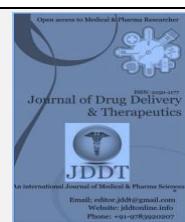
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Review Article

Solid lipid nanocarriers as alternative drug delivery system for improved oral delivery of drugs

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Abstract

Oral bioavailability of drugs is mainly limited due to the poor aqueous solubility, enhanced chemical degradation, reduced permeation and/or first pass metabolism. Various novel delivery systems are developed for improved oral bioavailability of these drugs such as modified orals, buccal, transdermal and osmotic delivery systems. Colloidal carrier systems such as nanoparticles, lipid nanoparticles, nanoeulsions, microspheres, liposomes, resealed erythrocytes and transfersomes were also developed to enhance the oral delivery. Among these, solid lipid nanocarriers (SLNs) also gain much attention on the enhancement of oral bioavailability. SLNs are submicron sized nanoparticles and composed of solid lipid, surfactants and cosurfactants. The enhanced oral bioavailability of poorly soluble drugs from SLNs might be due to the reduced particle size, bypassed presystemic metabolism, and enhanced gastric mucosa permeability. Vast literature is available for the advantages, limitations, preparation methods, evaluation parameters and application of SLNs in different routes. This review mainly focused on list of drugs developed as SLNs and considered as an alternative approach to enhance the oral bioavailability based on pharmacokinetic as well as pharmacodynamic parameters was discussed.

Keywords: Oral bioavailability, solubility, first-pass metabolism, solid lipid nanoparticles, pharmacokinetics, pharmacodynamics.

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INTRODUCTION

Different Drug Delivery Systems have been generally developed to improve the bioavailability of ineffectively assimilated drugs with a specific objective to enhance their clinical efficiency when administered orally. It is evaluated that in about 40 - 70% of all new drugs are developed as poor solubility in aqueous environment¹. The expansion in the extent of ineffectively dissolvable competitors is every now and again credited to upgrades in combination innovation, which has empowered the outline of extremely confounded mixes, and an adjustment in revelation system from a supposed phenotypic way to deal with an objective based approach². Different physicochemical properties which add to the poor dissolvability of different drugs incorporate their perplexing structure, estimate, high molecular weight, high lipophilicity, compound H-attaching to dissolvable, intramolecular H-holding, intermolecular H-holding (precious stone pressing), crystallinity, polymorphic structures, ionic charge status, pH, and salt shape^{3,4}.

Various approaches have been used to enhance the oral bioavailability of poorly soluble drugs. These approaches includes; i) enhance the solubility and dissolution rate using liquisolid compacts (Arun and Narendra, 2016), solid dispersion by complexation⁵⁻⁷, ii) by avoiding the pre-systemic metabolism using buccal delivery⁸⁻¹⁰, semi solid dispersions¹¹, iii) prolong the drug release using floating delivery¹²⁻¹⁵, sustained delivery and osmotic delivery^{16, 17}, multiunit dosage form¹⁸⁻²⁰; chrono and colon delivery^{21, 22}; iv) reducing the particle size by using micronization and nanonization such as self-emulsifying delivery²³, solid lipid nanoparticles²⁴, cubosomes²⁵, nanosuspension²⁶, transfersomes and ethosomes²⁷⁻²⁹, nanocrystals³⁰, nanoemulsion^{31,32} and microemulsions³³; Among various approaches, lipid nanocarriers (solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs)) considered to be as vehicle for one of the novel delivery system for improvement of oral bioavailability^{34, 35}. A vast variety of literature available on enhanced oral delivery in terms of pharmacokinetic and pharmacodynamic activity of poorly soluble drugs reported^{36,37}.

SLNs are defined as a sub-micron colloidal carrier with particle size between 50-1000 nm^{38, 39}. SLNs have the advantages over other colloidal carrier systems especially compared with polymeric nanoparticles, nanoemulsions and nanostructured lipid carriers^{40, 41}. Compared with other systems, SLNs has many benefits including ease of preparation, low cost, high-scale production, excellent physical stability, good release profile, chemical versatility, preparation in the absence of organic solvent, no toxicity of lipid carrier system, biodegradability of lipids, being cheaper than polymeric carrier, being easier to get approval and reliability and biodegradability of lipids^{42, 43}. In general, SLNs are made of combination of solid lipids which are solid at room temperature, surfactants and co-surfactants⁴⁴⁻⁴⁶.

SLNs enhance the bioavailability, sustained drug release, tumor targeting, surface modification and loading of both hydrophilic and lipophilic drugs⁴⁷⁻⁴⁹. SLNs have the additional advantage of reduced cytotoxicity, improved ocular delivery and enhanced pharmacodynamic activity^{50, 51}. Previously, Meharant and Mader,⁵² reported the systemic review on production methods and secondary steps for stabilization; Uner and Yaner, reported the application of SLNs in different routes and ocular delivery⁵³⁻⁵⁵; Jenning et al., discussed various evaluation methods⁵⁶; effect of SLNs in dermal applications as cosmetics^{57, 58} and used as vehicle for bioactive compounds reported⁵⁹. In this review mainly focus on the role of solid lipid nanoparticles to improve the oral bioavailability of poorly soluble drugs based on pharmacokinetic and pharmacodynamic parameters.

CASE STUDIES OF DRUG LOADED SOLID LIPID NANOPARTICLES

Müller et al.,⁶⁰ formulated and reported the enhanced oral bioavailability of cyclosporine form SLN formulation compared with nanocrystals and marketed microemulsion Sandman Neoral/Optoral® formulation as reference formulation. The AUC values >1000 and >12,000 ng/ml being 0.4 and 0.0% of the total AUC for SLN, but 6.5 and 2.9% in case of the microemulsion. Müller et al.,⁶¹ developed and reported the in vitro characterization of cyclosporine loaded SLNs using Imwitor 900 as lipid matrice. From the results, cyclosporine loaded SLNs exhibited more inclusion of cyclosporine and also more drug release. Based on wide angle X-ray scattering studies, cyclosporine is molecularly dispersed in between the fatty acid chains of the liquid-crystalline alpha-modification fraction of the loaded SLN.

Lopinavir (LP) loaded SLNs were used to enhance the lymphatic uptake of LA by overcoming the lymphatic transport. LP-SLNs were prepared by glyceryl behenate using hot homogenization coupled with probe sonication method. The particle size, PDI and zeta potential of optimized SLNs was found to be 230 nm, 0.27 and -27 mV, respectively. About 4.91-fold enhancement in the lymphatic uptake was observed with in vitro cumulative studies in 0.1N HCl followed by pH 6.8 phosphate buffer. In vivo studies in male albino rats showed 2.13-fold improvement when compared with LP suspension, as control formulation⁶².

Statistically optimized nisoldipine loaded solid lipid nanoparticles (ND-SLNs) were developed using central composite design to improve oral bioavailability. ND-SLNs were prepared by homogenization followed by ultra sonication method using Dynasan-114 as lipid matric, egg lecithin as surfactant and poloxamer 188 as co-surfactant. Particle size, PDI, zeta potential and entrapment efficiency of ND-SLN was found to be 104.4 ± 2.13 nm, PDI of 0.241 ± 0.02 and EE of $89.84 \pm 0.52\%$ respectively. Further N-SLN showed

sustained release for upto 24 h. The pharmacokinetic study revealed the about 2.35-fold enhancement in oral bioavailability and 36 h prolonged pharmacodynamic effect when compared with ND suspension in Albino Wistar rats⁶³.

Oral bioavailability of olmesartan medoxomil (OM) was improved by solid lipid nanoparticles delivery system. Nooli et al.,⁶⁴ reported the enhanced oral BA of OM 2.32-times more in male Sprague Dawley rats compared with OM plain drug solution. Similarly, Arun et al., 2018, reported the about 7.21-folds improvement and 3.52-folds improvement compared with OM coarse suspension and nanosuspension formulation, respectively⁶⁵. Recently, Pandya et al., 2018, developed the SLNs of OM to increase the oral BA by employing central composite design. From his findings, about 2.3-fold enhancement in the OM-SLNs were reported compared with marketed formulation⁶⁶.

Similarly, candesartan cilexetil, angiotensin receptor 1 antagonist, prescribed for the treatment of hypertension. The bioavailability of candesartan cilexetil was less than 20% owing to poor solubility and pre-systemic metabolism. Therefore, an attempt was made to enhancement in the bioavailability using SLNs delivery system. SLNs of CC were prepared by using triglycerides as solid lipid matrices. The BA of CC loaded SLNs were increased by more than 2.85-folds compared with coarse CC suspension formulation in albino Wistar rats at a dose of 10 mg/kg⁶⁷. Zhang et al., also reported the improvement in oral bioavailability of candesartan was 12-folds more after incorporation into solid lipid nanoparticles⁶⁸.

Felodipine is an antihypertensive drug with poor oral bioavailability due to the first pass metabolism. Solid lipid nanoparticles as considered as alternative delivery system to improve the BA. Therefore, felodipine loaded solid lipid nanoparticles (SLNs) were developed using triglycerides as lipid matrices and prepared by hot homogenization followed by sonication method. Pharmacokinetics of felodipine-SLNs after oral administration in male Wistar rats was studied. The BA of felodipine loaded SLNs was increased by 1.75-folds when compared to that of a felodipine coarse suspension⁶⁹.

Lacidipine (LD) loaded solid lipid nanoparticles (LD-SLNs) were reported by Sandeep et al.,⁶ for improving the oral bioavailability. LD-SLNs were prepared in two steps. First step was hot homogenization-ultrasonication method, using triglycerides (tripalmitin and tristearin), monoglyceride and surfactants (Poloxamer 188 and egg lecithin E80). LD-SLNs prepared with Dynasan-116 (F3) having the size of 141.86nm, PDI of 0.293, P of -22.3m with 94.75% of EE was optimized and was stable for 60 days. Further, pharmacokinetic studies were conducted in Wistar rats. The relative bioavailability of LD in SLNs was 2.03-times when compared with that of the LD suspension. The results are indicative of SLNs as suitable lipid based carrier system for improving the oral bioavailability of LD⁷⁰.

Rosuvastatin calcium (RC) is a hypolipidemic drug with poor oral bioavailability due to poor aqueous solubility and first-pass metabolism. Solid lipid nanoparticles are used to improve the oral bioavailability of RC. RC-SLNs were prepared by triglycerides using homogenization method. The SLNs showed sustained delivery of RC upto 24 h. In vivo studies revealed the 2-folds enhancement in oral bioavailability compare with suspension formulation in rats⁴⁹. Further, attempts were made to improve the oral bioavailability of RC using monoglycerides to reduce the cost of manufacturing and processing. RC-SLNs were developed using Dynasan-112, glyceryl monostearate and stearic acid. RC-SLNs prepared with Dynasan-112 showed below 100 nm

size with less than 0.3 PDI and -26 mV zeta potential. RC-SLNs showed more than 80% drug release in 24 h from dialysis method using 0.1N HCl followed by pH 6.8 phosphate buffer as release media. DSC and XRD studies confirmed the conversion of crystalline to amorphous state. TEM and SEM analyze the particle shape and were found to be nearly spherical in shape with increased polydispersity. The enhancement on the oral bioavailability from SLN was found to be 4.5-folds compared with suspension formulation in male albino rats. Further, pharmacodynamic studies exhibited reduced total cholesterol, LDL, VLDL and enhanced HDL levels for 36 h compared with suspension formulation⁷¹.

Simvastatin loaded solid lipid nanoparticles were prepared to improve the oral bioavailability. Glyceryl behenate and glyceryl palmitostearate used as solid lipids containing Tween 80 as surfactant. Entrapment efficiency and size of the particles were more than 96% and below 200 nm respectively. The electron micrographs indicated that lipid nanocarriers were almost spherical in appearance. X-ray diffraction and differential calorimetric studies proved that the drug was amorphous form in the lipid matrix. Pharmacodynamic studies of simvastatin solid lipid nanoparticles exposed superior reduction in total cholesterol values as compared to pure drug powder indicating enhanced oral bioavailability of Simvastatin⁷².

Sorafenib is poorly water-soluble drug with low oral bioavailability and reduced liver targeting property. SLNs were developed to enhance the oral bioavailability as well as liver targeting of sorafenib (SR-SLNs)⁷³. The EE and DL of SR-SLNs were 89.87 and 5.39% respectively. Particle size, PDI, and zeta potential of SR-SLNs were 77.16 nm, 0.28, and -18.1 mV, respectively. The liver-targeting and oral bioavailability results showed that the average drug selectivity index value of SR-SLNs was 2.20-times and 66.7% more than that of the SR-suspension formulation respectively, after oral administration to male Wistar rats (7.5 mg/kg).

Altretamine-loaded solid lipid nanoparticle (AL-SLNs) was developed by using Box-Behnken design to improve the oral absorption. The SLNs were evaluated for mean particle size, entrapment efficiency, and drug-loading. The optimized formulation, with a desirability factor of 0.92, was selected and characterized. *In vitro* release studies showed a biphasic release pattern from the SLNs for up to 24 h. The results of % EE (93.21 ± 1.5), %DL (1.15 ± 0.6), and mean diameter of (100.6 ± 2.1) nm, were very close to the predicted values⁷⁴.

Narendar and Karthik, developed the solid lipid nanoaprticles of zolpeplon to improve the oral bioavailability using response surface methodology⁷⁵. The prepared ZL-SLNs were spherical in shape with increased PDI after lyophilization. ZL was converted to amorphous form when loaded in SLNs, which was confirmed by DSC and XRD studies. Drug release was continued for more than 24 h through dialysis method. *In vivo* studies after oral administration of SLNs showed around 2.5-folds improvement in bioavailability compared with pure drug coarse suspension in rats.

Madhu et al., developed the lyophilized raloxifene hydrochloride (RH) solid lipid nanoparticles to improve the oral bioavailability due to its poor bioavailability⁷⁶. RH-SLNs were prepared using triglycerides as solid lipids and characterized for optimized system based on particle size, entrapment efficiency and zeta potential. Further, converted to powder form by subjecting to freeze drying. RH loaded into converted to amorphous form confirmed by DSC and XRD studies. *In situ* intestine perfusion studies exhibited

more drug permeation in GIT of rat. *In vivo* pharmacokinetic study evidenced for improved oral bioavailability of RH from SLNs, after oral administration to rats and compared with suspension as control.

CONCLUSIONS AND FUTURE PERSPECTIVES

Poor bioavailability of drugs is a major limitation in successful drug delivery by oral route of administration. Abundant research developments are in progressive, especially with novel delivery approaches and nano carriers is focused on enhancement of oral bioavailability of poorly absorbed drugs. Further, it is important to understand the purpose for the poor bioavailability before outlining delivery systems. The positive outcomes got with the utilization of different delivery systems or diverse methodologies of bioavailability improvement appear to guarantee. Accordingly, the commercial improvement of the SLN delivery systems significantly requires more research for overcome the difficulties; for example, scale up, cost viability and unsteadiness of a portion of the details. Various methods have been developed with a focus on enhancement of the scale up and manufacturing errors limitations. To complete development works within a limited amount of time, the establishment of a SLN strategy should be one of the best approach for the pharmaceutical development of poorly water-soluble drugs.

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