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Review Article

Case studies of enhanced pharmacodynamic activity of poorly oral bioavailable drugs via solid lipid nanoparticles

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Abstract

Solid lipid nanoparticles (SLNs) considered as an alternative vehicle for the enhanced oral absorption of drugs, and also to enhance therapeutic effectiveness after oral administration. Pharmacodynamic activity of drug is mainly describes the pharmacological and therapeutic activity of drug to the biological system. Lipid nanoparticles especially SLNs made of physiological inert lipid molecules and helps the lymphatic transport. Numerous literatures is available on the effect of SLNs and other colloidal carrier systems on the pharmacokinetic activity of poorly bioavailable drugs, to improve their oral absorption and also respective mechanisms for the improved oral bioavailability. However, very few literatures is reported on the pharmacodynamic activity and the effect of dose on the pharmacodynamic activity. Therefore, the current review is mainly dealing with the effect of SLNs on the pharmacodynamic activity discussed.

Keywords: Oral absorption, solid lipid nanoparticles, lymphatic transport, pharmacokinetics, pharmacodynamics.

INTRODUCTION

In general, drugs with low water solubility, difficulty in formulation development as conventional dosage forms, as they existent problems such as slow onset of action, low oral bioavailability, shortage of dose proportionality, failure to attain stable plasma levels (steady state concentration), and dislikable side effects¹⁻⁴. New approaches are developed and reported to enhance the oral bioavailability therapeutic efficiency by gastro retentive delivery⁵⁻¹⁰, through permeation by buccal delivery¹¹⁻¹⁴, solubility by complexation and liquisolid compacts¹⁵⁻¹⁷, osmotic drug delivery^{18,19}, transfersomes^{20,21}, colon delivery²², alternative delivery systems^{23,24} etc. Administration by the oral route of the drug is most prevalent strategy for drug transport. Regardless of the fame and flexibility of the oral course, huge issues endure. Not all drugs have the physical, chemical or biological qualities essential for the effective treatment by oral delivery²⁵. Issues, for example, poor solubility or chemical stability of the gastrointestinal tract, poor porousness through the organic films or affectability to digestion are outstanding to bring about the dismissal of potential medication hopefuls as useful items^{26,27}. Lipid based drug delivery have been proposed as a method for bypassing some of safer drugs or physical obstructions related with inadequately effectiveness of drugs^{28,29}. These potential drug deliveries incorporate the more traditional structures, for example, emulsions and microemulsions, and in addition later ones, for example, liposomes, microspheres, solid lipid

nanoparticles (SLNs)³⁰⁻³³ and nanostructured lipid carriers (NLC)³⁴⁻³⁸ and also reduction of particle size (nanosuspension)³⁹⁻⁴¹ to improve the oral bioavailability.

Lipid nanoparticles such as SLNs are emerging as alternative carriers to colloidal drug systems, for controlled systems and targeted delivery. These are in submicron size range (50-1000 nm) and are made of biocompatible and biodegradable materials capable of incorporating both lipophilic, hydrophilic drugs, protein delivery^{42,43} and also surface modification for enhanced delivery and stability⁴⁴. SLNs combine the advantage of different colloidal carriers, for instance, like emulsions and liposomes, these are physiologically acceptable and like polymeric nanoparticles, controlled release of drug from lipid matrix can be anticipated^{45,46}.

SLNs are particles made from solid lipids (i.e., lipids solid at room temperature and also at body temperature) and stabilized by surfactant(s). By definition, the lipids can be highly purified triglycerides, complex glyceride mixtures or even waxes. Through the work of various research groups, the SLN carrier system has been characterized intensively in various applications also⁴⁷⁻⁵¹.

Great progress has been made in the treatment of a variety of diseases by using drug delivery systems including solid lipid nanoparticles (SLN). Controlled drug delivery, enhancement of bioavailability of entrapped drugs via modification of dissolution rate⁵²⁻⁵⁴ and/or improvement of tissue

distribution and targeting of drugs⁵⁵⁻⁵⁸ by using SLNs and NLCs have been reported.

Extensive literature was reported in the development of drug loaded SLNs and NLCs to improve the oral bioavailability of poorly soluble and absorbable drugs⁵⁹⁻⁶². But, there is no specific review reported on the pharmacodynamic activity of SLNs reported. Therefore, in this review, mainly discuss about the pharmacodynamic effect of drug loaded SLNs of low bioavailability drugs.

CASE STUDIES

Simvastatin solid lipid nanoparticles

Simvastatin (ST) is a lipid lowering drug with low oral bioavailability of about 5%. The poor bioavailability

constraint requires the development of efficient delivery system, which could improve the oral absorption and transport of ST. ST-SLNs are prepared using homogenization method, employed Compritol and Precirol as solid lipids, Tween 80 as surfactant. The mean particle size, zeta potential (ZP), entrapment efficiency (EE) was observed to be below 200 nm, 96% and -25 mV respectively. The pharmacodynamic study of ST-SLNs is conducted in wistar rats at a dose of 0.1 mL in 1 g/kg of poloxamer F-127 solution induced hyperlipidemia. From the results, the formulation of ST reduced the total cholesterol, low density lipoproteins and increased high density lipoproteins compared with drug suspension⁶³. List of various drugs loaded SLNs on pharmacodynamic activity showed in Table 1.

Table 1: List of drugs loaded solid lipid nanoparticles on pharmacodynamic effect up on oral administration

Drug	Animal	Inference	Ref
Simvastatin	Female Sprague Dawley rats	Decrease in TC, LDL and increase in HDL	63
Nisoldipine	Wistar male rats	Reduced systolic blood pressure upto 36 h	64
Galantamine	Rats	Memory restoration	66
Candesartan cilexetil	Wistar male rats	Systolic blood pressure decreased upto 48 h	67
Dexamethasone- cholesteryl butyrate	Mice	additive anti-inflammatory	68
Isradipine	Wistar male rats	Reduced blood pressure	70
Rosuvastatin calcium	Rats	Reduced TC and LDL levels, increased HDL levels	69

Nisoldipine solid lipid nanoparticles

Kishan and his team mainly research focus on the pharmacokinetic and pharmacodynamic effect of drug loaded SLNs, SEDDS and nanoemulsions to tumor targeting. Same group also reported the nanodelivery systems of some drugs to improve the oral bioavailability⁶⁴. Initially, Nisoldipine (ND) loaded SLNs were developed and reported. ND is a calcium channel antagonist, used for the treatment of hypertension. The oral bioavailability of ND is only about 5% due to poor water solvency and also presystemic metabolism in gut wall. Therefore, an attempt was made to develop ND loaded SLNs (ND-SLNs) to enhance oral absorption using central composite design. ND-SLNs showed mean particle size of below 100 nm, PDI of 0.23, ZP of -25 mV and EE of 91%. Pharmacodynamic studies were conducted in male wistar rats in fructose induced hypertensive rats. The rats treated with 10 mg/kg of statistically optimized ND-SLNs in comparison with pure drug suspension. Reduced systolic blood pressure was observed up to 36 h in SLN treated group, whereas suspension group showed up to 12 h. Therefore, the bioavailability of ND was improved by using SLNs delivery system⁶⁵ (Narendar and Kishan, 2015).

Galantamine solid lipid nanoparticles

Medhi et al., investigated Galant amine loaded solid lipid nanoparticles (GM-SLNs) to improve the oral bioavailability and also memory function in amnesia induced mice⁶⁶. GM-SLNs were prepared by employing microemulsion method. Prepared SLNs have the particle size of below 100 nm with EE 83.4 ± 0.6%. Further, pharmacodynamic activity of the GM-SLNs were evaluated for brain targeting and memory enhancement in isoproterenol-induced amnesic rats using Morris water maze test. From the pharmacodynamic results,

noticed that enhanced or restoration of cognition function in memory loss rats, which is statistically significant.

Candesartan cilexetil solid lipid nanoparticles

Dudhipala and Veerabrahma, developed the candesartan cilexetil (CC) loaded solid lipid nanoparticles to prolong the drug release with improved pharmacokinetic and pharmacodynamic activity⁶⁷. CC belongs to BCS class II drug with poor oral bioavailability, hence, prone to improve the oral transportation using SLNs delivery system. CC-SLNs were prepared using hot homogenization coupled with sonication technique. Solid lipids, surfactant and cosurfactant selected for the making of SLNs are triglycerides (dynamisan 114, 116 and 118), egg lecithin and poloxamer 188 respectively. From the physical characteristics and in vitro release studies, optimized SLNs were identified. DSC and XRD studies revealed the conversion of crystalline to amorphous form of CC in SLN formulation. Particle size of the SLNs was nearly spherical in shape with increased polydispersity, performed by SEM and TEM analysis. Pharmacodynamic study of SLNs are conducted in fructose (10% w/v) induced hypertensive wistar rats at a dose of 10 mg/kg. CC-SLNs showed reduction blood pressure immediately and continued for up to 48 h. Hence, the results successfully demonstrate the role of SLNs as oral bioavailability enhanced carrier.

Dexamethasone cholesteryl butyrate solid lipid nanoparticles

Combination of dexamethasone cholesteryl butyrate loaded solid lipid nanoparticles (DC-SLNs) were prepared and characterized for enhanced anti-inflammatory activity. DC-SLNs were prepared by hot micro emulsion method. The pharmacodynamic activity of SLNs is tested by 4% (w/v) dextran sulfate sodium salt in mice. From the results, DC

nanoformulation administration was able to achieve a significant cytokine decrease compared to the cytokine plasma concentration of the untreated mice with dextran sulfate sodium-induced colitis. Specifically, DC-SLN induced a IL-1 β plasma concentration of 61.77% \pm 3.19%, whereas D or C used separately induced a concentration of 90.0% \pm 2.8% and 91.40% \pm 7.5%, respectively; DC-SLN induced a TNF- α plasma concentration of 30.8% \pm 8.9%, whereas D or C used separately induced ones of 99.5% \pm 4.9% and 71.1% \pm 10.9%, respectively⁶⁸.

Rosuvastatin calcium

Narendar and Kishan, also studied the effect of rosuvastatin calcium (RC) loaded SLNs on pharmacokinetic and pharmacodynamic activity, as a vehicle for improved oral absorption⁶⁹. RC-SLNs were prepared with dynasan 112, stearic acid and glyceryl monostearate. Previously, RC-SLNs also developed with triglycerides (dynasan 114, 116 and 18)⁶. In order to reduce the manufacturing cost, monoglycerides and triglyceride with low cost were used. RC-SLNs with dynasan 112 showed particle size, PDI, ZP and EE of below 75 nm, 0.23, -26 mV and 93%, respectively. Pharmacodynamic studies were conducted in wistar rats at a dose of 10 mg/kg. The hyperlipidemia in rats was induced by intraperitoneal injection of Triton-X-100 (100 mg/kg) in normal saline solution. RC-SLNs showed statistically significant reduction in the serum total cholesterol, low density lipoproteins, and slight increase in high density lipoproteins. These levels of changes were continued for 36 h and 24 h in RC-SLNs and RC suspension treated group respectively. Thus, RC oral bioavailability was enhanced by making in to SLN delivery system.

Isradipine solid lipid nanoparticles

Isradipine (ID) have the oral bioavailability of about 5% due to poor aqueous solubility and chemical instability. Therefore, SLNs of ID were developed to enhance the oral transport by avoiding first-pass metabolism too. ID-SLNs were prepared with probe sonication method. Prepared SLNs evaluated for optimized system with good stability properties. Pharmacodynamic studies in rats exhibited declined levels of systolic blood pressure in fructose induced hypertension model⁷⁰.

Conclusion and future prospective

Solid lipid nanoparticles are very multifaceted structure with distinguishable advantages and disadvantages related to other colloidal carriers. Due to the stability and drug expulsion problems of SLNs, the NLCs were emerge., SLNs offering virtuous release profile and it is made them widespread in nano pharmaceutical research field and other applications such as food and bioactive delivery. SLNs are produced with stable and reproducible properties by using known techniques. SLNs provides the enhanced pharmacodynamic effect in the preclinical studies in poorly oral absorbable drugs. The research on going on SLNs as well as of commercialization is possible and practicable in the laboratory and on the large scale. Additional efforts are needed to confirm the pharmacokinetic and pharmacodynamics of SLNs in human population and also in clinical point of view.

DECLARATION OF INTEREST

Author declares no conflict of interest.

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