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ADVANCEMENT IN ORAL DRUG DELIVERY; A PARADIGM SHIFT FROM CONVENTIONAL TO NANOFORMULATIONS

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ABSTRACT

Historically, medicinal substances were used in a crude form where proper preservation and dose accuracy were the apparent challenges. The conventional dosage forms are often inherited with limited bioavailability, less effectiveness, and more side effects. To overcome these challenges, advanced drug delivery systems and pharmaceutical nanotechnology resulted in enhanced solubility, dissolution, and oral bioavailability. Within the frame work of drug discovery and development proceeses, along with novel drug discovery and re-profiling, the re-formulation approach is of considerable importance. Drug re-formulation focuses on existing drugs to enhance their bioavailability, where the determinant factors are the drug solubility and dissolution in the the gastrointestinal tract (GIT), and its membrane permeability. Re-formulation of existing drugs enhances their pharmaceutical worth and cost-effectiveness as compared to novel drug discovery and development. Bioavailability through re-formulation could be enhanced by particle nanosizing, choice of excipients/method, or enhancing penetration utilizing a carrier. Therefore, incorporating multiple strategies simultaneously is of profound consideration to address current challenges and ensure future adaptable perspectives for fulfilling the rational needs of consumers and patients.

Keywords: *Advanced drug delivery, enhancing bioavailability, lipid-based nanoformulations, lipid-polymer hybrid nanoformulations, re-formulation*

INTRODUCTION

Since ancient times, plants have been used as medicines for the eradication of diseases, and modern medicines are based on traditional knowledge and practices of herbs as a source of therapy. Natural products possess distinguished characteristics such as chemical diversity, target specificity, and less toxicity for the biological system [1]. Although plants have been used as a remedy from ancient times, the credit for isolation of pure compounds from the plants in the modern world concerning drug discovery and development goes to the pharmacist “Friedrich Serturner” who isolated morphine from opium in the year 1805 A.D. [2, 3]. Since that, numerous medicinal entities/compounds, particularly in the era of the industrial revolution (from 1970 A.D. onward) have been discovered and developed, , in various dosage forms and formulations. The drug discovery from natural sources such as plants, animals [4, 5] and semi-synthetic/synthetic origin [6, 7] involves the identification of molecules by comprehensive evaluation to be used as possible drug candidates [8]. New drug development needs financial investment, human and technological expertise along with adherence to health authority regulations on quality control and manufacturing standards before a drug could proceed to the market [9]. A new chemical entity (NCE) costs approximately one billion US$ from the stages of drug screening, formulation, and dosage form development to the marketing. While the success rate attained by the pharmaceutical industry to bring a candidate drug to the market is not more than 10% as compared to the total investigated NCEs [10, 11]. Drug discovery and

development is a prolonged process and improved drugs are those which offer advantages in terms of safety, potency, tolerability, and ease of administration [12]. Even, then the conventional dosage forms possessing insufficient bioavailability, more side effects, frequent administration, and ultimately patient non-compliance as prominent limitations [13]. In the light of literature, 60% of those drugs coming to the market from synthetic sources are poorly water soluble, hence possessing poor bioavailability [14].

There are two basic scientific concepts regarding drug discoveries and investigations: either using novel drugs for the known targets (new drug discovery) or to explore new targets for existing approved drugs (drugs re-profiling or re-positioning). Re-profiling of drug investigation is an emerging field in drug development, where new targets/indications for existing medication could be determined. Novel drug discovery and development necessitates more cost, longer time (10-17 years), great efforts, and less possibility of success (overall less than 10%), while drug re-positioning is effective with respect to cost, time (3-12 years), efforts, as well as safety and pharmacokinetics concerns are fewer. On the otherhand, drug re-formulation focusing on overcoming the hurdles relevant to aqueous solubility and permeability of existing drugs. Drug re-formulation is among the drug development/investigation processes, where the delivery of an existing pharmaceutical entity could be improved. Moreover, it is less expensive in comparison to novel drug discovery and development [15-17]. The novel discovery and development process is complex and needs multifaceted paradigm checks for clinical trials and commercialization [18-21], while, re-formulation deal with the drugs possessing low aqueous solubility and/or low permeability i.e., represented by biopharmaceutics classification system (BCS) in BCS class II, III, or IV [15-17]. Pharmaceutical substances after development and approval for a disease could be subjected to additional clinical applications in any other disease (re-positioning) or there could be additional development of an equivalent pharmaceutical entity in a new formulation (re-formulation) to aid to the worth of pharmaceuticals. Both approaches (either re-positioning or re-formulation) are conventional, cost-effective, have an insignificant risk of safety, and have fewer chances of failure for drug development. In South Asian traditional medicines [22] and the allopathic system of medicines [23], the re-formulation of regime/pharmaceuticals is an area of indispensable research. Re-purposing is the collective term applied to re-positioning, re-formulation, and combination strategies (re-positioning with aided re-formulation). Four groups have been designated in drug re-formulation [23] that include:

Group-0: Where a chiral switch or excipient(s) are different, but the pharmacokinetic parameters remain similar. It also includes reformulations where none of the other classifications (from groups 1 to 3) could be applied.

Group-1: Where the pharmaceutical form and route of administration are similar, but the pharmacokinetic parameters are different (such as modified release formulations).

Group-2: Where pharmaceutical form is different but has the same route of administration and possesses the identical parameters of pharmacokinetics.

Group-3: Where the pharmaceutical form, as well as the administration route of the re-formulated drug, is different.

Rational Drug Delivery: A Vital Hallmark After Drug Discovery

The aim of rational drug delivery specifically to timely release drug in the desired concentration at the target site for pharmacological response, whereas drug delivery in general is the administration of pharmaceutical entity to exert therapeutic effect in the subject (human or animal) [13, 24, 25]. Within the body, the drug crosses many biological barriers and reaches the target of interest. During this transport, the drug may bind to non-target sites and produce undesirable effects or get inactivated. Therefore, effective drug delivery to the target site is of principal consideration to reduce unintended effects and ensure cost-effective drug therapy [25]. Drug administration through the oral route is preferred and safe, but there exist an insufficient understanding of mechanisms that could explain the critical processes necessary for oral drug absorption. It has been reported that the physiological barriers to oral drug delivery include the biochemical barriers (e,g, the degradation of a drug as a result of enzymatic or pH effect), the mucosal diffusion barrier, and the cellular permeability barriers [26]. To understand the gastrointestinal absorption-related processes,

variability occurs in patient/special populations, gastrointestinal tract regional differences, the effect of advanced formulations, and drug-food interactions [27]. Drug investigated by either means to be formulated in a suitable dosage form for comparatively long-term storage (stability), known composition/strength, availability, and efficacy for the treatment of ailment(s). Furthermore, it should ensure to achieve the desired therapeutic outcomes in a specific duration of time under a particular mechanistic approach. However, if the therapeutic goals of any drug formulation are not achieved, having hindrances, a higher dose or frequent doses are required. Then re-formulation of such drug(s) to enhance its delivery and maintain its concentration in the range of therapeutic index, necessitate fulfilling the therapeutic outcomes.

Transforming a pure drug or a chemical/compound into a formulation and dosage form to be used safely and effectively by patients [28], comes under the jurisdiction of the pharmacy profession particularly the discipline of pharmaceutics, which deals with the process of turning NCE into a drug product. Rational drug delivery could ensure optimal drug bioavailability. It is necessary for the biological response that the drug should achieve optimal concentration in the systemic circulation from the dosage form. The problems that result in poor bioavailability are either poor aqueous solubility, poor permeability, poor stability at physiological pH, or a greater level of pre-systemic metabolism. These problems could be overcome either by changing the route of drug administration, modification in formulation, or modification in chemical structure [29], as presented in Figure 1.

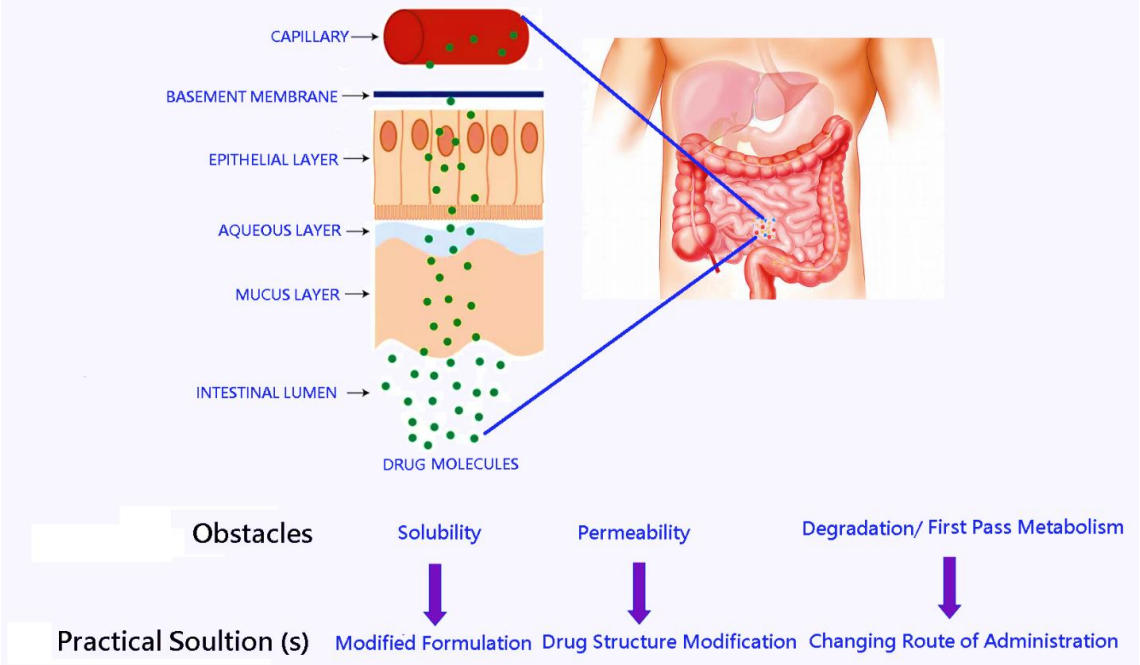
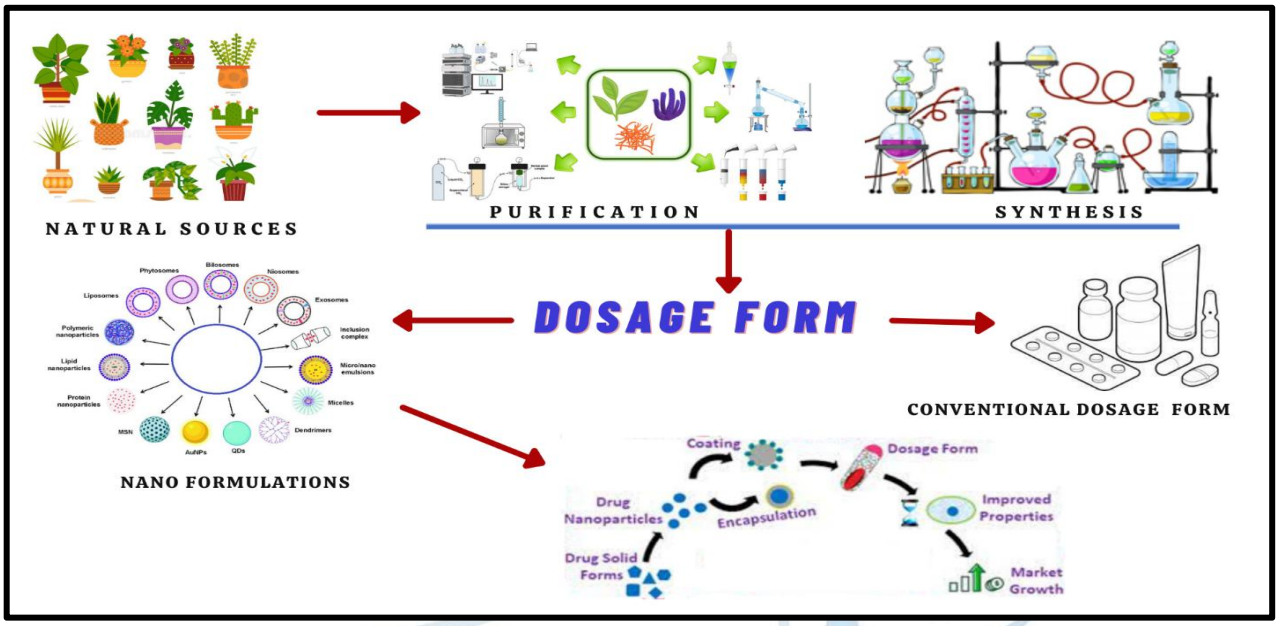


Figure 1. Oral bioavailability drug pathway, the inherent obstacles along with their measures

Conventional *versus* Enhanced Drug Delivery

The conventional dosage forms are inherited with limited bioavailability, less effectiveness, and more side effects. To overcome these hindrances, advanced drug delivery systems and pharmaceutical nanotechnology/particle technology resulted in greater solubility, dissolution rate, and enhancement in the oral bioavailability as well as a quick commencement of desired therapeutic effect and a lower dose requirement in comparison to conventional dosage-forms [30, 31]. The diagrammatic presentation of conventional versus nano-based formulation and the advancement involved are depicted in Figure 2.

Figure 2. Nanoformulations with improved characteristics compared to conventional dosage forms obtained from natural/synthetic sources



The World Health Organization (WHO) has introduced BCS classification, where each drug is designated a specific class on the basis of its potential aqueous solubilization and gastric permeation [32, 33], which are depicted in Table 1

Table 1: Drugs characteristics on the basis of Biopharmaceutics classification system

BCS Class	Aqueous Solubility	Gastric Permeability	Examples	Reference
I	High	High	Acetaminophen, Acyclovir, Amitryptaline, Captopril, chlorpheniramine, Diazepam	[33]
II	Poor	High	Ibuprofen, Ketoprofen, Carvedilol, Ketoconazole, Fenofibrate, Danazol	[34]
III	High	Poor	Amoxicillin, Erythromycin, Ciprofloxacin, Famotidine	[33]
IV	Poor	Poor	Acetazolamide, Amphotericin-B, Furosemide, Paclitaxel	[35]

The formulation role while focusing on modification in strategies in terms of choice of excipients and method of preparation is predominant for enhancing the class-II drugs bioavailability from the GIT, while formulation strategies could result in a slight improvement in the bioavailability of class-III and IV drugs due to their inadequate potential to cross GIT membrane. For drugs included in these two classes, modification in physicochemical properties through structural alteration could be required to cope with permeability hurdles. Furthermore, it is suggested for poorly water-soluble drugs, the desirable strategies are lipid-based, crystalline solid, or amorphous formulations [36]. The advancement in drug delivery systems started with liposome (lipid-based system) to various grades of polymers (biodegradable, block co-polymers, natural polymers), and protein-based drug carriers [37].

Drugs in BCS Class-I show high solubility (HS), high permeability (HP), and rapid dissolution (RD). To fulfill the HS, HP, and RD requirements, the criteria are better explained in the literature [38]. Drugs in BCS class-I possess good solubility and permeability but may have poor bioavailability (BA) due to considerable first-pass effect, where drug get metabolized somewhere in th body before reaching into the systemic

circulation [39]. Examples of some model drugs from BCS-I to IV and the techniques to improve solubility of BCS- II drugs has been illustrated here [33].

Drugs in BCS Class-II posses low solubility while permeability is high, and if these drugs are in solution form, it get completely absorbed from GIT. Therefore, *in-vitro* dissolution studies are essential prior to *in-vivo* absorption to determine bioavailability (BA). For BCS class-II and IV drugs, the pKa of active pharmaceutical ingredient (API) has considerable effect on the aqueous solubility in *in-vitro* and *in-vivo* studies. Weak acidic drugs with pKa ≤ 5 (e.g., BCS-IIa, ibuprofen, and ketoprofen) have poor solubility at acidic pH but posses better absorption in the small intestine. Weak basic drugs with pKa ≥ 6 (BCS-IIb, carvedilol, and ketoconazole) show high solubility in acidic medium but poorly absorb from the small intestine. Absorption of neutral drugs with no pKa or pKa < 0 and ~ >8 (BCS-IIc, fenofibrate, and danazol) not affected by changing the pH range. Other contributing factors for dissolution/absorption include particle size and solid form (crystalline/amorphous) investigated in *in-vitro* and *in-vivo* studies [34].

Drugs in BCS Class-III are highly soluble but their permeability across membranes is low leading to less absorption and poor bioavailability. The choice of excipients resulted enhancement in the permeability of drugs in *in-vitro* studies (e.g., either by altering the integrity of membrane, affect on transporter(s), or through modification of gastrointestinal transit time). Excipients suitability could be tested and validated through *in-vitro* and/or *in-situ* models that can be predicted as a substitute for *in-vivo* human investigations [39].

Drugs in BCS class-IV have low solubility and permeability, hence poor absorption and bioavailability. Examples of this class include acetazolamide, amphotericin-B, furosemide, and paclitaxel. The absorption of most drugs of this class are also affected by P-glycoprotein (leading to permeability hindrance) and CYP3A4 (potentiating drug metabolism before reaching to systemic circulation) that further compromises the therapeutic capability of drug substance [35].

Keeping in consideration the hindrance to solubility and permeability, bioavailability could be enhanced by particle nanosizing [31], intelligent choice of excipients/method [40], or enhancing penetration through a carrier/nanocarrier [41-44]. The lipid-based drug delivery system technology and its feasibility have been proven efficient in most poor water-soluble drugs formulations. Determining the solubility and permeability through multiple strategies including *in-silico, in-vitro*, and *ex-vivo* data necessitate the prediction of better bioavailability through oral route [27], and ultimately better response in consumers, i.e., the patients.

Nano-based Drug Delivery

In the novel drug-delivery approaches, the role of nanotechnology as well as material sciences have played significantly to potentiate the development of drug candidates for proven clinical therapeutic outcomes [45]. Drug delivery strategies from ancient to traditional/moderate, and currently nano-sized applications are of paramount interest. Drug particle nano-sizing improved its efficacy and has led to selective targeting of the drug molecules within the biological system. The macromolecular size of drug particles has limitations of *in-vivo* instability, poor bioavailability, target-specificity and consequently more adverse effects. On the hand, nano-sized drug particles exhibit unique physicochemical and biological properties to attain greater bioavailability as well as target specific body parts [1], hence ensure more efficacy with least side effects.

Nanomedicine being an emerging area of research incorporating knowledge with advance techniques in the field of medicine and pharmaceutical sciences. Recent developments in the field of drug delivery are nanostructures as delivery agents where either the drug is encapsulated or attached with therapeutic drugs for effective controlled release delivery to the target tissues. These nanostructures ensures greater bioavailability, longer stay in the blood circulatory system. Thus, enable the release of drugs as per therapeutic requirement with less plasma fluctuations and minimized adverse effects [1]. Nanomedicine investigations have also revolutionized anticancer therapy [46]. For this purpose, screening of nanomedicine through the exploitation of multicellular tumor spheroid (MCTS) as an *in-vitro* model [43, 47] is of appropriate interest to assess the penetrability of nanoparticles in tumor tissues [46]. Various drug delivery systems along with their examples and key findings are illustrated in Table 2.

By definition, the size of nanoparticles (NPs) varies from one discipline to another. In chemistry, NPs are categories of materials that incorporate particulate substances having a size less than 100 nm, while in pharmaceutical terms the size range below 1000 nm is considered a nanoparticle [1, 14, 48]. The subdivision in the field of medicine that exploits nanotechnology to prevent and treat ailments by the use of nanomaterials is termed as nanomedicine [1]. There are three layers of NPs; (i) the out-surface layer (consisting of small functional molecules, such as metal, surfactant(s), and/or polymer(s), (ii) the shell, and (iii) the central core (essential portion of NPs) [48]. The specifically engineered nanoparticulate sizes can selectively stimulate membrane receptors for the downregulation of their expression level, which modifies the signaling, hence cellular response. Due to this evidence, nanostructures could interact passively with cells, and facilitate the molecular processes for regulation of cell functions. Similar interactions of NPs with biological system occurs that provokes the need to design intelligent NPs or nanodevices, for molecular-based therapeutics or diagnosis. Research conducted on particle size from 2-100 nm, reveals that the size range 40-50 nm form the critical cut-off point for receptor-mediated endocytosis [49]. The cellular uptake of nanostructures is greater than uptake of large particles (1-10 μm), hence NPs directly interacting with cells treat a disease with improved efficiency and reduced or negligible side effects [1].

The intricacies of *in-vitro* assessment of novel drug delivery systems include estimation of formulations with respect to cytotoxicity, compatibility with biological system, and immunogenic effect. The routine *in-vitro* cytotoxic effect estimated using 2-D monolayer cell culture, but three-dimensional multicellular tumor spheroids (3-D MCTS) have become a promising tool because it better mimic *in-vivo* solid tumors as compared to 2-D monolayer cell culture. *In-vitro* cytotoxic effect of anticancer formulations (docetaxel nano-emulsion and methotrexate liposomal formulation) have been performed in MCTS model [50]. Targeted drug delivery especially of anticancer nano-formulations while focusing to reduce side effects and toxic effect on normal tissues is an area of concern. The better antitumor effect of nanocarriers resulted in monolayer cell culture frequently fails during *in-vivo* studies due to difference in microenvironment and physicochemical characteristics. Therefore, development of 3-D multicellular culture system incorporated with collagen for screening drug delivery of nanocarriers and obtaining more acceptable estimation in laboratory experiments could be of great interest for ultimate therapeutic outcomes [51]. It has been reported that the nanoparticle size from 10 -100 nm passively accumulates within the tumor and due to longer retention within the tumor leads to enhanced permeability [52].

For appropriate formulation designing in either drug delivery system; understanding of morphological and physico-chemical characteristics as well as interactions of drug play significant role. The nanocarriers composition (organic, inorganic, or combination) and the form of its association with drugs (core-shell or matrix system) are essential to understand the drug delivery pattern [1]. Nanosizing either by top-down approach (milling/attrition and high-pressure homogenization, and sonication) where larger particles split into nanosize, or bottom-up approach (microemulsion, antisolvent precipitation/crystallization, solvent displacement, supercritical fluid technology, and spray freezing into liquid) where reduced particles accumulated to nanosize [53, 54]. The top-down approach is advantageous to synthesize nanoparticles in a brief period in bulk quantity. Likewise, the bottom-up approach is used to synthesize homogenous nanostructure particles with ideal crystallographic and surface structure characteristics [55].

Types of Nano formulations

Nanoparticles are categorized as inorganic and organic-based. Inorganic nanoparticles include metal oxides (oxides of titanium, zinc, silver, and magnesium) have gained significant attention because of their physical and optical stability. Similarly, organic-based materials including lipids, polymers, and carbon nanotubes have wide applications [54]. Nanoparticles may be shaped in the form of nanospheres or nanoencapsulation [56]. various nanostructures particularly dendrimers-based, micelles, and liposomes have been often exploited for designing target-specificity in drug delivery. Drugs inherited with poor solubility and weaker absorption ability opted for nanoparticulate drug delivery systems. It is worth mentioning that, the nanostructures efficacy in terms of drug carriers depend on its size, shape, physico-chemical and biological features [1]. Metallic nanoparticles, particularly the noble metals (Gold “Au”, Silver “Ag” and Platinum

"Pt"), focus on green nanotechnology to ensure an eco-friendly environment [1, 55, 57]. Lipid [58] and polymeric nanoparticles [56] are the common approaches to enhance drug delivery.

Liposomes and Lipid Nanoparticles

The initiation of nano-based drug delivery systems were the development of liposomes and micelles. Liposomes were discovered in 1960. The investigated carrier systems for drug delivery have been exploited in the cosmetics and pharmaceutical industry to transport various molecules. Formulation of liposomes include processes of hydration, agitation, solvent-evaporation, and solubilization of surfactant(s). Drug is loaded in the liposomes by either active (drug encapsulation after formation of liposomes) or passive (drug encapsulation during the formation of liposomes) approach. Drugs that are hydrophilic in nature, characteristically restricted to aqueous core of liposome and independent of drug/lipid ratio. On the other hand, drugs that are hydrophobic, their engulfment or encapsulation depended on the characteristics of acyl chain of liposome. The compact lipid nanostructures and phospholipids including liposomes as well as micelles have been proved appropriate for targeted drug delivery. Although liposomes enhanced permeability that boosts the drug delivery efficiency, yet, opsonization, and immunogenicity are the main shortcomings to use liposomes for drug delivery purposes [1]. The liposome formulations are advantageous as compared to the rest of carrier systems because these are generally regarded as safe (GRAS) [36]. The azithromycin-liposome for vaginal therapy has shown potential effectiveness [59].

Solid-lipid-nanoparticles (SLN) [60], and nanostructured-lipid-carriers (NLC) [61] are recent approaches to prepare "stealth" nanoparticles to escape reticuloendothelial system (RES) and modify the release behavior of active constituent, most preferably for poorly water-soluble drugs. Nanoparticle preparation methods are based on high-energy, low-energy, and organic solvents. NLC has an advantage over SLN because of the better loading capability of the active ingredient and more stability. The solid-lipid core is encapsulating highly lipophilic drugs, protecting the drug from degradation and enhancing their stability. Moreover, due to high drug loading efficiency, physicochemical characteristics of lipids with negative charges to overcome the physiological barrier and efflux mechanism due to P-gp in GIT epithelia, retention for a longer time in GIT, results enhance bioavailability (BCS II & IV) of drugs [61] by rendering them lipophilic. In comparison to SLN, the NLC has high drug loading efficiency and longer retention time within the particles [61]. The lipid nanoparticle preparation methods have certain inadequacies, such as being more laborious, risk of phase inversion, production of non-uniform particle size, and inconsistent reproducibility [58]. While polymeric nanoparticles have the advantage to prevent inactivation as well as degradation of drugs by digestive enzymes and acidic pH of the gastrointestinal tract [62].

Polymeric micelles and Polymeric nanoparticles

The nanostructures of polymeric micelles constituted by amphiphilic polymers that in the aqueous solution form a core-shell structure. The hydrophobic drugs loaded in hydrophobic core, while hydrophilic shell solubilize in water and stabilizes the core. The polymeric shell also confines non-specific interactions with components of biological system, rendering a favorite drug delivery system for hydrophobic drugs, which encourages enhancement of stability and bioavailability of drugs [1]. Polymeric micelles have been reported to penetrate deeper into MCTS and delivered conjugated-drug more than the diffusion of the free drug [63, 64]. The preparation methods for polymeric nanoparticles and liposomes is explicitly elaborated in the literature [65].

The greater biocompatible and biodegradable properties of polymers including natural (e.g., alginate and chitosan), and synthetic polymers (e.g., polyvinyl alcohol (PVA), polyethylene glycol (PEG) etc.) have been extensively exploited in the fabrication of nanoparticles [1]. Polymeric nanoparticle preparations may proceed through polymerization or a pre-formed polymer. Polymerization need purification because of the risk of toxicity of the final preparation/medium. The pre-formed polymer includes natural (for example, albumin, gelatin, alginate, chitosan, and agarose) and synthetic (incorporated through emulsification, or solvent evaporation/displacement/diffusion methods etc.). Technological advancement in this field leads to the desolvation of macromolecules and supercritical/compressed fluids-based techniques. The nature of polymer/drug/formulation/method has its desirable requirements and advantages/disadvantages [56].

Cationic polymers posses inherited potential to seize physical barriers that prevent penetration in tumors [52]. While considering all these aspects, formulation design should be based on safety, economy, efficiency of the final pharmaceutical product, and patient compliance [56, 66].

Nanocrystals

Another approach to nano-based drug delivery is nanocrystals. It is purely drug particles within a range 1000 nm in solid crystalline form. It don't need attachment of carrier molecule and occasionally polymeric steric-stabilizers or surfactants are incorporated to stabilize them [1]. The main reasons for their greater solubility and enhanced bioavailability is the increase of the dissolution velocity as a result of greater surface area and saturation solubility. However, the saturation solubility of amorphous form of drug is higher than the equally sized crystalline form [14]. Yet, stability in the shelf-life will determine whether to formulate a drug in crystalline or amorphous form. The basic three methods for nanocrystal formation are milling, homogenization, and precipitation methods. Nanocrystal formulations are particularly advantageous for those drugs which have low doses and a narrow therapeutic window. Additionally, nanocrystal formulations don't need to incorporate surfactants and possess quick absorption capability for fast onset of action [14]. Due to these exceptional advantages, pharmaceutical nanocrystal formulations are of paramount interest.

Metallic nanoparticles

To protect society from rising environmental toxicity and provide ecosystem friendly, harmless and sustainable environment, the concept of "green nanotechnology" is materialized into existence for the purpose to produce novelty in techniques for nanoproducts. This concept excludes toxic chemicals like organic solvents to be used in generating nanomaterials, instead, noble metals (e.g., gold, silver, and platinum) have found greater applications with characteristic features by scientific platforms **[67]**. For pharmaceutical and biomedical applications, nanomaterials could be composed of noble metals (Au, Ag, Pt), semiconductors (CdS, ZnS, TiO_2, PbS), magnetic compounds (Fe_2O_3, Fe_3O_4, FePt, CoPt) and their combinations. The medicinal applications of gold has been started by Chinese since 2500 BC. Current revolution in nanotechnology has exploited gold for drug delivery, diagnosis, and especially in the cancer treatment. Due to biocompatibility feature of gold, the tumor-targeting technology has prioritized it for targeted drug delivery. Silver has antimicrobial potential and uses in cosmetics, toothpaste, wound dressings/soap, shampoos, detergents, and water purification systems. platinum derivatives include several anticancer agents like; cisplatin, carboplatin, hepatoplatin [68]. All these examples demonstrate the widespread biomedical, pharmaceutical and environment friendly applications of nobel metals, which has attracted the attention of scientists to a greater extent.

Lipid-polymer hybrid-nanoparticles

Although, lipids or polymers system has their advantages and shortcomings (when used alone) concerning discrete physicochemical, pharmaceutical and pharmacological aspects. The lipid-polymer hybrid-nanoparticles (LPHNs) or carriers concept comes up with the potential benefit, which are formulated by variety of methods to improve the drug delivery and therapeutic outcomes [45]. In LPHNs formulations, the drug particles are encapsulated within the lipid-polymer core(s) as presented in Figure 3.

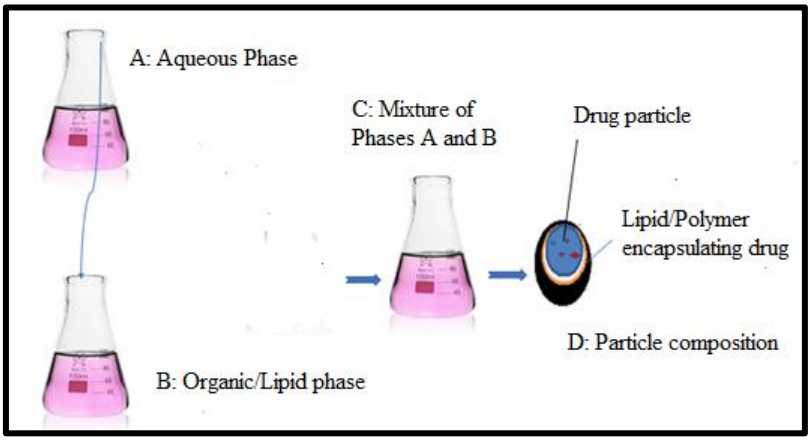


Figure 3. A schematic diagram of lipid-polymer-based nanoformulation

The investigations on lipid-dendrimer hybrid nanoparticles (LDH-NPs) with pH-responsive characteristics has revealed the delivery of vancomycin (VCM) more effectively. The findings of this study explored faster drug release at pH 6.0 as compared to pH 7.4. Furthermore, LDH-NPs expressesed antibacterial activity against methicillin-resistance staphylococcus aureus (MRSA) by 8-fold lower minimum inhibitory concentrations (MICs) at pH 6.0 and 7.4, in comparison to antibacterial activity of VCM alone. Additionally, the viability study of bacterial cell showed that LDH-NPs had an efficient killing of MRSA (84.19%), compared to VCM alone (49.26%) at the same MIC, which further confirms the worth of LDH-NPs in comparison to drug alone [69]. The effective drug delivery, smart and intelligent acting of this drug carrier system reflects its versatile application to be exploited and materialized to reduce potential adverse effects and ensure treatment effectively.

Applications of Nanoformulations

Nanotechnology is a multidisciplinary science to develop the novel treatment and diagnostic modalities [70]. Adopting nanotechnology as well as material sciences resulted in the development of numerous innovative drug-delivery systems that proved clinically as talented candidates in therapeutic outcomes [45]. The very small size of nanoparticles possesses a larger surface area in comparison to volume that causes modulation in characteristic functions [68]. Nanoformulation is preferred over conventional formulations due to improvements in drug solubility, stability, permeability, bioavailability, controlled release to prolong action, reduce dosing frequency, and targeted specificity to avoid toxicity [70, 71].

To conclude, nanoparticles and nano-formulations are advantageous which results in (a) enhancing pharmacokinetics and pharmacodynamic characteristics of drugs without modification in their molecular structure, (b) more effectiveness in the cell, tissue, as well as molecular targeting, and (c) overcoming the most inherent biological barriers [72].

Multiple Approaches to Design Formulation

Lipinski rules also called as Rule of Five (ROF) frequently used to discover novel drugs or to contribute improvement in the efficiency of existing/approved drugs [26]. ROF presents the basic criteria particularly with respect to structural modification to improve the quality of drug candidate. Method involved in the preparation of nanoformulations is key contributer to change the size and shape of formulation and improve drug delivery. The size of nanoparticles has distinct advantages compared to microparticles in terms of higher intracellular uptake, e.g., A particulate size of 100 nm has shown 2.5 times greater uptake in comparison to 1 µm, and 6 times greater uptake as compared to 10 µm particles investigated in Caco-2 cell line. Similarly, studies in rat *in-situ* intestinal loop model have shown greater efficiency of nano-formulation (15-250 times greater) as compared to microparticles. As for as the shape of particle is concerned, rods and sphere shape nanoparticles have greater cellular uptake followed by cylinderical and cube shapes [65].

Focusing on nanosizing, choice of excipients/method, and permeation enhancer/carrier are the combinative approaches for improving drug deliveries to the site of action through the stealth and intelligent pharmaceutically engineered formulation. For example, LPHNs, where the polymeric core and lipid shell exist, intensify double characteristics of both polymeric nanoparticles and liposomes, especially concerning their physical stability as well as biocompatibility [73]. LPHNs used as drug encapsulating and carriers have proven potential benefits, which are prepared using different approaches for the improvement in therapeutic outcomes [45]. A fast method for the formulation of LPHNs with an almost uniform particle size has been reported by the nanoprecipitation technique [73, 74]. Similarly, curcumin is a good anticancer agent but possesses poor bioavailability. A polymer-based nanocarrier incorporation with curcumin has resulted in good therapeutic outcomes [75]. The copolymer conjugate of curcumin (a hydrophobic drug) has showed "smart" tumor-targeting with greater internalization and subsequently release of drug to effectively kill the cancer cells. This study conducted in pancreatic and breast cancer spheroids where dose- and time-dependent efficiency was observed [76].

The three main challenges to nanoformulation are stability, mechanism related to drug delivery and degradation, and quality-based regulations by FDA. The selection of appropriate method for nanoformulation which possess precise control on the size and morphology of nanoparticles is the key determinant related to properties and application outcomes [65]. It is aimed to investigate such a method for drug nanoparticles to have reasonable drug entrapment efficiency, protection from degradation in gastrointestinal epithelia, and achievement of an effective bioavailability profile to the desired pharmaceutical, pharmacological, and population requirements. Subjected formulations, optimization, and characterization could be augmented by interlinking with computational and statistical tools. Computational studies play important roles in drug screening and design. For cost and time minimization in drug development, it is necessary to integrate theoretical background, computational methods, and laboratory experiments [77]. The Design of experiments (DoE) is a statistical computer-assisted optimization method that investigates the input variables to get the ideal target response [78]. As DoE is a systematic and efficient method for collecting data and getting findings that enable researchers tofind-out a relationship between the input variables (factors) and the output variables (responses), therefore, it is a synergistic tool to be exploited for experimentation and optimization.

Selection of a suitable dosage form

The selection and design of a pharmaceutical dosage form require a precise understanding to keep a balance between the quality target profile versus technical hurdles. The quality target profile includes safety, efficacy, and patient acceptability, while technical challenges include the product development capability, ease of manufacturing, transportation, storage conditions, and dispensing requirements. Therefore, formulation scientists should consider flexibility to select a dosage-form and its excipients to prioritize the patient's needs and ensure the drug properties in the final dosage-form [79]. Development of the generic drug into dosage-form based on specific market requirements (e.g., US or EU market, etc.) that can accelerate its market acceptability. If the manufacturer's goal is US market, then all formulating excipients must be of USP grade, as well as analysis and stability studies should also be conducted in accordance to the USP standards. While a "Patent Drug" or innovator manufacturer develops the medicinal product as a result of a series of experimentations and needs to conduct a human trial or bioavailability studies before marketing approval [80]. Regarding regulatory guidelines for the development of nanomedicines, global regulations have not yet been defined. Due to the non-availability of specified protocols for the pre-clinical studiest of nano-products, as an alternative, the guidlines applicable to the investigations of "conventional" pharmaceutical products have been commonly adapted for the evaluation purpose of nanomedicines [81]. For different dosage-forms, specific Good Manufacturing Practice (GMP) guidelines are of the greatest value to be adopted.

Conclusion

Appropriate formulation and effective drug delivery (either from formulation or final dosage-form) to the desired site of action are the ultimate necessary stages after drug discovery. The efficient bioavailability with

ensured safety, efficacy, and cost-effective therapy could be guaranteed through the incorporation of novel drug delivery technologies and individualization of therapy. Administration of drug to the patient through oral route is comparatively safe, patient-compatible, and advantageous in terms of the low cost of therapy. But the inheriting drawback is the low bioavailability either due to poor aqueous solubility, low gastric permeability, gastric degradation of drug, drug deactivation in the GIT, or a greater first pass metabolism which limits the oral route of medication.

An integrated approach for research study designing consisting of a relevant literature survey, predictive computational studies for formulation design, Quality by Design or Design of Experiment through the statistical model for screening /optimization /characterization, understanding of material sciences, and pharmaceutical technology could be adapted to synergize the research and development studies. Therefore, multiple approaches to enhance drug delivery by intelligent incorporation of the active pharmaceutical ingredient(s), pharmaceutical excipients, and particle technology are of vigorous importance in this respect to encounter the challenges and contribute to eradication of diseases.

Declaration of competing interest

The authors declare that they have no competing or financial interests to disclose.

Table 2: Drug delivery systems along with their examples and findings

Drug delivery system(s)	Drug (i) cum excipients	Findings	Reference(s)
Micelle	i. Paclitaxel ii. Glycyrrhizic acid iii. Docetaxel iv. Sodium taurocholate v. Lecithin NaCl and KCl	Resulted 90% encapsulation efficiency, enhanced *in-vivo* bioavailability.	[82]
Nanostructured Lipid Carrier (NLC)	i. Artemether cum Lumefantrine i. Glyceryl dilaurate i. Capmul MCM (medium chain mono- and di-glycerides) v. Oleic acid v. Tween 80 i. Sodium carboxymethyl cellulose i. Solutol HS 15	The NLC formulation reduced the daily dose by 10-fold, dosing frequency by 2-fold, while the soft gelatin capsules of NLC formulation reduced the number of unit doses required to be taken by 2-fold.	[83]
NLC	i. Flurbiprofen ii. Compritol® ATO 888 iii. Miglyol® 812 iv. Lecithin v. Poloxamer 188 vi. SDC and vii. Tween-80	Bioavailability of drug from NLC formulation showed improved characteristics than the commercial formulation.	[84]
Solid lipid nanoparticles (SLN)	i. Niclosamide ii. Stearic acid iii. Tween-80 iv. Polyethylene Glycol-400	SLNs shows significantly improved bioavailability compared to marketed drug, as well as possessing stable and sustained release performance	[60]
SLN	i. Famotidine ii. Stearic acid iii. Tween-80 iv. Polyvinylpyrrolidone (PVP-K30)	Famotidine in SLN formulation boosted the oral bioavailability, stability and confirmed a sustained drug release behavior	[85]

Polymeric formulation	i. Atorvastatin calcium ii. Pregelatinized starch iii. Lutrol iv. Kollidon 90F v. PEG 6000 vi. kollidon 12F	Polymeric formulation resulted higher drug release than pure drug and marketed product after one-hour of administration	[86]
Polymeric co-crystal	i. Artemisinin ii. Resorcinol iii. Potassium dihydrogen phosphate (KH_2PO_4), iv. Santonin v. Sodium hydroxide (NaOH) vi. Orcinol vii. Poly(vinylpyrrolidone) K-29/32 (PVP) viii. Copolymer poly(vinylpyrrolidone)/vinyl acetate (PVP-VA) ix. Hydroxypropyl methylcellulose K4M (HPMC) x. Hydroxypropyl methylcellulose acetate succinate (medium grade, HPMC-AS)	polymers significantly enhanced the dissolution and permeation, hence bioavailability of the Artemisinin cocrystals	[87]
Self-micro-emulsifying drug delivery system (SMEDDS)	i. Artemether ii. Capmul MCM iii. Cotton seed oil /Linseed oil /Olive oil /Castor oil iv. Tween 80 /Span 80 v. Polyethylene Glycol 400 vi. Propylene Glycol vii. Silicon dioxide viii. Magnesium sterate ix. Magnesium hydroxide x. Gelucire 43/01	Results indicate better bioavailability	[88]
Sustained release matrix with polymers incorporation	i. Cefpodoxime proxetil ii. Hydroxyl propyl methyl cellulose (HPMC K100 M) iii. Sodium alginate iv. Chitosan v. Microcrystalline cellulose vi. Magnesium stearate vii. Talc viii. PVP K30 ix. Isopropyl alcohol	Drug release maintained up to 12 hrs with 96.3% drug release, which could result in reducing the dose, frequency, and keep bioavailability of drug at therapeutic level for longer time.	[89]
Lipid-polymer hybrid nanoparticle formulation	i. Norfloxacin ii. Stearic acid iii. Eudragit RS-100 iv. Ethyl cellulose v. Sodium lauryl sulphate vi. Oleic acid	The bioavailability and sustained release rate of Norfloxacin from lipid-polymer hybrid formulation was greatly increased	[90]

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