# Novel approaches for solubility enhancement of BCS class II drugs

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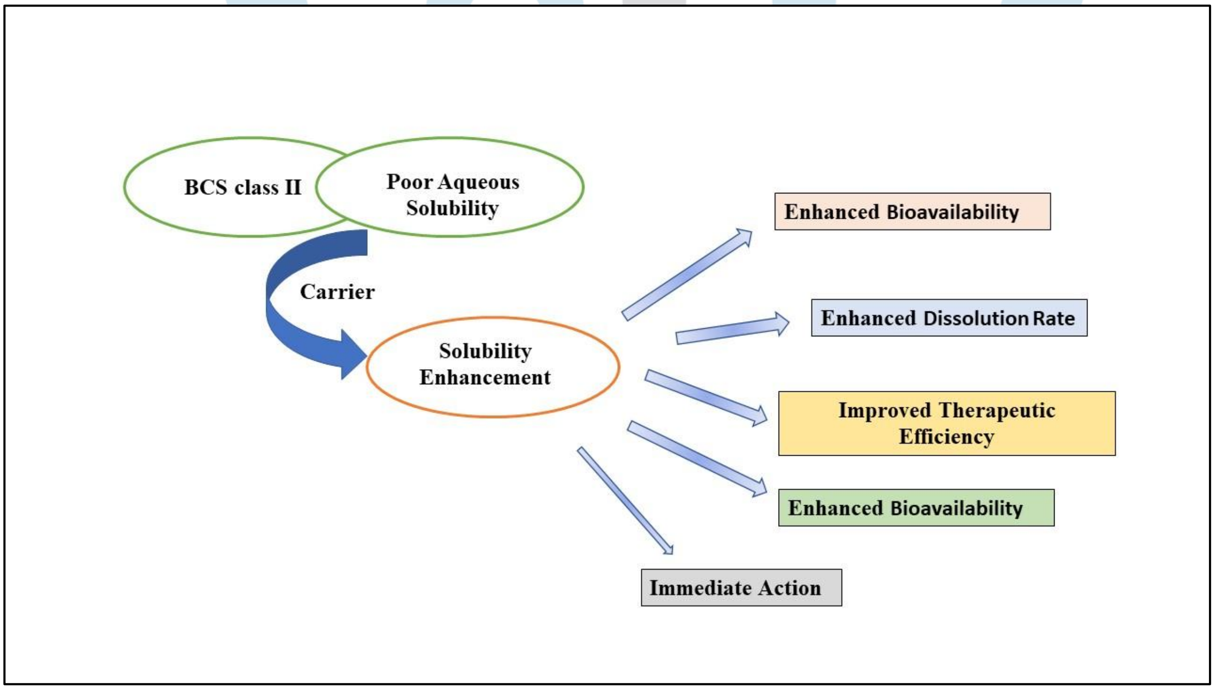
## Graphical Abstract



## Abstract

When creating oral dosage forms, the main problem is ensuring that the medicine is soluble and bioavailable. About 40% of new pharmacological entities with limited solubility are the result of pharmaceutical research worldwide. The main issue with poorly water-soluble medication design is lower bioavailability. A pharmacological product's efficacy is diminished by poor water solubility, which also increases adverse effects and patient variability (both intra- and inter-patient). We have discussed how solubility was improved for better therapeutic action in this paper. To help you better understand the notion of solubility improvement, we have also detailed the many research for some BCS class II medications, such as atorvastatin, aceclofenac, valsartan, and ketoprofen. Finally, a few instances of carriers utilized to improve solubility were covered. Researchers and scientists will benefit from this article's improved understanding of solubility enhancement.

**Keywords:** Solubility; BCS class II; Bioavailable; Carrier; Solubility enhancement.

## Introduction

About 40% of new pharmacological entities with limited solubility are the result of pharmaceutical research worldwide (1). Due to pharmacological and toxicological methods using high throughput screening and combinatorial chemistry, this figure will rise by up to 90% (2). Pharmacies invest enormous sums of money in everything from product development to medicine discovery. Failures can also occur during the product development process, which is why some medications fail to reach the market during post-marketing surveillance and others are recalled. Thus, only about 10% of newly developed pharmaceutical drugs with poorly soluble pharmacological molecules make it from clinical trials to the market. Oral medicine administration is widely recognized as a convenient method for ensuring patient compliance (3).

The oral route has several benefits, including easy drug delivery, repeat dose administration, and variety in formulation manufacture. Prior to permeability, which allows a medicine to eventually reach the systemic circulation, solubility is the main requirement for a drug (bioavailable) (4). Since the majority of these medications are lipophilic, their poor water solubility negatively impacts their bioavailability. Therefore, developing oral medication delivery methods for weakly water-soluble medicines is more difficult for pharmacists. The main factor influencing a drug's plasma concentration—which is required for its pharmacological action—is its solubility. During the medication development process, these compounds' in-vitro and invivo assays present additional challenges (5).

Without mentioning the biopharmaceutical categorization system, which classifies drugs according to their permeability and solubility, which can have an impact on their bioavailability, the term "solubility" is rendered meaningless. All medications are categorized into four classes by the biopharmaceutical classification system. The solubility of BCS class II and IV medications is an issue; nevertheless, of the two, the solubility of BCS class II drugs is the rate-limiting phase during dissolution (6). Other forms of dosage, such intravenous formulations, also heavily depend on solubilization. One important factor in achieving the requisite quantity of medications in the systemic blood circulation to produce the required reaction is solubilization (7).

When taken orally, water-insoluble drugs frequently need high dosages to reach therapeutic plasma concentrations. One of the main issues with general development and the creation of novel chemical formulations is low water solubility. The medication that is going to be absorbed needs to be present in the absorption area in an aqueous state. The liquid used in the mixture of liquid medications is water. Nearly all medications have limited water solubility, a weak acidic core, or a weak base. These poorly soluble in water drugs have a sluggish rate of absorption, which causes the gastrointestinal mucosa to be toxic and have insufficient and inconsistent bioavailability. The most significant constraint to achieving the necessary amount in the systemic blood circulation for reactions when it comes to oral drugs is their solubility (8).

Solubility is a big difficulty for scientists who study pharmaceuticals. One of the most challenging parts of the drug development process is improving drug solubility, which is followed by oral bioavailability, particularly for oral drug delivery systems(9). There are numerous methods for making poorly soluble medications more soluble in water. The features of the medicinal product in issue, the makeup of the chosen sample, and the anticipated dosage are some of the factors that go into choosing this technique. Many researchers have employed a variety of techniques (both conventional and contemporary) to improve the solubility of medications that are poorly soluble in water, including solid dispersions, cocrystals, nanospheres, nanoparticles, and self-emulsifying drug delivery (2, 10, 11). Thus, one of the key techniques for improving the solubility of BCS class II medications is solid dispersion.

## Need For Solubility Enhancement

Due to its ease of use, affordability, high and improved patient compliance, improved stability, ease of manufacturing, and flexibility in dosage form design, the oral route of administration is the most appropriate and widely used method of drug delivery. When creating oral dosage forms, the main problem is ensuring that the medicine is soluble and bioavailable (12). The main issue with poorly water soluble medication design is lower bioavailability. Drug permeability, metabolism, rate of drug dissolution, and water solubility all affect a medicine's bioavailability. A pharmacological product's efficacy is diminished by poor water solubility, which also increases adverse effects and patient variability (both intra- and inter-patient). As a result, solubility is now the main restriction in the medication development process (13, 14).

Better solubility is desirable, but so are increased efficacy, safety, and economical formulation design.

Certain medications, such as atorvastatin, aceclofenac, valsartan, ketoprofen, and carbazepine, are preferred for the treatment of specific disease classes. However, they are also regarded as poorly soluble in water medications. The solubility of these medicines determines both their therapeutic action and bioavailability (15-17). Enhancing the solubility of these drugs through innovative approaches will contribute to a higher bioavailability.

## Solubility Enhancement of Some BCS Class II Drugs

### Aceclofenac

Aceclofenac is a nonsteroidal anti-inflammatory medication (NSAID) derived from phenylacetic acid that exhibits strong analgesic and anti-inflammatory effects. With selectivity for the COX-2 isoform over the COX-1 isoform, it is a strong inhibitor of cyclooxygenase (COX), an enzyme essential to the manufacture of prostaglandins and thromboxanes (18). First authorized by the EU in

1990, aceclofenac was introduced in Spain in 1992. Since then, it has been given the go-ahead for usage in 69 nations, treating an estimated 171 million patients. Aceclofenac is a derivative of phenylacetic acid that is taken orally and acts on many inflammatory mediators (19).

In many painful situations, aceclofenac relieves symptoms by acting as an analgesic and an anti-inflammatory.Comparable to diclofenac, piroxicam, and naproxen, the medication lessens pain, lessens the severity of the condition, and enhances knee function in people with osteoarthritis. The list of approved uses for aceclofenac varies from nation to nation, but generally speaking, it is advised for the management of painful and inflammatory conditions like osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, odontalgia, scapulohumeral periarthritis, and extraarticular rheumatism (20).

Aceclofenac taken orally is quickly and totally absorbed; peak plasma concentrations are attained between 1.25 and 3.0 hours after dose. There has a 4-hour elimination half-life and a 25-liter distribution volume. Aceclofenac concentrations in the synovial fluid rise to around 57% of those in the plasma after penetration. Aceclofenac has a volume of distribution of around 25 L and is highly (>99%) protein bound.

### Valsartan

Angiotensin-receptor blocker (ARB) valsartan is used to treat heart failure, diabetic nephropathy, and hypertension, among other cardiac disorders. By competing with angiotensin II for binding to the type-1 angiotensin II receptor (AT1) subtype and blocking the blood pressure-raising effects of angiotensin II, valsartan reduces blood pressure by opposing the renin-angiotensin-aldosterone system (RAAS). Angiotensin-converting enzyme (ACE) inhibitors cause dry cough, a side effect that is not experienced by ARBs. Diabetes-related nephropathy, left ventricular hypertrophy, isolated systolic hypertension, and hypertension can all be treated with valsartan. It can also be used as a substitute medication to treat coronary artery disease, myocardial infarction, systolic dysfunction, and heart failure (21, 22).

Angiotensin II is specifically blocked from binding to the angiotensin II type 1 receptor by valsartan, a nonpeptide angiotensin receptor antagonist. Valsartan's effectiveness, safety, and tolerance have been proven in extensive research on heart failure (HF), post-myocardial infarction (MI), and hypertension. Between 85 and 99% of valsartan's plasma proteins are bound; its estimated volume of distribution and plasma clearance are 17 liters and 2.2 liters per hour, respectively. Following an 80 mg dose of valsartan, the mean elimination half-life (t½) was 7.05 hours. Of a dose of valsartan taken orally, around 86% is excreted through feces, and approximately 13% is eliminated by the kidneys. Two days after the treatment, most renal excretion is finished, but significant stool elimination lasts until day four. Most of the medication is eliminated unaltered (23).

In order to improve the antihypertensive drug valsartan's aqueous solubility and rate of dissolution by solvent evaporation technique, Balakrishnaiah et al.prepared and characterized solid dispersions of the poorly water soluble agent using water soluble carriers such as Kolliphor P 407, Kolliphor P 188, Kolliwax GMS II, Kolliphor HS15, HPMC AS, and Soluplus in the proportions of

1:1, 1:3, and 1:5 (Drug: Carrier). They also added 2% SLS to the mixtures. The solubility behavior and drug release of all the formulations were significantly enhanced. The acquired results demonstrated that when the drug was produced as a solid dispersion as opposed to a pure form, the water solubility and rate of dissolution were greatly improved (24).

Sapkal et al.utilizing the solvent evaporation approach, the scientists produced and studied solid dispersions of valsartan utilizing β-Cyclodextrin to increase its water solubility and rate of dissolution. The acquired results demonstrated that, when formed in a solid dispersion as opposed to a pure medication, the water solubility and rate of dissolution were greatly improved. The kind and quantity of the carrier determine how much the dissolving rate is enhanced, and this rate increases as the carrier's concentration rises. Reduced drug particle size deposited on the carrier's surface and improved drug particle wetability by the carrier may be the cause of the increase in dissolving rate (25).

Parvataneni et a.Surfactants are frequently added to tablets in order to enhance wetting, disintegration, and dissolution during wet or dry granulations, or in conjunction with directly compressible vehicles. The dissolution performance of valsartan tablets was enhanced by the application of Microparticle-entrapped micelles (MEM) technology, which resulted in tablets that showed a higher dissolution rate than controls and were marketed in all media used, regardless of pH levels and composition (26). Yan et al.created a novel valsartan-loaded solid dispersion with increased bioavailability and no crystalline alterations, several valsartan-loaded solid dispersions were prepared with water, hydroxypropyl methylcellulose (HPMC) and sodium lauryl sulphate (SLS). Unlike the traditional solid dispersion system, the valsartan-loaded solid dispersion had a rather rough surface and did not affect the crystalline form of the medication. The drug solubility was increased by approximately 43 times in the drug-loaded solid dispersion made up of valsartan/HPMC/SLS at a weight ratio of 3/1.5/0.75. When compared to valsartan powder and the commercial product, it produced a greater AUC, a shorter Tmax, and a Cmax (27). In order to increase the solubility of valsartan, Shirsath N et al. create valsartan-mannitol Solid Dispersions (SDs) using bottom-up process-based freeze drying (lyophilization) techniques. The ideal solubility and particle size parameters were 242.5 nm and 115.14µg/L, respectively.Simple lyophilization processes were used to successfully generate solid dispersions of valsartan-mannitol, which appear to have promise for improving the drug's oral bioavailability and rate of solubility (28). In order to enhance the solubility of Valsartan, Suhail et al. prepared carbopol 934-co-poly(itaconic acid) (CPcPIA) nanogels using the free radical polymerization technique. Polymeric nanogels were observed to significantly increase the solubility of Valsartan (2.002, 2.976, and 3.543 mg/mL) in pH 1.2, deionized distilled water, and pH 7.4 as compared to the reference product. The results of the toxicology study revealed that the prepared nanogels had no harmful effects on the species of rabbits. This suggests that synthesized nanogels are not only limited to a particular class of drug; rather, they can enhance the solubility of all low aqueous soluble drugs (29).

## Ketoprofen

An example of a non-steroidal anti-inflammatory medicine (NSAID) is ketoprofen (KP). Because of its capacity to treat inflammatory illnesses, musculoskeletal injuries, rheumatoid arthritis, osteoarthritis, and dysmenorrhea to reduce mild discomfort, it is commonly utilized in medical care. By inhibiting cyclooxygenase (COX), ketoprofen primarily functions by preventing arachidonic acid from being converted into prostaglandins and thromboxane A2, which are chemicals that trigger inflammation. Additionally, in both in vitro and in vivo models of glioma tumors, ketoprofen inhibits cell proliferation (30, 31). Ketoprofen also has the qualities of simple metabolism, rapid blood-brain barrier crossing, and rapid absorption. Abdominal pain, gastrointestinal erosions, ulcers, and significant adverse effects could all be exacerbated by using ketoprofen (32).

The goal of Devi et al.'s work is to use fumaric acid as a coformer to build a co-crystal that will increase the solubility of ketoprofen. By using a straightforward solvent-assisted grinding technique, the co-crystal of fumaric acid and ketoprofen was created. The drug and coformer were considered independent variables, while the solubility and percentage of drug release were considered dependent variables. Based on the findings of experiments on solubility and dissolution rate, the formulation demonstrated a significant improvement in both co-crystallization qualities. When compared to a standard medicine, the optimized batch of co-crystal formulation demonstrated a swift pharmacological response in Wistar rats and albino mice based on in vivo activities (anti-inflammatory and analgesic)(33). Ketoprofen (KTF) nanosuspension was created by Amin et al. using high-pressure homogenization (HPH). The objective is to produce a stable nanosuspension with a higher rate of dissolution and drug saturation solubility.According to the acquired results, HPH can be used to create aqueous drug nanosuspensions that have fine dissolving and solubility characteristics, making the created particles stable for up to one month. According to the data, the generated nanosuspensions exhibit a uniform distribution morphologically even after redispersion, demonstrating the product's stability (34).

Ketoprofen is a non-steroidal anti-inflammatory medication that causes gastrointestinal issues and is not readily soluble in water. Yiyun et al. looked into the possibility of using polyamidoamine (PAMAM) dendrimers to make ketoprofen more soluble in his work. Variables including pH level, concentration, and dendrimer production have all been studied for their effects. According to the experiment's findings, the concentration of dendrimers directly correlated with ketoprofen's solubility in the dendrimer solutions. PAMAM dendrimers can be utilized quite well, under the right circumstances, to increase the solubility of ketoprofen (35).

Devi et al. assessed the potential of a liquid-solid formulation to increase ketoprofen's rate of dissolution and, consequently, its bioavailability. Different batches of liquisolid were made with aerosil 200 as the coating material, microcrystalline cellulose as the carrier, and polyethylene glycol 200 as the solvent. The present study's findings demonstrated that the liquisolid formulation may be a useful strategy for improving ketoprofen's bioavailability and may be used to oral therapy (36). Ketoprofen (KETO), a BCS class-II medication that is poorly soluble in water, was made more soluble and dissolved faster by Yadav et al. via a solid-dispersion method. Polyvinylpyrrolidone K30 (PVP K30) and d-mannitol were used in various drug-to-carrier ratios to generate solid dispersions. Solid dispersions containing d-mannitol were made by kneading and melting processes, while dispersions containing PVP K30 were made by kneading and solvent evaporation techniques. The solid dispersions made with PVP K30 had the greatest increase in KETO dissolving rate. Better dissolving profiles were displayed by physical mixes of KETO produced with both carriers than by pure KETO (37).

## Carbazepine

1968 saw the approval of carbamazepine for the treatment of trigeminal neuralgia, and 1974 saw the addition of approval for the medication's usage in partial seizures. Numerous other first-generation medications have also received approval and are being used to treat different kinds of seizures. For example, ethosuximide is being used to treat absence seizures in the absence of generalized tonic-clonic seizures (38). Valproic acid is used to treat partial seizures and primary generalized epilepsies. Since the 1950s, carbamazepine has been the most commonly used medication. Benefits of carbamazepine include its ability to treat partial, secondary, and most likely primary generalized seizures; it has a less sedative effect than barbiturates; it is simple to detect blood levels; and increasing the dosage causes a gradual rise in blood levels (39).

Because carbamazepine has a low water solubility (17.7 mg/L), it has a low bioavailability. This makes a higher dose necessary, which increases the risk of related noncompliance and the drug's negative effects. Food may boost the medicine's dissolution, as carbamazepine is a BCS class-II medication that is extremely permeable and weakly soluble. This has been observed to increase the bioavailability of the drug. Nevertheless, by giving the medication in a more bioavailable form that tends to require a lower dosage, these problems can be mitigated. Because drug-loaded SLN solves carbamazepine's solubility issues, it can be used to increase bioavailability and decrease variability in fed and fasting states. Medarević et al. explore the possibility of using poloxamers as carriers of solid dispersions (SDs) to increase the rate of dissolution of carbamazepine (CBZ), a medication that dissolves poorly. Poloxamer 188 (P188) and poloxamer 407 (P407) were melted down to create solid dispersions at various drug-to-carrier ratios (1:1, 1:2, and 1:3). Because of its more pronounced hydrophilic qualities, P188 shows greater efficiency in raising the rate at which CBZ dissolves, whereas increasing the concentration of poloxamers led to a decrease in the rate at which drug release occurs because of their thermoreversible gelation (40). The effects of solid dispersion on the solubility, dissolution rate, and pharmacokinetic profile of carbamazepine were investigated physicochemically by Zerrouk et al. Studies on solubility revealed that the solubility of carbamazepine increased linearly as the concentration of PEG 6000 increased. When it comes to the increase in carbamazepine solubility caused by PEG 6000, there is no discernible difference between physical mixes and solid dispersions. In 90 minutes, less than 60% of pure carbamazepine was dissolved. In contrast to the parent medication, the dissolution rates of physical mixes (carbamazepine phase III) and solid dispersions (carbamazepine phase II) were higher. Phase III carbamazepine disintegration was more noticeable than phase II disintegration. The dissolution profiles showed that the amount of PEG 6000 was a determining factor in the percentage of medication dissolved (41).

Using PLGA as the polymer (with varying drug:polymer ratios) chosen at random by factorial method designing, Tummala et al. develop nanotechnology-based systems for a few poorly water-soluble drugs, such as carbamazepine, with the expectation of improving dissolution properties that may increase its bioavailability. Particle size, drug loading, and entrapment efficiency of the optimized batch in the drug:polymer ratio of 1:1 are 126.8±0.19m, 34.81±0.01%, and 64.28±0.09%, respectively. According to in vitro drug release studies, carbamazepine nanoparticles released the drug in two phases: first, in a burst of 50±0.12% within four hours, and then, over the course of 24 hours, in a continuous release of 89.92±0.01%, indicating an improvement in solubility (42). Feng et al. produced and characterized carbamazepine (CBZ) loaded SDs with outstanding dissolving and tabletability. Using Eudragit EPO as the carrier, hot-melt extrusion (HME) was used to create the CBZ SDs at a 4:1 drug to carrier ratio. The findings demonstrated that after being extruded at 140 °C, the crystalline form of the polymorph of CBZ in SDs changed from form III to form I. All of these findings demonstrated how much the CBZ SDs made by HME with 80% CBZ and 20% Eudragit EPO could enhance tabletability and dissolving (43). Heena et al. used various solubility enhancement strategies to increase the solubility and dissolution rate of the antiepileptic carbamazepine (CBZ). Although only a very tiny amount of CBZ (20 mg) could be added to SNEDDS, the necessary dosage of CBZ was effectively synthesized as a solid dispersion using Soluplus®. Based on the findings, it is possible to improve the bioavailability of CBZ by making a solid dispersion because of the higher solubility and dissolution (44).

### Atorvastatin

The hepatic enzyme HMG-CoA reductase is selectively and competitively inhibited by atorvastatin. Hepatic cholesterol levels consequently decline because HMG-CoA reductase is the enzyme that catalyzes the conversion of HMG-CoA to mevalonate in the cholesterol production pathway. Lower levels of hepatic cholesterol cause the liver's LDL-C receptors to become more highly expressed, increasing the liver's absorption of LDL-C and lowering blood levels of the metabolite (45). In aqueous solutions with a pH of 4 or lower, it is insoluble. The solubility of atorvastatin calcium in distilled water, pH 7.4 phosphate buffer, and acetonitrile is very minimal. The systemic availability of HMG-CoA reductase inhibitory action is approximately 30%, while the absolute bioavailability of AT (parent drug) is about 12%. First-pass metabolism in the liver and presystemic clearance by the gastrointestinal mucosa are the causes of the low systemic bioavailability (46). Shaker MA et al. created atorvastatin (AT) with amphiphilic carriers (Pluronic F127® and Pluronic F68®) to increase the drug's oral bioavailability in vivo as well as its solubility and dissolution in vitro. Up to 93% of the AT content was dissolved in 30 minutes, according to dissolution profiles, which also demonstrated a rise in the rate and maximum amount of dissolved AT. The addition of Pluronics® to AT formulation significantly increases AT's absorption and dissolving behavior, and it may be a helpful strategy for enhancing AT's therapeutic and clinical efficacy (47).

To improve atorvastatin calcium solubility, Ali AH et al. create a nanosuspension of the drug. Furthermore, the freeze-dried material's saturation solubility In distilled water, 0.1N HCl, and phosphate buffer pH 6.8, nanosuspension demonstrated increases of 3.3, 3.8, and 3.7 folds, respectively. When atorvastatin calcium, which is weakly soluble in water, was prepared as a nanosuspension, the drug's solubility and rate of dissolution were greatly increased (48). Shahraeini et al.used an ultra-sonication process to manufacture atorvastatin solid lipid nanoparticles (ATR-SLNs). The synthesized SLNs exhibited a PDI value of less than 0.5, with nanoparticle sizes ranging from 71.07 ± 1.72 to 202.07 ± 8.40 nm. It was observed that drug entrapment efficiency and nanoparticle size increased in tandem with an increase in lipid concentration in ATR-SLNs. The results of in vitro skin penetration demonstrated that atorvastatin-containing SLN might improve atorvastatin dermal delivery, where a greater concentration of atorvastatin was found in skin layers (49). Naqvi et al.created and described atorvastatin calcium co-crystals using liquid-assisted grinding, utilizing nicotinamide and citric acid as co-formers to improve solubility. Zeta size research revealed that the vast surface area of small particle sizes helps to promote solubility. The formulations' solubility was found to be boosted several times in all mediums when compared to the solubility of the medicine that is currently on the market, according to investigations on its dissolution and solubility. Based on all of these investigations, it can be said that the co-crystallization approach improved the calcium atorvastatin solubility through the use of a liquid-assisted grinding process (50). In order to enhance drug breakdown, Maleki A et al.developed mesoporous silica composites that included the weakly water-soluble medication atorvastatin calcium (AC), which was meant to be administered orally. The effects on drug release rate of mesocellular siliceous foam (MSF) with continuous 3D pore system and 2D-hexagonal silica nanostructured SBA-15 were also compared. It verified a notable improvement in the atorvastatin calcium release profile when using SBA-15 and MSF as the drug carrier. Furthermore, MSF demonstrated a quicker rate of AC release in an enzyme-free simulated stomach fluid (pH 1.2) as compared to SBA-15 (51). By employing the conventional fusion and microwave-induced fusion methods, Taral et al. developed a solid dispersion of atorvastatin calcium in varying ratios. The carrier used for this process was PEG 6000. There is no chemical interaction between the medication and the polymer, according to the FTIR measurements. As the concentration of PEG 6000 increased, all of the formulations demonstrated a noticeable improvement in drug solubility. However, compared to the traditional hot melt process, the dispersion made using the microwave-induced fusion method is more soluble (52).

## Fenofibrate

The mechanism of action of fenofibrate is the activation of peroxisome proliferator activated receptor α (PPARα). This decreases apoprotein C-III synthesis and activates lipoprotein lipase, increasing lipolysis and removing triglyceride-rich particles from plasma. The drop in triglycerides that follows causes the size and makeup of LDL to change from small, dense particles to large, buoyant particles (53). These bigger particles are quickly catabolized and have a higher affinity for cholesterol receptors. The digestive system absorbs fenofibrate efficiently. Following absorption, metabolites—mainly fenofibric acid and fenofibric acid glucuronide—are the principal way that FE is eliminated in the urine (54).

For fenofibrate that is poorly soluble in water, Yousaf et al. create a unique electrosprayednanospherule that has the best oral bioavailability and aqueous solubility. When compared to free medication, all of the electrosprayednanospherule formulations exhibited noticeably improved aqueous solubility and dissolution. It exhibited the maximum solubility at 32.51±2.41 μg/mL, a superb dissolving rate of ~85% in 10 minutes, and an oral bioavailability that was almost 2.5 times greater than the free drug. When compared to the traditional solid dispersion, it demonstrated a comparable oral bioavailability. Improved solubility and bioavailability offered by electrosprayednanospherules make them a feasible drug delivery option for oral administration of fenofibrate, which is not very water soluble (55). FBT nanocrystals are created by Ige P et al. to improve oral bioavailability and solubility. In 1% sodium lauryl sulfate (SLS) media, formulation FNS3 and pure medication demonstrated in vitro dissolution rates of approximately 73.89% and 8.53%, respectively. It was discovered that the pure drug's saturation solubility in 0.5% and 1% of SLS was 6.02 ± 1.51 μg/ml and 23.54 ± 1.54 μg/ml, respectively. Fenofibrate nanocrystals' improved absorption and solubility suggest that this may be a viable oral administration method (56). Fenofibrate (FF), a medication that dissolves slowly in water, was dissolved more quickly thanks to Ghosh et al. A dissolving research was first conducted on solid dispersions of fenofibrate (SDFs) that were made with Carplex-80, PEG-4000, or both at different weight ratios.Therefore, compared to pure FF, the amount of medication released by SDF-7 was maximized by a factor of 2.5.The solid dispersion approach significantly improved FF release, according to the results (57). A successful supercritical drying approach along with the sol-gel method were used to manufacture supercritical processed starch nanosponge (SSNS) by Jadhav et al. The generated SSNS material has a high surface area (180 m2/gm) and pore size (40 nm to 200 nm), according to the results. When compared to ordinary medication, an in-vitro drug release research revealed a significant improvement in the SSNS formulation's solubility (58). In order to improve the oral bioavailability of fenofibrate (FNB), Quan G. et al. looked into the use of mesoporous silica Santa Barbara amorphous-15 (SBA-15), which is derived from supermolecular assemblies of the surfactant Pluronic® P123 with well-ordered 2-D hexagonal pores, as a reservoir to create a novel solid self-emulsifying matrix. Compared to raw powder and commercial capsules, the in vitro release rate of the solid SEDDS matrix was quicker. Beagle dogs exhibited a considerable improvement in the absorption of FNB supplied by solid SEDDS matrix; its Cmax and AUC values were approximately 8- and 4-fold higher than those of commercial goods, respectively. A novel approach for advanced therapeutics may be offered by SBA-15, which has shown promise as a reservoir for SEDDS to increase the bioavailability of poorly water-soluble medications (59). In order to improve the solubility of fenofibrate (FB), a BCS II medication, Tran et al. devised several adsorption techniques for FB onto high-surface-area carriers (Ae200). Physical adsorption and supercritical fluid procedures demonstrated the highest dissolving rates (over 80% in 30 minutes and over 90% in 60 minutes) with the largest surface area values when compared to physical mixing and spray drying. The supercritical solvent impregnation technique (SCF1), one of the two best approaches, provided superior dissolving behavior and was linked to the FB physical state shift from crystalline to amorphous. This enhancement raises the possibility that SCF1 may be useful in the creation of hydrophobic medications (60).

## Carriers Used for Solubility Enhancement

### Polyethylene glycol (PEG)

PEGs fundamental characteristics Polyethylene glycols (PEG) are polyesters composed of ethylene oxide with a molecular weight ranging from 200 to 3,00,000. PEGs with molecular weights ranging from 1500 to 20,000 are frequently employed in the manufacturing of solid solutions and dispersions. As the MW rises, PEG's viscosity increases. At room temperature, PEGs with a molecular weight (MW) of 2000 or more form hard, brittle crystals; those with a MW of 800 to 1500 are best described as Vaselinelike. PEGs with a MW of 600 or less are fluid. Their water solubility is generally very good, however it gets worse as MW increases. PEGs dissolve in a variety of organic solvents, making them especially helpful for producing solid dispersions (61). The PEGs of relevance have no melting point above 65 oC. For instance, PEG 1000, PEG 4000, and PEG 20 000 all have melting points between 30 and 40 °C, 50 and 58 °C, and 60 and 63 °C. The melting method can be used to create solid dispersions due to their low melting temperatures. Additionally, PEGs can solubilize some molecules and make other chemicals more wettable. Even a medication that dissolves well in water, like aspirin, can have its rate of dissolution accelerated with PEG 6000. PEGs with MWs between 4000-6000 are most frequently used to create solid dispersions since water solubility is still comparatively high in this range (62). The drug-to-carrier ratio is one of the most significant variables influencing a solid dispersion's effectiveness. An overly high concentration of the drug will cause it to solidify instead of remaining molecularly dispersed in the dispersion. However, an excessive carrier percentage may result in the drug losing all of its crystallinity, which would greatly enhance its solubility and release rate (63).

### Polyvinylpyrrolidone (PVP)

When vinypyrrolidone is polymerized, polymeric compounds with molecular weights ranging from 2,500 to 3,00,0000 are produced. Similar to PEGs, PVPs are highly soluble in water and can improve the hydrophilicity of dispersed molecules in a variety of contexts. The rate of flufenamic acid wetting and dissolving was accelerated by the use of PVP-based solid dispersions (64). The higher chain length of high molecular weight PVPs further reduces their water solubility, which is already poor due to their significantly greater viscosity at a given concentration. PEG and other solid dispersions with a high PVP content have a better drug release profile and solubility than dispersions with high drug concentrations. With PEG, this is also true (65).

### Cellulose Derivatives

Celluloses, a kind of polysaccharides present in plants, are widely distributed across the plant kingdom. High molecular weight unbranched chains are joined by b-1, 4-glycoside bonds forming between the saccharide molecules.

### Hydroxypropyl methylcellulose (HPMC)

In HPMCs, 4-32 percent of the hydroxyl groups are derivatized with hydroxypropyl groups, and 16.5–30% of the hydroxyl groups are methylated. Mixed cellulose ethers make up HPMCs. HPMCs are soluble in water, ethanol/dicloromethane mixtures, and methanol/dicloromethane combinations. Their molecular weight ranges from 10,000 to 1,500,000.

### Hydroxypropyl cellulose (HPC)

Chloroform (hydroxypropyl cellulose), methanol, ethanol, water (up to 40 °C), and other solvents could all be successfully solubilized using HPC. In fact, the diameter of HPCs ranged from 37,000 MW (Type SSL) to 1,150,000 MW (Type SSB) (Type H). Numerous studies have recently been conducted to examine the effects of chain length and HPC fraction in the solid dispersion on the release behavior of flurbiprofen. The release rate increased as a result of the use of lower MW HPCs as carriers (66, 67).

### Carboxymethyl ethyl cellulose (CMEC)

Carboxymethylethylcellulose (CMEC) resists disintegration by the stomach's acid, unlike most cellulose-ethers, which dissolve in the stomach. The grade of CMEC determines the lowest dissolving pH; above pH 5–6, it dissolves quickly. Furthermore, CMECs dissolve readily in a 1:1 mixture of dichloromethane and ethanol (i.e., 70% isopropanol, 60% ethanol, and 30% acetone). At pH 6.8, nifedipine and spironolactone dissolve much more quickly in amorphous solid dispersions. Additionally, it's probable that the medication under investigation, MFB1041, will have a significantly higher bioavailability in beagles (68).

### Urea

Urea is a byproduct of human protein metabolism that is generally regarded as harmless and has a modest diuretic effect. It is easily soluble in a variety of typical organic solvents in addition to being highly soluble in water. Even though urea is no longer frequently used as a carrier in the pharmaceutical business, ofloxacin's solubility rate may be increased more than thrice when co-evaporated with urea (69).

### Polyols, sugar, and their polymers

Notwithstanding their low toxicity and high water solubility, sugars, polyols, and their polymers are not suitable carriers for the synthesis of solid dispersions. Because most sugars have a high melting point and are poorly soluble in organic solvents, preparing hot melts and co evaporates can be problematic.

### Emulsifiers

Emulsifying chemicals can also be used to improve the way that many drugs release. This could be due to a number of things, such as improved wetting qualities and drug solubilization. Using them in combination with another carrier is standard procedure due to the possibility of toxicity problems, like damage to the mucosal membrane.

### Derivatives of organic acids

In order to improve the oral bioavailability of griseofulvin in solid dispersions, organic substances like citric and succinic acids were first employed. Liquids become solids when they are ensnared in cyclodextrins, which enhances solubility and offers flavor masking, chemical protection, and simpler handling.

## PATENTS RELATED TO SOLUBILITY ENHANCEMENT

Some patent which related to solubility enhancement are given in table 1.

**Table 1.** List of Patents which related to Solubility Enhancement

| Patent Number | Title of Patents | Summary | Inventor and Year of Application |
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| EP2878311 A1 | Solubility Enhancement for Hydrophobic Drugs | The goal of the innovation is to offer an enhanced formulation with better bioavailability for active ingredients that are either water soluble or poorly soluble in water. Therefore, another goal is to create a unique composition with active ingredients that are either water insoluble or poorly soluble in water yet have improved profiles of absorption and dissolution. | Freund Pharmatec Ltd, 2013 |
| US9186338 B2 | Solubility enhancer and use thereof | This invention discloses a novel solubility enhancer that can be used to create safe and efficient pharmaceutical formulations of partially soluble drugs. The solubility | Ramachandran Radhakrishnan, 2006 |

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| | | enhancer is made of dialkyl substituted amides of fatty acids with carbon chains ranging from C6 to C16, most commonly N,N-dialkyl hexanamide, N,N-dimethyl octanamide, N,N-dialkyl decanamide, N,N-dialkyl dodecanamide, or N,N-dialkyl hexadecanamide. | |
| TW-201216962-A | Formulation for solubility enhancement of poorly soluble drugs | The present invention offers a preparation for oral absorption of hardly soluble drug that improves its solubility. It is characterized by the following components: (A) a granulated substance that consists primarily of the hardly soluble drug with an acidic group in its molecule, along with an alkali agent, surfactant, and a disintegrator; and (B) a disintegrator that is only present outside the granulated substance. | Sakuma Satoshi, Ueda Hiroshi, 2010 |
| CA2746887 A1 | Methods for enhancing the release and absorption of water insoluble active agents | In one or more molten fatty acids, conjugated fatty acids, (semi-) solid surfactants with high HLB value, and/or hydrophilic polymers, a poorly water soluble active ingredient is dissolved, melted, or suspended. To create microparticles suspended in a hydrophilic or lipophilic carrier, the molten active agent mixture is subsequently suspended and homogenized in the hydrophilic or lipophilic carrier. Hard, soft, or non-gelatin capsules can contain the particles suspended in the hydrophilic or lipophilic carrier. It is anticipated that the above-described approach will yield microparticles with improved dissolving characteristics. Cilostazol dissolved 100% in 15 minutes and fenofibrate over 90% in 35 minutes, according to in vitro release trials of formulations including both drugs. | Aqeel Fatmi, Tae Kyoung Kim, 2009 |

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| CN1156461 C | Improved aqueous solubility pharmaceutical formulations | This paper describes a formulation of a pharmaceutically active drug that is crystalline and sparingly water soluble. The active agent is stabilized in its amorphous form by solidifying it in a typically hydrophobic medium. The formulation's composition stabilizes the amorphous state, extending the enhanced composition's shelf life. Additionally, the active agent's solubility and bioavailability are enhanced by this stabilized formulation. The composition of the active agent stabilizes its solutions, preventing the less soluble, crystalline form of the active agent from precipitating out of its aqueous solutions and recrystallizing. | Elkoponic, 2009 |
| WO2006046623A1 | Solid medicinal preparation improved in solubility and stability and process for producing the same | a stable medical preparation that has been given enhanced solubility while retaining preparation stability by the use of a formulation technique based on the use of a chemical component that is only partially soluble in water as the active ingredient. The solid preparation has enhanced water solubility and consists of an inorganic porous material, a water-soluble polymer, and an active component that is only partially water soluble. The process for making the solid preparation involves dissolving an inorganic porous substance and an active ingredient that is only partially water soluble in an organic solvent. The resulting solution is then mixed with the inorganic material while stirring, and the mixture is then granulated and dried. | Shogo Yamane, Hirofumi Yamane, 2005 |
| US20040058956A1 | Pharmaceutical composition having an improved water | A hydrophilic polymer and a HER2 inhibitor that is rarely or not soluble in water are combined to create solid dispersions. The oral absorption, blood bioavailability, and | Yohko Akiyama, Satoshi Iinuma, |

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|---|---|---|---|
| | solubility | HER2 inhibitor solubility of these solid dispersions have all increased. | 2001 |
| WO1996019239A1 | Solid composition with improved solubility and absorbability | A solid composition with enhanced solubility and absorbability that consists of a polymer base, a nonionic surfactant, and an extremely hardly water soluble drug in the form of an amorphous substance with a solubility of 10 vg/ml or less. When this mixture is dissolved in water, it forms fine particles with a particulate size of 1 vm or less that contain the extremely hardly water soluble drug while maintaining its amorphous form. The exceedingly rarely water soluble medicine exudes from the small particles in the solid composition, improving drug absorption through the digestive tracts. | Katsuhiko Yano, Atsushi Kajiyama, 1995 |
| JP2009506027A | Pharmaceutical composition of pranlukast solid dispersion with improved initial dissolution rate and method for producing the same | The pharmaceutical composition of a pranlukast solid dispersion with an enhanced initial dissolve rate and the process for making it are the subjects of the current invention. More precisely, the invention concerns a pharmaceutical composition of a solid dispersion of pranlukast made by heating and combining a solid dispersion of pranlukast with an anticoagulant whose HLB falls within a certain range. By addressing the significant issue of pranlukast solid dispersion sticking to the capsule wall, the initial dissolve rate of the medication was increased. When supplied in the same volume as the pharmaceutical composition, the bioavailability can be enhanced due to the superior in vivo absorption concentration (Cmax) and maximum absorption concentration (AUC). | Jun Gyo Oh Young , 2005 |

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| JP2008184393A | Improvement of water solubility of hardly water-soluble medicine by mix-grinding with acrylic copolymer, and preparation of sustained release type particle | To improve the solubility of a medication that is hardly soluble in water in order to produce sustained release type particles that release a medication under particular conditions. The feature of this sustained release type particulate composition is that it is made by spraying and drying an aqueous suspension of the uniform mixture made up of the hardly water-soluble medicine, acrylic acid-methyl acrylate copolymer, and anionic surfactant on the surface of the particulate material. This layer of the uniform mixture is made up of the hardly water-soluble medicine, the acrylic acid-methyl acrylate copolymer, and an anionic surfactant. | Hiroaki Fukamizu, 2007 |

## Conclusion

To sum up, improving the solubility of pharmaceuticals in oral dosage forms is essential to improving their bioavailability and therapeutic efficacy. The substantial influence of solubility on drug efficacy, together with the related problems of side effects and patient variability, have been brought to light in this work. We have illustrated workable solutions to these problems by examining numerous strategies for increasing solubility, especially through the case studies of BCS class II medications like atorvastatin, aceclofenac, valsartan, and ketoprofen. In order to improve the solubility of pharmaceutical formulations, scientists and researchers can get important insights from the discussion of various carriers. These developments significantly raise the possibility of better patient outcomes and less variation in medication response.

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