Nanoparticulate drug-delivery systems: lymphatic uptake and its gastrointestinal applications

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ABSTRACT

One of the important challenges of modern drug therapy is the optimization of the pharmacological action of a drug along with the reduction of its toxic side effects in vivo. One response is the use of drug carriers that can provide site specific or targeted drug delivery combined with optimal drug release profiles. Nanoparticulate systems (NPS) as a drug delivery system is an emerging field in medical sciences since they are believed to target the delivery of the drug in cells reduce dose and thus reduce side effects and dose related toxicities. The gastrointestinal tract (GIT) uptake of nanoparticulate systems is nowadays well accepted phenomenon. Uptake of Nanoparticulates from the gut can provide an additional drug administration route with its own pharmacokinetic parameters and specific drug-carrying ability. The drug is transported into the GIT by carriers whose physico-chemical characteristics must be taken into account, although the physico-chemical and pharmacological characteristics of the drug remain intact. In this article we concentrate particularly on the translocation of NPS via the lymphatic system, and their use.

INTRODUCTION

One of the important challenges of modern drug therapy is the optimization of the pharmacological action of a drug along with the reduction of its toxic side effects in vivo. One response is the use of drug carriers that can provide site specific or targeted drug delivery combined with optimal drug release profile (Kreuter, 1991). Among these carriers, liposomes and nanoparticles have been most extensively investigated. A decade ago as a drug delivery system, nanoparticles were first studied because of their size-dependent physical and chemical properties (Hussain, 2001). Some nanoparticles as formulations have already entered into a commercial exploration (Florence and Hussain, 2001; Nishioka and Yoshino, 2001). Liposomal formulations have some technological limitations such as poor stability, low residence time and low drug entrapment efficiency. To overcome them, polymeric nanoparticles have been tried as alternative drug carriers. The predominant area of research using polymeric nanoparticles is controlled delivery system of drug following parenteral, oral, pulmonary, nasal, and topical routes of administration. By virtue of their small size and by functionalizing their surface with polymers and appropriate ligands, polymeric nanoparticles can also be targeted to specific cells and specific locations in the body. Polymeric nanoparticles have been reported to overcome stability issues for certain drugs, reducing the therapeutic dose and thereby minimizing drug induced side-effects (Florence, 2004; Hans and Lowman, 2002).

The primary objective of this review article is to highlight various advantages offered by lymphatic targeting of orally administered nanoparticulate systems (NPS) in drug delivery systems. This review further enlightens how NPS are relatively efficient and therapeutically beneficial alternatives to conventional dosage forms besides affording means of targeted drug delivery via a convenient route of administration.

Intestinal Lymphatic Targeting

The epithelial lining of GI tract is made of a mosaic of cells, among which enterocytes (absorptive cells) and goblet cells (secreting the mucus) may be distinguished. These cells are held together tightly forming a strong barrier covered by a mucosal layer. A part of the gut associated lymphoid system(GALT) namely lymphoid follicles which are involved in the development of the mucosal immune response, are interspersed in the enterocyte layer.
These follicles are diffusely distributed or clustered in so-called Peyer's patches, whose number and location vary widely between species and individuals besides being age dependent. These follicles are overlaid by the follicle-associated epithelium (FAE) which comprises enterocytes, M cells differentiated from the enterocytes, and a few goblet cells. These sites serve as the first checkpoints for antigens. FAE and the M cells have been described as most suitable places for particle uptake (Delie and Blanco-Prieto, 2005).

These are characterized by the presence of M-cells which helps in endocytosis, transport into intraepithelial regions and adjoining lymphoid tissue. Usually, nanoparticulates bind to the apical membrane of M-cells, followed by rapid internalization and transportation to the lymphocytes (Florence and Hussain, 2001; Hans and Lowman, 2002). In such cases, absorption of a drug via GALT offers a distinct advantage in avoiding presystemic hepatic first-pass metabolism and thereby preventing drug loss. The factors which affect NPS absorption via the GALT are not only limited to properties of the loaded drug but also the physical characteristics of the carrier like size, shape, specific surface, surface charge, chemical stability of both NPS and loaded drug along with potential interactions with gut contents, transit time through the GIT, transport through the mucosa, adhesion to epithelial surfaces, and particulate aggregation when coming in contact with the gut fluid. The path of transit and translocation of NPS depend quite significantly on their average diameter, surface charge, and rele

This in turn may reduce efficacy of such formulations via specific drug delivery approach leading to reduced feasibility of same. Besides the above listed properties of NPS, loading capacity also plays a critical role. Loading capacity bears a directly proportional relationship with bioavailability wherein higher loading is associated with higher bioavailability per absorbed particle (Hussain, 2001). Apart from these issues, biocompatibility and biodegradability of the NPS components plays an important role in determining the relative usefulness of such formulations. (Figure 1).

Lymphatic targeting of NPS affords (i) oral delivery of nano-encapsulated GIT labile molecules, (ii) oral delivery of nanoparticle-polymer conjugates and nano-solubilized poorly soluble molecules, (iii) improved bioavailability of poorly absorbed drugs due to increased residence time and surface specificity of NPS (Khan et al., 2013), (iv) oral delivery of vaccine antigens to gut-associated lymphoid tissue (Reddy et al., 2007), (v) translocation of antineoplastic drugs for treatment of lymphomas (Cho et al., 2014), (vi) delivery of diagnostics for the lymphatic system, (vii) sustained/controlled drug release, particularly important for toxic drugs (e.g., antineoplastic drugs) (Cho et al., 2014), (viii) reduction of drug-related GI mucosal irritation and cause avoidance of the hepatic first-pass effect. The formulations that have been reported for lymphatic targeting are given in Table 1 (Khan et al., 2013; Cho et al., 2014; Shah et al., 2011; Alex et al. 2010; Almeida and Souto, 2007; Wu et al., 2011). Various research activities have been conducted which further underline the advantages of lymphatic targeting.

<table>
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<th>Table 1: Nanoparticulate drug formulations reported for Lymphatic targeting.</th>
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**Colonic Lymphatic Targeting**

Lymphatic tissue in the colon is usually found in aggregated masses spread irregularly. The presence of M-cells in the colon increases the possibility of nanoparticulates being absorbed in colon (Uchida, 1988). Development of Colon-specific drug delivery intended for targeting lesser proteolytically active colon can help improve bioavailability of drugs like proteins and peptides. Colonic targeting offers advantages of therapeutic intervention in pathological processes of the gut, such as ulcerative colitis or Crohn’s disease with increased possibility of targeting of labile molecules such as peptides and small proteins to the colon (Watts and Illum, 1997).

**Factors affecting NPS efficacy**

Gastrointestinal labile molecules such as peptides, anticancer, anti-HIV and immunosuppressant compounds have been incorporated into NPS. Efficient incorporation of bioactive molecules in NPS requires an in-depth study of the factors that may affect the encapsulation. Factors that may affect efficacy of NPS are: drug loading, acceptable physicochemical characteristics such as size, zeta potential or surface charge, molecular weight, hydrophilicity and composition which help for translocation of NPS to lymph and drug release pattern from them.
The size and composition of NPS play an important role in lymphatic uptake and particle retention in lymph nodes. Carriers such as colloidal, polymeric and lipid particles show more efficiency in lymphatic uptake. Several drug molecules, including anticancer and monoclonal antibodies, have been incorporated into dendrimers and lipid-based nanoparticles, such as liposomes, SLNs, and NLCs, on the basis of their size and the nature of the preparations for lymphatic targeting. Reports suggest that a particle size of 100-500 nm is optimal for lymphatic uptake via the GI lymphatic system but at a slower rate than particles of size 50-100 nm. However, the uptake of particles with size larger than 500 nm has not been clearly defined (Khan et al., 2013).

Surface charge on NPS

The charge on NPS is also an important factor in lymphatic uptake. Negatively charged carriers, such as dendrimers encapsulated proteins, polyactic-co-glycolic acid nanospheres, and anionic lipid nano-liposomes have been reported to show higher lymphatic uptake than neutral or positively charged surfaces, which may be ascertained to presence of negatively charged interstitial matrix leading to more drainage into lymphatic system (Kaminskas and Porter, 2011; Rao et al., 2010). Thus, anionic NPS will encounter electrostatic repulsive forces from the negatively charged matrix leading to faster drainage. However, negatively charged particles have been reported to be retained for a longer period of time in the lymph nodes (Khan et al., 2013; Kaur et al., 2008). Conversely, positively charged NPS are more attracted to wards the negatively charged interstitium and face electrostatic repulsion in the positively charged lymphatic drainage leading to slower movement in them. Further, zeta potential of the particles provides an insight regarding the ionic nature of NPS. Zeta potential values lesser than -30 mV indicates strong anionic nature, while values between +10 and -10 mV indicate neutral behavior, whereas values more than +30 mV indicate a cationic nature. Positively (ie, stearylamine) or negatively (ie, dicetyl phosphate) charge surfactant incorporated Zidovudine-liposome intended for lymphatic targeting showed that negatively charged liposomes improved lymphatic uptake compared with the positively charged liposomes (Kaur et al., 2008).

Hydrophobicity of NPS

Hydrophobicity plays major role in facilitating lymphatic uptake of NPS. The hydrophobicity of the particulates can be correlated with their surface properties, and is mainly responsible for phagocytosis and lymphatic uptake. Reports suggest that decrease in the hydrophobicity of NPS leads to decrease in
phagocytosis, decrease in opsonization leading to decrease in lymphatic uptake. Consequently, more the hydrophobicity of NPS, more will be the phagocytosis and lymphatic uptake will increase (Khan et al., 2013).

**Choice of NPS**

Factors that must be examined in order to obtain the best formulation type of NPS are: (i) sufficient drug loading to achieve therapeutic levels; (ii) good translocation of NPS to lymph (i.e., small size, biocompatible, biodegradable components, chemophysical stability of carrier and drug, zeta potential, etc.); (iii) sustained/controlled drug release from NPS; and (iv) increased oral bioavailability to enhance efficacy (Khan et al., 2013).

**Nanoparticulates for lymphatic targeting**

Various research activities have been conducted which highlight the relative advantages of NPS lymphatic targeting via oral route. The nanoparticulates studied for such an approach include Dendrimers, Polymeric nanoparticles, Liposomes, Self-microemulsifying drug-delivery systems and Solid lipid nanoparticles among others.

**Dendrimers**

Dendrimers have been used to prepare nanoparticulates (with diameter below 50 nm) to study the relationship between diameter and uptake from the GIT (Florence, 2004). Study in rats examining the absorption through Peyer’s patches and enterocytes of dendrimers having lipidic external character along with a series of cationic dendrimers have shown their preferential uptake through Peyer’s patches. In-vivo study of Phospholipid coated polyamidosamine dendrimers entrapped with 5-Fluorouracil in albino rats have shown to be more effective orally than free drug with increase in lymphatic uptake, indicating absorption of the dendrimer through the lymphatic route (Tripathi et al., 2002).

**Polymeric Nanoparticulates**

Polymeric (natural or synthetic) nanoparticulates are particles of diameter below 1 μm. Natural polymers (i.e., proteins or polysaccharides) are not widely used for this purpose, because of chances of variation in purity, requirement of cross-linking and chances of denaturation of drug (Hans and Lowman, 2002). The most widely used synthetic polymers are poly (lactic acid), poly (glycolic acid), their copolymers poly (lactide-co-glycolide acid) (PLGA) and polyalkylcyanoacrylates (PACA) (Bala et al., 2004; Vauthier et al., 2003). These polymers, offer the advantage of sustained delivery of drugs and avoiding repeated dosing. The major target zone for lymphatic uptake of the nanoparticles are Peyer’s patches in GALT. Microparticles have been reported to remain in Peyer’s patches, while nanoparticles are systemically disseminated permitting a wide range of drugs to be delivered via the oral route (Hans and Lowman, 2002). In the last decade, a lot of research has focused on the absorption enhancement of peptides proteins (Almeida et al., 2010; Delie and Blanco-Prieto, 2005), and vaccine antigens. Mucoadhesive polymer (chitosan or Carbopol) coated nanoparticulates have shown prolonged action and are more effective (Takeuchi et al., 2001).

Prolonged hypoglycemia is produced by PACA nanospheres entrapped Insulin and dispersed in an oily phase with a surfactant (Damge et al., 1997). Insulin loaded Poly (isobutylcyanoacrylate) nanocapsules upon oral administration to rats while being monitored by fluorescence and transmission electron microscopy (TEM) showed absorption through the epithelial mucosa in the intestine (Pinto-Alphandary et al., 2003, Li et al., 2004). PACA nanocapsules incorporated with a peptide, octreotide showed improved and prolonged therapeutic efficacy (Damge et al., 1997). PLGA nanoparticles loaded with Salmon calcitonin and complexed with amphiphilic molecules on oral administration to rats showed increased absorption efficiency and reduction in the required dose for production of desired therapeutic action (Sang and Gwan, 2004).

Heparin is generally administered by the parenteral route as it has no oral bioavailability. Heparin-loaded polymeric nanoparticles, prepared with biodegradable poly-e-caprolactone and PLGA and nonbiodegradable positively charged polymers (when used alone or in combination) on oral administration to rabbits showed anti-factor Xa activity for a longer period than when a heparin solution was administered intravenously (Jiao et al., 2002). It would be ideal to have an oral delivery system for vaccines. Following the oral administration of antigens, they are usually taken up by the Peyer’s patches primarily through the M-cells and these are sufficient for mucous immunization. For producing IgA antibody response, oral delivery of antigens may be considered as an ideal means (Reddy et al., 2007; Foster and Hirst, 2005). These delivery systems will be effective in the oral delivery of antigens only if they are able to protect the molecule. It has been found that oral administration of antigens incorporated in nanoparticulates induces a stronger antigen-specific immune response than do antigens in the water soluble formulations. This may be attributed to the protection from proteolytic enzymes and the acidic pH of the stomach (Fooks, 2000; Tabata, et al., 1996).

Positively charged nanoparticles carrying cyclosporin A (prepared by the emulsification solvent diffusion method and nanoprecipitation method with nonbiodegradable polymers) showed relative bioavailability of cyclosporin A ranging from 20% to 35% that of Neoral (El-Shabouri, 2002; Ubrich et al., 2005). Polybutylcyanoacrylate nanoparticles (PBCNs) loaded with Peurarin increased the oral bioavailability to up to 550% as compared to the tablet formulation, thereby providing a more effective alternative for the delivery of such poorly water soluble drugs (Zhao et al., 2011). Tacrolimus loaded PLGA/ PLGA-PEG nanoparticles when administered intravenously in rats for lymphatic targeting showed more promising results as compared to commercial product of tacrolimus Injection (Prograf®) (Shina et al., 2010).

Doxorubicin loaded PLGA nanoparticles administered orally in rats have shown improved bioavailability and reduced toxicity as compared to intravenous route (Kalaria et al., 2009).
Current research gives strong indication that both cyclodextrins and polymeric nanoparticles could be highly useful in the search for a suitable method for such successful oral delivery of proteins and peptides (Kanwar et al., 2001).

Liposomes

Liposomes provide a simple and convenient formulation for oral drug administration. However, their stability in acidic pH of stomach and gastrointestinal medium needs to be ascertained (Allen, 1997; Barratt, 2000). Stability in the physiological conditions after oral drug delivery has been studied for determining the lipid components which shall be able to withstand the harsh conditions associated with GIT (Taira et al., 2004). Polyethylene glycol coated liposomes containing recombinant human epidermal growth factor were administered orally to rats and compared to that of the solution form of same in terms of area under the concentration–time curve (AUC). It showed an increase of 1.7-fold and 2.5-fold for phosphatidylcholine and dipalmitylophosphatidylcholine liposomes, respectively (Cansell et al., 2003). Liposomes encapsulating an extract of natural marine lipids with large amounts of N-3-polyunsaturated fatty acids (PUFA) when administered to thoracic lymph duct-cannulated rats showed absorption of fatty acids were higher than with fish oil (Takeuchi et al., 2003). Chitosan or Carbopol coated liposomes containing calcitonin (both negatively and positively charged liposomes) showed that pharmacological efficacy of the intestinal absorption in rats of coated liposomes was more than twice that of non-coated liposomes (Li et al., 2003). Cationic charged double liposomes containing salmon calcitonin on administration to rats showed higher hypocalcaemic effects than on administration in solution (Yamabe et al., 2003).

Self-(Micro) Emulsifying Drug-Delivery Systems

Self-(micro) emulsifying Drug-Delivery Systems [S(M)EDDSs] are isotropic mixtures of oils, surfactants, solvents, and cosolvents/surfactants which are used for the improvement of oral absorption of highly lipophilic drugs. Paclitaxel supersaturable self microemulsifying drug-delivery system (S-SEDDS) formulation with hydroxypropylcellulose as precipitation inhibitor (Gao et al., 2003), showed a 5-fold increase in the oral bioavailability than the oral Taxol formulation in rats. Coadministration of P-glycoprotein inhibitors (cycloropin A) with paclitaxel S(M)EDDS to rats showed improved oral bioavailability as compared to commercially available Taxol (Gursoy and Benita, 2004). Oral administration of simvastatin [S(M) EDDS] to beagle dogs showed 1.5-fold increase in bioavailability over conventional oral tablet (Kang et al., 2004).

The systemic bioavailability of a poorly water soluble drug Puerarin increased significantly when formulated as microemulsion drug delivery system as compared to other formulations. This may be attributed to the improved the lymphatic transport and portal absorption of such formulations (Wu et al., 2011). S-MEDDS in sustained-release pellets of Puerarin developed using castor oil as the oil phase, Cremophor® EL as the emulsifier, and 1,2-propanediol as the co-emulsifiers showed 2.6 fold increase in absolute oral bioavailability and 259.7% increase in relative oral bioavailability as compared to Puerarin tablet when tested in beagle dogs. These results demonstrate that pueraarin–S-MEDDS sustained-release pellets had a sustained-release effect, and could remarkably improve the oral bioavailability of pueraarin (Zhang et al., 2012). Raloxifene loaded microemulsions/S-MEDDS with Capmul MCM C8 (oil), Tween-20 and Akrysol K140 (as solvents) and PEG-200 (cosolvents) as excipients; on administration to rats exhibited significantly higher intestinal permeation (lymphatic uptake) and increased bioavailability as compared to drug suspension of raloxifene leading to decrease in dose, dosing frequency and lesser side effects (Thakkar et al., 2011).

Solid–Lipid Nanoparticles

Solid–lipid nanoparticles (SLNs) are submicron sized particles composed of biocompatible and biodegradable materials, such as triglycerides and fatty acids (Bummer, 2004; Manjunath et al., 2005; Muller et al., 2000). They offer a prominent advantage over other NPS as they are made of physiological lipids and surfactants which are recognized as safe. Per oral administration of camptothecin-loaded SLNs (produced by high-pressure homogenization) to rats, showed enhanced availability of the drug compared to solution with significant increase in AUC and mean residence time (MRT) (Yang et al., 1999). Orally administered piribedil SLNs in rabbits showed more than 2-fold increase in drug bioavailability as compared to pure piribedil (Demirel et al., 2001).

Poorly soluble all-trans retinoic acid when administered orally to rats in form of SLNs showed significantly increased absorption as compared to other formulations (O’ Driscoll and Giffin, 2008; Khan et al., 2013). Clozapine SLNs when administered by intravenous (IV) and intraduodenal routes showed increased bioavailability with increase in area under the curve (AUC) by 3 and 4.5 times respectively as compared to clozapine suspension. Thus, administration of clozapine SLNs orally can offer better more efficacious alternative as drug delivery system as compared to other routes (Manjunath and Venkateswarlu, 2006).

After IV administration, SLNs and stealth nanoparticles (to avoid reticuloendothelial system recognition) have been found to be able to cross the blood–brain barrier, increasing the MRT (to a greater extent with stealth SLNs) of the loaded drug compared to solution (Gasco, 2000). Further, SLNs are taken up quickly by neoplastic and non-neoplastic cell lines (Serpe et al., 2004; Serpe et al., 2004; Dianzani et al., 2006). Tobramycin loaded SLNs (Tobramycin is not absorbed in GI tract and is administered through parenteral route) after administration to rats into the duodenum showed 100 and 20 times higher AUC compared to solution with significant increase in AUC and mean residence time (MRT) (Yang et al., 1999). Orally administered piribedil SLNs in rabbits showed more than 2-fold increase in drug bioavailability as compared to pure piribedil (Demirel et al., 2001).

Idarubicin is an anthracycline anticancer agent (effective in the treatment of various kinds of tumors), usually administered
via intravenous route which leads to distribution of idarubicin to heart, lung, spleen and kidneys while being the primary cause for its cardiotoxicity. Idarubicin containing SLNs on administration to rats duodenally showed higher 21 fold increase in AUC than after intravenous route and thereby enhancing bioavailability. Further, due to 30 fold increase in elimination half life in case of SLNs as compared to solution, it may be suggested that SLN could be useful for prolonged drug delivery. Additionally, these changes can help to reduce toxicity and increase clinical efficacy of drugs (Zara et al., 2002; Khan et al., 2013).

Methotrexate loaded SLNs containing Compritol 888 ATO when administered intraduodenally showed a 10 fold increase in methotrexate concentration as compared to that of Methotrexate solution. This was due to superior lymphatic uptake of Methotrexate SLN and thereby into systemic circulation, which increased bioavailability and improved toxicity profile of the drug (Paliwal et al., 2009; Khan et al., 2013). The poor oral bioavailability of Docetaxel (potent anticancer agent) has limited its development in oral formulations. The P-glycoprotein (Pgp)-mediated efflux in intestine and cytochrome P450 (CYP)3A-mediated first-pass metabolism in intestine (and/or liver), together with poor aqueous solubility (0.025 μg/mL), are primarily responsible for low oral bioavailability of docetaxel. Docetaxel loaded SLNs surface modified with Tween 80 or D-alpha-tocopheryl polylethylene glycol 1000 succinate (TPGS 1000) showed a sustained-release profile of docetaxel from the SLNs compared with an intravenous docetaxel formulation (Taxotere®). Tween 80-emulsified SLNs showed enhanced intestinal absorption, lymphatic uptake, and relative oral bioavailability of docetaxel compared with Taxotere in rats. These results may be attributed to the absorption-enhancing effects of the tristearin nanoparticle. Further, TPGS 1000-emulsified SLNs as compared to Tween 80-emulsified SLNs showed relatively better intestinal absorption and oral bioavailability of docetaxel in rats, probably due to better inhibition of drug efflux by TPGS 1000, along with intestinal lymphatic uptake. Thus surface modified SLNs can serve as effective oral delivery systems for docetaxel (Cho et al., 2014).

Colonic Targeting

One way to target the colon is to incorporate drugs in appositely charged nanoparticulates. Rolipram loaded PLGA nanoparticles (with size 200-500 nm) were studied for the treatment of experimentally induced inflammatory bowel disease (Lamprecht et al. 2001). The particles were administered to rats for five days with drug solution administered for comparative evaluation. Both were found to be equally efficacious with no significant difference in measured parameters. However, after the treatments were stopped, a severe relapse was observed in case of drug solution treated rats while the nanoparticle treated group showed reduced inflammatory levels. This may be attributed to ability of nanoparticles to retain the drug from systemic absorption while providing a targeted sustained release profile of the drug leading to enhanced efficacy (Lamprecht et al., 2001). Tacrolimus loaded PLGA NPS entraped into pH-sensitive microspheres (NPMS) were designed to reduce the occurrence of premature uptake or degradation of NPS during their passage through GIT. Such NPS achieved greater selectivity to their site of action providing greater efficacy than when administered orally (Lamprecht et al. 2005).

CURRENT STATUS AND FUTURE ADVANCES

In order to obtain desired results after administration of nanoparticulates orally, NPS should be able to withstand the adverse conditions in the GIT. For the last two decades, active research has been able to minimize the effects of GIT on such systems. From the pharmaceutical standpoint, most nanoparticulates targeted to the lymphatic system have increased bioavailability versus the referee drug; which is particularly appreciable for labile drugs and molecules with poor solubility. However, one major factor affecting the efficacy of any selected NPS is incorporation efficiency, which must be increased in order to administer required therapeutic dose without affecting the safety and efficacy of the patients. Although, some polymeric biodegradable nanoparticles are already on the market, to date they are only restricted for parenteral route. Studies on the oral route have chiefly addressed the administration of vaccine antigens, peptides, and small proteins. Provided that the choice and selection of the polymer is appropriate, the in vivo results can prove to be promising for delivering drugs efficiently into the human system. Lipid-based systems have achieved some of these desired results. Some antiprotease drugs, ritonavir, and saquinavir, carried by S(M)EDDS, are now on the market and provide better bioavailability than the referee drug (Yamabe et al., 2003). Tobramycin or Idarubicin loaded SLNs administered duodenally show better pharmacokinetic parameters than the same drug administered IV as a solution. Tobramycin SLN administered duodenally may have permitted more efficient absorption of tobramycin by the GIT. This is of particular interest as this drug is mostly administered by the parenteral route. Interest in the oral administration of chemotherapeutic agents via NPS has been further stimulated by the discovery that oral fluoropyrimidines have nearly equivalent efficacy with potential to reduce toxicity, when compared to administration of these drugs by the IV route. Thus using rational nanoparticulate design, several antineoplastic drugs could be developed for oral use (Royce et al., 2000, Khan et al., 2013, Cho et al., 2014). Although studies on nanoparticulates targeting the colon are relatively few, some interesting results have been achieved using liposomes and PLGA nanoparticles (Xing et al., 2003; Lamprecht et al., 2001). Conventional intravenous administration of cytotoxic drugs has limited tumor uptake because of minimal access to the tumor, decreased circulation time due to faster clearance by the phagocytic system, and increased targeting (Cai et al., 2011; Khan et al., 2013). Conversely, absorption via lymphatic route for delivery of cytotoxic agents offers to overcome the limitations of nonspecificity, drug resistance, and severe toxicity.
CONCLUSION

Orally administered NPS are administered by a well-accepted easy route. They are generally intended either to protect drug susceptible to the adverse effects of the GI tract or to release the drug from the formulations in a sustained manner over a prolonged period of time. This helps in reduction in dose and frequency of dosing, which in a way helps in reducing the harmful side effects of drugs and minimizing the dose related toxicity, thereby preserving the safety and the efficacy of the patient. Nanoparticulates targeting lymphatic uptake, encompassing the before mentioned attributes offer a lucrative means of oral delivery of both hydrophobic and hydrophilic drugs including peptides, anti-cancer agents, hormones, CNS drugs among others. Such delivery systems not only afford comparable bioavailability and therapeutic efficacy of drugs through oral route but also may in many cases show increase in them as compared to other routes besides increasing the patient compliance and reducing the unintended side effects related to other routes of administration. Further, lymphatic uptake of these particles could be utilized for targeting many diseases causes and their amelioration. Research Studies focused on this targeting strategy can show a new approach to treat and combat diseases. Thus, lymphatic route of drug uptake can serve as a superior alternative route of administration and further investigation is desired in this area of drug delivery.

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