CODEN: WJAPAC Impact Factor: 3.87 ISSN: 3049-3013

World Journal of Advance Pharmaceutical Sciences

Volume 2, Issue 1. Page: 104-116 Review Article www.wjaps.com

THE EFFECTS OF EXCIPIENTS ON DRUG SOLUBILITY & PERMEABILITY: A BIOPHARMACEUTICAL PERSPECTIVE

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How to cite this Article Aditya R. Kirmirwar (2025). THE EFFECTS OF EXCIPIENTS ON DRUG SOLUBILITY & PERMEABILITY: A BIOPHARMACEUTICAL PERSPECTIVE. World Journal of Advance Pharmaceutical Sciences, 2(1), 104-116.

Article Info

Article Received: 12 April 2025,

Article Revised: 02 May 2025,

Article Accepted: 22 May 2025.

DOI: https://doi.org/10.5281/zenodo.15519640

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ABSTRACT

Despite being thought of as inert substances, excipients are essential for improving drug permeability and solubility, which has a big impact on bioavailability and therapeutic results. Optimizing solubility and permeability is crucial in biopharmaceutics, particularly for medications that fall into Classes II and IV of the Biopharmaceutical Classification System (BCS) and are poorly soluble in water and have low permeability. The mechanisms by which excipients affect drug permeability and solubility are examined in this review, with a focus on how they affect formulation development. To increase drug solubility, excipients such lipid-based carriers, polymers, and surfactants have been used widely. By decreasing surface tension and improving drug particle wetting, surfactants, for instance, improve solubility and make it easier for drugs to dissolve in gastrointestinal (GI) fluids. Solid dispersions are produced by hydrophilic polymers such as polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP), which stabilize medications in an amorphous state that is more soluble than crystalline forms. By increasing its dispersion in GI fluids, lipid-based formulations like liposomes and self-emulsifying drug delivery systems (SEDDS) provide other ways to increase the solubility of hydrophobic medications. Excipients are essential for boosting medication permeability in addition to improving solubility. Drug transport across intestinal barriers is facilitated by penetration enhancers including bile salts, fatty acids, and surfactants, which alter the integrity of biological membranes. These excipients function by promoting fluidity in membranes, facilitating tight junctions, or blocking efflux transporters, such as P-glycoprotein, which actively remove medications from cells. These excipients greatly enhance drug absorption by removing permeability barriers, particularly for medications with limited permeability in their native condition. Even while excipients have benefits, using them might provide difficulties. Formulation development must take into account safety issues, legal barriers, and the possibility of interactions between excipients and active pharmaceutical ingredients (APIs). Furthermore, physiological variables including pH variations and GI tract enzyme activity might cause excipient performance to vary, which could affect the uniformity of medication absorption. Excipients are essential to contemporary medication formulation, especially when it comes to enhancing the permeability and solubility of difficult drug candidates. New opportunities for improving medication absorption and bioavailability are constantly presented by developments in excipient technology. Nonetheless, further investigation is required to tackle safety, stability, and regulatory issues, guaranteeing that excipients efficiently enhance drug delivery in biopharmaceutical applications.

KEYWORDS: Biopharmaceutical Classification System (BCS), low permeability.

INTRODUCTION

In medication preparations, pharmaceutical excipients are inert materials that are combined with active pharmaceutical ingredients (APIs). Previously thought to be pharmacologically inert, excipients are now acknowledged for their important function in regulating the solubility, permeability, stability, and general bioavailability of drugs. This comprehensive essay examines excipient kinds, uses, and processes, all of which are backed by current scientific research.[8,9]

Types of Excipients

Excipients are divided into groups according to their chemical characteristics and uses

- Binders (such as cellulose derivatives and starch): provide tablet cohesiveness.
- Diluents and fillers, such as lactose and microcrystalline cellulose, increase the weight of tablets.
- Disintegrants: Encourage the digestive tract to break up tablets (e.g., croscarmellose sodium).
- Lubricants: Help tablets (like magnesium stearate) come out of molds.
- Coatings: Preserve and regulate the release of APIs (such as hydroxypropyl methylcellulose).
- Preservatives: Stop microorganisms from growing (parabens, for example).
- Solvents and co-solvents, such as ethanol and propylene glycol, increase solubility.
- Surfactants, such as sodium lauryl sulfate and polysorbates, help in solubilization and absorption.[8,9]

Traditionally regarded as inert elements in pharmaceutical formulations, excipients are essential for adjusting the permeability and solubility of active pharmaceutical ingredients (APIs). Excipients are carefully chosen in contemporary drug delivery systems to improve drug solubilization, stabilize drug molecules, and make it easier for them to pass through biological membranes. For many medications, particularly those in classes II and IV of the Biopharmaceutics Classification System (BCS), poor water solubility and restricted membrane permeability are significant obstacles to oral bioavailability. While permeability enhancers like bile salts and absorption modulators can help with transcellular or paracellular drug transport, functional excipients like surfactants, co-solvents, cyclodextrins, and lipid-based carriers can greatly increase solubility. Therefore, a crucial component of developing pharmaceutical formulations that maximizes drug distribution and therapeutic efficacy is the careful selection and design of excipients.[1]

The preferred method of medication delivery is still oral administration since it is non-invasive, simple to dose, economical, and highly patient-complied with.[2,3] However, two physicochemical characteristics—intestinal permeability and water solubility—have a significant impact on the effectiveness and bioavailability of medications taken orally. Adequate permeability guarantees transport through the membranes, whereas the dissolved form of the active pharmaceutical ingredient (API) is necessary for absorption from the gastrointestinal tract (GI).[4,5]

About 40% of commercial medications and 70% to 90% of novel drug candidates have poor aqueous solubility; as a result, they fall under either BCS II (low solubility, high permeability) or BCS IV (low solubility, low permeability).[6,7]

Excipients are essential for altering the permeability and solubility of active pharmaceutical ingredients (APIs), which in turn affects how bioavailable oral medication formulations are. They are especially important for poorly soluble medicines, which are a big problem in drug development.

Excipients in drug formulation

In rare cases, active ingredients are used alone. To treat hypothyroidism, for instance, levothyroxine, a synthetic type of thyroid hormone, is given at very low dosages, ranging from 15 µg to 200 µg. It is impossible to make tablets using just this medication because of the extremely tiny amounts of powder. Because of this, levothyroxine tablets must be made with the hormone in addition to one or more non-pharmaceutical substances known as pharmaceutical inactive components or excipients, which have a variety of particular pharmaceutical uses.[10]

Excipients are essential to the creation of stable dosage forms, their administration, and the medication development process. As demonstrated by epileptic patients in Australia in the late 1960s using phenytoin capsules, a poor excipient selection can even result in serious intoxications2. Lactose, which is thought to be a harmless substitute for calcium sulphate, which was used as a diluent in the capsule, caused the mean serum phenytoin concentration to rise by a factor of 4.5. This is significant for an active ingredient with a narrow therapeutic index like phenytoin. Lactose is easily soluble in water, but calcium sulphate (dehydrate) is very weakly soluble in the same medium. This difference in solubility provides the reason. Therefore, lactose caused an instantaneous and enormous release of phenytoin over the hazardous threshold, while calcium sulphate functioned as a matrix forming and extended the drug's release in the original formulation. Another instance of excipient confusion that might be lethal is when pharmaceutical makers in Panama used diethylene glycol—thinking it was glycerine—to make cough syrup in 2007. Antifreeze contains diethylene glycol, a nephrotoxic and hepatotoxic substance that can cause multiple organ dysfunction syndrome, particularly in youngsters.[10,11]

Many drug metabolism research organizations have the significant challenge of determining bioavailability, or

the actual quantity of medication that is accessible to the body following the administration of a certain dose of the drug in a pharmaceutical dosage form. Numerous substances may be mainly inaccessible following oral delivery due to specific pharmacological and/or dosage form features, according to a wide body of data. Numerous pathways contribute to a drug's biological availability. Poor availability may be caused by a number of factors, including low solubility, slow rate of dissolution or release, poor permeability, gastrointestinal degradation, and fast biotransformation. Experience has demonstrated that each of these elements may be examined separately and that several potential issues can be foreseen before the medication is delivered to the clinic.[12]

Excipients usually serve several purposes in a formulation. For instance, in a solid dosage form, microcrystalline cellulose might function as a disintegrant, binder, or filler/diluent.

Diluents/fillers, lubricants, glidants, and other excipients can be added to a formulation to increase powder flow or compression and, consequently, improve manufacturability. Additionally, some excipients are used to improve drug stability (such as low moisture grades of common fillers in cases of hydrolytic instability or antioxidants in cases of oxidative instability); improve disintegration and consequently dissolution (such as disintegrants); and improve palatability (such as flavorants and sweeteners). Additives, such as aqueous film coating components, can enhance the final dosage form's appearance. Lastly, by altering the permeability or solubility of the medicine, excipients can also be employed to improve oral bioavailability. Therefore, the goal of this study is to give a summary of the excipient regulation procedure and emphasize that, from a biopharmaceutical standpoint, excipients are frequently not "inert." Additionally, work that is pertinent to industry and uses high-throughput or contemporary in silico techniques for pharmaceutical excipient selection is reviewed.[13]

Classification of Excipients and their role in drug delivery

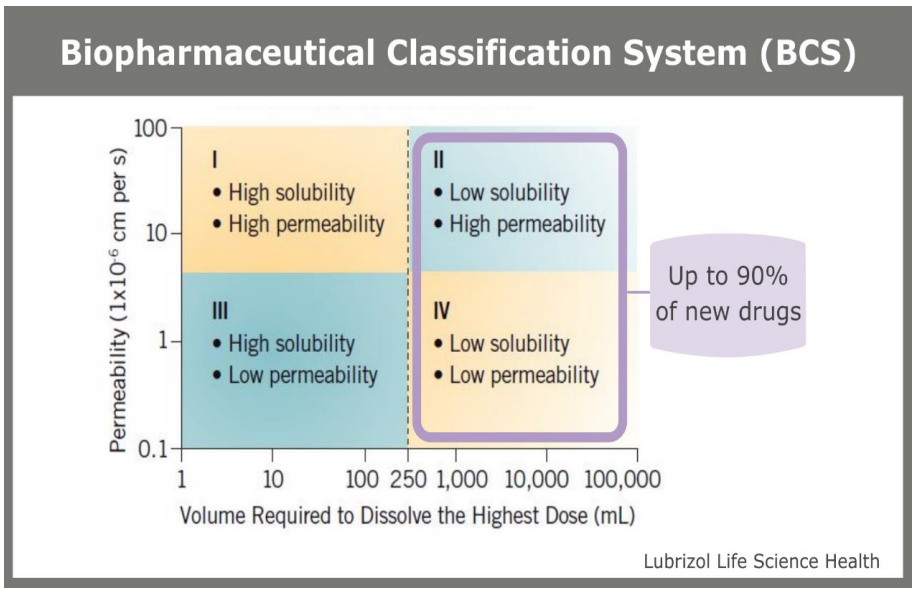
Historically thought of as inert ingredients in pharmaceutical formulations, excipients have come to light for their active roles in regulating drug distribution, especially when examined from a biopharmaceutical standpoint. Their impact on active pharmaceutical ingredients' (APIs') pharmacokinetics and therapeutic efficacy goes beyond that of simple fillers.

Classification of Excipients in drug delivery

Based on their functional functions and interactions with APIs, excipients may be divided into the following categories

1) Functional excipients are made to carry out certain tasks in medication formulations, such increasing stability, regulating release rates, or boosting solubility. For example, polymers can be employed to regulate the drug's release over time, and surfactants can make poorly water-soluble medications more soluble.[14]
2) The BCSE, or Biopharmaceutical Classification System of Excipients, Excipients are categorized using this method according to how well they interact with intestinal metabolism and efflux processes, which are essential for medication absorption. Four courses make up the BCSE.[14,15,16]:

 Class I: Excipients that do not affect intestinal metabolism or efflux mechanisms.
 Class II: Excipients that can interfere with intestinal metabolism but not with efflux mechanisms.
 Class III: Excipients that can interfere with efflux mechanisms but not with intestinal metabolism.
 Class IV: Excipients that can interfere with both intestinal metabolism and efflux mechanisms.[16]



From a biopharmaceutical standpoint, excipients influence drug delivery through various mechanisms

- Improving Solubility and Permeability: Drugs that are poorly soluble in water can have their solubility and permeability improved by excipients such as cyclodextrins and surfactants, which will aid in improved absorption.
- Modulating Drug Release: To ensure long-lasting therapeutic benefits, polymers like hydroxypropyl methylcellulose (HPMC) are utilized to regulate drug release.
- Interacting with Efflux and Metabolic Pathways: Some excipients can increase medication bioavailability by blocking transporters or enzymes involved in efflux and metabolism. For instance, it has been demonstrated that excipients such as polysorbates and PEG fatty acid esters block P-gp, a crucial efflux transporter.
- Enhancing Stability and Compatibility: By shielding medications from environmental elements like light and moisture, excipients can prolong the stability and shelf life of formulations.[14,15,17]

Excipients are essential to medication delivery because they affect the pharmacokinetics and therapeutic results of APIs. Creating safe and efficient pharmaceutical formulations requires an understanding of their classifications and modes of action from a biopharmaceutical standpoint. The dynamic roles of excipients continue to influence the development of drug delivery systems as the area progresses.

Impact of Excipients on drug solubility: Mechanism and Strategies

One of the most important problems in pharmaceutical research is making poorly water-soluble medications more soluble, especially for substances that fall into Classes II and IV of the Biopharmaceutics Classification System (BCS). Excipients are essential for increasing these medications' solubility and, in turn, their bioavailability. With the help of pertinent examples, this paper examines the ways in which excipients affect medication solubility and describes methods used to improve solubility.[18,19]

Mechanism by which Excipient enhance drug solubility

- Cyclodextrin Complexation: Cyclodextrins are cyclic oligosaccharides that may form inclusion complexes with hydrophobic medicinal molecules because of their hydrophilic exterior and hydrophobic center. The drug's stability and solubility are improved by this complexation. Sulfobutylether-β-cyclodextrin, for example, has been used to increase the solubility of the antiviral drug remdesivir.
- Systems of Solid Dispersion: The medication is distributed in a carrier matrix, frequently in an amorphous condition, in solid dispersions, increasing the surface area and rate of disintegration. Commonly utilized carriers include polymers like chitosan, hydroxypropyl methylcellulose (HPMC), and polyvinylpyrrolidone (PVP). For instance, a solid furosemide and crospovidone dispersion significantly accelerated the rate of disintegration.
- Nanosizing and Micronization: A drug's dissolving rate is increased when its particle size is decreased since it has a larger surface area. Nanosuspensions, which are made using methods like wet bead milling, have been demonstrated to increase the solubility of a number of medications.
- Utilizing Surfactants: Surfactants can promote medication solubility by lowering surface tension and encouraging wetting of the drug particles. Additionally, they have the ability to create micelles that encapsulate hydrophobic medications, increasing their solubility. Polysorbates and sodium lauryl sulfate are examples of common surfactants.
- Drug delivery systems that self-emulsify (SEDDS): SEDDS are oils, surfactants, and co-solvent mixes that improve the solubility and absorption of lipophilic medications by forming fine emulsions when they come into contact with gastrointestinal fluids. To increase the solubility of medications like simvastatin, SEDDS have been used.
- Solid Amorphous Dispersions (ASDs): By spreading a medication in an amorphous form inside a polymer matrix, ASDs enhance solubility and inhibit crystallization. ASDs are made using methods including hot-melt extrusion and spray drying. In ASDs, polymers such as HPMC and Soluplus® are frequently used.

Strategies for Enhancing Drug Solubility Using Excipients

- Selecting the Right Excipients: It's critical to pick excipients that can work well with the medication molecule to improve solubility. For instance, solubilization efficiency can be increased by using surfactants with low critical micelle concentrations.
- Optimization of Formulation Parameters: The solubility improvement that excipients give can be affected by varying variables including pH, temperature, and solvent composition. For example, manufacturing some medications under acidic pH settings can boost their solubility since these circumstances make the pharmaceuticals more soluble.
- Combination of Strategies: A synergistic impact might result from utilizing a variety of solubility improvement approaches. For instance, the solubility and bioavailability of poorly soluble medications can be greatly increased by combining solid dispersion with surfactants.[19]

In order to improve the solubility and bioavailability of medications that are not very soluble in water, excipients are essential. Excipients can greatly increase medication solubility through processes including complexation, solid dispersion, micronization, and the application of surfactants and SEDDS. Excipients must be carefully

chosen and optimized in order to create pharmaceutical formulations that guarantee both patient compliance and therapeutic efficacy.

Role of Surfactants in improving drug solubility and permeability

Oral drug administration has significant obstacles due to poor water solubility and restricted membrane permeability, particularly for medications in Biopharmaceutics Classification System (BCS) Classes II and IV. Through a variety of methods, surfactants—amphiphilic compounds with hydrophilic heads and hydrophobic tails—can greatly increase solubility and permeability.

Mechanisms by Which Surfactants Enhance Drug Solubility

1) Formation of Micelle: Above their critical micelle concentration (CMC), surfactants create micelles and lower surface tension. The apparent aqueous solubility of hydrophobic medications can be increased by solubilizing them within the micelle core.

Example- polysorbate 80 increases paclitaxel's solubility.[20]

2) Enhance Wetting and Dispersion: Surfactants reduce interfacial tension between drug particles and the dissolution medium, increasing the drug's surface area for solubilization.[21]

Mechanisms Enhancing Permeability

1) Membrane Fluidization: Surfactants interact with lipid bilayers of biological membranes, altering membrane integrity and enhancing paracellular and transcellular transport.

Example**:** Sodium lauryl sulfate (SLS) increases membrane permeability by disrupting tight junctions.[22]

2) Efflux Pump Inhibition: Some surfactants inhibit efflux transporters like P-glycoprotein (P-gp), enhancing intracellular drug accumulation.

Example**:** Cremophor EL inhibits P-gp, improving the bioavailability of substrates like cyclosporine A.[23]

Commonly used Surfactants

Surfactant	Type	Applications
Polysorbate 80	Nonionic	Micellar solubilization
Cremophor EL	Nonionic	Solubilizer and P-gp inhibitor
Sodium lauryl sulfate (SLS)	Anionic	Permeability enhancer, wetting agent
Solutol HS15	Nonionic	Enhancing bioavailability

Surfactants are critical excipients in modern drug formulation strategies, significantly improving the solubility and permeability of poorly water-soluble drugs. Their versatile functionality makes them key to developing effective oral, transdermal, and injectable formulations.

Polymers and their effects on drug release and absorption

The ability of polymers to regulate drug release rates, increase stability, and improve bioavailability makes them popular in drug delivery systems. The design and content of polymers can be changed to customize medication absorption to meet certain therapeutic requirements.

1. Controlled and Sustained Drug Release

Drugs can be released from polymers at regulated rates, increasing patient compliance and treatment effectiveness.

- Biodegradable Over time, the body breaks down polymers like PLGA (polylactic-co-glycolic acid) to release medications. Implants and injectable formulations frequently employ them.[24]
- In oral controlled-release tablets, hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) create gel layers that regulate drug dispersion.[25]

2. Enhancement of Drug Solubility and Absorption

Many medications have limited oral bioavailability due to poor water solubility. Solubility can be enhanced by polymers via:

- Solid Dispersions: To keep medications in an amorphous form and improve solubility, polymers such as PVP (polyvinylpyrrolidone) are utilized.[26]
- Micellar Systems: Hydrophobic medications are encapsulated in micelles made of amphiphilic block copolymers, such as PEG-PLA, which enhances their solubility and systemic circulation.[27]

1. Mucoadhesion and Targeted Absorption

By sticking to mucosal surfaces or facilitating targeted distribution, certain polymers can improve medication absorption:

- Chitosan is a naturally occurring mucoadhesive polymer that temporarily opens tight junctions to improve medication transport across epithelial layers.[28]
- Targeted Polymers: By conjugating polymers with ligands (such as peptides or folate), medications can be delivered to certain cells, enhancing absorption and therapeutic results.[29]

2. Stimuli-Responsive Drug Release

- Drugs can be released in a controlled way at certain places using polymers that react to environmental factors like pH, temperature, or enzymes:

Drugs are released in the gut via pH-sensitive polymers (Eudragit L100 dissolves at pH > 6).[30]

Polymers are indispensable tools in drug delivery science. They control drug release profiles, enhance solubility, improve mucosal adhesion, and enable site-specific absorption. Their versatility supports innovations in oral, transdermal, injectable, and nanoparticle formulations.

Lipid-Based Excipients: enhancing solubility and intestinal absorption

Many active pharmaceutical ingredients (APIs), especially those in BCS Class II and IV, exhibit poor water solubility, limiting their oral bioavailability. Lipid-based excipients offer a powerful strategy to enhance drug solubility and facilitate intestinal absorption through various mechanisms including emulsification, micellization, and lymphatic transport.

Mechanisms of Lipid-Based Excipients

1. Solubilization via Lipid Media

Oils and surfactants are examples of lipid excipients that solubilize poorly water-soluble medications, enabling them to stay dissolved in the gastrointestinal system.

Long-Chain Triglycerides (LCTs) and Medium-Chain Triglycerides (MCTs) aid in keeping the medication soluble.

These lipids combine to generate emulsions of water and oil that have a lot of surface area for absorption.[31]

2. Self-Emulsifying Drug Delivery Systems (SEDDS)

Oil, surfactant, and co-solvent mixes known as SEDDS spontaneously create emulsions in the gastrointestinal system. When tiny oil droplets (nano- or microemulsions) come into contact with GI fluids, they improve dissolution. Keep the medication supersaturated in digestive fluids to facilitate absorption.[32]

3. Efflux and Metabolism Inhibition

Some lipid excipients decrease drug efflux and first-pass metabolism by inhibiting CYP and P-glycoprotein (P-gp) enzymes Cremophor EL and Labrasol improve intracellular medication retention by blocking efflux transporters.[33]

4. Transport of Lymph

Bypassing the liver and increasing bioavailability, highly lipophilic medications (log P > 5) can be absorbed by intestinal lymphatics when taken with long-chain triglycerides.

Examples include danazol, halofantrine, and cyclosporine A.[34]

Lipid-based excipients offer a powerful biopharmaceutical strategy to address the challenge of poor solubility and limited intestinal absorption. Through mechanisms like micelle formation, lymphatic transport, and metabolic inhibition, they significantly enhance drug bioavailability. These systems are particularly valuable for oral delivery of lipophilic drugs and continue to evolve with advanced lipid carrier technologies.

Solid Dispersion and Solubilizing agents in Formulation design

Drug solubility and permeability are critical determinants of oral bioavailability, particularly for Biopharmaceutical Classification System (BCS) Class II and IV drugs, which suffer from poor aqueous solubility. Pharmaceutical excipients can significantly enhance solubility and/or permeability, influencing drug absorption and therapeutic efficacy. Among these, solid dispersions and solubilizing agents are widely adopted formulation strategies. This review focuses on the biopharmaceutical role of these excipients and their mechanisms in improving drug performance in vivo.[35]

Solid Dispersions in Drug Formulation

One or more active pharmaceutical ingredients (APIs) are dispersed at the molecular level in an inert hydrophilic carrier matrix in solid dispersions (SDs). This method improves the bioavailability of medications that are poorly soluble in water by increasing their solubility and rate of dissolution. In order to improve medication absorption, the process mainly depends on the production of supersaturated solutions and the decrease of particle size following delivery.[36,38]

Carrier Selection

When creating SDs, the carrier selection is crucial. Water-soluble or swellable, pharmacologically inert, non-toxic, and chemically compatible with the medication are all desirable qualities in a carrier. Polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), and polyvinylpyrrolidone (PVP) are often utilized carriers. These carriers inhibit recrystallization by stabilizing the drug's amorphous state in addition to improving solubility.[36]

Method of Preparation

SDs are made using a variety of methods, including as solvent evaporation, melt extrusion, and spray drying. Because of its scalability and capacity to create fine powders with improved dissolving qualities, spray drying is preferred among them. The drug's physical condition and the formulation's stability are impacted by the technique selection.[36,38]

Difficulties and issues with Stability

Despite their benefits, SDs have drawbacks such scale-up issues, moisture-induced crystallization, and physical instability. The drug's amorphous state is thermodynamically unstable and may eventually return to a crystalline form, which would decrease its solubility. Stabilizing agents and ideal storage conditions are therefore necessary to preserve the effectiveness of SD formulations.[36]

Solubilizing Agents in Drug Formulation

Excipients known as solubilizing agents are used to make poorly water-soluble medications more soluble, making it easier to formulate them into injectable and oral dosage forms. These substances, which each have a unique function in solubilization, include complexing agents, cosolvents, and surfactants.[37]

Types of Solubilizing Agents

- Surfactants: Non-ionic surfactants, such as polysorbates and Cremophor EL, are frequently used to form micelles, encapsulating the drug and increasing its solubility
- Cosolvents: Organic solvents, such as ethanol, propylene glycol, and polyethylene glycol (PEG), are used in combination with water to increase the solubility of lipophilic drugs
- Cyclodextrins: These cyclic oligosaccharides enhance the solubility and stability of drugs in water by forming inclusion complexes.[37]

Mechanisms of Action

The solubilizing effect of these agents can be attributed to various mechanisms

- Micelle Formation: Surfactants form micelles that encapsulate hydrophobic drugs, increasing their solubility.
- Hydrotropic Solubilization: Cosolvents increase the polarity of the solvent system, enhancing the solubility of lipophilic drugs.
- Inclusion Complexation: Cyclodextrins form inclusion complexes with drugs, reducing their crystallinity and increasing solubility.[37,38]

Considerations in Formulation

The selection of solubilizing agents must consider factors such as the drug's physicochemical properties, the intended route of administration, and potential interactions with other excipients. Additionally, the safety and regulatory status of these agents are paramount in ensuring the acceptability of the final formulation.[37]

Case studies: Successful use of Excipients to improving Bioavailability.

Excipients play a pivotal role in enhancing the bioavailability of pharmaceutical formulations by improving drug solubility and permeability.

1. Enhancing Drug Solubility

Due to inadequate rates of dissolution, medications that are poorly soluble in water sometimes have restricted bioavailability. Excipients can lessen this restriction in a number of ways:

- Hydrotropic Agents: By decreasing water activity, substances such as sugar alcohols (such as mannitol and sorbitol) can improve solubility and raise the solubility of ionized drug forms. Their effects, however, can differ depending on the drug's ionization state and be concentration-dependent.
- Surfactants: By creating micelles that enclose hydrophobic drug molecules and speed up their dissolution, substances like sodium lauryl sulfate (SLS) and Tween 80 can solubilize medications. The essential micelle concentration of surfactants and the physicochemical characteristics of the medication determine how effective they are.
- Polymers: By keeping the medication in an amorphous state, inhibiting crystallization, and speeding up dissolving, polymers such as polyvinylpyrrolidone (PVP) and its copolymer PVPVA 64 may increase solubility. The solubility improvement is greatly influenced by the polymer's molecular properties and choice.[39,40]

2. Modulating Drug Permeability

Poor permeability can restrict medication absorption even in cases when solubility has been improved. Permeability can be affected by excipients in the following ways:

- Enhancers of Permeation: Some excipients have the ability to temporarily relax intestinal epithelial tight junctions, which makes it easier for drugs to be absorbed. SLS, for example, has been demonstrated to improve drug permeability by reversibly opening tight junctions in Caco-2 cell cultures.
- Complexation Agents: By making it easier for medications to pass across biological membranes, cyclodextrins can combine with medications to create inclusion complexes that increase their permeability and solubility.
- Lipid-Based Systems: By changing the gastrointestinal environment, lipid excipients can improve permeability and encourage medication solubilization.[41]

3. Interplay Between Solubility and Permeability

Permeability and solubility have a complicated connection. Improving one property might have a negative impact on the other. By creating micelles that limit the amount of free medication accessible for absorption, SLS, for instance, may inhibit permeability at specific doses even if it can improve solubility. On the other hand, SLS can weaken the intestinal barrier and increase permeability at greater doses.[42]

4. Biopharmaceutical Considerations in Formulation Development

To balance the drug's permeability and solubility, excipient concentration and selection must be carefully considered. The performance of the formulation depends on a number of important factors, including the physicochemical qualities of the medication, the excipient, and the planned method of administration. More and more sophisticated methods, like as molecular dynamics simulations and high-throughput screening, are being used to forecast and assess how excipients may affect medication bioavailability.[43]

Regulatory Considerations for Excipients in pharmaceutical products

Excipient regulations are essential in the biopharmaceutical industry to guarantee the quality, safety, and effectiveness of medication formulations. Despite being thought of as inert, excipients have the ability to affect the pharmacokinetics and pharmacodynamics of active pharmaceutical ingredients (APIs). In order to reduce any dangers, regulatory bodies need thorough analyses of excipients.

1. Regulatory Frameworks and Guidelines

Guidelines for the assessment and application of excipients have been created by regulatory organizations such the European Medicines Agency (EMA), the U.S. Food and Drug Administration (FDA), and the International Council for Harmonization (ICH). To make sure that excipients don't negatively impact the drug's performance or patient safety, these criteria cover things like quality control, safety evaluations, and compatibility tests.[44]

2. Safety and Toxicity Assessments

Excipient safety is crucial, particularly when used to susceptible groups like children and the elderly. Toxicology studies are necessary for regulatory bodies to evaluate the possible hazards related to excipients. These studies assess variables like as dosage, delivery method, and possible API interactions. For example, some excipients might result in gastrointestinal issues or hypersensitivity responses. Consequently, it is crucial to choose excipients with known safety profiles.[45]

3. Compatibility with Active Pharmaceutical Ingredients

To keep the medication formulation stable and effective, excipients and APIs must work well together. In order to identify possible interactions between excipients and APIs, regulatory guidelines advise doing compatibility studies utilizing methods such as Nuclear Magnetic Resonance (NMR), Fourier Transform Infrared Spectroscopy (FTIR), and Differential Scanning Calorimetry (DSC). These interactions may cause the API to degrade or produce hazardous byproducts.[46]

4. Impurities and Residual Solvents

Patient safety may be at stake when excipients include contaminants and leftover solvents. Regulatory bodies divide solvents into many groups according on how harmful they are. Class 2 solvents are restricted because of their neurotoxic or teratogenic effects, whereas Class 1 solvents should be avoided because of their propensity to cause cancer. Although they still have limitations, class 3 solvents have a minimal risk for toxicity. One important regulatory requirement is that excipients adhere to predetermined limits for contaminants and residual solvents.[47]

5. Pediatric and Geriatric Considerations

Due to variations in metabolism and organ function, extra consideration must be given while using excipients in juvenile and geriatric populations. Some excipients, such polysorbate 80, have been linked to negative outcomes in newborns and young children. Regulatory recommendations advise carrying out comprehensive safety studies and restricting the use of such excipients in formulations meant for these groups.[48]

6. Global Harmonization Efforts

Global initiatives aim to harmonize regulatory requirements for excipients to facilitate international trade and ensure consistent quality standards. The ICH plays a significant role in developing guidelines that are adopted by regulatory agencies worldwide. These efforts help streamline the approval process for drug formulations containing excipients and ensure that they meet safety and quality standards.[49]

Challenges and Limitations of Excipients using in Drug Formulation

1. Excipient Variability

The performance of a medicine can be greatly impacted by excipient variability. Drug solubility and permeability can be affected by variables such contaminants, moisture content, and particle size. For example, changes in hydroxypropyl methylcellulose's (HPMC) viscosity might impact the active pharmaceutical ingredient's (API) rate of dissolution, resulting in uneven bioavailability. Furthermore, variations in the excipient sources—such as plant or animal origins—can add unpredictability to the finished product, impacting its stability and performance.[50,51]

2. Regulatory Challenges

Significant regulatory obstacles stand in the way of the development and approval of innovative excipients. Novel excipients now need to be authorized as part of a medication dosage formulation; there is no special approval procedure for them. The introduction of novel excipients that potentially improve medication solubility and permeability may be delayed by this absence of a streamlined process. Furthermore, the approval procedure is made more difficult by the lack of worldwide harmonization in excipient laws, which might result in higher prices and delays in the market.[52]

3. Safety Concerns

Even if they improve a drug's permeability and solubility, some excipients can be dangerous. For instance, using large amounts of glycerol as a solvent might have negative consequences such diarrhea, electrolyte imbalances, and mucositis. The use of sulfites as antioxidants might also result in hypersensitivity responses, especially in young people. Because of these potential issues, excipient safety profiles must be carefully considered and tested throughout formulation development.[53]

4. Manufacturing Complexities

Manufacturing difficulties may arise when excipients are added to medication formulations. For example, excipients that improve drug solubility, such as cyclodextrins, might make production more difficult because of their intricate structure and requirement for exact control over formulation parameters. Furthermore, careful optimization is needed when combining excipients with APIs to guarantee homogeneity and avoid problems like segregation or irregular drug release patterns.[51,54]

5. Stability and Compatibility Issues

For the medicinal product to be stable and effective, excipients and the API must work well together. API deterioration, decreased bioavailability, or the production of hazardous byproducts can result from incompatibilities. For instance, Maillard reactions can occur when amine groups in APIs and reducing sugars in excipients interact, resulting in discoloration and decreased effectiveness. Therefore, while developing a formulation, comprehensive compatibility studies are crucial.[55]

6. Economic and Market Considerations

The process of creating new excipients is expensive and time-consuming; it sometimes takes more than 10 years and involves a large financial outlay. Despite their potential advantages, innovative excipients only make up a small portion of pharmaceutical sales worldwide, which means there are little incentives to develop and use them. The introduction of novel excipients that might enhance medication solubility and permeability may be hampered by the current economic climate.[55]

Future Directions in the use of Excipients for Optimizing Drug Solubility and Permeability

1. Amorphous Solid Dispersions (ASDs) with Advanced Excipients

The use of amorphous solid dispersions (ASDs) to improve the solubility of medications that are not very soluble in water has grown in popularity. High molecular weight polyacrylic acid excipients, such Lubrizol's ApinovexTM polymers, have been demonstrated to stabilize amorphous forms of active pharmaceutical ingredients (APIs) and greatly increase dissolving rates. These polymers provide a strong option for improving solubility by facilitating high drug loading and maintaining stability under accelerated settings.[56]

2. Nanotechnology-Based Excipients

Novel strategies to improve medicine delivery and bioavailability are provided by nanotechnology. More surface area and regulated release profiles are offered by the creation of nanocarriers such liposomes, solid lipid nanoparticles, and mesoporous silica. By encapsulating APIs, these nanocarriers can increase their permeability and solubility while facilitating targeted distribution to certain bodily locations.[57]

3. Natural Deep Eutectic Solvents (NADES)

A new family of excipients known as natural deep eutectic solvents (NADES) has surfaced with possible uses in medication formulation. Research has shown that NADES, which are made up of substances like glycerol and choline chloride, may greatly improve the stability and solubility of hydrophobic medications like curcumin. These solvents provide a biocompatible and efficient drug delivery medium, especially for topical and oral formulations.[60]

4. Self-Microemulsifying Drug Delivery Systems (SMEDDS)

SMEDDS are isotropic blends of oils, co-solvents, and surfactants that, when they come into contact with aqueous media, spontaneously create microemulsions. By encouraging the breakdown of lipophilic medications in the gastrointestinal tract, these systems improve their solubility and bioavailability. In order to increase stability and regulate release patterns and boost therapeutic efficacy, recent developments have concentrated on formulation optimization.[58,59]

5. Regulatory Considerations and Safety Profiles

The development of new excipients necessitates rigorous safety evaluations to ensure patient safety and regulatory compliance. The FDA and other regulatory bodies require comprehensive toxicity studies and human exposure data for excipients used in drug formulations. The absence of standardized guidelines for excipient safety evaluation can pose challenges in the development of novel excipients, highlighting the need for harmonized regulatory frameworks.[61]

DISCUSSION

The biopharmaceutical performance of a drug—its absorption, distribution, metabolism, and excretion (ADME)—is strongly influenced by its solubility and permeability. These two parameters are especially critical for drugs falling under Biopharmaceutics Classification System (BCS) Class II (low solubility, high permeability) and Class IV (low solubility, low permeability). Excipients, though historically considered “inactive” ingredients, play an increasingly recognized role in modifying these characteristics. Their impact can be both beneficial and limiting, depending on the formulation strategy, drug-excipient compatibility, and administration route.

Through a number of processes, including as micellization (surfactants), complexation (cyclodextrins, for example), salt generation, and conversion to amorphous forms, excipients can improve medication solubility. In aquatic conditions, surfactants like sodium lauryl sulfate (SLS) and polysorbates create micelles that solubilize lipophilic medications. However, by encasing hydrophobic drug moieties in their hydrophilic outer shell, cyclodextrins increase solubility.

For BCS Class II medications, amorphous solid dispersions (ASDs) utilizing hydrophilic polymers like as hydroxypropyl methylcellulose (HPMC) or polyvinylpyrrolidone (PVP) are frequently used. By preventing drug crystallization, these polymers maintain the drug's supersaturated, more soluble form. Physical instability and return to the crystalline state after storage, however, continue to be major obstacles.

Some excipients may unintentionally decrease drug permeability, while others may increase it by altering membrane fluidity or blocking efflux transporters such as P-glycoprotein (P-gp). For instance, micellar entrapment may cause high solubilizing agent concentrations to reduce the percentage of medication in free, permeable form.

Bile salts and medium-chain fatty acids are examples of penetration enhancers that can momentarily relax intestinal epithelial cells' tight junctions, enhancing paracellular transport. However, their reversibility and safety need to be thoroughly described to prevent jeopardizing the integrity of the mucosa.

Excipient variability—differences in grade, source, particle size, and impurity profile—is one of the most important issues in pharmaceutical development. Changes in dissolving rates, disintegration durations, and bioavailability may result from these variances. For instance, in controlled-release formulations, HPMC's viscosity may have an impact on the drug's release profile. Therefore, to guarantee repeatability in medication performance, excipient consistency from batch to batch is crucial.

Excipients can improve permeability and solubility, however not all of them are without disadvantages. Some surfactants have the potential to irritate or hypersensitively affect mucosal tissue. APIs and polymers may interact negatively, resulting in stability problems. Furthermore, at larger dosages, excipients such as sodium lauryl sulfate and polyethylene glycol (PEG) have been linked to negative gastrointestinal symptoms. Excipient safety profiles must thus be thoroughly assessed, particularly in specific groups like children or the elderly.

The creation of innovative multipurpose excipients that concurrently enhance stability, permeability, and solubility is the key to the future of excipient science. Promising developments include mesoporous carriers, nanostructured lipid carriers (NLCs), and natural deep eutectic solvents (NADES). Predictive modeling and machine learning are also being investigated to improve formulation design and forecast excipient performance.

Regulations are gradually changing to enable separate approval processes for new excipients. Innovation and the use of novel functional excipients in pharmaceutical development will probably be encouraged by this.

The dualistic character of excipients in medicine formulation is highlighted in this debate. Although they can greatly increase the solubility and permeability of drugs, their effects are not always favorable and need to be carefully evaluated from a biopharmaceutical and safety perspective. The next generation of excipient-enhanced formulations will be shaped by developments in material science, computer modeling, and a better mechanistic understanding of excipient-API interactions.

CONCLUSION

Excipients are now essential components of contemporary drug delivery systems, having previously been regarded as pharmacologically "inactive". Their capacity to alter permeability and drug solubility has a major effect on the bioavailability and therapeutic effectiveness of pharmaceuticals taken orally, especially those that are poorly soluble in water.

From a biopharmaceutical standpoint, excipients contribute to the stability and manufacturability of drug products; they affect permeability by altering membrane fluidity, blocking efflux transporters, or opening paracellular pathways; and they improve solubility through processes like micelle formation, complexation, and amorphous dispersion. Their effects, however, might differ depending on concentration, chemical makeup, and interaction with active pharmaceutical ingredients (APIs), and they are extremely formulation-dependent.

Notwithstanding the benefits, there are still a lot of excipient-related issues. These include possible toxicity, batch-to-batch variability, physical and chemical instability, and regulatory restrictions on the use of new excipients. A thorough, mechanistic knowledge of excipient activity in vivo is necessary because to these constraints, particularly with regard to their effects on pharmacokinetics and drug transport across biological membranes.

In the future, many of the current obstacles should be removed with the creation of innovative and multipurpose excipients including deep eutectic solvents, smart polymers, and nanocarriers. Furthermore, to promote innovation in excipient research, it will be crucial to integrate high-throughput screening, computational modeling, and regulatory harmonization.

In conclusion, optimizing excipient selection and formulation design is not just a matter of enhancing solubility and permeability—it is a critical component in ensuring efficacy, safety, and patient-centric drug delivery. As our understanding deepens, excipients will increasingly be recognized not merely as formulation aids, but as active enablers of drug performance.

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