INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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**Review Paper**

# Liquid-Solid Compacts: Approach for Improving Drug Solubility and Bioavailability

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ARTICLE INFO

Published: 18 May 2026
Keywords:
Liquid-solid compacts, solubility improvement, poor water solubility, dissolution rate, bioavailability, drug delivery systems
DOI:
10.5281/zenodo.20267338

## ABSTRACT

One significant challenge in oral drug delivery is the inadequate aqueous solubility of numerous active pharmaceutical ingredients (APIs), which results in slow dissolution rates and diminished bioavailability. Approximately 40% of drugs in development experience poor water solubility, making the formulation process particularly challenging. Among new techniques, liquid-solid compacts (LSCs) have attracted interest as a potentially effective method to improve the solubility and dissolution rate of drugs with low water solubility. This investigation examines the formulation and assessment of LSCs utilizing a model hydrophobic drug. While techniques such as micronization and solid dispersion are available, many are hindered by issues related to scalability and stability. The LSC approach provides a distinctive advantage by transforming liquid medications into dry, non-sticky, free-flowing and compressible powders by employing carriers (such as microcrystalline cellulose) and coating agents (like colloidal silicon dioxide). In this study, various LSC formulations were developed utilizing non-volatile solvents. The dissolution behavior of these formulations was evaluated against the pure drug and physical mixtures. The optimized LSC exhibited a notable increase in the dissolution rate-over three times higher than that of the pure drug—due to enhanced wetting, increased surface area, and molecular dispersion within the matrix. In summary, liquid-solid compacts offer a feasible, scalable, and cost-effective solution for improving the solubility and oral bioavailability of drugs that are poorly soluble in water. This method could serve as an important tool in the development of pharmaceutical formulations.

## INTRODUCTION

There is increasing interest in liquid-solid compacts as a new and effective pharmaceutical formulation technique that can improve the solubility and dissolution rates of poorly aqueous soluble drug compounds. The aim of this

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**Relevant conflicts of interest/financial disclosures**: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

investigation was to examine and ascertain the importance of liquid-solid compacts and other methodically designed tablets and their dissolution behavior.[1] The term "liquid-solid compacts" has been recently given a new meaning and is being used to refer to physical mixtures of powders coated with a water-immiscible liquid on their surface to produce free-flowing dry granules. The basic construction and manufacture process resembles that of the ordinary wet-granulated tablets, but there are some important differences. The most important of these is that since the coated powder compacts are hard granules instead of soft ones, they can remain as powders for long periods of time and still give no agglomeration.[2] This makes it possible to store them and to build them up by compounding with other powders, either solid or liquid. Liquid-solid compaction has been investigated as a method whereby powder compact size and hardness can be controlled, while the powder water-solubility rate can be modified; this is especially significant in controlling or retarding the solubility of the smaller-scale particles. To treat powder compacts with a liquid simply means to dip them in a liquid and endeavor to design the compaction of powder materials in the presence of unbound water. Compressed tablets are conventionally made from powders that are dry and highly compressible.[3] It is by combining these two factors that tablets can be prepared by wet and/or liquid compaction. Such double or dual-compression tablets have applications in sustained-release drug delivery since the coat layer might be an aqueous insoluble gel, which then engenders drug release via swelling methods rather than simply porosity. Perhaps the most notable and radical examples are liquid-compacted powders, where aqueous-dissolving water-immiscible liquids can be applied in a new mode of tabletting where the products are either a dry powder or a disc.[4]

Biopharmaceuticals, or therapeutic agents that are based on biomolecules, have recently gained more attention. Biopharmaceutical compound exhibit unique performance characteristics, being highly efficacious and selective against their physiological target, in being able to be produced large volumes of production, in their inability to survive orally, and in broader therapeutic applications.[5] Unfortunately, most biopharmaceuticals incur significant solubility and/or bioavailability issues. Spreading and disintegration of a liquid medication is one method for improving dissolution and perhaps bio-availability. In this context, solid compacts have been suggested as a new high-volume tablet formulation technique, where the high solubility liquid is absorbed onto the high surface area powder drug particles, thereby instantly creating a larger surface area for dissolution. Liquid-solid compacts aid in the disintegration and dissolution of both liquid and solid pharmaceutical formulations is discussed. [6][2]

## 2. Background on Drug Solubility

Medical science has progressed significantly with the introduction of new drugs; yet, many of these drugs have low solubility and poor bioavailability, leading pharmaceutical companies to optimize bioavailability during the product development stage. Many formulations have been developed and are available in the market, indicating that the optimization of bioavailability is still a topic of challenge and interest in pharmaceutical science.[7] Many poorly soluble drugs can be successfully formulated using solid dispersions, and such formulations are available as marketed products. Solid dispersion systems can provide numerous benefits: to increase the solubility of poorly soluble drugs, thereby increasing the dissolution rate, absorption, and bioavailability; to stabilize unstable drugs against hydrolysis, oxidation and other decomposition procedures; to reduce a side

effect of certain drugs; to mask unpleasant taste and smell of drugs; to improve drug release from ointment creams and gels; to avoid undesirable incompatibilities; to obtain a homogeneous distribution of a small amount of drug in solid state; to dispense liquid or gaseous compounds in a solid dosage; to formulate a fast release primary dose in a sustained release dosage form; to formulate a sustained release regimen of soluble drugs using poorly soluble carriers.[8] Water soluble Solid dispersions can be prepared by selecting any water-soluble carrier. The enhancement of solubility of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Solubilization of drugs is the rate determining step for oral absorption, which can subsequently affect the in vivo absorption. Many drugs face solubility problems, affecting their bioavailability, making solubility enhancement necessary. Solid dispersions are one of the most attractive processes to improve poor water solubility.[9][10]Hot melt method, solvent evaporation, ball mill method, electrospinning process, and supercritical CO2 method are the techniques used to fabricate solid dispersions.[11][12] Here solid dispersion is described in detail, using pharmaceutical formulations as examples, and new ideas are proposed for manufacture and development of solid dispersion systems.[13][14]

## 3. Challenges in Drug Bioavailability

Many formulations containing innovative excipients are presently accessible. The distribution systems are made of biodegradable lipid excipients created using one or a combination of different materials that expand on macro- or sub-microscopical structures while remaining economically relevant based on the API's needs, production, and intended therapeutic use.[7] These new excipients vary greatly in their hydrophilicity, viscosity, gelation, and structural characteristics, thereby modifying their performance.[15] Along with the standard pre-formulation tests, a few more specialized assessments are required to determine the excipient's suitability in contract.[16]Using these evaluations as a guide for searching available excipients, the formulator can feel more confident in their selection.[17][18]

As the most common oral delivery method, many formulations of drugs, particularly lipophilic compounds, are developed in this way. A significant challenge in drug discovery for pharmaceutical formulations is the solubility of compounds in the gastrointestinal tract to achieve desired systemic levels and efficacy. In this regard, poorly soluble drugs are one of the most significant development issues because they are a common cause of late-stage formulation failure. A pharmaceutical compound's bioavailability is determined by its solubility in the gastrointestinal tract after oral administration.[19] Solubilization is a dynamic process whereby molecules dissolve from a solid phase into a liquid phase.[20][21] The resolution is promoted primarily by the enhancement of energetic factors: efficiency of the intermolecular interaction energies, mixing energies, and solute solvent surface area.[22][23][24] There are two primary stages to drug solubilization: nucleation and growth.[25] The first stage is supersaturation associated with a free energy barrier involving critical crystalline dimensions. Solutions in the nucleation state are metastable and are thus aversive systems prone to convert to the relatively lower energy state of saturation.[26]These decrease in supersaturation with time and can precipitate the solute. Drug formulations are generally selected on an empirical basis from the many approaches available because the precise mechanism of drug absorption is poorly understood.[27] Further, careful attention must be paid to the routes of administration; methods can vary drastically in

efficacy and tolerability based on the physicochemical properties of the API.[28]

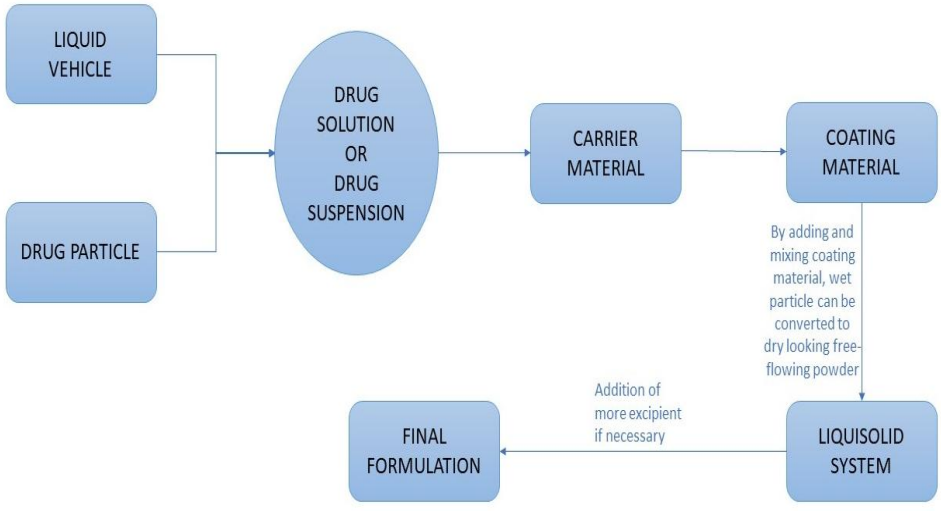
## 4. Overview of Liquid-Solid Compacts

The objective of this study was to formulate liquid-solid compacts utilizing oil, pharmaceutical aids, and drug substance using a direct compression technique while assessing the effects of the composition of the liquid-solid compacts on their release properties.[29][1]

Liquisolid compacts have recently become a viable method for increasing the rate of dissolution.

of medications that are poorly soluble.[30] The concept of "liquisolid systems" defined by Spireas *etal*. (1999) can be used to change a liquid into a powder that flows freely, compresses easily, and seems to be dry through basic physical mixing with specific excipients known as the coating and carrier substance. To share a new mathematical model that introduces a redefined fundamental flow property for powders, called the flowable liquid-retention potential (d-value). It also presents a new fundamental compression property known as the compressible liquid-retention potential (P-number).[31] This model helps us figure out the ideal amounts of carrier and coating materials needed to create well-flowing and compressible liquid/powder mixtures. Additionally, we've developed two new testing procedures: the "Liquisolid Flowability Test" and the "Liquisolid Compressibility Test," which are essential for evaluating the d-values and P-numbers of powder excipients.[32] To top it off, we've included various examples of immediate and sustained-release liquisolid tablet formulations, along with their flowability and compressibility assessments, comparing their in-vivo and in-vitro release profiles to those of commercial products.[33]

Liquisolid compact technology has been effectively used to enhance the physical and chemical stability designing moisture resistant solid dosage form of poor like as Ranitidine Hydrochloride is a highly water-soluble drug. It is used in the treatment of gastric and duodenal ulcers and gastroesophageal reflux disease (GERD) and other drugs also.[34]




## 5. Mechanisms of Enhanced Solubility

To improve the solubility of drugs in aqueous media is a challenging task for formulators. Solid dispersions, in which drugs are dispersed in a hydrophilic carrier in a solid state, have been used to improve the solubility of poorly soluble drugs for decades. Working in line with this concept, liquid-solid compact (LSC) was formulated in this study.[1]Such systems are prepared by compacting a mixture of solid carrier and drug dissolved in a liquid vehicle. At a certain weight ratio of solid carrier to liquid vehicle, compacting of a liquid-

solid blend results in lost liquid fraction from the resulting compact with a uniform porous structure. When finely divided, such porous systems provide a continuous water channel professed to allow superior solvent access to the drug in contrast to solid dispersions prepared by a melting or solvent processes.[29]For this reason, hypromellose acetate succinate or Eudragit L, soluble polymers often used for film coating of pellets, were sought to provide LSC due to their retention and porous properties upon drying. [7] The proof-of-concept study conducted with probucol in this study demonstrated that such systems can be successfully fabricated and they have potential for enhanced solubility and dissolution.[35]

Here, the merit of this formulation approach is highlighted in terms of easy and controlled preparation, improved solubility and bioavailability, and the mechanism of enhanced solubility with dry, porous systems.[36] Solid dispersions have been devised to prepare a solid-state mixture of drugs with a hydrophilic carrier, expected to accelerate drug dissolution by instant wetting of the carrier upon contact with aqueous media.[37] Such solid systems can enhance the solubility of poorly water-soluble drugs in aqueous media via one (or more) of the following mechanisms. External surface area of the system increases instantaneously, in turn providing pharmaceutical powders entailed by high porosity, large surface area, and roughness, aiding the contact with medium and facilitating interfacial diffusion of solvent species.[4]

External surface primary particles of a compacted system are subject to crack formation caused by liquid vehicle loss, so that smaller particles predominantly with a denser yet porous structure are exposed at the surface, facilitating greater wetting resulting in faster drug release.[38] Redistribution and deposition of surface active carriers on the surface of the compacts increase coverage roughness even with low total surfactant ratios, promoting contact to form a thin liquid film, increasing solubility and wettability, and lessening the dissolution time needed to attain 90% drug concentration.[39]

### 5.1. Role of Particle Size

The bioavailability of poorly soluble drugs is highly contingent upon particle size. A reduction in particle size yields a greater surface area, thereby enhancing the dissolution rate. This improvement facilitates the development of a wider array of formulation designs and drug delivery systems.[40] Beneficial effects of particle size reduction on solubility may also be responsible for the improved bioavailability of some compounds.[41] However, general size-benefit results can be deceptive. Reduction of drug size is not uniform, and micronized powder can contain a small percentage of fine material. Moreover, fines can agglomerate. Hence, a substantial portion of the drug is delivered at a size greater than would be ideal. Historically, fine powders (i.e. sub-45-µm) are frequently re-agglomerated due to surface forces, which leads to poor dissolution.[42]It is critical that the given API is fully available. Several methods for control of particle size were developed and included homogenization, antisolvent precipitation and rapid freezing.[43]

### 5.2. Impact of Surface Area

The release performance of a liquisolid system is governed by the state of the drug within the liquid vehicle. A completely dissolved drug achieves a molecular dispersion in the carrier powder, maximizing the surface area available for release and enhancing the rate. Conversely, drug concentrations surpassing the solubility limit result in a particulate suspension, diminishing the release rate.[44][45] This relationship is quantified by the Fraction of molecularly dispersed drug (FM), a key parameter calculated as FM = Sd/Cd, where

Sd is the drug's solubility and Cd is its concentration in the vehicle. An FM value of 1 signifies complete dissolution.[46]

## 6. Formulation Techniques

In the liquisolid technique, the drug is dissolved in a non-volatile liquid vehicle and mixed thoroughly with non-volatile carrier material. A mixture of a liquid drug and liquid vehicles, which is mixed with powder excipients is compressed to obtain liquisolid tablets or capsules. Whereby liquisolid technology has advantages over approaches such as solid dispersion and solid lipid nanoparticles.[30] The liquisolid compact technique for solubility and dissolution enhancement was firstly put forward by Spireas,S. and Bolton, S. (1999).[47] The formation of a solid-liquid (or liquid-solid) blend made of a powder substrate consisting of carrier [Microcrystalline cellulose( AvicelPH 101/ 102 ), lactose, starch, sorbitol]and coating material [Colloidal Silicon dioxide( Aerosil 200 ) , Magnesium aluminometasilicate (Neusilin), a liquid (Polyethylene glycol 200, 400, 600 , Propylene glycol , glycerin , polysorbate (Tween 20,80), Labrasol ,Transcutol) and a drug (in the liquid state) is known as a liquid-solid compact, and the preparation of such a blend is called liquid-solid technique.[48] On the basis of physical characteristics, the general use of liquid-solid technique can be classified into powder and compact dosage forms. Liquisolid-system-based powder dosage forms are usually prepared by converting a normally liquid drug or a drug solution by liquisolidding.[49] Liquid-solid technique (LST) employs the adjuvant use of powder excipients. The conversion of liquid drug or drug solution into powder is achieved by their systematic blending with powder excipients of prescribed physical characteristics and proportions.[40] Since the liquid-solid technique is particularly adapted to the generation and formulation of powder tested liquigranules , it can be further subdivided into powder granule or powder systems. The liquid-to-solid systems can be also compressed into tablet dosage forms. Dissolution and bioavailability of liquid-solid dosage forms depended on the release of drug from liquid-solid matrices. And hence there is need for solid dosage forms which release drug at controlled rate and extent.[50] The release of drug from liquid-solid matrix is highly regulated by solubility of drug in liquid-liquid matrices, drug-to-excipient and liquid-to-excipient ratio, permeability of drug and adhesive-bonding interaction at solid-solid, liquid-solid and solid-liquid interfaces. Other physicochemical properties of drug and excipients have also been reported to affect their release.[51]

### 6.1. Melt Granulation

Melt granulation (MG) is a sheet-to-granule process widely used in the pharmaceutical industry for sprayable and compressible granule production.[52][53] In the MG process, the granule is prepared by disintegrating a melt sheet coated by a hot melt binder, which is formed from a drug-excipient blend using a roller compactor or a hot melt fluidized bed.[54][55][56] With MG, the final drug form is successfully manufactured as a melt sheet. After coating with a melt binder, the melt sheet is bundled in a sheet-to-granule device to manufacture the granule.[57][58]

In the MG process, the melt sheet is disintegrated using mechanical energy to prepare the granule.[59] A granule device is built, and the granulation process is controlled with operating parameters, e.g. rotating speed of the cylinder and exit height. The performance of the granule devices is evaluated using the granulation efficiency, granule size distribution, and particle size reduction ratio.[60][61] The preparation process and characterization methods of both melt and non-melt granules are discussed. The granulation mechanism of the liquid-solid compact formation

process is studied. [62] The resultant granules show dissimilar morphology, and all the granules exhibit a similar dissolution profile. As a novel approach, melt granulation is used to substantially improve the solubility and bioavailability of poorly water-soluble drugs. Effect of the granulation device, as well as granulation parameters, on the resultant granules is intensively investigated.[63][64]

To increase the solubility of poorly water-soluble drugs, a hybrid preparation employing a melt-freeze technique and a melt-spray drying technique is developed.[65][66] All the resultant granules exhibit a similar particle size, and a dissimilar morphology is observed between the granules prepared by the two techniques. To augment the solubility of a poorly water-soluble drug by ~25 times, a unique granulation process is developed with two FDA-approved excipients.[67] The drug loading in the resultant granules reaches ~30%. To enhance the solution flux of poorly water-soluble drugs, a simple coating technique is used to improve the wettability of compacted granules.[68]The coated compacted granules exhibit higher solution flux than the uncoated ones.[69]

### 6.2. Co-Solvency Methods

The solubility of drugs is one of the major factors affecting their bioavailability. Many drugs show less solubility in gastric and intestinal fluids due to their high hydrophobicity or low lipophilicity. Many approaches have been developed during the last few decades to increase the solubility of poorly soluble drugs.[70] The solubility of drugs can be improved by salt formation, co-solvency, complexation, chemical modification, particle size reduction, solid dispersion techniques, solvent evaporation techniques, and liquisolid compacts.[71][72] The term liquisolid compacts is used to define formulations obtained by converting liquids (either liquid drugs or drug solutions in non-volatile solvents) into dry looking, free-flowing, and compressible powders by simple blending with selected excipients in a simple one-step procedure.[73][74][75]

Co-solvent systems are usually developed to improve the solubility of poorly soluble compounds. Especially, organic solvents can be used in combination with specific additives to obtain solubility enhancement.[76][77] However, the effect of the co-solvent system features a saturation limit and usually causes severe neurotoxic and cardiotoxic side effects. For these reasons, this approach does not appear to be a meaningful one for the development of safer and more efficient oral formulation systems capable of solubility enhancement.[78][79]

### 6.3. Spray Drying

The spray drying is one of the commonly used approaches and an effective method for the formulation of liquid-solid compacts. Spray drying has been used widely to produce solid forms of pharmaceutical compounds suitable for tabletting.[80] It consists mainly of a drying chamber in which liquid containing drugs or excipients droplets are introduced. The moisture content of the material has been reduced, causing the droplets to dry and forming powder comprising solid material. Spray coating of the tablet surface at the end of the process is also achievable through that method.[81]In formulating liquid-solid compacts, the use of substantial water-soluble excipients is a concern in terms of both the compaction studies and spray drying feasibility.[82] The solid dispersion formation improves the solubility and bioavailability of a poorly soluble drug when combined with an appropriate amount of excipients.[83]Oftentimes, polymer coating solutions of normal and reverse coacervation techniques are used. Further thermal processing is required due to the existence of residual solvent in the plastic form powder.[84][85]

## 7. Characterization Methods

Characterization methods were divided into various groups based on the nature of the material used and technique. Flow property evaluation methods were as follows: angle of repose, Carr's Index was determined using flowability number , Griffith's compressibility and cohesive index (or strength), and the same for mixtures.[86][87] Evaluating the powder coating on the core was additionally divided into Dorr's analysis, Kjeldahl's nitrogen determination, and optical examination methods. The latter operates by determining the reflection coefficient from the cut surface and the time knots.[88][89] The results of time knots obtained with grades of slow or immediate release cores were compared with pure excipients. Solid state analysis was performed with infrared spectroscopy.[90] The materials were introduced into cells. The cohesion of the pellets was tested by adding them into a mortar bowl with water droplets. Operating solid-state analysis methods were infrared spectroscopy, ultraviolet spectroscopy, and a polarising microscope for crystallisation.[91]

### 7.1. X-ray Diffraction

X-ray diffraction (XRD) was the primary technique used to gain information regarding the solid state and structural level properties of the co-crystals formed. The same solid state techniques were used to determine the structural consequences of solvent for an improvement in dissolution and solubilizing properties.[92] The drug's transformation into an amorphous form or into a solubilized state is supported by X-ray diffraction. This is verified by the simultaneous appearance of peaks matching to the carrier material and the removal of the drug's distinctive crystalline peaks.[93]

### 7.2. Differential Scanning Calorimetry

It is commonly known that Differential Scanning Calorimetry (DSC) is a useful method for evaluating potential interactions between medicinal components and excipients in pharmaceutical formulations. To avoid incompatibilities that can jeopardize the stability and functionality of the finished product, it is crucial to identify such interactions during the preformulation phase. DSC was used in this investigation to assess the thermal characteristics of the prepared liquisolid system and the pure components.[94] DSC can provide information on the thermal behaviour of a formulation on a bulk level.[95] An indium standard was used for calibration, and the analysis was carried out at a heating rate of 10 °C/min between 30 and 300 °C. Although DSC provides a through understanding of a formulation's bulk thermal properties, it is crucial to recognize that local variability that can arise at micro- or nanoscopic dimensions may not be adequately captured. [96]

### 7.3. Scanning Electron Microscopy

Liquisolid compacts (LSCs) are frequently studied using scanning electron microscopy (SEM), which examines the surface morphology of the LSCs and confirms drug adsorption onto coating and carrier materials. SEM pictures of liquisolid formulations usually show smoother, amorphous-like surfaces without apparent crystals, indicating molecular-level dispersion or homogeneous liquid adsorption, in contrast to pure medicines, which typically have sharp crystalline structures.[98]Despite liquid inclusion, carriers with porous structures, like silica and microcrystalline cellulose, appear coated or packed in LSCs, producing a dry, free-flowing powder. SEM pictures of the pure drug, carrier, physical mixture, and final compact can be compared to gain qualitative information on structural changes that enhance wetting and dissolving.[99][100]

Future work will focus on microstructural and mechanical studies of the bed structure and the compacts, increased productivity of new methods, and broadening processability to more drug/excipient combinations. The study on pharmacopoeias should extend the understanding of the applicability of different processes on a larger set of formulations.[101]

## 8. Advantages of Liquid-Solid Compacts

Since the first description of the liquisolid technique for the formulation of liquisolid systems in 2003, numerous times have been published over various aspects of the technique, including the formulation development, physicochemical properties and characterization of the liquisolid system, the methods for evaluation of liquisolid systems for their potential to improve the dissolution characteristics of poorly water-soluble compounds and the efficacy assessment of their performance in an in-vivo model.[102][103] A wide variety of liquid, non-volatile, water-insoluble carriers (or vehicles) have been used, including the lipids from the SEDDS dimensions like oils and surfactants, as well as organic solvents and other surfactants such as PL 6060 and Cremophore RH 40 .[29][104]

The following is a non-exhaustive list of the liquid vehicles that have been used in liquisolid formulations.[105] Specifically designed liquisolid wettable carriers with a particular chemical composition that would not only absorb the liquid vehicle to form non-drug aqueous “solids” similar to indirect cleaving of liquid.[106][107] But also retain surface properties and hydrophilic characteristics similar to ion-exchange resins. Biopolymeric polypeptides, polysaccharides, and chitosan bases have been used as carriers and hydrophilizing diluents for liquisolid compacts sprinkled over disgusting taste pronouncing on tablets.[108]

A concise design rationale is proposed based on the chemical and physicochemical principles governing the interactions involved in the carrier-diluent-liquid component environments. This design rationale elucidated and validated on multiple dimensions may lead to more sophisticated and innovative liquisolid formulations with enhanced approaches for new drug entities as a part of the pharmaceutical science research pipeline to enable safe and effective therapy for patients. The liquisolid technique is a novel and exciting technology. It is easy to utilize, cost-effective, and provides numerous advantages.[109]

### 8.1. Improved Bioavailability

Oral drug delivery route is the most common and widely used route for systematic drug delivery. The major obstacle faced by drugs in the oral delivery route is its poor solubility in aqueous medium.[110] Thus, improvement in the solubility of the drug is a must requirement for any therapeutic entity with poor solubility in aqueous medium. The problem of poor solubility and/or palatability can be costs effectively tackled via smart formulations like tablets, capsules, nanoemulsions, up to LSVs.[111][112] Oral administration of powder formulation of liquid super saturated micro/emulsion is an advance formulation with significant solubility and bioavailability enhancement.[113]

It is sumrised that, in LSVs loaded with MS, the lipid content provides a solubilization effect to the poorly soluble APIs, improving their solubility. This effect was furthered by the surfactant component, which not only maintains the nanosized nature of the obtained L-fLIVs, but also affects the overall solubilization mechanism for MS and SLX.[114][115] Thus formulated LSVs formulations containing 4% surfactant with a 76:24 % oleic acid and capryol 90 mixes were thermodynamically stable, with entrapment

efficiencies 95.49 ± 0.21% SLX and 89.85 ± 0.34% MS provided the optimal emulsifying performance. In vitro dissolution studies illustrated significantly improved rates of dissolution.[116] In comparison to the wider range of bioactive entities, lipophilic APIs, this significant enhancement in the solubility of MS and SLX by LSVs was illustrated. LSVs promisingly enhance the solubility and bioavailability of poorly soluble lipophilic molecules, offering a novel alternative to emulsion systems with potential for drug development.[117][118]

### 8.2. Enhanced Stability

Physical stability is the most significant obstacle faced by solid dispersions, affecting both the drug and the carrier. Choosing an appropriate polymer and processing method is pivotal in producing a successful product as it will greatly affect the stability.[119]If the drug is in the form of a co-processed excipient such as a sugar-based Liqui-Vehicle enabled compacts the solid dispersion stability may primarily reside with the excipient rather than the processing method.[120] Packaging and storage conditions can also play a role in the physical stability of solid dispersions but may also depend on the physical state of the carrier. The polymer is the predominant component that regulates solid dispersion stability, and thus the primary focus will be on its stability. Storage of the solid dispersion below the Tg if desired is known to enhance stability; conversely, with storage of the solid dispersion temperature above the Tg instability becomes apparent.[121] Conventional solid dispersions are amorphous matrices in which the poorly soluble drug is molecularly dispersed in a water-soluble polymer/carrier that can adjust the drug solubility in GI fluids and modulate the drug release. When fully released from the compact mold, the drug content will disperse in a gel state.[122] However, for many dispersions, the drug-polymer failure might take place very soon and often during the manufacturing process.[123][124] This occurs due to the aqueous extraction, dehydration of the gel state, general incompatibility of polymer and drug moieties, or confinement in the porous structure of the sugar-based LVE carriers.[125] Once the drug is released from the gel state, it may either dissolve in organic solvents and/or crystallize. further, which either case will deteriorate the product performance. The dissolution process may also involve a rapid and large calorimetric reaction and/or crystallization from supersaturated conditions, which may cause batch-to-batch variation in performance. The crystalline expelled drugs will also cause poor processing and storage stability.[41][80]

## 9. Case Studies

In the present investigation, an attempt was made to enhance the solubility and dissolution rate of an oxicam derivative (Piroxicam) an NSAID by liquisolid compact technique. Five liquisolid compact batches of Piroxicam were formulated using different non-volatile solvents, which were evaluated for their flow properties and drug release characteristics. Out of five liquisolid compact formulations, batches with 15 % of Neusilin US 2 were found to be the best formulations as they exhibited 98. 4 % drug release in 60 minutes. The results indicated that liquisolid technique can be successfully employed for improving the solubility and dissolution rate of a high dose drug like Piroxicam which is an API that undergoes dissolution rate limited absorption & has low solubility in case of solid dosage forms.[30] Orally bioavailability of drugs is a major concern for researchers and pharmaceutical industries due to low solubility of newly discovered molecules. When it comes to drug development, lead compounds are purified and subsequently modified for optimal bioavailability.[93][94]

However, the majority of these compounds suffer from low solubility as they are hydrophilic in nature. Hence, several methodologies are investigated for solubility enhancement. The current delivery system aims to improve solubility of poorly soluble drugs in the oral formulation stream using carbon dioxide, polar aprotic solvents, coating and surface adsorption techniques. Supercritical carbon dioxide, non-coating solvents or polymeric excipient, microscopic technique was utilized to enhance the virally-inspired nanoparticulate solid lipid delivery system of lysozyme for inhalation [29][126]

### 9.1. Case Study 1: Antihypertensives

Antihypertensives constitute a major group of therapeutic agents used in the treatment of arterial hypertension. Application of an appropriate prodrug or an effective salt form with high pKa can enhance solubility and bioavailability of biopharmaceutics classification system (BCS) class II, III and IV drugs.[127][128] The common antihypertensives in the descaling application include amlodipine besylate, lercanidipine hydrochloride, telmisartan, atorvastatin calcium, and their salts or prodrugs.[129][130]

Amlodipine besylate is a dihydropyridine-derivative antihypertensive agent licensed for treatment of mild-to-moderate essential hypertension. Amlodipine besylate is a BCS class II drug with a pKa of 8.6, very low solubility of <0.5 mg/mL in simulated gastric fluid, and a high log P of 5.08, which poses a challenge for its formulational development.[131][132] Liquisolid compacts of amlodipine besylate were prepared with PEG 200 and PEG 400 as the co-solvents and evaluated. [133][134] This study demonstrated that the drug solubility and dissolution can be significantly enhanced by using a combination of liquisolid technique and non-volatile liquid vehicle.[135]

Lercanidipine hydrochloride is a highly lipophilic 1,4-dihydropyridine derivative calcium channel blocker with a pKa of 4.22 and a high lipid solubility of log P of 5.83, being in BCS class II, with poor solubility in water which makes it an incomplete oral bioavailability of approximately 10%. [137] The aim of the present investigation was to prepare and characterize the liquisolid compacts of lercanidipine hydrochloride to increase the dissolution rate. Different liquisolid formulations were prepared using PEG 400 and Tween 80 as liquid vehicles.[138] The prepared liquisolid compacts were characterized for flow properties, drug content, weight variation and in vitro drug release study.[139] The results indicated that liquisolid technique could significantly enhance the drug dissolution rate. Although the rapid and complete dissolution of drug could not be achieved, overall liquisolid compacts of lercanidipine hydrochloride produced improved dissolution with early onset compared to pure drug.[140]

### 9.2. Case Study 2: Antidiabetics

Diabetes mellitus is a chronic illness characterized by the buildup of hyperglycemia. There are different classifications of diabetes, with Type 1 and Type 2 being the principal formulations. Type 1 diabetes corresponds to the absolute lack of insulin, thus requiring chronic insulin therapy. Type 2 diabetes, in turn, may have diverse origins but fundamentally entails insulin resistance, where the body either has reduced insulin secretion and/or insulin action, leading to failure to control glucose homeostasis.[141] A cornerstone in the treatment of type 2 diabetes are oral antidiabetic drugs, which are divided into eight major groups including biguanides, sulfonylureas, Glinides, AGI, DPP-4i, thiazolidinediones, SGLT2-i, and GLP-1 receptor agonists.[142]

Gliclazide is a representative compound of the sulfonylureas group. It is used to treat type II

diabetes and is a weakly water-soluble drug with a low aqueous solubility of less than 60 µg/mL. However, after being introduced into the market in 1999, its bioavailability decreased to 30%. There is a huge demand to reformulate gliclazide. The aim of this study is to enhance the solubility of gliclazide. In order to achieve the desired effect, evaluating several parameters such as excipient selection, method selection on the solubility of gliclazide were performed. Thus, consuming the new formulation would treat type II diabetes and it would be able to improve the poor bioavailability of gliclazide. A suitable combination of excipients and formulations dosage forms is important, and generally leads to improvement in therapeutics. However, the present formulation developed by using microcrystalline cellulose does not enhance drug solubility.[143]

In order to obtain an insight into the physicochemical properties and in vitro release of produced LSCs from fumed silica as an excipient of gliclazide-carplex solid dispersion, studies along with in vitro dissolution tests were performed. Recently developed integrated system provides a new insight into the analysis of glycerin esters in edible oils and fats. A set of conditions to conduct analysis of various glycerol-plain and glycerol-diglyceric esters was successfully developed. In order to obtain reliable mass quantifications of the compounds of interest, detectors were employed. The newly assessed method was validated using several oil samples. According to the analysis of the vegetable fats this online derived knowledge supports the theoretical background of the investigation of their quality and composition integrity.[144]

## 10. Regulatory Considerations

Food and Drug Administration (FDA) approval of a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) is a requirement for commercial distribution of a new drug product in the US. Both the NDA and ANDA submissions must contain sufficient data to demonstrate that the drug product is safe and effective under its proposed conditions of use. In the current pharmaceutical industry, there are stringent regulations governing the drug approval and delivery processes controlled by organizations like FDA, WHO, MHRA, EMA, etc. These guidelines or principles for drug approval and delivery vary depending on type of dosage form, potency and destination region.[144]

Novel drug delivery systems that would typically fall under Pre-Clinical or Investigational New Drug Application (IND) regulations would require additional data and testing beyond what is needed for more traditional technologies. However, in some regions, there may be existing regulations that can be utilized to take a Liquid-Solid Compact delivery system to market without conducting additional studies that would be required for a full NDA application.[145]

Hydrophilic Liquid-Solid Compacts exhibit a specific released behaviour in in vitro testing with an initial rapid dissolution phase followed by a slower controlled dissolution. In addition Liquid-Solid Compacts and Bioavailability studies in Beagle Dogs were conducted with Rapacurium designed such that they would closely emulate the conditions and approaches envisaged for the product. The results do show a much closer correlation in both Rat and Dog studies indicating both the potential of the delivery system to control the oral bioavailability of drugs and also the compatibility of some of the rapid solidification flotation-based technology with batch production of Compact dosage forms.[146]

Liquid-Solid Compacts can have a greatly increased mean dissolution time and a significantly reduced peak height and apparent clearance when compared to conventional solid dosage forms. This behavior is potentially beneficial in terms of managing both the onset and

incidence of adverse effects as a more constant kinetic profile may translate to a reduction in peak plasma drug concentration and an increase in maintenance of the trough. [147]

## 11. Future Directions in Research

While various strategies may be applied to prepare and characterize LSCs, future studies can be developed in several directions. With regard to the preparation methods, they can be combined with each other to optimize the choice of the method and to investigate the effects on the properties of LSCs as drug carriers.[148] Alternatively, new formulations or methods can also be developed. Furthermore, popular technologies, such as extrusion, electrospinning, hot-melt extrusion, rotary evaporators, and lyophilization may also be employed. Nevertheless, the principles of preparation remain the same.[149] The LSCs of a solid oral dosage form can also be prepared via batch-wise tube technology, where the compact mixture can be heated with a liquid medium (if required), and the temperature may then be decreased. Fast compacted tablets can also be prepared via current excipient transfer methods, including injection-molding and compression molding, followed by subsequent granulation if wet granulation is involved. Other 3D printing methods, including fused deposition modeling and selective laser sintering, may also be used.[150]

In terms of the characterization methods, protocols can be established in accordance with the guidelines of the International Conference on Harmonisation and USP General Chapter 1225. The methods settled in this strategy must be fully elaborated on and applied to well-characterized products appropriate for each analytical technique. Once these protocols are established for all of the characterization techniques in advance, they can be applied in a time-saving manner to varied application products. Additionally, with regard to the biodegradable excipients in wider pharmaceutical research, LSCs composed of the mixture of FDA- and EMA-approved excipients may be included. Routine safety assessments may be carried out on each newly selected excipient. The newly developed excipients may then be characterized generally using standard reference modeling compounds revealed in this report, and they can be utilized to prepare and validate dosage forms for the aforementioned application studies. To check for the generality of the approach, LSCs composed of fixed comminution conditions may also be used. Comminuted dispersions composed of excipients with varied chemical structures may be investigated. The approach may then be further extended to solid composites of LSCs and poorly soluble compounds prepared in other salty and condensed forms. The primary most functional or promising excipients or preparation/characterization methods may be selected for pharmaceutical research via other approaches, including chemometrics. Selective excipients may be screened on tabletability via the facility in preparation for LSCs by melt-injection or pregrinding.[7]

### 11.1. Innovative Formulation Strategies

Mucoadhesive drug delivery systems are an important area of research because of the growing interest in polymers that can bind to mammalian tissues and delivery formulations to the required sites of action.[151] In recent years, the therapeutic effects of mucoadhesive polymers have been examined on the targeting and timing of drug release, while enhancing the targeting, efficacy and bioavailability of drugs.[152] Hydrophilic or hydrophilic grafted polymers are known to incorporate drugs with attached or adsorbed portion, while the association of mucoadhesive polymers in the formulation, combined with the mucoadhesive drug carriers like buccal gel formulations, are mainly considered in delivering drugs through/onto mucosal sites.[153][154]

While long acting and controlled release delivery systems have their own limitations, there is a need for sustained delivery of instantaneous release or fast onset drugs. This can be achieved by incorporating minute quantities of a poorly water soluble/-permeable drug in newly developed liquid-solid compacts (LSC), using mucoadhesive polymers in the formulation. The advantages of such formulations are, namely, that they will prevent the unanticipated absorption changes occurring when the wrist watch is removed from a subject, and they will prolong the effective therapeutic concentration of an instantaneous-release drug for many hours without inducing side effects. [155]

The term "liquid-solid compacts" (LSC) refer to granules produced by wet granulation of a powdered, crystalline substance without any solid excipients, followed by a melting or solvent evaporation step in which poorly soluble component(s) and/or solid surface modifiers are incorporated into the granules. The novelty of the LSC formulation approach lies in their design, and the amphiphilic liquid-solid carriers which characterize them are an innovation in formulation approaches to enhancing dissolution/bioavailability.[156]

### 11.2. Personalized Medicine Approaches

With high-throughput screening of genomics and proteomics that produces vast quantities of new data regarding disease biology and its potential mechanism detection, personalized approaches for different diseases or drug adaptation are expected to improve overall therapeutic indices. However, one of the most daunting issues confronting therapeutics design is the development of drugs with good solubility and bioavailability. Various strategies or approaches regarding solubilization of poorly soluble or bioavailability insight are proposed.[146]

Drug Formulation-Tableting: The pharma pipeline produces many chemical entities with unknown solubility and permeability. Besides potential efficacy and safety concerns, medicine repositioning such as dosage form conversion is also an interesting strategy for drug repurposing.[157] Even though more than two thirds of NDAs were based on 505(b)(2) applications for different dose strengths, dosage forms or drug combinations, literature is still scarce regarding detailed case studies on successful product transformations. Therefore, a generous characterization of various drug dissolution technologies which may affect solubility and bioavailability of complex compounds is provided here.[158]

Improving Drug Solubility & Bioavailability–Liquid-Solid Compacts (LiSCs): Tunable solubility, excellently improved bioavailability and solid-state stability using LiSCs are described. By generating unique combinations of melting-extrusion and liquid-assisted granulation processes, LiSCs can be fabricated using a vast variety of widely available pharmaceutical excipients with orthogonal solubility profiles such as cellulose, surfactants, sugars/starch, and organic solvents. LiSCs are stable at elevated temperatures and humidity and yet are readily soluble in aqueous media to quickly disintegrate and rapidly dissolve (within 1 min for ~98% drug release).[159] For most tested formulations, LiSCs outperform the FDA-approved formulations in both in vitro dissolution and in vivo bioavailability. LiSCs were created not merely individual examples of process and proven to be robust formulations, but facilitate the search for inhibition of gastric acid secretions as a new frontier for gastric diseases.[160]

## 12. Limitations of Current Research

Despite the large numbers of literatures focused on LSC, many concerns should be addressed. LSC is usually done under binary liquid-solid states. In

addition, in current conditions, LSC is used in a selective way to lyophilizing agent, i.e., one side is lacy, by variant solvent evaporation rates, complicating how to apply LSC in a more diverse class of solid-form processes like injection molding and 3D printing. Both direct compaction techniques and compaction-on-granules methods need the LSC powder blend >90% of total mass, limiting LSC and less likely to affect existing form options. For advanced techniques like tablet-in-capsule, layered tablets, and bilayer tablets, additional design work is also required. When using auxiliary digestive-stimulating agents in the present LSC, attention should be paid to the safety of excipients. The LSC of multiple drugs or excipients is still underexplored [7].

Current LSC proof-of-concept studies have limited insights into structure-performance relationships. Conductor-to-insulator groups could only happen on each paradigm of the two-curve, homogeneous mixtures of HPMCP 6 and PVPVA in both dry and liquid states, none in combinations.[161] Further microscale multiscale structure-performance studies will be necessary to generalize to the powder level, and a better understanding of structure-performance relationships will help in the unabated development of new formulations.[162] To facilitate further improvements in the LSC method, a failure diffusion model is proposed along with its multiscale extension to assist in optimization of mixed batch formulation and introduction to both nascent and less common powder excipients. All existing compacts could alternatively serve as templates for the systematic design of powders with even lower limits for both drugs and excipients.[163]

## 13. Comparative Analysis with Other Methods

Liquid-solid compacts (LSC) using either streaming or spray drying as processing is a new novel concept in which a liquid is heated at elevated temperatures to make a compact and then subjected to sublimation under vaccum to produce porous and free-flowing LSC powder. Initially, a matrix formulation was prepared and subsequently prepared into tablets or compacts using LSC processing. LSC or LSC compacts contain a larger amount of hydrophilic excipients (≥70%), can produce a large porous volume (>35%), and show improved flowability (<15.5 as angle of repose) compared to products prepared by blend-compaction. Recent attempts to improve solubility and bioavailability for BCS class-II and -IV drugs are focused on the alternative biconvex slow-release tablet (BSRT) or a liquid-solid (LS) tablet which is produced by an unconventional compression process.[164] The LSC tablet is made from the compact, in which one part of the effervescent agent/filler of size ≥500 μm is mixed with a powder of biphasic co-formulating a low- and high-solubility drug before blending with the rest of the excipients for direct compression, whereas the BSRT is produced by the re-adjusting the high-speed mixer and the resultant pre-gelatinized starch by the extrusion-spheronization method. A new patented 3D printed tableting technique is also developed. The main solution is produced a mixture in which part of the binder is replaced with a molten active pharmaceutical ingredient (API) under heating to generate the liquefied mass, while part of the excipients is fed into the mixture followed by cooling and 3D printing into tablets. During the printing process, the moisture is sublimated to produce fast-disintegrating tablets. The 3D printed tablets with two API loadings, which deliver a zero-order release up to 10–12 hours, show a good linearity between the predicted and measured velocities. Recently, LSC or LSC compacts prepared using either streaming or spray-drying as processing is developed.[29]The LSC compacts containing a liquid and solid phase can be used, in which a liquid, after preheating, is sprinkled into and

mixed with a base powder, followed by steaming in an evaporator. After sealing and further steaming again in a high-temperature melting process at 100–115°C and blasting in a high-temperature pin mill, the LSC single-unit powder exhibits a large porous volume and pore diameter (14.8 μm), expansion ratio (±80%), and flowability (HAs <40 °C).[165]

### 13.1. Solid Dispersions

Drugs which are poorly soluble in water are most common in pharmaceutical industry. More than 40% drugs in pipeline and 70% of the newly developed drugs are poorly soluble in water. This leads to poor bioavailability of these drugs. Solid dispersion was invented to increase the solubility of poorly soluble drugs which involve dispersing drug in suitable carrier at liquid state or melt state. This technique has several advantages and use various carriers which can be selected as per drug profile. There are many methods for preparing solid dispersions being used by research employees but there are few commercial products.[7]

Melt or liquid state dispersions let to obtain solid dispersions in heterogeneous (carrier and drug crystallization) situation. Difficulty to obtain drug and carrier homogeneity is the major problem for preparing solid dispersions in solid state mixing. Due to high molar volume and low melting point of drugs on the other hand preparation of solid dispersions through solvent evaporation is very expensive and time consuming. However the drug in liquid state homogeneously disperses the carrier due to low viscosity and high surface area of drugs. Also it is possible to utilize such carriers which can absorb water only after obtaining solid dispersions. Hence this is more effective and simpler approach than the normal solid dispersions preparation methods.[166]

Strong hydrophilic raw materials are available as carriers. In order to use it carriers should lose its water at human want temperature. Complex solid dispersions were discussed i.e. one type of drug is present in multiple state which leads to unmatched above consideration.[167] It may be advantageous or disadvantageous to dissolve in non bioactive carriers or use prodrugs of carriers for enhancing bioavailability or solubility. This combination carrier system has become interesting and attractive in the eyes of researchers. Research is now focused on selecting such drug propyl or carrier possibilities which can use multiple aspects of drug development or formulation design.[168]

### 13.2. Nanosuspensions

Nanosuspensions are sub-micron colloidal dispersions consisting of poorly water-soluble drugs, stabilizers, and/or surfactants. Nanosuspensions formulations contain drugs with a size range of less than 1000 nm. The small size of drug particle leads to enhancement in dissolution rate due to the increased surface area and accelerated mass transport of nanocrystals.[169] The technique can be applied with different methods used to prepare nanosuspension-based formulations. Recently, various injectable nanosuspensions have been developed and tested preclinically. Formulating poor aqueous solubility drugs in nanosuspension formulations significantly improves bioavailability.[170] Nanocrystalline formulations of carvedilol marketed for an oral route showed FDA approval. The purpose of this review study is to provide detailed information on nanosuspensions as a promising approach for enhancing bioavailability of poorly soluble drugs. Nanosuspensions have a great deal of interaction at the mucosal membrane due to a large surface area that leads to enhanced permeability across the intestinal membrane.[171] Nanosuspensions can be administered efficiently through the oral, parenteral, buccal, nasal, transdermal, and intravitreal routes. Sample studies were conducted to expand the applications

of nanosuspensions by various routes. There is a growing consensus that nanosuspensions are promising delivery systems to enhance the solubility and bioavailability of poorly water-soluble drugs. These nanosuspensions can be developed by several techniques. Unfortunately, the large-scale production and commercial manufacture of nanosuspensions remain a challenge.[172]

## CONCLUSION

Liquisolid compact technique is an innovative method to increase the solubility and bioavailability of poorly soluble drugs. Liquisolid compacts have the capacity to contain solutions of non-volatile and high melting point liquids. An ideal liquisolid formulation should be fluffy, free flowing, and effective in solubility enhancement for drug delivery.[173] Many approaches including use of salt form, amelioration of pH, use of surfactants, micronization of drug, solid dispersions, emulsions, inclusion complexes, lipid-based systems etc., have been explored by researchers. But they all have limitations in terms of cost and feasibility. By using simple design and formulation liquisolid compact technique enhances solubility and hence bioavailability of poorly water soluble drugs, as food and drug interaction, prolonged effect and sporadic delivery of drug may be reduced.[174]. Liquisolid technique for the improvement of dissolution of a poorly soluble drug, which can be utilized as an alternative formulation design for enhancing the solubility and dissolution properties of poorly water soluble drug. Various drug delivery systems were prepared using a well-absorbed drug. They provide a brief overview of liquid-solid compacts, methods of preparation, optimizing variables and constituent compounds, evaluating the solubility of poorly soluble drugs. Recent and future trends in liquisolid technique, either its application or preparation, were covered. The improvement of solubility and dissolution rate of a poorly-soluble drug, efavirenz, using liquisolid compacts was highlighted [30]. Atorvastatin Calcium is a poorly soluble drug, which is practically insoluble in water. The liquisolid compact technique was an alternative formulation for the enhancement of solubility and dissolution of atorvastatin calcium. The recent advances made in the field of liquid-solid compacts through the literature from the beginning till date were discussed along with possible future trends as well. Solid dispersion, microencapsulation, inclusion complexation, liposome, use of surfactant oils, liquisolid compacts, and various other techniques were discussed [146]. Among various methods, the liquisolid compact technique is a novel, effective, cost-effective, and best approach for enhancing the solubility and bioavailability of poorly water-soluble drugs.

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HOW TO CITE: Deeksha Agarwal, Anjali Singh, Lakshya Veer Singh, Liquid-Solid Compacts: Approach for Improving Drug Solubility and Bioavailability, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 5, 4357-4383, https://doi.org/10.5281/zenodo.20267338