 35000, for example, the amount of carrier and coating material required can be reduced.
iii. The medication must be highly soluble in the liquid vehicle in order to prepare liquid solid systems.

Formulation and preparation of a liquisolid system

The Liquid vehicle

Nonvolatile organic solvents that are water miscible, inert, and safe to consume orally should be used as the liquid vehicle in liquisolid systems. Such solvents include propylene glycol, glycerin, PEG 200 and 400, polysorbate 20 and 80, and PEG 200 and 400. The drug's solubility in nonvolatile solvent influences tablet weight and dissolution profile significantly.
A higher FM value (the fraction of molecularly dispersed drug) on the other hand is associated with higher drug solubility in the solvent, which increases the rate of dissolution. The liquid vehicle chosen is primarily determined by the purpose of the investigation. When dissolution augmentation is used, a liquid vehicle with a high ability to solubilize the medication is chosen. If the goal is to delay drug release, a liquid vehicle is preferred.

Carriers

The carriers surfaces should be porous and have a high liquid absorption capacity. Carrier properties such as (SSA) and liquid absorption capacity are extremely important in the development of a liquisolid system formulation because they allow the incorporation of a large amount of liquid medication into the liquisolid structure. The SSA value has a large influence on liquid adsorption capacity. It is influenced by the type of coating used as well as the physicochemical properties of the liquid vehicle such as polarity, viscosity, and chemical structure. The carriers' surfaces should be porous and have a high liquid absorption capacity.

Because they allow the incorporation of a large amount of liquid medication into the liquisolid structure, carrier properties such as (SSA) and liquid absorption capacity are extremely important in the development of a liquisolid system formulation. The SSA value has a significant impact on liquid adsorption capacity. It is influenced by the type of coating used as well as the liquid vehicle's physicochemical properties such as polarity, viscosity, and chemical structure.

Materials for coatings

Coating materials include powdered Aerosil 200, Neusilin, calcium silicate, and magnesium aluminometasilicate, which are ultrafine and highly adsorptive substances. These materials aid in the coverage of wet carrier particles by adsorbing any excess liquid, resulting in the appearance of a dry, non-adherent, free-flowing powder. It was discovered that using Neusilin US2 as a coating material instead of Aerosil 200 in a liquisolid system increased liquid adsorption capacity while decreasing tablet weight.

Additives

The proclivity of solid dose forms to degrade has a direct effect on the amount of medication released. Disintegrants are commonly added to liquisolid pills to aid in rapid disintegration. In liquisolid systems, disintegrants such as sodium starch glycolate, croscarmellose sodium, and low substituted hydroxypropyl cellulose are commonly used. Polyvinylpyrrolidone (PVP) is another intriguing addition because of its ability to absorb large amounts of medication into liquisolid systems and thus reduce tablet weight Furthermore, because PVP inhibits crystal development, liquisolid tablets containing PVP dissolve more quickly. The HPMC additive is another component found in liquisolid systems that often acts as a release retarding agent to extend medication release.

Procedures for General Liquisolid System Preparation

Blending or total solubilization In the following step, the resulting liquid medication is combined with the additional excipients used in the liquisolid formulation. Spireas and Bolton state that calculated drug and liquid carrier dosages are combined, followed by three steps of heating or sonication. During the first stage, the liquid medication is poured onto the calculated amount of carrier material and blended for one minute at an approximate mixing rate of one rotation per second to ensure that the liquid medication is evenly distributed throughout the carrier powder.

The coating material is then added and thoroughly mixed in the calculated amount. The prepared powder mixture is applied in a uniform layer to the surface of a mortar in the second stage and allowed to stand for 5 minutes to allow complete absorption of the drug medication into the interior framework of the carrier and coating materials. In the third stage, the disintegrant is added and thoroughly mixed with the above powder mixture to produce a final liquisolid system.

The prepared liquisolid system can be compressed or encapsulated further. It should be noted that the mixing speed, mixing time, and standing time are all adjustable.

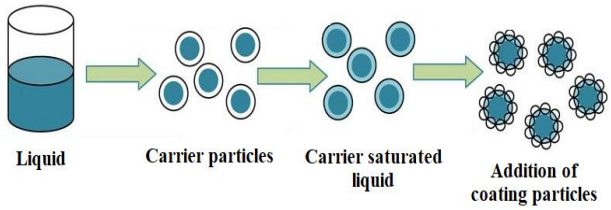


Fig. Scheme for Liquisolid Technique

Applications

- Liquisolid compact technology can significantly improve the bioavailability of drugs that are insoluble in water. Several water-insoluble drugs were formulated into liquisolid compacts after being dissolved in various non-volatile solvents.
- According to the literature, several drugs have been successfully incorporated into liquisolid compacts.
- Rapid release rates are achieved with liquidsolid formulations.
- These are useful for insoluble solid drugs in water or liquid lipophilic drugs.
- Reliable
- This method has resulted in the release of water-soluble drugs such as propranolol hydrochloride.
- Improved dissolution and solubility.
- Compressibility and flowability.
- Creating Controlled Release Tablets
- Increased bioavailability.

The liquidsolid technique as an aid to drug dissolution

In the literature, three potential mechanisms of liquisolid system dissolution enhancement have been proposed: increased drug surface area, increased drug solubility, and increased wetting properties. Despite the fact that the drug is in a solid dosage form, it is either solubilized or dispersed. As a result, the drug surface area available for dissolution has significantly increased. In addition to the preceding mechanism, drug solubility in the aqueous diffusion layer could be increased. It is acknowledged that the liquisolid system's relatively small amount of liquid vehicle may be insufficient to increase overall drug solubility in the dissolution medium. However, a liquid vehicle may exist between the individual liquisolid primary particle and the dissolution medium in the diffusion layer microenvironment.The liquisolid technique was used to improve the dissolution of tadalafil, a drug that is poorly water soluble.

The liquidsolid technique for maintaining drug release

The liquidsolid technique was created to hasten the dissolution of drugs that were insoluble in water. Extensive research in recent years has suggested that the liquisolid technique could be used to create drug formulations with prolonged release. Sustained release formulations are designed to gradually release the drug over a set period of time while maintaining high efficacy, patient compliance, and minimal side effects. The ability to create a liquisolid system with zero order release kinetics is one of the primary advantages of using the liquisolid technique to prolong drug release.The main limitation is the large tablet weight, which results from the high drug dose used in sustained release liquisolid formulations (which is usually higher).

The liquidsolid technique can be used to reduce the effects of pH change on drug release

The ionisation constant (pKa) of the compound and the pH of the surrounding environment determine the solubility of weak acids and bases. As a result, the pH of gastrointestinal fluids influences the dissolution and bioavailability of these drugs significantly.As a result, drug bioavailability and therapeutic effects are highly variable . El-Hammadi *et al*. investigated the use of the liquisolid technique to reduce the effect of pH variation on loratadine release. Propylene glycol was used as a liquid vehicle, MCC as a carrier, and silica as a coating material to create several liquisolid formulations. According to the findings, the liquisolid technique is a promising tool for reducing the impact of pH variation on dissolution rate.

The liquidsolid technique has been identified as a potentially useful tool for increasing drug photostability in solid dosage forms

Photostability studies for photosensitive drugs are important because drug potency loss during photodegradation can result in toxic degradation products and potential side effects]. The liquisolid technique's photoprotective action is based on the photoprotective property of silicon dioxide (a common coating material in liquisolid systems), which has a high refractive index and the ability to diffract light waves of various energies. The liquidsolid technique is not only useful for increasing the dissolution rate of poorly water-soluble drugs, but it is also a novel and excellent method for preparing zero order release sustained release tablets.Furthermore, the technique has demonstrated promising results in terms of decreasing the effect of pH variation on drug release and improving drug photostability in solid dosage forms. This technique's potential applications in pharmaceutics will be researched further in the future. More research is being done to develop superior solvents, as well as modern carrier and coating materials for loading high-dose drugs.

Evaluation of liquisolid systems

Characteristics of flow

Powder flowability is critical in the production of pharmaceutical dosage forms in order to reduce high dose variations. Angle of repose, Carr's index, and Hausner's ratio were used to ensure the flow properties of the liquisolid systems.

Precompression experiments on prepared liquisolid powder systems

Differential scanning calorimetry, X-ray diffraction, and scanning electron microscope studies are performed to ensure the suitability of the selected excipients. Flowability studies are also carried out in order to find the best compression formulae. Prior to the formulations being compressed into tablets.

***Calorimetry by differential scanning* (DSC)**

DSC is used to evaluate the thermotropic properties and thermal behaviour of the drug, excipients used in the formulation, and the finished liquisolid system. The thermotropic properties and thermal behaviour of the drug, excipients used in the formulation, and the finished liquisolid system are evaluated using DSC.

Calculating the contact angle

The imaging method is used to assess wettability by measuring the contact angle of liquisolid tablets. The most common imaging method directly measures the contact angle of a liquid drop resting on the plane surface of a solid. In dissolution media, a saturated solution of the drug is prepared, and a drop of this solution is placed on the surface of the tablets. To calculate contact angles, multiply the height and diameter of a sphere drop on the tablet by the number of sphere drops.

SEM (scanning electron microscopy) (SEM)

The scanning electron microscope (SEM) is used to assess the morphological properties of raw materials and drug-carrier systems (SEM).

X-ray Diffraction (XRD)

X-ray diffraction (XRD) patterns are determined for the drug, excipients used in formulation, the physical mixture of drug and excipients, and finally the prepared liquisolid system to characterize the crystalline state. The absence of constructive specific peaks in the drug's liquisolid X-ray diffractogram indicates that it has almost completely converted from crystalline to amorphous or solubilized form.The absence of constructive specific peaks in the drug's liquisolid X-ray diffractogram indicates that it has almost completely converted from crystalline to amorphous or solubilized form.

The lack of crystallinity in the liquisolid system was thought to be due to drug solubilization in the liquid vehicle, which resulted in the drug forming a solid solution within the carrier matrix. The drug's amorphization or solubilization in the liquisolid system may contribute to an increase in apparent solubility and thus the drug's dissolution rate.

Dissolution tests in vitro

Numerous studies have shown that the liquisolid compacts technique may be a viable option for the formulation of water-insoluble drugs. This liquisolid compacts technique has been successfully used to improve the in-vitro release of poorly water soluble drugs such as hydrocortisone, prednisolone and piroxicam. Several water-insoluble drugs, including nifedipine, gemfibrozil, and ibuprofen, have shown higher bioavailability in rats when compared to commercial counterparts. Liquidsolid compacts with lower R-values (carrier: coating ratio) have less carrier powder (microcrystalline cellulose) and more fine drug-loaded silica particles, and their liquid medication per powder substrate ratios are higher. Liquidsolid compacts with higher R-values, on the other hand, have low liquid/powder ratios, a high cellulose content, and a low silica content.

Testing in vivo

In beagle dogs, the absolute bioavailability of hydrochlorothiazide liquisolid tablets was 15% higher than that of commercial tablets, according to in-vivo testing.

CONCLUSION

This method could be used to create water-insoluble solid drugs as well as liquid lipophilic drugs. The increased rate of drug dissolution from liquisolid tablets is most likely due to an increase in the wetting properties and surface area of dissolvable drug particles. Rapid disintegration rates are observed when compared to conventional tablets, resulting in improved release rates and thus higher bioavailability. Drugs are released from liquisolid tablets over time due to the use of certain agents in the formulation.

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