Journal of Advances in Medical and Pharmaceutical Sciences

21(4): 1-18, 2019; Article no.JAMPS.53071
ISSN: 2394-1111

Various Challenges and Opportunities in Oral Delivery of Anticancer Drugs

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/JAMPS/2019/v21i430144
Editor(s):
(1) Dr. Amr Ahmed El-Arabey, Department of Pharmacology and Toxicology, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt.
Reviewers:
(1) Jacilene Silva, State University of Ceará, Brazil.
(2) Paras Nath Yadav, Tribhuvan University, Nepal.
(3) Portia Osborne, University of Yaounde 1, Cameroon.
(4) Rakesh K. Sindhu, Chitkara University, India.
Complete Peer review History: http://www.sdiarticle4.com/review-history/53071

Review Article

Received 05 October 2019
Accepted 09 December 2019
Published 25 December 2019

ABSTRACT

Oncology is that area of medicine where patients are usually treated intravenously. Researchers are trying to find alternative drug delivery methods of anticancer drugs due to the pain associated with conventional drug delivery methods. Studies estimate that a majority of patients (up to 89%) prefer oral anticancer medications to traditional IV fluid or injection therapies when available. Better patient compliance, tolerability, reduced cost; greatest safety and possible increased efficacy are the main reasons for increased attention towards oral delivery of anti-cancer drugs. But oral bioavailability of this class is limited because of its idiosyncratic physicochemical properties and biological barriers such as pre-systemic metabolism and gastrointestinal instability. The various challenges to oral delivery of anticancer drugs are discussed extensively in this paper including peculiar physicochemical properties, biological barriers and adverse drug-drug interactions. Further, the emerging innovations in addressing the challenges to oral delivery of anticancer drugs are discussed. These mainly include absorption enhancers and nanocarriers based drug delivery systems.

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Keywords: Patient compatibility; oral drug delivery; anticancer; absorption enhancer; nanocarriers.

1. INTRODUCTION

Cancer continues to be a major threat to human beings. According to WHO, the global cancer burden is estimated to have risen to 18.1 million new cases and 9.6 million deaths in 2018. In oncology, major chemotherapy has invariably been given intravenously and therefore hospital services and clinical activities have been designed according to this administration [1]. There is a need for novel and more efficient methods of anticancer drug delivery. Scientists are constantly trying to introduce new and less painful methods of anticancer drug delivery. Among them, oral delivery has managed to get major attention. There has been a steady increase in the number of oral anticancer drugs available in past. In the United States alone, more than 20 oral antineoplastic agents have been approved [2]. Moreover, more than one-quarter of anticancer drug molecules under development are oral route [1]. The oral route is considered the most convenient and preferable method of drug delivery by the patients because of its various advantages over others.

The major advantages of oral route drug delivery over others are as follows [3]:

1. Required plasma drug concentration can be maintained for a prolonged period to increase the efficacy and decrease the toxicity of anticancer drugs.
2. We can modulate the delivery of drug-using oral dosage form which is a major advantage over other drug delivery methods.
3. Oral chemotherapy is painless and can be self-administered at home. This approach can increase patient compliance and quality of life of the patient during chemotherapy.
4. There is no risk of infection or extravasations involved with oral delivery of anticancer drugs as in the case of intravenous drugs.
5. There is no need for hospitalization, sterile manufacturing or trained personnel in case of oral delivery which can lead to a huge reduction in costs of treatment for patients.
6. Oral anticancer drugs can also be used as a prophylactic measure due to the ease of administration.

Furthermore, due to decreased costs, the treatment can be availed by people who cannot afford the existing expensive parenteral treatment. According to a research conducted, 78.7% of total patients wanted themselves to be treated by oral route for recurring breast cancer disease, whereas nearly 2.7% preferred parenteral route while 18.6% landed with no preference [4]. Considering these results the current research on developing new drug molecules has rapidly shifted to oral delivery of anticancer drugs.

However, this preference of people for oral delivery is conditioned by efficacy and toxicity-related issues. Approximately two-thirds of patients require that the efficacy of oral formulation has to be equivalent to iv, with 70% and 74% of patients not willing to accept less response rate and duration of survival, respectively [4]. Now, this efficacy of oral anticancer drugs is limited because of physicochemical properties, and physiological barriers such as pre-systemic metabolism and gastrointestinal instability. For example, only a fraction of dose is available in systemic circulation after oral administration of these drugs. For example, the oral bioavailability of docetaxel was 26% [5] and paclitaxel was 6.5% [6]. This poor bioavailability of the taxanes (paclitaxel and docetaxel), can be ascribed to their poor solubility, metabolism by cytochrome P-450 (CYP-450) enzymes and good affinity with drug efflux pump P-glycoprotein (P-gp) [7].

Concomitant medications may significantly affect the bioavailability of orally delivered drugs. Thus, the drug interaction profile of oral anticancer drug must be well studied, since failure to recognize potential and real drug-drug interactions may lead to adverse outcomes [1]. However, recent advances in technology and sciences have made it possible to overcome these limitations. This includes Absorption enhancers (P-gp inhibitors and Functional excipients), Nanocarrier based approaches (Drug nanocrystals, Polymeric nanocarriers, Lipid-based nanocarriers, Dendrimers, Smart nanocarriers, Integrated nano-hybrids) and Nano Devices (Nanovectors, Nanowires arrays, Nano cantilevers arrays).

The therapeutic efficacy of the formulation depends upon its capability to deliver the drug, at the right place and at the right time in an amount adequate to yield a therapeutic response. Comparative therapeutic equivalence of oral and intravenous routes has been studied for a wide variety of drugs and promising results were

Table 1. Physicochemical properties of various anticancer drugs

Drug	Challenges					Solutions	Improvement	Reference
	Solubility	LogP	Permeability	P-gp substrate	Stability			
5-Fluro uracil	No	Yes	No	Yes	Rapid degradation into dihydro-5-fluorouracil when catalyzed by dihydropyrimidine dehydrogenase (DPD).	Capecitabine is a novel oral fluoropyrimidine carbamate was developed (Prodrug). Conversion of capecitabine to 5-fluoro uracil is mediated by three enzymes.	Improved concentration observed	[8]
Paclitaxel	Yes	Yes	Yes	Yes	affinity for the intestinal and liver cytochrome P450 (like CYP3A4) metabolic enzymes	P-gp inhibitors used such as cyclosporine A used which inhibits CYP3A4 also. development of lipidic formulations, such as supersaturate, self-emulsifying drug delivery systems (S-SEDDS) or self-micro emulsifying drug delivery systems (SMEDDS),	The values of Cmax for paclitaxel coadministered with verapamil and for paclitaxel-loaded LNC were 237 ± 121 and 368 ± 326 ng/mL, respectively, which were higher than the Cmax of paclitaxel\ alone (103 ± 82 ng/mL).	[9]
Docetaxel	Yes	Yes	Yes	Yes	-	P-gp inhibitor OC144-093 was used	Bioavailability increased from <10% to 26%	[5]
Capecitabine	No	No	No	No	-			[10]
Doxorubicin	No	No	Yes	Yes	Affinity to cytochrome P450.	Nanoparticles prepared from biodegradable polymers	Reduced cardiotoxicity	[11]
Atorvastatin	Yes	Yes	No	No	Affinity to CYP3A4	Solid lipid nanoparticles	Reduced toxicity, prolonged release.	[12]
Temozolomide	No	Yes	No	No	Hydrolysis in aqueous medium of pH>7	Cocrystals of temozolomide were prepared with acids to maintain the environment around it acidic.	The co-crystals with succinic acid were stable until 1 year time period.	[13]

Solubility is considered a challenge if the solubility of the drug in the aqueous medium is less than 60 µg/ml, LogP is considered a challenge if the value is not between 0-3 (Edward.H.Kerns, Li Di., 1965). Permeability is considered a challenge if less than $10x10^{-6}$ cm/s [14]. All the calculations were performed at pH 6.8

observed in most of the cases. Cyclophosphamide yields no statistical significant difference in the area under the plasma disappearance curve (AUC) and generated similar cytotoxic metabolic products upon administration through oral and parenteral routes thereby suggesting the therapeutic equivalence, irrespective of the route of delivery. Paclitaxel in nanoparticulate dosage form administered by oral route had shown promising tumour reduction in animals compared to a commercially available intravenous formulation at 50% reduced dose [15]. There are many such examples which will be further discussed in this paper. The results suggest that the natural limitations of the drug molecules can be overcome using suitable formulation development techniques.

The present review covers various challenges encountered for efficient oral delivery of anticancer drugs. The correlation between n the physicochemical properties and in vivo performance of the drugs are also discussed. Furthermore, various emerging trends to overcome these challenges have also been discussed in detail. Table 1 gives a summary of anticancer drugs given orally, challenges encountered during their delivery and solutions developed or proposed to overcome them.

2. CHALLENGES TO ORAL DELIVERY OF ANTICANCER DRUGS

Bioavailability is the fraction of drug that is available in systemic circulation after administration. The key factors affecting the oral bioavailability of drug include its aqueous solubility, dissolution rate from the dosage form, intestinal epithelium permeability, stability against intestinal and liver cytochrome P450 metabolic enzymes, and P-gp efflux pump [14]. Based on these grounds the principal challenges to the oral delivery can be categorized broadly into physicochemical properties of the drugs and physiological barriers posed by the body.

2.1 Physicochemical Properties

A highly complex system of parameters associated with absorption, distribution, metabolism, and excretion (ADME) determines the pharmacokinetic profile of orally administered drugs in relevant test species or man. The critical physicochemical properties of the drug affecting its oral deliverability include solubility and permeability which are further dependent on the fundamental properties such as log P and pKa.

2.1.1 Permeability

There are two main mechanisms of drug transport across the gastrointestinal epithelium: transcellular, i.e. across the cells, and paracellular, i.e. between the cells. The transcellular pathway is further divided into simple passive diffusion, carrier-mediated transport (active transport and facilitated diffusion) and endocytosis. All of them are shown in Fig. 1.

Passive diffusion is the preferred route of transport for most of the drugs. In this process, drug molecules pass across the lipoidal membrane via passive diffusion from a region of high concentration in the lumen to a region of lower concentration in the blood. Now, Passive transcellular permeability is defined as a concentration gradient-driven mass transport of a compound from one side of the cellular membrane to the other through the lipid bilayer [16]. This tradeoff was explained by the equation:

$$P = DK/\square$$

where P is the drug's permeability coefficient, D is the diffusion coefficient of the drug through the membrane, K is the partition coefficient of the drug between the aqueous intestinal milieu and the GI wall, and h is the thickness of the membrane. The process initially involves the partitioning of the drug between the aqueous fluids within the gastrointestinal tract and the lipoidal-like membrane of the lining of the epithelium. The drug in solution in the membrane then diffuses across the epithelial cell/cells. Upon reaching the blood the drug will be rapidly distributed, so maintaining a much lower concentration than that at the absorption site. If the cell membranes and fluid regions making up the gastrointestinal- blood barrier can be considered as a single membrane, then the stages involved in gastrointestinal absorption could be represented by the model shown in Fig. 2.

Candidates with sufficient solubility but poor permeability are categorized as III in BCS classification. Many anticancer drugs come under this classification and include cyclophosphamide, anastrozole, letrozole, doxorubicin, methotrexate, etc. The permeability values less than $10*10^{-6}$ cm/s are considered poor and need appropriate efforts for improvement.

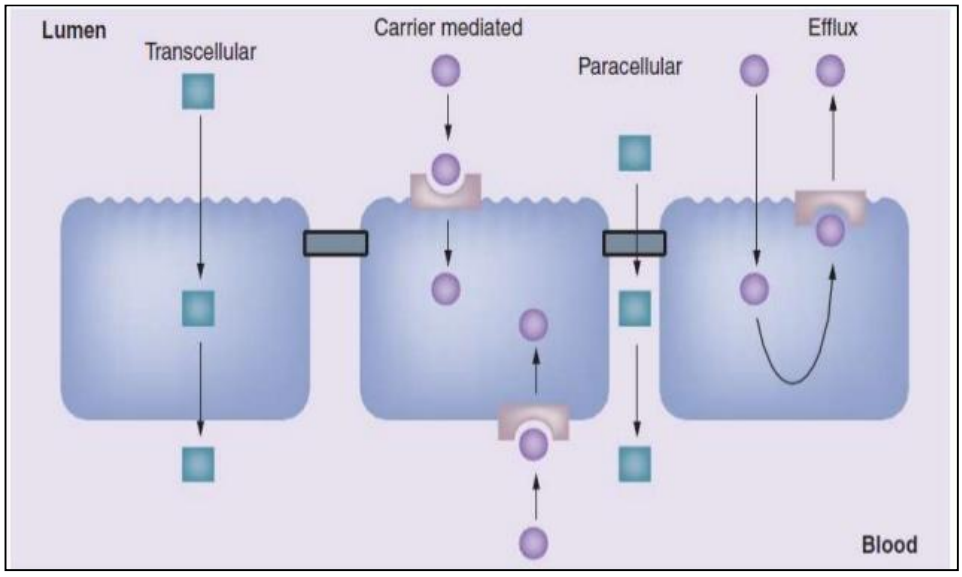

Fig. 1. Passive (transcellular and parracellular) and active (carrier-mediated uptake, efflux) mechanisms of drug absorption across the intestinal epithelium

The outlined bars represent the tight junctions between the cells

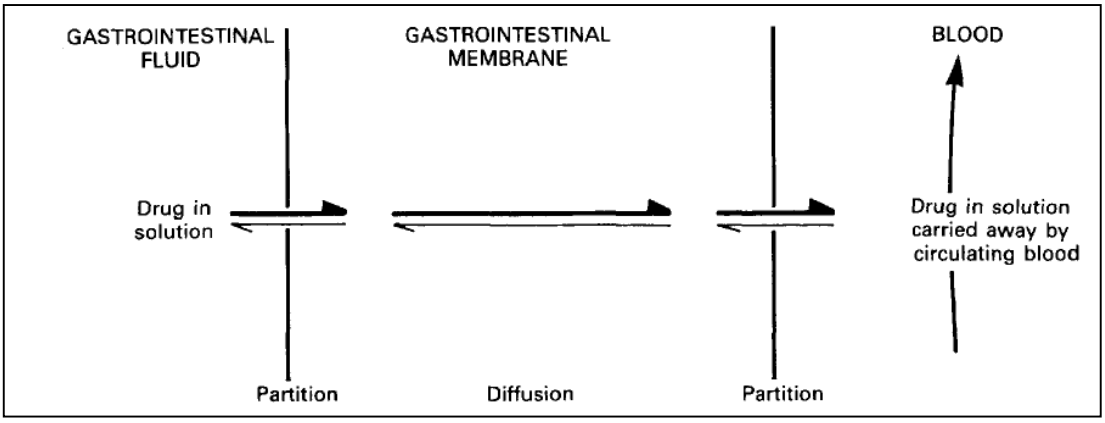

Fig. 2. Diagrammatic representation of absorption via passive diffusion [17]

2.1.2 Solubility

The solubility of a drug at a given temperature is defined as the concentration of the dissolved drug, which is in equilibrium with the solid drug. The solubility depends on the nature of solute and solvent as well as the temperature, pH and pressure. The solubilizing of the drug is necessary for the absorption of the drug.

High solubility in BCS is defined as (a) 85% dissolution of the dose within 30 minutes at all pH values from 1 to 7.5 and (b) does/solubility (D/S) ≤ 250 mL (Edward.H.Kerns,Li Di., 1965). Therefore, drugs not abiding by these criteria are considered poorly soluble. According to BCS classification, these candidates are categorized as II and need attempt for solubility enhancement which could otherwise result in either solubility or dissolution limited absorption leading to poor bioavailability. Classical examples include tamoxifen, rubitecan, sorafenib, gefitinib, etc.

2.1.3 Stability

It needs to be chemically stable to withstand the pH of the gastrointestinal tract, and it must be resistant to enzymatic degradation in the gastrointestinal tract. Most of the anticancer drugs are metabolized even before reaching the systemic circulation. This is due to their instability

in the gastrointestinal pathway or hepatic portal circulation [14]. For example, 5-fluoro uracil it is rapidly degraded into dihydro-5-fluorouracil when catalyzed by dihydropyrimidine dehydrogenase (DPD). Paclitaxel and doxorubicin have an affinity for the liver and intestinal cytochrome P450 and that is why are metabolized even before reaching the systemic circulation.

2.2 Pharmacological Barriers

2.2.1 Gastrointestinal transit time and effect of food

It is known that the small intestine is the major site of drug absorption, and thus the time a drug is present in this part of the gastrointestinal tract is extremely significant. Normal gastric residence times usually range between 5 minutes and 2 hours, although much longer times (over 12 hours) have been recorded, particularly for large single units. Many factors influence gastric emptying, as well as the type of dosage form and the presence of food: these include the postural position, the composition of the food, the effect of drugs and disease state. In general, food, particularly fatty foods, delays gastric emptying and hence the absorption of drugs [17].

Small intestinal transit is relatively constant, at around 3 hours. For example, chlorambucil undergoes hydrolysis in the aqueous medium. So in the fed state, the prolonged gastric residence time would accelerate its hydrolysis and lead to slower or decreased absorption [18].

Another example can be of estramustine phosphate sodium, it forms a poorly absorbable complex with calcium-containing foods (ex. Milk). Due to this chemical binding with food, the absorption is decreased [18].

2.2.2 P-gp efflux of drugs

It is now known that there are counter transport efflux proteins that expel specific drugs back into the lumen of the gastrointestinal tract after they have been absorbed. One of the key counter transport proteins is P-glycoprotein. It is extensively distributed in intestinal epithelia, hepatocytes, kidneys, various glands and capillary endothelial cells comprising blood-brain and blood-testis barriers. Most of the anticancer drugs are the substrates for P-gp including Paclitaxel, Docetaxel, Etoposide, Vinblastine, Vincristine and Doxorubicin.

Pgp is a member of the ABC (ATP binding cassette) family of transporters with the molecular weight of 170 kDa and N terminal glycosylation, which utilize the energy from cleavage of two molecules of ATP to ADP and inorganic phosphate for the transport of each drug molecule. Its structure constitutes two homologous chains of equal length, each comprising six units of transmembrane domains and an ATP binding sites separated by a flexible linker polypeptide region between the two homologous chains.

P-gp has been described as a hydrophobic vacuum cleaner. The first step in transport involves binding of the drug to the inward-facing conformation from the cytosolic side of the membrane. This is followed by a switch to the outward-facing conformation, which reorients the binding site to the extracellular side, resulting in drug release.

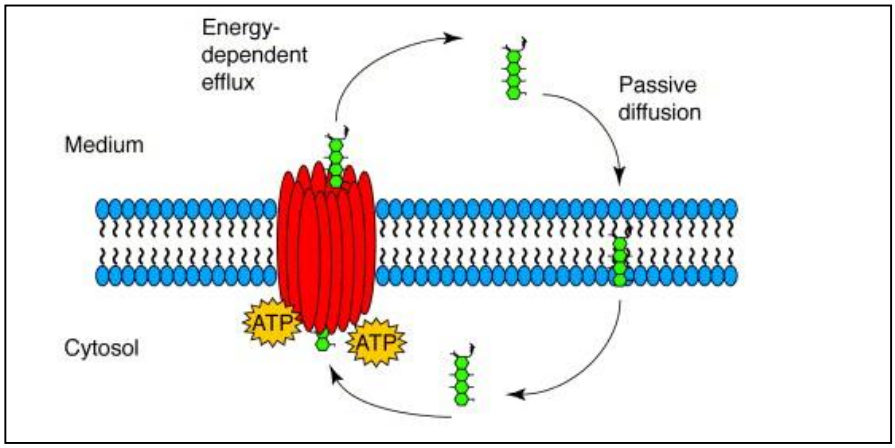

Fig. 3. P-gp mechanism for efflux of molecules

2.2.3 Pre-systemic metabolism

All drugs that are absorbed from the stomach, small intestine and upper colon pass into the hepatic portal system and are presented to the liver before reaching the systemic circulation. Therefore, if the drug is going to be available to the systemic circulation it must also be resistant to metabolism by the liver. Hence, an oral dose of the drug could be completely absorbed but incompletely available to the systemic circulation because *of first-pass* or *presystemic* metabolism by the gut wall and/or liver [19]. For example, 5-fluoro uracil it is rapidly degraded into dihydro-5-fluorouracil when catalyzed by dihydropyrimidine dehydrogenase (DPD). Paclitaxel and doxorubicin have an affinity for the liver and intestinal cytochrome P450 and that is why are metabolized even before reaching the systemic circulation.

3. EMERGING TRENDS IN ADDRESSING THE CHALLENGES TO ORAL DELIVERY OF ANTICANCER DRUGS

Nevertheless, in spite of the above-mentioned challenges, oral delivery of various anticancer drugs has been evaluated for their efficacy and toxicity profiles. The most conventional approach includes co-administration of a therapeutic agent or functional excipient that either circumvent the biological barriers or facilitates the absorption of the drug across the gastrointestinal tract by altering the physicochemical properties of drug substances. Recently, carrier-based approaches have been implemented which can bypass the majority of the challenges and can achieve desired delivery in the most efficient form. However, the selection, design and development of drug-specific carrier system are a state-of-art and require a thorough understanding of the physicochemical properties of drug substances and its behaviour in physiological conditions. The subsequent sections report various such approaches implemented to achieve oral delivery of various difficult-to-deliver anticancer drugs.

3.1 Absorption Enhancers

3.1.1 P-gp inhibitors

Transmembrane efflux of drugs can be tackled by co-administration of various P-gp modulators or inhibitors along with the drugs. The potential mechanisms by which the inhibition of efflux pump occurs include altered membrane fluidity, inhibited ATPase activity, blocking of drug binding site, decreasing P-gp expression (e.g. Peceole), depletion of ATP (e.g. Pluronics), interaction with membrane (e.g. Triton X 100) and interference with the ATP binding sites [20]. Fig. 4. reflects various P-gp based approaches for improving the oral bioavailability of drugs.

Examples

a) CyclosporinA, which inhibits the functions of both P-gp and CYP3A4, has been shown to improve Paclitaxel oral bioavailability in vivo by enhancing oral absorption and decreasing elimination. If calculated relative to the area under the plasma concentration-time curve (AUC) of intravenously administered Paclitaxel (Taxol\) in mice treated without CsA, the oral bioavailability of paclitaxel increased from 9 to 67% with the coadministration of CsA [17].
b) The calcium channel blocker, verampil was the first drug found to inhibit p-gp efflux pump in vitro. In an in vivo study in rats, the area under the curve of paclitaxel was multiplied by 5 and 7.5 with the coadministration of verapamil or KR30031, respectively [17].

This approach is scarcely used clinically owing to associated clinical complications such as suppression of the immune system thus causing long term medical complications.

3.1.2 Functional excipients

A large variety of functional excipients have been studied to increase the oral bioavailability of drugs. Mechanistically, they are found to modulate the activity of the P-gp efflux pump, facilitate wetting, increase solubilization, increase permeability across the gastrointestinal tract, etc. These include polysaccharides, polyethene glycols and derivatives, surfactants, lipids, thiolated polymers and amphiphilic block copolymers to name a few.

3.1.2.1 Natural polymers

The natural polymers such as dextrans, anionic gums and sodium alginate are reported to inhibit the P-gp efflux pumps [21]. Anionic gums such as xanthan gum, gellan gum, alginates, flavicam and Ascophyllum with carboxyl functional groups or salts thereof increase the transport of drugs such as vinblastine and doxorubicin by inhibiting their efflux.

Recently, a member of the flavonoid class, quercetin, has been evaluated as a potential P-gp modulator and CYP modulator [22]. Quercetin is found to interact either with the ATP binding site or with the substrate-binding site of P-gp. Co-administration of quercetin with tamoxifen citrate has led to an increase in relative bioavailability by about 1.5-fold, indicative of its inhibitory effect on transmembrane efflux and CYPs [23].

3.1.2.2 Polyethene glycol (PEG) and its derivatives

These are well reported to inhibit the P-gp efflux of drug compounds, although the mechanistic understanding is still elusive [24]. However, PEGs with molecular weight < 200 lacked the P-gp interaction capability while satisfactory P-gp inhibition was observed in the case of >300 molecular weight [25]. The P-gp inhibition capability is also retained when PEGylation of the drug is practised, e.g. PEGylated paclitaxel poses higher oral bioavailability as compared to plain paclitaxel [6]. Apart from efflux inhibition, solubilization potential of PEGs also contributes significantly to increasing the oral bioavailability of drugs. Substrate competition or ATP depletion was proposed to be the probable mechanism of P-gp inhibition by such novel grafted polymer systems [26].

PEGs were found to inhibit the efflux of various compounds such as rhodamine123, paclitaxel, doxorubicin, etc. irrespective of the molecular weights when tested against Caco-2 cell monolayers [27].

3.1.2.3Thiolated polymers

Thiolated polymers have recently been studied for their P-gp and CYP enzyme inhibitory activity. The rationale for such studies was based on the feasibility of the covalent binding of sulfhydryl substituted purines with P-gp.

Example: The thiolated polymer chitosan-4-thio-butylamidine (chitosan-TBA) significantly increased the absorptive transport (+118%) and markedly reduced the secretory transport (−37%) of rhodamine 123 [28]. This inhibitory effect was attributed to the capability of the sulfhydryl group to react with the cysteine residues located within the Walker A consensus sequences of each of the two ATP binding domains of P-gp. While these cysteine residues are not important for P-gp function there lays a probability of steric hindrance at the catalytic activities of the P-gp.

3.1.2.4 Surfactants

Surfactants have been widely used in formulations with the intention of enhanced drug absorption using wetting and solubilization. However, their P-gp inhibition capability has recently gained widespread acceptance [29]. Mechanistically, these alter the membrane fluidity and bind with the hydrophobic domain of P-gp thereby changing its conformation leading to reduced functionality. On the other hand, some surfactants such as Labrasol open the tight junctions of intestinal epithelium via interaction with F-actin and ZO-1 [30].

Mainly polysorbates, castor oil derivatives, fatty acid ester surfactants such as hydroxyl stearates e.g. Solutol HS 15, Cremophor EL,etc. and vitamin E derivatives have been evaluated for their P-gp efflux inhibition.

Example: Among the tested surfactants, Cremophor EL, Tween 20, Span 20 and Brij 30 exhibited significant increase in the uptake of [3H] mitoxantrone in BCRP-expressing cells whereas Cremophor EL, Cremophor RH40, Tween 20, Tween 80, Span 20, Brij 30, Myrj 52 and Gelucire 44/14 posed significant increase in the uptake of [3H] mitoxantrone in P-gp expressing cells [31].

3.1.2.5 Cyclodextrins

Yet another class of functional excipients, cyclodextrins, has been evaluated for their P-gp interaction capability. Methylated cyclodextrins have been reported to interact with the lipid components of the biological membranes, especially cholesterol, modifying their fluidity and permeability. Furthermore, the solubility advantage also contributes to overall bioavailability enhancement by these cyclodextrins.

Examples:

a) Significant increase in the susceptibility of MCF-7 and MDA-MB-231 cell lines to carboplatin and 5-fluorouracil was observed when pretreated with methylated cyclodextrins [32].
b) Furthermore, a significant increase in the in vitro cytotoxicity against cancer cell lines was observed when paclitaxel was complexed with cyclodextrins; probable reason identified was increased solubilization and permeation and inhibition of efflux pumps.

c) Extrapolating these findings, the permeation study across excised intestinal epithelium of the rats were performed and an about 12-fold increase in the apparent permeability of paclitaxel was found from cyclodextrin-polyanhydride nanoparticles as compared to Taxol® [33].

3.2 Nanocarrier Based Approaches

Nano-engineered drug delivery systems have shown their potential to increase the oral delivery of various anticancer drugs. Substantial efforts have been made to improve oral bioavailability. It has now become quite evident that a variety of nanocarriers have gained substantial attention for enhancing the oral deliverability of anticancer drugs. The principal advantages of nanocarriers include their increased solubilization potential, superior encapsulation, altered absorption pathways, prevention of metabolic degradation within the gastrointestinal tract, chemical versatility of materials eligible for nanomedicines, flexibility in surface functionalization, drug and disease-specific tailor-made design capability, targeting potential and ability to incorporate a wide variety of drug substances. It prevents the cytotoxic effects to the gastrointestinal tract which is very critical for patients on chronic cancer therapy via the oral route.

Briefly, particle size, shape and surface properties of the nanoparticles play a crucial role in the uptake across the gastrointestinal membrane and were found to significantly affect the absorption profile. The nanocarriers with the particle size of 50–300 nm, positive zeta potential and hydrophobic surface were found to have preferential uptake from the gastrointestinal tract as compared to their counterparts [34]. Various identified absorption mechanisms through which nanocarriers increase the oral bioavailability of drug molecules include increased absorption from enterocytes (due to increased solubilization and dissolution), mucoadhesion (interaction between the positively charged nanocarrier with negatively charged mucin) [35], tight junction modulation (capability of nanocarriers to interact with the tight junction proteins) [36], receptor-mediated endocytosis and transcytosis (clathrin- and caveolae-dependent and -independent endocytosis) [37], phagocytosis via specialized microfold cells (M cells) of the Peyer's patches and other mucosa-associated lymphoid tissues (MALT) [38] and lymphatic absorption via chylomicron uptake mechanism from the enterocytes (mediated by lipase for various lipid-based drug delivery systems) [39].

The subsequent sections convey the information on recent developments in the formulation of a variety of nanocarriers which were employed for the oral bioavailability enhancement of anticancer drugs.

3.2.1 Drug nanocrystals

Recently, nanocrystal approach has gained a great deal of importance considering its capability to impart higher saturation solubility, enhanced dissolution and reproducibility for oral absorption of drug molecules, encompass high dose drugs, thereby increasing the overall bioavailability [39].

The residence time of nanocrystals in GI tract can be increased by incorporating with mucoadhesive polymers in them. Various approaches have been reported to impart mucoadhesion to the nanocrystals which include suspension layering, spray drying, etc. However, there is always a limitation in the choice of excipients with dual functionality of mucoadhesion and nanocrystal stabilization. Hence, a novel approach of incorporating the nanocrystal in mucoadhesive gels was implemented [40]. The other advantages with nanocrystal approach include high drug payload, drug stability, improved drug efficacy, high level of scalability and widespread industrial adaptability. The other advantages with nanocrystal approach include high drug payload, drug stability, improved drug efficacy, high level of scalability and widespread industrial adaptability.

Examples:

a) Liu et al. have reported the development of paclitaxel nanocrystals by surface stabilization with Pluronic F127 [41].
b) On the similar line, novel nanocrystal formulation of paclitaxel and camptothecin has been developed using three-phase nanoparticle engineering technology (3PNET technology), which includes a 3 step process: amorphous precipitate; hydrated amorphous aggregate and finally stabilized nanocrystal utilizing F127 as polymer stabilizer [42]. The efficacy was 3-fold greater as compared to that of a free drug suspension, clearly indicative of

advantage of nanocrystal in the drug absorption.

3.2.2 Polymeric nanocarriers

3.2.2.1 Polymeric nanoparticles

Polymeric nanoparticles are nano colloidal cargos, preferably in the size range of 10–1000 nm, made up of a wide variety of polymers. A large number of polymers including the co-polymers have been employed for the preparation of polymeric nanoparticles (nanocapsules and matrix-based nanoparticles).

These include natural polymers such as gelatin, dextran, albumin, chitosan and alginate to name a few, among which chitosan and its derivatives have been widely explored. Latest trend include utilization of the synthetic biodegradable polymers such as polylactic acid (PLA), polyglycolic acid (PGA), copolymers of lactic and glycolic acid (PLGA), poly (ε-caprolactone) (PCL), poly-alkyl cyanoacrylate (PACA), polyethyleneimine (PEI), poly (L-lysine), poly (aspartic acid), etc.

Advantages:

a) Robust structural characteristics imparting very high stability in the gastrointestinal tract.
b) Furthermore, the hydrophobicity and hydrophilicity within the polymeric system can be manipulated to accommodate a wide variety of drug molecules.
c) The polymeric nanoparticles tend to show a very high degree of sustained release of drug molecules, which could be of special significance for oral delivery in terms of ensuring that no drug is released from the formulation till it reaches systemic circulation thereby bypassing various physiological barriers to oral delivery of difficult-to deliver drugs.

Example: Tamoxifen loaded PLGA nanoparticles (TEM-NPs) were prepared by the double emulsion diffusion evaporation with slight modifications [43]. About 3.84-fold and 11.19-fold increase in the oral bioavailability of tamoxifen was observed upon incorporation into PLGA nanoparticles as compared to commercial analogue, tamoxifen citrate and free base, respectively. Furthermore, the significantly higher antitumor efficacy of tamoxifen and reduced hepatotoxicity were also observed from PLGA nanoparticles as compared to free base [44].

3.2.2.2 Polymeric micelles

Polymeric micelles are the systems containing hydrophobic cores surrounded by hydrophilic corona that is exposed to the aqueous environment. Various mechanisms of drug absorption via polymeric micelles include alteration in the membrane permeability, absorption of micelles via fluid-phase pinocytosis, receptor-mediated endocytosis (upon attachment of specific ligands to the micellar structures), inhibition of the efflux transporter proteins (majority of the polymers forming micelles are reported to interact with efflux transporter proteins) and mucoadhesion along the gastrointestinal tract.

The cores of the polymeric micelles are generally made of a biodegradable polymer such as poly (β-benzyl-L-aspartate), poly (DL-lactic acid), poly (ε-caprolactone), etc. whereas the shell is made up of biocompatible polymers such as polyethylene oxide. The micelles may either be functionalized with certain polymers such as poly (N-isopropylacrylamide) which is temperature-sensitive or poly (alkyl acrylic acid) to which is pH-sensitive or can further be conjugated with ligands to impart targeting characteristics.

Advantages:

a) They are more stable, have enhanced solubilizing power and longer circulating time due to outer hydrophilic shell, small size and targeting capability as compared to surfactant micelles.
b) The hydrophobic cores act as a reservoir for lipophilic drug molecules and corona acts as the steric stabilizer of the overall system thereby assuring the integrity of the system in aqueous environment holding the adequate amount of guest drug molecules.

Example: Sophisticated systems utilizing Dequalinium, as a targeting ligand for preferential co-localization in the mitochondria, guided by the transmembrane electric potential within the cell has been developed. The permeability studies revealed about 36.4-fold higher transport of these functional micelles as compared to the free drug [14].

3.2.2.3 Polymer-drug conjugates

Polymer–drug conjugates are the novel drug delivery systems comprised of covalently linked drug molecules to the polymer backbone. Along

with the drug molecules, additional functional excipients such as diagnostic agent, targeting ligand, PEG chains to improve hydrophilicity, excipients to inhibit drug efflux can also be accommodated in the polymer backbone. The principal types of linkages include amide linkages, ester linkages, sulfhydryl linkages, hydrazone linkages, enzymatically degradable linkages, etc [41]. It should be noted that ester and hydrazone linkages are acid labile and should be less favoured while designing an oral drug delivery system.

Advantages

a) Targeting potential offered by polymer-drug conjugate is beneficiary in case of cancer therapy owing to highly toxic effects of anticancer agents to the normal tissues of the body.
b) Increased solubilization, enhanced plasma half-life, bioavailability enhancement and reduced excretion by kidneys, protection towards degrading enzymes and prevention or reduction of aggregation or immune responses can be achieved by using Polymer-drug conjugates.

Example: PEGylated paclitaxel showed about a 4-fold increase in the oral bioavailability as compared to free drug, which could be attributed to increased solubility, permeability and reduced presystemic metabolism.

3.2.3 Lipid-based nanocarriers

Since many decades, lipids have been widely used for improving the oral bioavailability of various difficult-to-deliver drugs. The lipidic excipients principally comprise of monoglycerides, diglycerides, triglycerides, oils constituting various combinations of glycerides, phospholipids, sphingolipids and even high-fat meal.

The mechanism by which lipid is absorbed in the systemic circulation is shown in Fig. 6.

1) Gastric and lingual lipases digest triglycerides, diglycerides and fatty acids in the stomach and are responsible for the generation of the crude emulsion of lipids.
2) After gastric emptying, the crude emulsified lipidic system gets exposed to bile salts, phosphatidylcholine secreted by the gall bladder and pancreatic lipase/co-lipase secreted by the pancreas. The secreted components then get adsorbed on the surface of the crude emulsion droplets and the adsorption leads to further digestion and formation of stable small-sized emulsion droplets.
3) These small-sized lipid emulsion droplets are further acted by lipid digestion products to form mixed micelles of lipidic system, thereby making the process of lipolysis self-promoting [14].
4) The formed micelles will then be absorbed by enterocytes, where it gets converted to the chylomicrons upon re-esterification via monoacyl glycerol or phosphatidic acid pathway and subsequent stabilization by phospholipids.
5) The formed chylomicrons are then subjected to lymphatic transport system via mesenteric lymph and ultimately enter the systemic circulation by lymphatic drainage at thoracic duct.

Advantages:

a) The usual problem associated with most of the drugs includes either low aqueous solubility or poor intestinal permeability, both of which can adequately be taken care of by lipid-based drug delivery systems.
b) Some unique properties of lipids such as high solubilization potential, biocompatibility, manufacturing scalability, industrial adaptability, and distinct route of absorption eliminate various physiological barriers such as pre-systemic metabolism, gastrointestinal degradation, P-gp efflux and permeability related issues, etc.

Various types of lipid-based nanocarriers implemented for improving the oral delivery of drugs include microemulsions, nanoemulsions, lipid nanocapsules, self-emulsifying systems, lipid nanoparticles, hybrid lipid nanoparticles, liposomes and surface engineered liposomes to name a few.

3.2.3.1 Emulsions

Presently two versions of emulsions viz. microemulsions and nanoemulsions have been employed for improving the oral deliverability of BCS class II. These systems comprise of an appropriate blend of oil, surfactant and co-surfactant dispersed in aqueous phase tailor-

made as per the physicochemical properties of drug substances.

The most common oils used for the preparation of nanoemulsions include omega 3- and 6-containing polyunsaturated fatty acids (PUFA) such as pine seed oil, fish oil, flaxseed oil, safflower oil, hemp and wheat germ oil, etc. The principal reasons for their widespread usages in preparation of nanoemulsions could be attributed to their preferential absorption across the gastrointestinal barrier due to paucity of these agents in physiological conditions.

Advantages: The unique characteristics include thermodynamic (microemulsions) or kinetic (nanoemulsions) stability, supersolvency, small droplet size, high industrial scalability (as low energy requirements for manufacturing) and can use lipidic excipients as absorption enhancers.

Example: Nanoemulsion of Melphalan in Melphalan Capmul MCM, Tween 80 and Transcutol P was made and about 4.83-fold increase in oral bioavailability and 2-fold higher distribution in ovaries as compared to the free drug [45].

3.2.3.2 Self Emulsifying Drug Delivery System (SEDDS)

SEDDS are the most advanced approach of emulsion-based drug delivery systems and rely on the physiological fluids for the in-situ formation of micro/nanoemulsion. This formulation strategy comprises of drug dissolved in oils and stabilized by surfactants and co-surfactants, which upon exposure to the aqueous environment under gentle agitation leads to the spontaneous formation of the emulsion. Although the exact mechanism of self emulsification is yet to be understood and is unclear however it has been postulated that it happens when entropy change for dispersion exceeds the energy required to increase the surface area of dispersion.

Different types of oils that are known to form SEDDS include long- and medium-chain triglycerides with different degrees of saturation.

A newer generation of SEDDS based on supersaturation principle has been designed to exclude the side effects of surfactants and enhance the rate of absorption of drugs from the gastrointestinal tract. These formulations include low levels of surfactants and polymeric precipitation inhibitors to yield and stabilize a temporary supersaturated state of drug. HPMC and other cellulosic polymers are well recognized for their capability to inhibit the crystallization of drugs and thereby leading to the formation of the supersaturated state of the drug for a prolonged duration.

Example:

a) Recently, solid supersaturate SEDDS of docetaxel via spray drying technique have been prepared and it was found to have about 8.77-fold and 1.45-fold higher oral bioavailability as compared to free drug and conventional SEDDS [46].
b) Self-emulsifying drug delivery system was developed of tamoxifen which showed about 3.8-fold and 9-fold enhancement in oral bioavailability as compared to clinically used tamoxifen citrate and tamoxifen free base, respectively [14].

3.2.3.3 Solid lipid nanoparticles (SLNs)

SLNs are the alternative version of emulsions in which the liquid oil is replaced by solid lipids. These are generally prepared by various commonly used techniques such as hot homogenization, cold homogenization, microemulsion technique, solvent emulsification/evaporation, spray drying and so on.

The lipids that are used to prepare SLNs to include fatty acids (e.g. stearic acid), fatty acid esters (e.g. glyceryl monostearate, glyceryl behenate), triglycerides (e.g. tristearin, trilaurin), steroids (e.g. cholesterol) and waxes (e.g. cetyl palmitate). Depending on the charge, molecular weight and their capability to stabilize the dispersion, single or combination of emulsifiers are chosen and incorporated into the system. Commonly used emulsifiers and co-emulsifiers include lecithin, poloxamers, cholates, and so on.

Advantages:

a) Drug release can be modulated
b) Increased drug stability
c) Exclusion of organic solvents from the manufacturing process,
d) Manufacturing scalability and industrial adaptability.

It has been generally found that the drug release is often retarded due to high lipophilic nature of the overall system, but considering the urge to increase the drug release rate; polymer lipid hybrid nanoparticles were developed. These are based on the same principle of SLNs, and incorporation of the ionic polymers helps in improving the encapsulation of water-soluble ionic drugs such as doxorubicin hydrochloride [46].

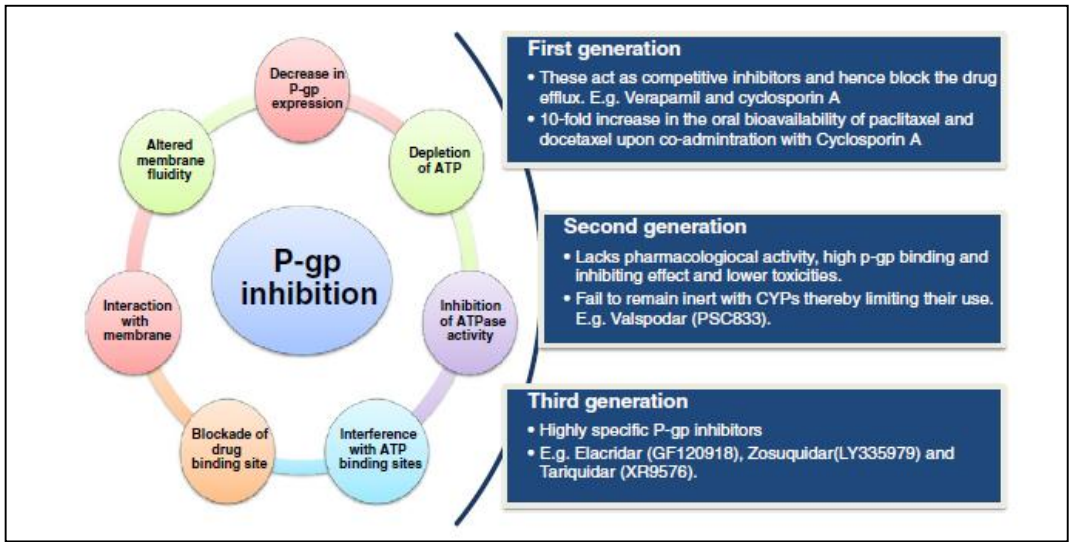

Fig. 4. Various mechanisms of P-gp inhibition [14]

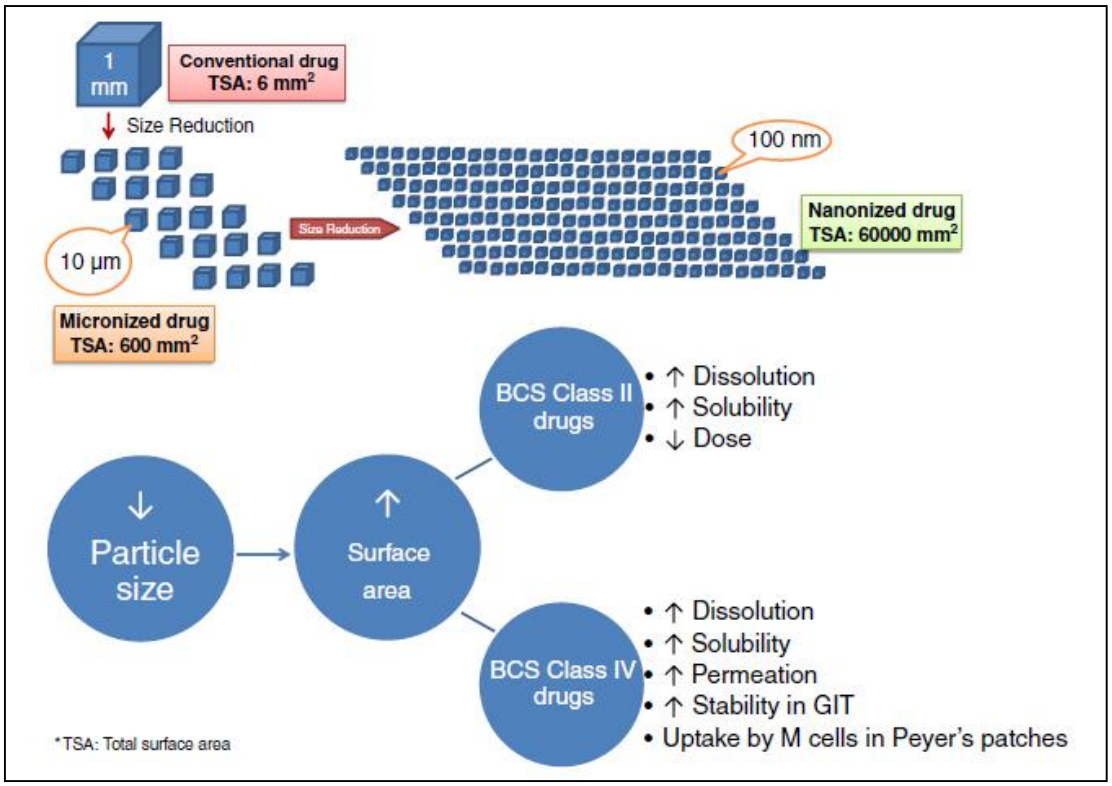

Fig. 5. Mechanistic representation of absorption via nanocrystals

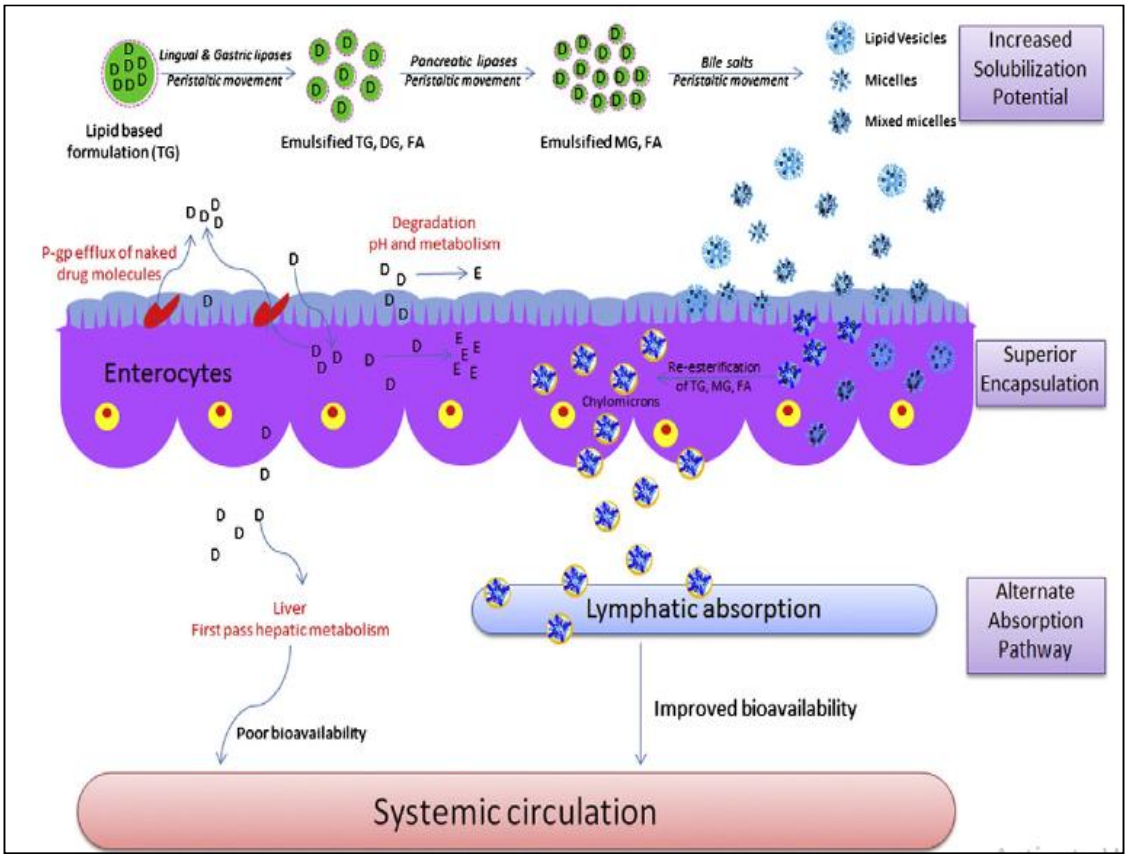

Fig. 6. Absorption of lipid-based nanocarriers

3.2.3.4 Nanostructured lipid carriers(NLCs)

NLCs are the advanced generation of SLNs, NLCs are prepared by similar technique as reported for SLNs with the only difference that both solid lipid and liquid oil are mixed in the formation of NLCs in contrast to only solid lipid for SLNs. This leads to the formation of porous matrix structure resulting in higher drug payload that is entrapped throughout the shelf life of the product. The stability of NLCs can further be enhanced by the addition of preservatives such as propylene glycol, pentylene glycol, etc.

Advantages: SLNs have limited drug loading capacity and subsequently results in the expulsion of the drug during storage. So NLCs can higher solubility as drugs can dissolve more easily in oils as compared to solid lipids.

Example: NLCs have also been implemented for oral delivery of etoposide and about 3.5-fold increase in the oral bioavailability was observed as compared to free drug. Increased permeation across, decreased the clearance and specialized uptake of nanoparticles was attributed for the probable reasons for increased oral bioavailability [47].

3.2.3.5 Liposomes

These are vesicular structures prepared from phospholipids and are capable of accommodating both hydrophilic and lipophilic drug substances within them. These are reported to have huge potential in the delivery of various anticancer agents especially in targeted drug delivery [48]. However, they are not stable in the harsh gastrointestinal environment. The principal reasons for their instability comprise of an acidic environment in the stomach (that leads to aggregation of constituent phospholipids) and presence of degrading enzymes in the intestine (such as pancreatic lipase). But their oral bioavailability can be increased by using surface modification such as PEGylation, transphosphatidylation, mucin coating (mucin

liposomes), polymer coatings (polymerized liposomes), polyelectrolyte coatings (nanocapsules) and chitosan coating.

3.2.4 Dendrimers

Dendrimers are the hyperbranched and uniformly distributed macromolecules that possess definite molecular weight, shape, size and specific chemical and physical properties including host-guest entrapment properties. The tailor-made design makes these sophisticated systems eligible for the incorporation of a wide variety of drugs that otherwise pose potential delivery challenges. The drug molecules can be either physically entrapped or chemically conjugated to the dendritic structures during or after synthesis of macromolecular systems. Furthermore, the encapsulation of drug molecules within the dendritic structures selectively eliminates solubility and permeability related issues. Henceforth, these systems can be exploited to accomplish the oral delivery of anticancer agents.

Advantages:

a) High solubilization capacity
b) Increased permeation capability across the gastrointestinal tract via the paracellular or transcellular pathway
c) Encapsulation of the drug molecules, thereby protected from the harsh gastrointestinal environment.
d) High drug payload

4. CONCLUSION

With the advent of nanotechnology in the drug delivery applications for improving the deliverability of various difficult-to-deliver drugs, there arise obvious concerns that need to be addressed. The principal concern is the safety profile of these nanocarriers for chronic treatment which is already under consideration and dedicated efforts are being made by the scientific community and health care agencies. The results so far seem to be promising which is evident from the fact that there are numerous nanotechnology-based products approved by regulatory agencies and are in clinical use. Furthermore, attempts can also be made to further exploit the targeting potential of nanocarriers to increase their uptake from the gastrointestinal tract to an extent comparable to that of parenteral administration. Also, the utilization of the functional excipients within the carrier systems can be exploited to a greater extent to design and develop rationalized drug delivery systems for various difficult to treat diseases such as cancer.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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