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Formulation Strategies To Optimize Drug Pharmacokinetics And Improve Therapeutic Outcomes

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Abstract
Poorly water-soluble drug candidates are becoming more prevalent. It has been estimated that approximately 60–70% of the drug molecules are insufficiently soluble in aqueous media and/or have very low permeability to allow for their adequate and reproducible absorption from the gastrointestinal tract (GIT) following oral administration. The molecules are withdrawn at various stages of discovery and development process for reasons such as poor ADME properties, lack of efficacy, and safety reasons. Formulation scientists have to adopt various strategies to enhance their absorption. Over the years, a wide range of compounds have been investigated for their permeation-enhancing effect in order to circumvent these challenges. There is also a growing interest in developing nanocarrier-based formulation strategies to enhance drug absorption.

Keywords: *Poorly soluble, permeability, absorption, efficacy, formulation strategies.*

Introduction

Pharmacokinetics is the study of how drugs are absorbed, distributed, metabolized, and eliminated by the body. It is an important aspect of drug formulation as it helps determine the appropriate dosage and frequency of administration. Pharmacodynamics, on the other hand, describes the mechanism of action or effect of a drug [1]. Understanding pharmacokinetics is crucial in evaluating and understanding the actions of drugs. Clearance, half-life, and protein binding are important concepts in pharmacokinetics that impact drug efficacy and toxicity. Overall, understanding pharmacokinetics is essential in optimizing drug therapy and ensuring patient safety. The development of drug delivery systems has undergone significant advancements over the years, heavily influenced by pharmacokinetic considerations. Pharmacokinetics, which encompasses the absorption, distribution, metabolism, and excretion (ADME) of drugs, plays a crucial role in the design and evaluation of drug formulations. Understanding these principles is fundamental to predicting drug behavior within the body and optimizing therapeutic efficacy [2].

The discovery of a new drug is a multi-stage complex process, each stage lasting for years. In addition to complexities in the science of making new safe and efficacious drugs, the political and economic factors coupled with stringent regulatory requirements and review process, the drug discovery has become even more complex and long-lasting [3]. The pharmaceutical industry is being criticized for not bringing more innovative medicines into the market for the treatment of unmet medical needs [4]. The sharp decline in the number of new drug approvals in the last decade can be attributed to the attrition of molecules during discovery and development. The attrition rate is very high in the drug

development process, with only 15% of molecules entering the clinical trials receiving marketing approval. The success rate from phase-III clinical trial to market translation is reported to be 50–70%. The molecules are dropped during the preclinical stage and withdrawn from further development during clinical studies for various reasons, such as lack of efficacy, toxicity, poor absorption, distribution, metabolism, and elimination (ADME) properties, commercial interest, and market competition [5]. Several approaches have been discussed in the literature to reduce attrition of drug candidates in clinical development. Identification of the right target and strong mechanism of action would reduce the failure of efficacy, and the attrition due to toxicity and safety can be reduced by eliminating molecules with mechanism-based toxicity, identifying biomarkers, selecting appropriate animal models for efficacy testing, and evaluating proof of concept at early clinical studies [6].

The failure of drug candidates may not be limited to the aforementioned reasons; there are several other factors contributing to attrition, such as the discovery and development of drug candidates for central nervous system (CNS) disorders facing additional barriers compared to those intended for other therapeutic applications [7]. Several drug candidates were reported to be dropped due to their inability to cross BBB. Gavestinel, which had completed phase III clinical trials but was failed to demonstrate clear efficacy due to its poor permeation across the Blood brain barrier (BBB). Although there have been significant innovative solutions to address the ADME issues, such as enhancing the solubility and permeability of molecules. However, issues such as rapid metabolism, especially first-pass effects, have met with limited success [8].

Formulation and drug delivery technologies have been tested for their utility in enabling drug candidates to progress from preclinical to clinical developmental stages [9]. Few reports suggest how formulation strategies are explored in drug discovery and development; however, most of them tend to focus on solubility and permeability issues. Hence, this review aims to provide comprehensive information on how formulation and drug delivery technologies can be explored to overcome various challenges in drug discovery and development [10]. The review discusses the examples of drug delivery technologies applied for enhancing the therapeutic utility and safety profile of already marketed drugs, and provides insight into how drug delivery can be better explored in the early stage of discovery and development to reduce attrition.

Formulation/drug delivery strategies for addressing ADME issues

The discovery and development of drugs involve various stages. The hunt for new drugs starts with selecting a disease and identifying of target. The molecules from synthesis or biological origin would normally be screened for *in vitro* biological activity [11]. The selected molecules then move to further preclinical testing such as *in vivo* activity in animal models, *in vitro* metabolism, and pharmacokinetic profiling in animals. During this stage, molecules will also be tested for physicochemical properties such as solubility, ionization, and partition behavior. The molecules with desired activity, ADME, and physicochemical properties will undergo stringent safety and toxicity testing before they enter clinical testing [12]. The physicochemical parameters coupled with ADME testing will assist in determining the drugability of molecules. The biopharmaceutics classification system (BCS) groups molecules into four classes based on solubility and permeability. The molecules belonging to Class I are believed to be more development-friendly as they possess desired characteristics that make them more drugable [13]. The molecules belonging to Classes II-IV will have problems associated with either solubility and/or permeability. Lipinski's rule of five also provides useful information on the biopharmaceutical behavior of molecules based on molecular weight, H-bond donors/acceptors and log *P* values [14]. The molecules that lack the desired ADME profile will fail to elicit pharmacological activity *in vivo*. The importance of early ADME prediction and profiling

has been reported in the literature, and early ADME profiling has been found to improve discovery output. The many hits during discovery fail to become lead candidates for clinical development due to poor ADME properties [15].

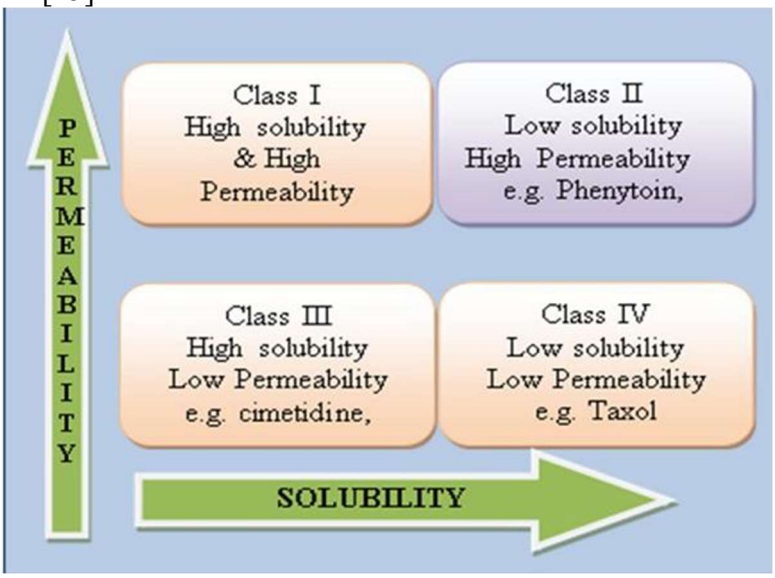

Figure 1. BCS classification system

Formulation approaches for improving solubility

Poor solubility leads to incomplete absorption, and the solubility of molecules becomes a problem in the early stages of discovery [16]. An estimated 70% of molecules in the developmental pipeline are believed to be poorly soluble, and 40% of already approved drugs are poorly soluble. Several innovations in the formulation science have led to viable technologies for the formulation of poorly soluble drugs to improve delivery [17].

The buffering/salt formation, cyclodextrin complexation, nanosuspensions, emulsion/microemulsion systems, cosolvency, and surfactant solubilization are commonly used technologies to deliver insoluble drugs.

Salt formation has been considered the simplest and most effective method for improving the solubility and dissolution rate of weakly acidic and basic drugs [18]. The salt formation provides viable strategies for molecules with solubility as a rate limiting factor in their development. There are several drugs on the market as salt forms, such as nelfinavir mesylate, atazanavir sulfate, ziprasidone hydrochloride and mesylate, imatinib mesylate, indinavir sulfate, metformin hydrochloride, amlodipine besylate, losartan potassium, diclofenac sodium and potassium, sodium valproate, and ketorolac tromethamine. For many of these molecules, the selection of appropriate salt forms enhanced their developability into clinical candidates and finally led to marketing approval [19]. Apart from the salt approach, the buffering/pH adjustment is widely used in the preclinical formulation development of insoluble molecules [20]. Nearly 85% of molecules from one of the Pfizer research facilities were formulated with pH adjustment and cosolvency in the year 2000. Similarly, many of the parenteral formulations on the market contain counter ions for pH modifications, examples include Ciprofloxacin Injection, Leurolide, Vincristine, Trimethoprim/Sulfamethoxazole and Methylprednisolone Injections.

Cyclodextrins have been explored extensively for the formulation of insoluble molecules. Cyclodextrins are versatile excipients used in oral and parenteral formulations and a choice of

excipient for solubilization of new chemical entities (NCEs) in the preclinical development. The DRF-4367 a weakly acidic NCE, had an oral bioavailability of 20% after oral administration as a suspension to rats; however, a solubilized formulation with hydroxypropyl-β-cyclodextrin and meglumine enhanced the bioavailability of the molecule nearly to 100%, thus enabling the molecule for further development [21].

The administration of molecules in the form of nanosuspension has been shown to increase oral bioavailability. The formulation of molecules as nanosuspension in the early preclinical development offers simple, safe, and cost-effective formulation strategies for the formulation of insoluble NCEs. There are many simple lab-based instrumentation and techniques described in the literature to produce nanosuspension for preclinical applications [22]. The nanosuspension of DRF-4367 with a mean particle size of 100–300 nm, prepared using bead milling followed by high-pressure homogenization, has shown a significant improvement in the oral bioavailability in rats (65% at 30 mg/kg) as against a plain suspension (35%).

Emulsions/microemulsions-based drug delivery systems have been found useful in enhancing oral bioavailability of insoluble molecules. The microemulsions have also been used in the preclinical formulation development of insoluble NCEs. Torcetrapib, which was considered to be a blockbuster molecule for the treatment of elevated cholesterol, inherently had poor absorption due to limited solubility in GI fluids [23]. The development of self-microemulsifying drug delivery system (SMEDDS) formulations consisting of oils/surfactants/cosurfactants has led to increased absorption of molecules in dogs as compared to aqueous suspension. There was 30–40-fold increase in C_{max} and AUC when administered as SMEDDS under fasted conditions [24]. Poor solubility was considered one of the problems in preclinical development, and the appropriate formulation development ensured the progress of the molecule to clinical testing. However, the molecule was discontinued from late-stage clinical testing due to safety reasons.

The cosolvent and surfactant-based formulation approach has been widely used to address the solubility issue in preclinical development [25]. The *N*-Epoxymethyl-1,8-naphthalimide (ENA) a novel antiproliferative drug candidate with potent anticancer activity, was found to have poor solubility and stability in aqueous systems; however, the use of ethanol and Cremophore® EL has resulted in a viable formulation necessary for further preclinical development of the molecule. A similar solvent/surfactant-based system was used for the formulation of taxol. The general template for screening formulation for insoluble NCEs at the discovery stage has been described in the literature [26]. These examples have demonstrated that formulation/drug delivery technologies can overcome the issue of solubility in drug discovery/development. However, in our experience, given the advent of these many technologies for solubilization, it is not always possible to formulate all insoluble molecules. Certain highly insoluble molecules may still pose problems and go undeveloped.

Formulation approaches for improving permeability

Permeability of drugs across the GI membrane is one of the rate-limiting steps in the absorption of drugs. The solubility and permeability of drugs together determine the extent of oral absorption. The physicochemical factors such as log *P*, molecular weight, polar surface area, charge/ionization, and number of hydrogen bond donors and acceptors determine the permeability of the molecule [27]. In general, hydrophobic small molecules with higher log *P*, and lesser polar surface area will have greater permeability across biological membranes. Unionized species are more favored for absorption than ionized species. In addition, drug efflux mediated mainly by transporters such as P-glycoprotein (P-gp), multidrug-resistant proteins (MRP) and organic cation transporters (OCT) leads to poor absorption of drug molecules. The low permeability of molecules may hinder their development, and

several NCEs are reportedly dropped during the discovery stage [28].

There are several methods reported in the literature for enhancing permeability and preventing the efflux of drug molecules by transporters. The permeation of molecules occurs by two pathways, transcellular uptake across epithelial cells and paracellular passage through intercellular space [29]. The improvements in both paracellular and transcellular absorption have been accomplished by the use of chemical enhancers. Diverse classes of compounds including detergents, surfactants, bile salts, Ca^{2+} chelating agents, fatty acids, medium-chain glycerides, acylcarnitine, alkanoyl cholines, *N*-acetylated a-amino acids, *N*-acetylated non-a-amino acids, chitosans, mucoadhesive polymers, and phospholipids have been investigated for permeation enhancement. Many of these agents act as detergents that disturb the structure of the lipid bilayer, leading to increased membrane fluidity and permeability [30]. On the other hand, certain agents act as calcium chelators and disrupt tight junctions between epithelial cells. The trimethyl chitosan was reported to bind to components of tight junctions and widen the intercellular space. Various excipients that are commonly used in pharmaceutical formulations are reported to be potent inhibitors of Pgp mediated efflux of drugs. Cosolvents such as polyethylene glycol, surfactants such as polysorbates, Vitamin E TPGS, Cremophores, Poloxamers, and dendrimers have been reported to significantly reduce P-gp efflux of drugs. Coadministration of cyclosporine, a P-gp substrate, with paclitaxel has resulted in enhanced absorption of paclitaxel in humans. Increased and consistent absorption of cyclosporine from SMEDDS formulation, Neoral® could be partially due to bypassing of P-gp efflux during the absorption [31]. The scientific efforts in enhancing the permeability of molecules have been successful to a considerable extent. Several techniques described in this section can be utilized in the early stage of drug discovery for salvaging molecules with poor permeability. However, these techniques have limitations, and not all molecules can benefit from them.

Formulation/drug delivery approaches for addressing metabolism and elimination

The fate of a drug in the body depends on its susceptibility to metabolizing enzymes. Most drugs undergo metabolism before excretion, and very few drugs are excreted unchanged. Phase I metabolism includes reactions such as hydroxylation and oxidation. Phase II metabolism involves derivatization reactions such as glucuronidation and sulfation [32]. The metabolism renders the molecules more hydrophilic and amenable to excretion. The rate of metabolism determines the plasma half-life of the molecule. A faster metabolism leads to a shorter half-life. The optimum plasma residence time of molecules is essential to elicit pharmacological action. Molecules that show significant activity *in vitro* often fail to produce meaningful activity in *vivo* conditions due to rapid metabolism, and resveratrol is one such molecule [33]. Molecules best in class, in terms of activity, may not progress to further development due to various issues such as ADME; rather, molecules with balanced properties will move forward.

Many of the commonly used excipients have been shown to reduce the metabolism of drugs in *in vitro* conditions. The surfactants such as Tween 80, Cremophore® EL, and Solutol® HS have reduced the metabolism of midazolam when co-incubated with rat liver microsomes. The reduction of metabolism was up to 50% in the case of Solutol® HS and Cremophore® EL at 0.3% *w/v* surfactant concentration, and similar results were reported for colchicine with these surfactants. Intravenous pharmacokinetic studies revealed that Solutol® HS had a significant effect on the clearance of colchicine, as clearance was significantly reduced and C_{max} was increased; however, the effects were minimal on midazolam [34]. The weak cytochrome p450 (CYP) inhibitory effect of the surfactant was sufficient to affect the moderately metabolized colchicine. In contrast, the pharmacokinetic profile of midazolam was unchanged because of its rapid rate of clearance through metabolism. The amount of

surfactant below the CMC after dilution with blood was also attributed to a lack of effects on metabolism as against *in vitro* results. Surfactants have been reported to affect the pharmacokinetic profile of anticancer drugs such as paclitaxel, docetaxel, etoposide, and doxorubicin. The intravenous administration of 2.5 mL/kg Cremophore® EL, 10 minutes before dosing of either doxorubicin or doxorubicin, has resulted in a doubling of AUC and Cmax, and a reduction of clearance to half for both drugs [35]. Hence, co-administration of surfactants can be considered to reduce the metabolism of molecules during discovery stages; however, hypersensitivity reactions towards surfactants need to be considered. Surfactants with better clinical tolerability must be used.

Another simple, safe, and effective approach to stabilize the molecule against metabolism is polymer conjugation. Reversible or irreversible covalent attachment of a polymer to small molecule non-peptide drugs can result in reduced metabolism, increased circulation time, improved activity, and reduced toxicity [36]. The shielding effects of the polymer on drug molecules against enzymes/chemicals result in reduced degradation. However, not all molecules may be feasible for polymer conjugation. The molecules with functional groups such as OH, COOH, NH_2, SH can be explored for polymer conjugation. Various polymers, such as dextrans, polyethylene glycol (PEGs), *N*-(2-hydroxypropyl) methacrylamide (HPMA), and polyglutamic acid, have been explored for conjugation with drugs. The polymer conjugation approach has been successfully applied to improve the safety, efficacy, and pharmacokinetic profile of small molecule drugs such as doxorubicin (DOX), norfloxacin (NOR), camptothecin (CAMP) and paclitaxel (PTX) [37].

The camptothecin–PEG conjugates were prepared using a glycine linker. The electronegativity of the linker was found to increase the stability of the conjugates. The alkylated glycine linker further enhanced the stability of the conjugates. The activity of these conjugates was similar to camptothecin-20-PEG without a glycine linker, which hydrolyzed rapidly in plasma [38]. These results demonstrate that despite being stable in plasma, camptothecin–glycine–PEG conjugates demonstrated good activity because of the probable hydrolysis of the conjugates in cells to release the parent molecules. This way, the circulation half-life can be increased without affecting activity and improving overall efficacy.

Paclitaxel has been conjugated to soluble polymers such as polyethylene glycol and the micelle-forming diblock polymer polyethylene glycol–polylactide (PEG–PLA). The paclitaxel–PEG conjugate made *via* an ester link was found to undergo rapid hydrolysis in plasma with $t_{1/2}$ of 30 min. The PTX–PEG ester conjugates were considered ideal for prodrugs and for parenteral formulation to overcome solubility issues [39]. However, PTX–PEG prodrugs were found unsuitable for use as long-circulating drug delivery systems. Paclitaxel was conjugated to PLA–PEG with an ester bond, and the conjugate was found to be active against the H7402 liver cancer cell line. The authors concluded that paclitaxel was released in the cells and that polymer conjugation did not affect the activity of paclitaxel. However, data on the pharmacokinetics and *in vivo* activity were not reported.

Recently, polymer conjugates of the metabolically unstable molecule, resveratrol, were prepared and evaluated. It was observed that RSV–PLA–PEG ester conjugates were found to be relatively stable in plasma and displayed a better pharmacokinetic profile with multifold higher C_{max} and AUC than plain RSV.

Drug delivery strategies for addressing efficacy/safety *via* targeting

The ability of a drug to exert pharmacological actions depends on the rate and extent at which the drug reaches the site of action. The desired biological action can be achieved if an adequate amount of the drug is available in the affected tissues. The presence of the drug molecule at levels beyond the tolerable limit in body tissues other than the site of action would precipitate unwanted biological responses, leading to toxicity. Discontinuation of many molecules in the discovery and development

program could be attributed to poor accumulation of molecules at the site of action and wide distribution to other parts of the body, leading to lack of efficacy and increased toxicity. In this section, we discuss briefly the examples of successful drug targeting and their possible application during discovery/development stages [40]. Drug targeting is usually achieved by either passive targeting or active targeting. Passive targeting involves the spontaneous accumulation drug delivery systems in the diseased parts of the body. On the other hand, active targeting involves attaching a targeting a moiety to the drug or drug carrier to enhance uptake by target cells. Tumors are highly vascularized in response to the increased demand for nutrient supply from rapidly growing tumor cells. The tumor vascular endothelium is more porous, which allows leakage of nano-drug carriers into the tumor through the pores. The inefficient lymphatic drainage and slow venous blood return allow drug carriers to remain in the tumor for a longer time. This process is regarded as enhanced permeation and retention (EPR). The cancer drug candidates are usually more toxic than other therapeutic molecules, and hence, drug targeting has been extensively applied to cancer treatment [41].

The Doxil® was first liposomal formulation approved by the United States Food and Drug Administration (FDA), the formulation is a PEGylated liposome encapsulating doxorubicin. The free doxorubicin has a circulating half-life of 0.2 h and an AUC of 4 μg·h/mL; in contrast, Doxil® has a half-life of 55 hours and an AUC of 900 μg·h/mL. More than 90% of the doxorubicin remained in the liposomes during circulation. The liposomal formulation avoided repeated administration of the drug and showed reduced clinical cardiotoxicity. Myocet® is another doxorubicin liposomal formulation with a circulating half-life of 2.5 h. It is reported to be safer than doxorubicin. DaunoXome® and Onco-TCS® are approved non-PEGylated liposomal formulations of daunorubicin and vincristine. Genexol-PM, a novel polymeric micelle encapsulating paclitaxel, exhibited significant efficacy and a better safety profile than Cremophore® EL-contained formulations. Preclinical studies in mice revealed that the concentration of paclitaxel in the tumor for the micelle formulation was higher than for plain paclitaxel.

Active targeting to the tumor has also been investigated. Abraxane®, albumin-bound nanoparticles containing paclitaxel, demonstrated higher response rates, a better safety profile compared to conventional paclitaxel, and improved survival in patients receiving it as second-line therapy. The albumin nanoparticles were reported to be actively transported into cancer cells *via* secreted protein acidic and rich in cysteine (SPARC) mediated transport. Oxaliplatin is a novel cisplatin derivative with reduced kidney toxicity; however, this drug is only effective when administered with 5-fluorouracil. Oxaliplatin is reported to partition rapidly into erythrocytes, and has been attributed to its a lack of anticancer activity when given alone [42]. Transferrin–PEG–liposomes containing oxaliplatin showed improved circulation time, reduced partitioning, and increased localization of oxaliplatin in the tumor. Intravenously administered transferrin–PEG–liposomes containing oxaliplatin suppressed tumor growth more effectively than PEG–liposomes, bare liposomes, and the free drug. The increased efficacy with transferrin liposomes could be due to their increased circulation time and transferrin-mediated endocytosis of the liposomes into cancer cells.

Formulation Strategies to Improve Pharmacokinetics Profile

- **Solid Lipid Nanoparticles (SLN)**

Solid lipid nanoparticles (SLN) have garnered great interest in their ability to improve the oral absorption of poorly soluble drugs. They are a colloidal system derived from a matrix of lipids that retain their solid state at a temperature below 140 °C, with sizes ranging from 50 to 1000 nm, and are able to disperse in an aqueous medium with the aid of surfactants. Some of the advantages of

employing SLN as a drug delivery system for oral administration include mitigating the degradation of entrapped drugs, as well as providing some control over the rate of drug release. Another advantage of utilizing this formulation approach is the ability to avoid hepatic first-pass metabolism through intestinal lymphatic uptake [43]. This is because the lipophilic nature of the SLN causes the nanocarrier to drain into the thoracic lymph before entering the systemic circulation near the left subclavian vein, thus circumventing the hepatic first-pass metabolism. One of the reasons for the absorption-enhancing ability conferred by SLN is attributed to the interaction of the P-gp efflux pump, which causes the substrate to be unavailable for transport. This was confirmed by Garg et al. (2016), who discovered that by formulating lumefantrine as the SLN, they were able to enhance the oral bioavailability of the drug, which is a substrate for P-gp, by 2.7-fold relative to when the lumefantrine was delivered in 0.25% *w/v* Na CMC suspension by oral gavage. The SLN used consisted of a binary lipid mixture of stearic acid and caprylic acid stabilized with the non-ionic surfactant, D-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS) and formulated with Poloxamer 188. Another advantage of formulating poorly soluble drugs by using SLN is the ability of the nanocarrier to increase the dissolution rate of the drug within the gastric lumen, thus generating a concentration gradient to promote absorption across the gastrointestinal membrane. Such an enhanced dissolution rate is attributed to the submicron size of the SLN, which provides a large surface area for drug dissolution [44].

- **Dimers**

A dendrimer is a synthetic polymer with a highly branched amidoamine structure and an ethylenediamine core. The repeated branching results in the dendrimer having a hollow interior and a dense exterior surface [45]. It also has a nanosized and spherical structure. Drugs may be bound to the polymer surface or loaded into the central core, depending on the physicochemical properties of the drug.

Yan et al. investigated the effects of an acetylated G2 PAMAM dendrimer on the intestinal absorption of poorly absorbable water-soluble drugs, using an in situ closed-loop method in rats. The acetylated G2 PAMAM was synthesized by reacting with acetic anhydride with G2 PAMAM to produce a primary amine-acetylated G2 PAMAM dendrimer (Ac-G2), in which the primary amine group on the dendrimer surface was converted to acetamide. Among the various acetylation levels, Ac50-G2 displayed the greatest absorption-enhancing effect on the permeation of the fluorescein isothiocyanate-labeled dextrans (FD4), 5(6)-carboxyfluorescein (CF), and alendronate. However, the same result was not observed for the macromolecular drug, FD10. The possible reason for such an observation may be attributed to the effect of the PAMAM dendrimers on loosening the tight junctions along the gastrointestinal tract. Although the dendrimer may loosen the tight junctions and enable the permeation of fluorescein isothiocyanate-labeled dextrans (FD4), 5(6)-carboxyfluorescein (CF), and alendronate, the size of the pores formed were insufficient to allow the paracellular transport of the macromolecular drug, FD10. It was also discovered that different generations of dendrimers had differing effects on absorption-enhancing effects, with G2- and G3-acetylated PAMAM dendrimers being more effective than G0- and G1-acetylated PAMAM dendrimers [46]. Yan and co-workers also highlighted that the dendrimer was shown to be safe and did not result in any observable damage to the intestinal lining following intestinal administration when the concentrations of acetylated PAMAM used were below 0.50 w/w.

- **Nanoemulsions**

Nanoemulsions are translucent or transparent water-in-oil (w/o) or oil-in-water (o/w) droplets that are

thermodynamically stable nanoformulations prepared from a mixture of water, oil, and surfactants, co-surfactants in an aqueous phase with droplet sizes ranging from 1 to 200 nm. The addition of a co-surfactant improves the emulsion stability by increasing the fluidity, as well as by a disordering effect on the surfactant film that increases the drug loading and the formation of an extemporaneous nanoemulsion [47]. The diameter of the oil droplets is usually in the range of 50–200 nm, as compared to conventional emulsions which have a size range from 1 to 100 μM. The use of a pseudo-ternary phase diagram aids in the identification of the optimum composition of water, oil, and surfactant that results in the formation of a nanoemulsion region via the titration method. Nanoemulsions are widely used due to their advantages, which include the protection of therapeutics against chemical and enzymatic degradation, high solubilization capacity, improved drug absorption, rapid onset of C_{max}, ease of fabrication, and the facile scale-up of the manufacturing process. In addition, the enhanced colloidal stability conferred by a nanoemulsion mitigates the propensity of the formulation to coalesce and flocculate over a long storage period [48].

- **Double emulsion**

Multiple emulsions are complex systems, which can be termed "emulsions of emulsions". Among multiple emulsions, a double emulsion is the simplest, in which a primary emulsion is re-emulsified into a dispersion medium [49]. These formulations have proved to be promising oral bioavailability enhancers of proteins, peptidomimetics, or BCS class III drugs, as these formulations may directly get absorbed as oil droplets from the intestine. Since no organic solvents are required in their preparation, these emulsions are also safer to administer and easier to prepare. In double emulsions, the drug is present in the inner hydrophilic core, which serves as a protection and storage chamber. Due to their instability during shelf-life, their industrial application is limited [50].
Koga et al., 2010, developed multilayer emulsions capable of enhancing intestinal absorption of calcein as a model BCS class III compound. They reported that the absorption-enhancing effects of w/o/w emulsions on intestinal calcein absorption in rats were significantly higher than that of the calcein control.

- **Niosomes**

Niosomes are described as a class of molecular clusters formed by the self-association of non-ionic surfactants in an aqueous phase. Their unique structure presents an effective novel drug delivery system with the ability to load both hydrophilic and lipophilic drugs. Niosomes can prove to be an effective delivery system in enhancing the oral bioavailability of the BCS class III group of drugs. Attai et al. 2007, prepared acyclovir niosomes which were unilamellar and spherical in shape. The nonionic surfactant vesicles were prepared by the conventional thin film hydration method. It is reported that the niosomal formulation exhibited significantly retarded release compared with the free drug, whereas the in vivo study performed by them revealed that the niosomal dispersion significantly improved the oral bioavailability of acyclovir by more than 2-fold increase as compared to the free drug solution [51].

- **Self- double emulsifying systems (SDEDDS)**

SDEDDS are formulations that can spontaneously emulsify in the gastrointestinal aqueous fluid, forming water-in-oil-in-water (w/o/w) double emulsions with drugs encapsulated in the inner aqueous core. SDEDDS are stable systems, as compared to conventional thermodynamically unstable double emulsions. SDEDDS can be directly filled into soft or hard gelatin capsules, which are easy to administer and store. Formulation of pidotimod SDEDDS is reported by Qi et al., 2013, in vivo study

results indicated that plasma concentration-time profiles in rats dosed with SDEDDS showed 2.56-fold increased absorption of pidotimod, compared to the pidotimod solution [52].

- **Liposomes**

The first liposomes, i.e. closed bilayer phospholipid systems, were described in 1965 and soon were proposed as drug delivery systems. Over almost 5 decades, the pioneering work of countless liposome researchers led to the development of important technical advances, such as extrusion for homogeneous size, remote drug loading, long-circulating (PEGylated) liposomes, triggered release liposomes, liposomes containing nucleic acid polymers, ligand-targeted liposomes, and liposomes containing combinations of drugs. These advances have led to numerous clinical trials in the delivery of anti-cancer, anti-fungal, and antibiotic drugs, gene medicines, and anesthetics, and anti-inflammatory drugs.

Manconi et al., 2013 designed metformin-loaded liposomes coated with chitosan cross-linked with the biocompatible β-glycerophosphate, the in vivo oral bioavailability performed by them suggested that the microcomplexes are effective carriers of the highly water-soluble antihyperglycemic drug, thus, allowing its controlled delivery and improved oral availability [53].

- **Crystalline Solid Formulations**

Modification of the physicochemical properties, such as salt formation and micronization of the crystalline compound to increase the surface area and thus dissolution, may be one approach to improve the dissolution rate of the drug. The particle size of about 2–5 μm can be achieved by micronization using an air-jet mill. The nanocrystal technology can reduce the crystalline particle size to 100–250 nm using ball-milling, dense gas technologies, and so forth [54,55]. However, these methods have their limitations. For instance, the formation of salt compounds is not feasible Particle size reduction may not be desirable in situations where poor wettability and handling difficulties are experienced with very fine powders.

Conclusion

The advancement of technologies, design, and development of new chemical moieties with targeting potential is leading to the emergence of new drug molecules with therapeutic effects but unfavorable physicochemical properties for their drug absorption in the body. There are many challenges that formulation science has not addressed, leaving ample scope for further investigations. The challenges associated with formulations include selecting the appropriate excipients, considering their solvent capacity, miscibility, chemical stability, compatibility, self-dispersibility, and regulatory issues. Various issues hindering the development of molecules into drug candidates can be overcome by employing different formulation or drug delivery strategies.

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