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# A REVIEW ON USE OF SUBLINGUAL FILMS AND SOME OTHER METHODS TO INCREASE THE BIOAVAILABILITY OF POORLY SOLUBLE DRUGS

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*Abstract :* Pharmaceutical researchers have long been exploring methods to increase the bioavailability of poorly soluble drugs, as this can significantly impact the effectiveness of a drug. One such method that has gained attention is the use of sublingual films. Sublingual films are thin strips that are placed under the tongue, allowing for rapid absorption of the drug into the bloodstream. This route bypasses first-pass metabolism in the liver, leading to higher bioavailability compared to traditional oral administration. The prodrug approach is an exciting way to improve the oral bioavailability of BCS class II drugs with low solubility and reasonable permeability, but extensive studies are needed to establish the safety profile of prodrugs in humans. Thin film drug delivery has emerged as an innovative alternative to traditional pills, capsules, and liquids commonly used for both prescription and over-the-counter medications. Dissolvable oral thin films (OTFs), also called Oral Strips (OS), originated in the confectionery and oral care industries as breath strips but have recently become a popular and innovative method for delivering vitamins and other personal care products. OTFs are gaining acceptance as a novel dosage form in pharmaceutical technology. ODFs may become the preferred delivery method for treatments requiring rapid absorption, such as those for pain, allergies, insomnia, and central neurological disorders. Self-emulsifying drug delivery systems are isotropic solutions of oil and surfactant that form oil-in-water microemulsions on mild agitation in the presence of water. SCF technologies are promising for eliminating organic solvent use in drug-cyclodextrin complexes. Overall, while sublingual films offer a convenient and effective method for increasing bioavailability of poorly soluble drugs, other innovative approaches like nanotechnology-based methods also hold potential for enhancing drug solubility and absorption. Nanotechnology-based approaches, such as nanoemulsions and nanocrystals, have shown promise in increasing drug dissolution rates and improving absorption. These techniques involve reducing drug particle size to enhance surface area and promote quicker dissolution.

***IndexTerms*** - Sublingual films, microemulsions, Nanotechnology-based approaches, nanoemulsions and nanocrystals.

## 1.INTRODUCTION

Hospital or health The oral bioavailability of BCS (biopharmaceutics classification system) class II drugs with poor solubility and reasonable permeability is limited by the drug dissolution step from drug products. Though prodrug approach is an exciting way of improving the oral bioavailability, it requires extensive studies to establish the safety profile of prodrugs in humans. In view of the increasing market share of oral drug products, a variety of technologies are developed to enhance the oral bioavailability of poorly soluble drugs using the excipients with approved or GRAS (generally regarded as safe) status. Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost-effectiveness, least sterility constraints and flexibility in the design of dosage form. As a result, many of the generic drug companies are inclined more to produce bioequivalent oral drug products. The high costs and time involved in new drug development, expiry of patents for a significant number of drug molecules, ease of manufacturing and ready availability of technology for the production of oral drug products are also driving the generic pharmaceutical companies towards the development of bioequivalent oral dosage forms. However, the major challenge with the design of oral dosage forms lies with their poor bioavailability. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, pre-systemic metabolism and susceptibility to efflux mechanisms (1, 2, 3). The most frequent causes of low oral bioavailability is attributed to poor solubility and low permeability (4). The tremendous pharmaceutical research in understanding the causes of low oral bioavailability has led to the development of novel technologies to address these challenges. One of the technologies is to design a prodrug with the required physico-chemical properties to improve the oral bioavailability (5).

The prodrug method is the best choice to increase the bioavailability of BCS class IV medications with poor solubility and poor membrane permeability and BCS class III drugs with good solubility and low permeability (6).
Nevertheless, although the prodrug strategy is an intriguing means of enhancing the oral bioavailability of BCS class II medications, it necessitates substantial research to determine the prodrug safety profile in humans, which could eventually lead to failure. The decreased solubility of the prodrug is another possible disadvantage of this strategy. Poorly soluble medications are present in over 40% of oral medicinal products on the market today, and over 30% of pharmacopoeia contains such drugs (7).
For these class II BCS medications with low solubility and reasonable permeability, is the rate-liming procedure of drug uptake. The pharmaceutical formulation is essential to the absorption of oral dose forms of medication from the gastrointestinal tract. For BCS class II medications, a range of pharmaceutical formulation strategies are employed to improve oral bioavailability. They make use of GRAS components and existing approved excipients. Thus, the price and development time are decreased. Micronization, nanosizing, crystallisation, solid dispersions, cyclodextrins, solid lipid nanoparticles, and other colloidal drug delivery systems like microemulsions, self-emulsifying drug delivery systems, and liposomes are the main technologies used to increase the oral bioavailability of drugs with poor aqueous solubility (8).

**2. THIN-FILM DRUG DELIVERY**

The administration of medications through dissolving films or oral drug strips allows for absorption in the mouth via buccal or sublingual routes, as well as enteric absorption in the small intestine. These films, made with hydrophilic polymers, quickly dissolve on the tongue or in the buccal cavity, releasing the medication into the bloodstream upon contact with fluids. Thin-film drug delivery has emerged as an innovative alternative to traditional pills, capsules, and liquids commonly used for both prescription and over-the-counter medications. These thin-film strips are primarily designed for oral administration. Users place the strip on or under the tongue (sublingual) or along the inside of the cheek (buccal). Resembling postage stamps in size, shape, and thickness, these strips allow the medication to bypass the first-pass metabolism, thereby increasing the drug's bioavailability. When the strip dissolves, the medication can enter the bloodstream through buccal, sublingual, or enteric routes. The buccal mucosa is preferred over the sublingual mucosa for systemic transmucosal drug delivery [9, 10].
Various buccal administration solutions have been commercialized or proposed for conditions such as trigeminal neuralgia, Meniere's disease, diabetes, and addiction. Thin films like Mr. Mint and Listerine PocketPaks breath-refreshing strips are widely available commercially. Since then, thin-film versions of several gastrointestinal drugs, cold and flu treatments, and other breath fresheners have also been introduced to the market. To create oral medication strips, a variety of ingredients are required, including strip-forming polymers, plasticizers, active pharmaceutical ingredients, sweeteners, saliva stimulants, flavoring agents, coloring agents, stabilizing and thickening agents. From a regulatory standpoint, all excipients used in the production of oral medication strips must be approved for use in oral pharmaceutical dosage forms [11].

**3. FAST-DISSOLVING DRUG-DELIVERY SYSTEMS**

In the late 1970s, fast-dissolving drug-delivery devices were developed to aid juvenile and elderly patients who struggle with swallowing traditional oral solid-dosage forms such as pills, capsules, and syrups. These devices include fast dissolve, rapid dissolve, rapid melt, and quick dissolving tablets, which, despite their different names, all share a similar principle and function. By definition, an oral fast-dispersing dosage form is a solid dosage form that rapidly dissolves or disintegrates in the mouth to create a solution or suspension, eliminating the need for water [12].
Oral films, also known as oral wafers, fall under this category. Dissolvable Oral Thin Films (OTFs), also called Oral Strips (OS), originated in the confectionery and oral care industries as breath strips but have recently become a popular and innovative method for delivering vitamins and other personal care products. Pharmaceutical companies have increasingly focused on developing novel dosage forms for existing medications. One such form is the oral strip, a thin film made with hydrophilic polymers that quickly dissolves on the tongue or in the buccal cavity [13, 14].
Formulating medications for children has proven challenging, with one of the key factors affecting adherence to therapy being the palatability of pediatric oral drug formulations. The fear of choking deters many young and elderly patients from taking traditional solid preparations. While oral disintegrating tablets offer the advantage of quick breakdown and administration without the risk of choking, their fragmented elements remain insoluble until swallowed. In these situations, fast-dissolving film formulations are particularly beneficial. Techniques such as solvent casting, semisolid casting, hot melt extrusion, solid dispersion extrusion, and rolling have been employed to create these oral thin films [15].

**4. ORAL THIN FILMS**

The oral mucosal epithelium, consisting of 40-50 cells, produces proteins and carbohydrates. Its thickness varies between 100-200 micrometers in different regions. The submucosal layer produces mucus, while the sublingual and submandibular regions secrete saliva and parotid fluids. Saliva consists of mucus, water, enzymes, and other substances. The mucosal structure has two distinct regions: a lipophilic membrane and a hydrophilic area. For a drug to be absorbed, its active pharmaceutical ingredient (API) must dissolve first. If the API is particularly lipophilic, absorption may be lower than anticipated due to its poor water solubility. Thus, balancing the drug's solubility and lipophilicity is crucial. The most common absorption route for medications is passive diffusion, influenced significantly by molecular weight, partition coefficient, and ionization level. When evaluating bioavailability, the API's pKa and its ionization state at the ambient pH must be considered. Typically, the degree of absorption correlates with the API's lipophilicity or partition coefficient. However, the drug's solubility is also a critical factor. The nonionized form of the drug can diffuse through cellular membranes more easily due to its higher lipid solubility. For water-soluble APIs, consistency in delivery is not an issue [16].
Conversely, for water-insoluble APIs, achieving consistent dispersion is essential to maintain the desired content homogeneity. APIs to be used in OTFs: It should only be taken in small doses, the sensation and taste left in the mouth should be suitable, the molecular weight must be minimal and the substance must be stable and soluble in saliva. Drug absorption through the mucosal epithelium occurs via two main pathways: the paracellular (intercellular) route and the transcellular pathway. The lipophilic cell membranes facilitate the passage of molecules with a high partition coefficient, whereas the hydrophilic nature of the intercellular space allows for the penetration of more hydrophilic molecules. The absorption efficiency of a drug depends on whether its molecule is hydrophobic, hydrophilic, or amphiphilic [17].
Pharmaceutical formulations include tablets, granules, powders, and liquids. Tablets are typically designed to be chewed or swallowed, but this can be challenging for elderly or young individuals who may have difficulty with solid dosage forms due to fear of choking. Orally dissolving tablets (ODTs) were developed to address this issue, but some patients still fear swallowing

solid forms. As a result, oral thin films (OTFs) have emerged as a superior alternative. Many drugs have low oral bioavailability due to stomach enzymes, first-pass metabolism, and pH variations. Such drugs have traditionally been administered parenterally, often with poor patient compliance. To overcome these challenges, the pharmaceutical industry has developed thin, dispersible, and oral-dissolving films as alternative drug delivery methods. These films are especially suitable for patients who fear choking, as they dissolve or disintegrate rapidly in the mouth [18].

Other important elements to take into account while selecting an API are its potential and therapeutic effectiveness. The best APIs for OTFs include anticancer medications, antitussives, antihistamines, antipsychotics, antianginal medications, nsaids, cardio-vascular medications, neuroleptics, painkillers, anxiolytics, anti-allergic medications, hypnotics, sedatives, antifungals, anti-drugs, Alzheimer's diuretics, and expectorants. OTFs dissolve immediately upon contact with saliva on the tongue, allowing the drug to be absorbed either locally or systemically. Unlike ODTs, which are fragile and can break during transport, OTFs provide a more robust and patient-friendly solution [19].

Oral disintegrating/dissolving films (OTFs) or strips are described as "drug delivery methods that quickly release medication by dissolving or adhering to the mucosa with saliva within a few seconds" due to their inclusion of water-soluble polymers. Oral thin films working like conventional orodispersible tablets, OTF dissolves within seconds in the mouth and the drug substance is swallowed together with saliva and takes the same route as a tablet. The sublingual mucosa, with its thin membrane structure and extensive vascularization, boasts high membrane permeability and rapid blood supply, enhancing bioavailability by bypassing the first-pass effect. Additionally, the oral mucosa's large surface area and ease of application make it an efficient and selective route for systemic drug delivery [20].

OTFs are typically thin, flexible polymer layers that may include plasticizers. Their natural form makes them less intrusive and more palatable for patients. Thin films meet many requirements of drug delivery systems, enhancing a drug's efficacy, reducing dosing frequency, and prolonging and improving the initial impact. The development of various biocompatible polymers and manufacturing processes has led to different types of OTFs. Consequently, OTFs are gaining acceptance as a novel dosage form in pharmaceutical technology. Significant efforts have been made to create polymeric OTFs for oral, buccal, sublingual, ocular, and transdermal administration. Among these, buccal and sublingual mucosa drug transport via OTFs has garnered considerable interest [21].

By combining polymers in different amounts, the mechanical strength, mucoadhesive properties, and drug release rate of thin films can be modified. The appealing characteristics of OTFs are influencing the pharmaceutical industry, driving the development and patenting of these formulations. For treatments requiring rapid absorption—such as those for pain, allergies, insomnia, and central neurological disorders—oral mucosal administration via OTFs may become the preferred delivery method. Originally used for confections and oral care products, dissolvable OTFs have evolved into an innovative delivery method for vitamins and personal care items [22].

The oral route is the most popular due to its ease of administration, comfort, adaptability, and patient compliance. Innovations have provided alternative delivery methods for juvenile, geriatric, ill, and non-compliant patients. These advances include bioadhesive mucosal structures like adhesive tablets, gels, and patches. Recently, polymeric films for drug delivery into the buccal cavity have shown significant potential. Orally disintegrating films (ODFs) quickly hydrate in saliva, releasing the active pharmaceutical ingredient after disintegration. ODFs are formulations that dissolve rapidly in saliva, using hydrophilic polymers [23].

Oral disintegrating tablets (ODTs) and ODFs are two types of these drug delivery systems. Developed in the late 1970s as alternatives to traditional dosage forms for patients who have difficulty swallowing, ODFs have the advantage of being less prone to patient misuse. Unlike ODTs, which required specific instructions to avoid biting or swallowing, ODFs eliminated these issues, providing a more reliable delivery method [24].

Orally dissolving films (ODFs) can incorporate a variety of medications such as antihistamines, antidepressants, vasodilators, asthma antagonists, antiemetics, and more. The taste of ODFs can be masked using agents like dimenhydrinate. Common medications found in ODFs include indomethacin, cetirizine, pilocarpine, rizatriptan benzoate, verapamil, ondansetron, dexamethasone, and rofecoxib. Plasticizers are used to enhance mechanical properties like stiffness and elasticity, typically comprising 0 to 20 percent of the film's total weight. Common plasticizers include PEG, glycerol, diethyl phthalate, triethyl citrate, and tributyl citrate [25].

Oral films, also known as oral wafers, are thin films designed to dissolve in the mouth. Although the technology for fast-dissolving oral film systems has existed for some time, it has recently gained renewed interest in pharmaceutical drug delivery. Initially marketed as breath strips in the confectionery and oral care sectors, dissolvable oral thin films (OTFs) have evolved into a popular delivery method for vitamins and personal care products. Companies experienced in creating polymer coatings with active pharmaceutical ingredients (APIs) for transdermal drug delivery have adapted this technology for OTFs. Currently, OTFs are in the early to mid-development stages for prescription medications and are a proven and recognized method for the systemic administration of APIs in over-the-counter (OTC) products [26, 27].

## 5. EXCIPIENT USED IN FORMULATION OF OTFS

### 5.1 Film-forming polymers used in OTFs

Selecting the appropriate polymer is crucial for the successful production of oral films due to their tensile strength, which is influenced by the type and amount of polymers used. The dry film should contain at least 45 percent polymer by weight, with 60 to 65 percent being ideal to achieve the desired properties. Polymers can be used individually or in combination to attain the necessary film characteristics. Since oral thin films (OTFs) are designed to quickly disperse and dissolve in the oral cavity, the polymers employed must be water-soluble. However, the resulting films must also be durable and able to remain intact during storage and transportation. Some are Methylcellulose, hydroxypropyl cellulose, and carboxymethyl cellulose, Polyvinyl pyrrolidone ,Polyvinyl Alcohol [28].

### 5.2 Surfactants used in OTFs

Surfactants as dispersing or wetting agents helping the film to dissolve in a short time and release the API quickly. It is preferable to use poloxamer 407, sodium lauryl sulfate, and polysorbate [29].

### 5.3 Sweeteners used in OTFs

Both natural and artificial sweeteners are utilized to sweeten OTFs (oral thin films). The most commonly used polyhydric alcohols include mannitol, sorbitol, maltitol, and isomalt. These polyhydric alcohols, when combined, produce a pleasant flavor and a cooling sensation on the tongue. Additionally, they do not leave a strong aftertaste and are considered less carcinogenic. Most polyols have a sweetening power less than half that of sucrose, with the exceptions of xylitol and maltitol, which have a sweetness similar to sucrose. The use of natural sugars in these formulations is restricted for diabetic patients, making artificial sweeteners more prevalent in food and medicinal products. OTFs often incorporate artificial sweeteners like aspartame and saccharin [30].

**5.4 Saliva stimulants used in OTFs**

Chemicals that stimulate saliva production can accelerate the breakdown of formulations. Acids commonly used in food preparation can serve as saliva stimulants. Among these are ascorbic acid, malic acid, citric acid, tartaric acid, and lactic acid [31].

**5.5 Superdisintegrants used in OTFs**

When superdisintegrants are incorporated into OTF formulations, their swelling and water absorption properties work together to rapidly disintegrate the material. These agents accelerate disintegration and breakdown by absorbing water and swelling due to their high water absorption capacity. Significant contact with saliva is essential for this breakdown process. Some examples are sodium starch glycolate, xanthan gum and croscarmellose sodium [32].

## 6. PREPARATION METHODS OF OTFS

**6.1 Solvent and semisolid casting method**

Orally Disintegrating Films (ODFs) are created using dissolvable projecting, a method where medicines, polymers, and excipients dissolve in deionized water. The mixture is then arranged on a petri plate and dried at high temperatures. Different grades of Lycoat and HPMC were used to produce an orodispersible film of tianeptine sodium. The formulation of ODFs is based on the optimal dissolvable based on its physicochemical properties, such as melting point, shear responsiveness, and polymorphism structure. The compatibility of the drug with the dissolvable and other excipients is evaluated before finalization. Trapped air bubbles can affect the uniformity of the film, which can be addressed by deaerating the mixture. Pullulan concentrates ranging from 2% to 8% provide a thin solution for film projection. Quick-dissolving films of anastrozole were successfully produced using the dissolvable projecting technique [33]. Solvent casting is a widely used method for creating Oral Thin Films (OTFs) due to its simplicity, cost-effectiveness, and ease of use. Components are mixed in a heated magnetic stirrer to form water-soluble components, and the drug and excipients are combined to create a viscous solution. The films are then left at room temperature for 20-25 hours or 24-48 hours, or at 40-50°C in an oven. After solvent evaporation, the films are cut into appropriate size pieces based on active ingredient content [34].

**6.2 Hot melt extrusion method**

Dry ingredients for the film are heated and blended using an extruder screw until they transform into a liquid, which is then amalgamated in a hot-liquefy ejection process. A level ejection pushes the extrudate into the desired film shape. While the film remains hot and pliable, stretching rollers can adjust its thickness and tensile strength. The process of hot melt extrusion is elaborated upon following the cooling and cutting of the extruded film. This technique is commonly employed for the production of sustained-release tablets, granules, subcutaneous, and transdermal delivery devices. The formulation's components are mixed and melted using an extruder equipped with heaters, resulting in the transformation of the liquid blend into film form using molds [35].

**6.3 Solid dispersion extrusion**

In this method, both the medication and the formulation components are combined and extruded to form a solid dispersion. This dispersion is then shaped into thin films using molds. Initially, a water-soluble film-forming polymer arrangement is created, followed by bonding it with a corrosion-resistant, insoluble polymer arrangement such as cellulose acetate phthalate or cellulose acetate butyrate. A suitable amount of plasticizer is incorporated to achieve a gel-like consistency. The gel mass is then molded into films or strips using heat-controlled drums. It is advised to maintain a film thickness ranging from 0.015 to 0.05 inches. The recommended ratio of the insoluble polymer to the film-forming polymer is 1:413 [36].

**6.4 Rolling method**

The process involves creating a preliminary blend of film-framing polymer, polar dissolvable substance, and other additives, excluding drugs. The mixture is directed to a professional clump feed tank and mixed with drugs to achieve a uniform consistency. A predetermined amount is dispensed onto a dish, then the film is framed and transferred onto a substrate support roller. Controlled air drying is used to dry the wet film, typically using water or water/alcohol blends as solvents. The active ingredient and other components are dissolved in aqueous solvent using a high shear processor. The resulting viscous mixture is spread onto the carrier roller, and the films are cut to the required dimensions and cured under regulated atmospheric conditions [37].

## 7. OTHER METHODS TO INCREASE THE BIOAVAILABILITY OF POORLY SOLUBLE DRUGS

Increasing the bioavailability of poorly soluble drugs is a crucial aspect of pharmaceutical research and development. Poor solubility can limit the absorption and therapeutic effectiveness of drugs, leading to suboptimal treatment outcomes. Various methods have been explored to enhance the solubility and ultimately the bioavailability of these drugs. One common approach is the use of solubilizing agents such as surfactants and co-solvents, which can improve drug dissolution by increasing its dispersibility in aqueous media [38]. Another strategy involves micronization or nanosizing of drug particles to increase their surface area and facilitate faster dissolution rates. Additionally, complexation with cyclodextrins or other carriers can improve drug solubility by forming inclusion complexes that enhance drug stability and release. Lipid-based delivery systems such as emulsions, liposomes, and solid lipid nanoparticles have also shown promise in improving the bioavailability of poorly soluble drugs by enhancing their solubility in lipid matrices and facilitating transport across biological membranes. Furthermore, novel technologies like nanocrystals, co-crystals, and amorphous solid dispersions are being explored to further enhance drug solubility and bioavailability through controlled release mechanisms [39].

**7.1 Micronization**

The oral bioavailability of drugs presented in a solid dosage form depends mainly on size, size distribution and morphology of particles. This is due to enhanced surface area of drug particles available for dissolution. Hence, a variety of micronization technologies such as spray-drying, freeze-drying, crystallization and milling processes were developed to decrease the particle size. However, the disadvantages associated with these traditional technologies are production of coarse particles with broad size

distribution, degradation of the product due to thermal or mechanical stress and contamination of the particles with toxic solvents. In the recent times, supercritical fluid (SCF) technologies are developed to overcome these disadvantages so as to produce a solvent-free drug product with improved dissolution, bioavailability and stability [40]. These greener SCF technologies have been demonstrated to produce particles with residual solvent content below the FDA-permitted levels. Furthermore, control over the morphology and crystallographic purity of the particles is shown to be better than several other conventionally used processes.

**7.2 Nanosizing**

This involves the reduction of drug particle size to the submicron range. The advances in milling technologies made it possible to produce drug particles in the range of 100 to 200 nm in a reproducible manner. While reduction of particle size has been employed in pharmaceutical industry for several decades, nanosizing can provide a further enhancement of dissolution rate. Nanosizing involves mechanical attrition to render large crystalline particles into nanoparticles. Elan's NanoCrystal® wetmilling technology and SkyePharma's Dissocubes® high-pressure homogenization technology utilize these principles for producing nanoparticles. An important requirement is that the nanoparticles are to be stabilized and formulated rigorously to retain their nature and properties. This is achieved with surfactants or polymers in nanosuspensions which can be further processed into standard dosage forms such as capsules or tablets suitable for oral administration [41].

**7.3 Solid dispersion**

The effective surface area is one of the important factors governing the dissolution rate of poorly soluble drugs. In addition to the micronization and nanosizing technologies, as described above, solid dispersion is the other way of enhancing the effective surface area available for dissolution. Solid dispersion involves the dispersion of one or more active ingredients in an inert carrier or matrix at solid state. These are usually prepared by heating mixtures of the drug and carrier to a molten state, followed by resolidification by way of cooling. A solid dispersion of nitrendipine prepared by a melt-mixing method using silica particles as carriers showed remarkably improved dissolution properties compared with that of the original nitrendipine crystals. This melt method often requires relatively high temperatures (>100°C), which may lead to thermal degradation of the drug. Solvent evaporation method is another technique of preparing solid dispersions which involves dissolving the components in a mutual volatile solvent followed by evaporation [42].

The effective surface area is a crucial factor in determining the dissolution rate of poorly soluble drugs. Solid dispersion is another method to enhance this surface area, which involves dispersing active ingredients in an inert carrier or matrix at a solid state. This is typically achieved by heating mixtures of the drug and carrier to a molten state and cooling them. For example, a solid dispersion of nitrendipine prepared using a melt-mixing method with silica particles improved dissolution properties compared to the original crystals. However, this method often requires high temperatures, potentially leading to thermal degradation of the drug. The solvent evaporation method is another technique for preparing solid dispersions, which involves dissolving components in a volatile solvent and evaporating. This method has shown to enhance the dissolution rate of spironolactone, itraconazole, and prednisolone. However, it is time-consuming, expensive, and not environmentally friendly due to its use of organic solvents and potential toxic residual solvents in the final product [43].

**7.4 Cyclodextrins**

Cyclodextrins are widely used to improve the solubility and dissolution rate of poorly soluble drugs. These starch derivatives, with their lipophilic interior and hydrophilic exterior, can incorporate apolar molecules or parts of molecules, resulting in better stability, high water solubility, increased bioavailability, or decreased side effects. The mechanism for enhanced solubilization is cyclodextrin's ability to form non-covalent dynamic inclusion complexes in solution, aggregate formation, and stabilization of supersaturated drug solutions. βcyclodextrin was the first cyclodextrin used to enhance dissolution rate, but its low aqueous solubility and nephrotoxicity led to the development of high water-soluble and less toxic derivates like 2-hydroxypropyl-β-cyclodextrin, methyl-β-cyclodextrin, and sulfobutyl ether-β-cyclodextrin [44].

**7.5 Self-emulsifying drug delivery systems (SEDDS) and selfmicroemulsifying drug delivery systems (SMEDDS)**

Self-emulsifying drug delivery systems (SEDDS) and selfmicroemulsifying drug delivery systems (SMEDDS) are isotropic solutions of oil and surfactant that form oil-in-water microemulsions on mild agitation in the presence of water. These novel colloidal formulations on oral administration behave like oil-in-water microemulsions and have been shown to improve the physical stability profile in long-term storage compared to ready-to-use microemulsions. SEDDS have been reported to enhance the oral bioavailability of paclitaxel, griseofulvin, and dexibuprofen, while SMEDDS have been shown to enhance the oral bioavailability of poorly soluble drugs such as simvastatin, acyclovir, and exemestane. Solid SEDDS are advanced formulations that can be filled directly into soft or hard gelatin capsules for conventional drug delivery. One challenge in formulating microemulsions, SEDDS, or SMEDDS is the limited availability of formulation components with GRAS status. Liposomal formulations may be preferred over colloidal drug delivery systems for solubilizing drugs and enhancing oral bioavailability due to the GRAS status of phospholipid constituents used in liposomal formulations. Liposomes offer a dynamic and adaptable technology for enhancing drug solubility due to their biphasic characteristic and diversity in design, composition, and construction [45].

**7.6 Solid Lipid Nanoparticles (SLNs)**

Solid lipid nanoparticles have a mean diameter as measured by photon correlation spectroscopy (PCS) ranging from 50 to 1000 nm and are made of solid lipids. SLNs may be obtained from emulsions that are used for parenteral administration by replacing the lipids in the liquid state by lipids in the solid state. SLNs are normally stabilized physically using surfactants. The major advantage that makes SLNs unique compared to polymeric nanoparticles, is that they can be produced/manufactured using high-pressure homogenization techniques used industrially for preparing emulsions. The emulsion production is generally equipped with temperature control units since elevated temperature sometimes favor emulsion production, which is equally applicable for producing SLNs by the hot homogenization technique [46].

The drug loading capacity of SLNs depends on certain parameters such as molecular weight of the drug, solubility of the drug in the lipid, hydrophobicity of the drug, the lipid matrix structure, stability of the drug and the polymorphic state of the lipid matrix. Use of complex lipids results in better drug entrapment, as the incorporated drugs are located within the fatty acid chains, crystal imperfections and also in between lipid layers. Large amounts of drug cannot be accommodated by the highly ordered crystal lattices. Drug expulsion may result during transition to highly ordered lipid particles. Lipids crystalize with higher energy modifications (α and β) directly after the nanoparticles are formed. This leads to more imperfections in the crystal lattice of lipids thereby facilitating larger mounts of drug entrapment [47]. A triggered and controlled release of the drug is exhibited if the

αmodification is preserved during storage and transformed (e.g. due to change in temperature). But, if the polymorphic transition leads to a β –modification, the drug will be discharged from the matrix of the lipid which may further lead to degradation of the drug and uncontrolled release of the drug [48].

**8.CONCLUSIONS**

Pharmaceutical companies are focusing on developing innovative technologies to improve oral drug solubility. The prodrug approach is an exciting way to improve the oral bioavailability of BCS class II drugs with low solubility and reasonable permeability, but extensive studies are needed to establish the safety profile of prodrugs in humans. Greener SCF technologies are expected to replace traditional micronization methods, offering precise control over particle size, distribution, and product quality. The scale-up of SCF technologies is expected for industrial production of micronized particles to enhance the bioavailability of poorly soluble drugs. Advancements in milling technologies, such as Elan's NanoCrystal® technology, could result in the production of nanosized drug particles in the range of 100 to 200 nm. Crystal engineering techniques, such as SCF technologies, are being developed for controlled crystallization of drugs, producing polymorphs, hydrates, solvates, nanoparticles, and pharmaceutical co-crystals with enhanced oral bioavailability. Research on solid dispersion techniques has led to the development of novel technologies like melt extrusion and SCF technologies. These methods overcome the disadvantages of traditional methods, such as the melt method and solvent evaporation method. Cyclodextrins can incorporate poorly soluble drugs or molecules, resulting in high water solubility and increased bioavailability. The solubilizing ability can be further enhanced by incorporating other water-soluble excipients. Traditional methods of preparing drug-cyclodextrin complexes involve the use of organic solvents, potentially containing toxic solvents. SCF technologies are promising for eliminating organic solvent use in drug-cyclodextrin complexes. Solid lipid nanoparticles (SLN) can entrap lipophilic drugs and stick to the gut wall, enhancing oral bioavailability. High-pressure homogenization and microemulsion technology are considered feasible for large-scale production of SLN. Pharmaceutical companies like SkyePharma AG and Vectorpharma are working to produce commercially feasible products using their own technologies.

**9. CONFLICT OF INTEREST**

None

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