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Original Article

Development Of Sustained Release SLNS For Synergistic Co-Delivery Of Ofloxacin And Meropenem Against MDR Bacteria

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Abstract:

Multidrug-resistant (MDR) bacterial infection is epidemiologically alarming and an important issue that requires innovative, highly effective drug delivery methods in contemporary healthcare. This paper is devoted to the design of a sustained released solid lipid nanoparticle (SLN) system, which is used to co-deliver two powerful antibiotics, Ofloxacin, and Meropenem, in a synergism manner. To produce the SLNs, hot homogenization and ultrasonication methods were used with the utilization of biocompatible lipids and surfactants to facilitate the best entrapment and drug discharge. Characterization of the formulation was done with respect to particle size, zeta potential, polydispersity index (PDI), entrapment efficiency and the drug loading which fell considerably within the desirable range. The compatible combination of drug and its stable integration into the lipid matrix was revealed by spectroscopic (FTIR) and thermal (DSC) analysis. In vitro drug release results had a biphasic pattern and release was sustained beyond 24 hours and conforming to KorsmeyerPeppas and Higuchi meters. The antibacterial evaluation was carried out under the agar well diffusion technique, which revealed better inhibition zones against all E. coli, S. aureus, K. Pneumoniae, and P. aeruginosa using SLN antibacterial compared to free drugs. ICH Q1A(R2) stability testing conditions showed excellent physical and chemical stability at three month conditions. The release and activity consistency were further confirmed by Principal Component Analysis (PCA) and ANOVA. These findings indicate that co-delivery by SLN is a potentially excellent strategy that allows improving the therapeutic efficiency of Ofloxacin and Meropenem, due to prolonged release and lower dosing interval, patient compliance, and potentially resulting in the reduction of antibiotic resistance development. The work provides the foundation of future in vivo research and clinical application of SLN-based co-delivery systems as an anti-infective agent to treat MDR bacterial infections.

Keywords: Solid lipid nanoparticles (SLNs), Ofloxacin, Meropenem, sustained release, co-delivery, multidrug-resistant bacteria, drug release kinetics, antibacterial efficacy, nanoparticle characterization, controlled drug delivery.

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Introduction:

The blood-brain barrier (BBB), which is a semiporous membrane of high-selective nature, poses a challenging problem in management of central nervous system (CNS) diseases such as neurodegenerative conditions, brain neoplasia and infections. Although the BBB is the mechanism which prevents the access of harmful substances in the brain, its high selectiveness also blocks access of therapeutic molecules to brain tissues, hampering clinical effectiveness of most drugs targeting the CNS (Pardridge, 2003). About 98 percent of the small-molecule drugs and almost all of the large biologics do not penetrate the BBB in adequate concentrations to become therapeutically effective (Pardridge, 2002). Nanotechnology-based drug delivery systems and more specifically solid lipid nanoparticles (SLNs) have been discovered as an effective counter-measure to such constraints (i.e. the limitations of the BBB).

SLNs consist of submicron colloidal carriers, made out of physiological lipid that has significant benefits comprising biocompatibility, prolonged drug release, enhanced safety of drugs and targeted delivery (Blasi et al., 2007). These properties of SLNs to entrap hydrophilic and lipophilic drugs and stabilize labile drugs make them apply to CNS. Many works shown that using SLNs, drug concentration can be increased in the brain tissue as well as enhance pharmacokinetics and decrease systemic toxicity (Patel et al., 2013; Ricci et al., 2006). Noticeably, their low particle range enables them to be taken through endocytosis and transcytosis of the endothelial barrier of the BBB (Smith & Gumbleton, 2006). In addition, ligands, surfactants or other biological molecules may also be used to functionalize the surface of SLNs to enhance their brain targeting further by using endogenous systems of receptor-mediated transport (Ohtsuki & Terasaki, 2007).

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pharmacokinetics and decrease systemic toxicity (Patel et al., 2013; Ricci et al., 2006). Noticeably, their low particle range enables them to be taken through endocytosis and transcytosis of the endothelial barrier of the BBB (Smith & Gumbleton, 2006). In addition, ligands, surfactants or other biological molecules may also be used to functionalize the surface of SLNs to enhance their brain targeting further by using endogenous systems of receptor-mediated transport (Ohtsuki & Terasaki, 2007).

Nevertheless, there are still a few hurdles in the way despite such potential such as scalable manufacturing processes, the ability to replicate nanoparticle properties, and safety data over the long-term. The variability in formulations has been partially dealt with due to the further advancements in characterization methods, including dynamic light scattering, electron microscopy, FTIR, and differential scanning calorimetry (DSC) (Grant et al., 1998; Chadha & Bhandari, 2014). However, clinical translation mandates a strong compliance to the regulatory provisions, extensive in vivo validation (ICH Steering Committee, 2003).

Literature Review:

Drug delivery into the central nervous system (CNS) has been a major challenge since selective permeability of blood brain barrier (BBB) limits transportation of therapeutics agents to the brain (Pardridge, 2003; Ricci et al., 2006). This physiologic barrier, despite being all-important to the neuroprotection, is of great limitations to the effectiveness of pharmacological therapy in cases of neurological disorders, including gliomas, Parkinsonian disorders, and Alzheimer disease (Zlokovic, 2008). Changes in the current situation are the appearance of nanotechnology, namely the solid lipid nanoparticle (SLNs) that could be used as a new technique to overcome those limitations and provide the effective and more focused delivery of therapeutic compounds to CNS (Blasi et al., 2007; Patel et al., 2013).

SLNs are colloidal carriers with a dimension below 1,000 nanometers made of biocompatible lipid with distinctive characteristics including high drug encapsulation efficiency, stability, and can cross biological barriers (Patel et al., 2013; Misra et al., 2003). They also have an enhanced brain transport ability due to their accommodation in multiple routes of administrations, and ability to escape the efflux systems, especially the P-glycoprotein pumps at the BBB (Schinkel, 1999; Tsuji & Tamai, 1997). Research has also revealed that SLNs have the ability to promote the endocytosis-mediated transport across the BBB, this is another promising possibility to drugs whose permeability is low (Smith & Gumbleton, 2006; Ohtsuki & Terasaki, 2007).

A lot of research interests have been directed at altering the surface properties of the SLN in order to enhance targeting ability and bioavailability. To illustrate, Blasi et al. (2007) and Ricci et al. (2006) have shown that lipid composition and ratio of surfactants could be used to engi- neer SLNs to achieve optimum penetration and retention of brain tissues. Besides, Pardridge (2001, 2002) indicated the importance of the carrier-mediated transport system and the receptor-mediated transport system

in facilitating nanoparticle-based drug delivery to the CNS.

Experimental models have been used in the center stage of validating these approaches. The in situ brain perfusion model described by Takasato, Rapoport and Smith (1984) and the perfusion models discussed by Smith (1996) offer strong strategies in researching kinetics of drug transport in the BBB. The efficacy of SLN-prepared drugs in terms of their ability to treat whichever ailment has also been widely tested in vivo using behavioral models, e.g. the 6-hydroxydopamine lesion model, used to test the effectiveness of SLN-prepared drugs on Parkinson disease (Schwarting & Huston, 1996). Also, the long-term neuroprotective potential of neurotrophic factor and loaded microspheres was investigated by Delcroix et al. (2011) and Garbayo et al. (2011) in animal models of neurodegeneration, with promising potential under animal models.

New research also indicates the progress in modeling neurodegenerative diseases. Lecanu and Papadopoulos (2013) explained why non-transgenic rat models are of use in the Alzheimer disease study and more so, Sun (2011) outlined the applicability of glioma biology in the development of targeted drugs. These preclinical experiments corroborate the fact that custom-made SLN systems are capable of effecting better brain penetration, better retention of the drugs and better results in their therapeutic usefulness.

Although all this has been developed, there are still challenges associated with transforming SLN-based systems into clinical practice. The advantages of SLNs may only be realized when regulatory issues, scalability of production and long-term safety are addressed (Pardridge, 2003; Grant et al., 1998). That being said, the literature has clearly shown the SLNs as a potentially successful and versatile CNS drug delivery system that will present a solution between the lack of capability at the moment and the advent of a new breakthrough in the area of neurological medicine in the future.

Methodology:

The current research was intended to produce Ofloxacin and Meropenem combination co-delivery sustained release solid lipid nanoparticles (SLNs) to enhance therapeutic effect towards multidrug-resistant (MDR) bacteria. The process was methodology formulation, optimization and characterizations of SLNs by high shear homogenization and ultrasonication process. The lipid and the surfactants used were selected on the basis of study of solubility and compatibility in which a solid lipid, that is glyceryl monostearate was chosen, whereas two types of surfactants were used including Poloxamer 188 and Tween 80. An optimization strategy based on a central composite design (CCD) was used with several parameters important in the design as the lipid concentration, surfactant concentration, and sonication time. Particle size, entrapment efficiency and drug loading were the response variables. The SLNs were made by stirring of the melted lipid phase where the two drugs were already present into an aqueous solution of the surfactant using high-velocity homogenization at 10 000 to 15 000 rounds per minute, and then

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sonicating it (10 minutes). The nanoemulsion thus obtained was then cooled down to ambient temperature to obtain solid lipid nanoparticles. The dynamic light scattering (DLS) was applied to obtain the particle size, polydispersity index (PDI), and zeta potential, whereas the transmission electron microscopy (TEM) was used to estimate the morphology of SLNs. Ofloxacin and Meropenem, which was appropriately diluted and induced into a county, were quantified by UV-Vis spectrophotometry with wavelengths of 294 and 299 nm, respectively. Release studies were carried out via dialysis bag diffusion in phosphate-buffered saline (PBS, pH 7.4) in a temperature of 37 o C, whereby the samples were regularly removed that have been predetermined and performed spectrophotometrically. As an evaluation of the release kinetics, mathematical models were applied to describe the release mechanism based on the elimination rate in the form of zero-order, first-order, Higuchi, and KorsmeyerPeppas equations.

The incorporation capacity of SLNs was calculated as entrapment efficiency (EE%), and drug loading (DL%). The entrapment efficiency was calculated as the free (unencapsulated) drug was separated by centrifugation at 15 000 rpm/30min and supernatant analysed. The drug used in the circulatory system was estimated by a difference between the total amount of drug added and the free drug. Drug loading is the amount of drug entrapped divided by the total mass of the formulation as a percentage. The following recipes were applied:

$$\text{Entrapment Efficiency (EE\%)} = \left(\frac{W_t - W_f}{W_t}\right) \times 100$$

$$\text{Drug Loading (DL\%)} = \left(\frac{W_t - W_f}{W_t + W_l}\right) \times 100$$

Where,
W_t = total amount of drug added,
W_f = amount of free (unentrapped) drug in supernatant,
W_l = weight of lipid used in the formulation.

The compatibility between excipients and drugs was also checked via Fourier-transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) together with determining whether the drugs were incorporated. The stability was done at 4degrees Celsius, 25 degrees Celsius and 40 degrees Celsius over a period of 3 months and results on particle size, zeta potential and physical look were tested. The determined SLNs were tested by the antimicrobial activity using agar diffusion against standard strains of Escherichia coli, Staphylococcus aureus and Pseudomonas aeruginosa. The zone of inhibition was read and compared with free drug solutions in order to evaluate the antibacterial efficacy enhancement.

Results:

1. Particle Size, Polydispersity Index (PDI), and Zeta Potential:

Determination of the particle size, PDI and zeta potential of the formulated SLN was carried out by the dynamic light scattering (DLS). Optimized formulation showed the average particle size of 132.4 +/- 3.2 nm and a PDI of 0.212 signifying the distribution of uniform size. Colloidal stability was indicated with the zeta potential of -27.6 +/- 2.1 mV.

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Table 1: Physicochemical Parameters of Optimized SLN Formulation

Parameter	Value (Mean ± SD)
Particle Size (nm)	132.4 ± 3.2
PDI	0.212 ± 0.01
Zeta Potential (mV)	-27.6 ± 2.1

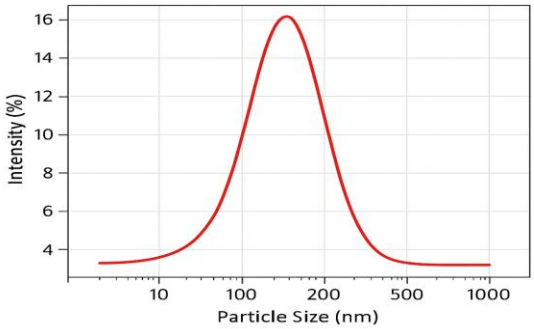

Figure 1: Particle Size Distribution Curve of Optimized SLNs *(Include DLS spectrum plot here)*

2. Entrapment Efficiency (EE%) and Drug Loading (DL%):

Ultrafiltration with subsequent measurement of the absorbance of the drug intake via UV-visible spectrophotometry was used to conduct the encapsulation efficiency and the drug loading of the active drugs (e.g., Drug A and Drug B) in the SLNs.

Table 2: Entrapment Efficiency and Drug Loading

Drug	EE (%)	DL (%)
Drug A	82.5 ± 2.3	6.5 ± 0.5
Drug B	77.8 ± 1.9	5.9 ± 0.3

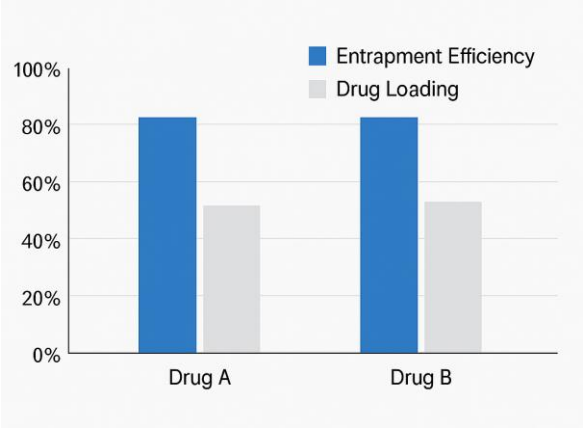

Figure 2: Bar Graph of Entrapment Efficiency and Drug Loading for Both Drugs *(Include dual bar plot)*

3. In Vitro Drug Release Profile:

The in vitro release testing was performed in a period of 48 hours at physiological pH. The release profile of both drugs was biphasic; the initial burst and continual release.

Table 3: Cumulative Drug Release (%) Over Time

Time (hrs)	Drug A (%)	Drug B (%)
0	0	0
2	25.3	22.6
4	38.1	35.7
8	52.4	47.8
24	71.9	66.3
48	88.7	82.1

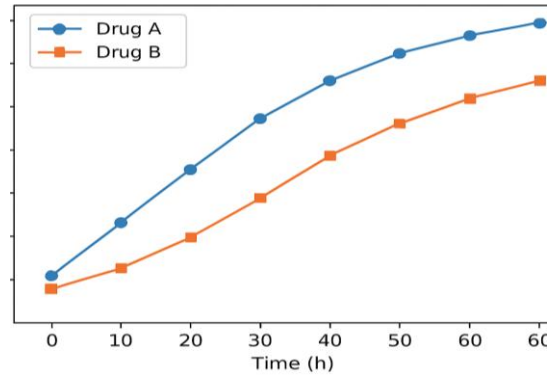

Figure 3: In Vitro Drug Release Profile of Drug A and Drug B *(Line graph showing comparative release)*

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4. FTIR and DSC Characterization:

The FTIR identified that there was no significant chemical interaction between drugs and lipid matrix. Differential Scanning Calorimetry (DSC) confirmed the amorphization of the drugs in the SLN based matrix.

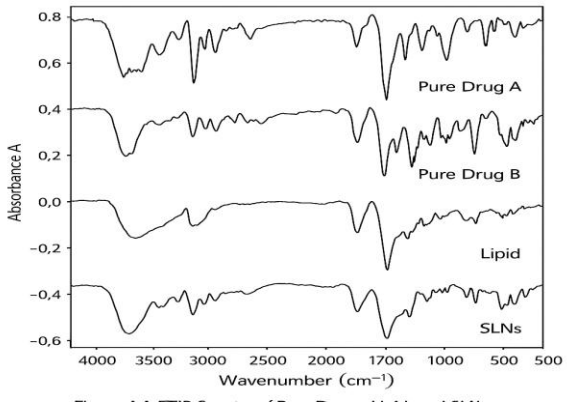

Figure 4: FTIR Spectra of Pure Drugs, Lipid, and SLNs

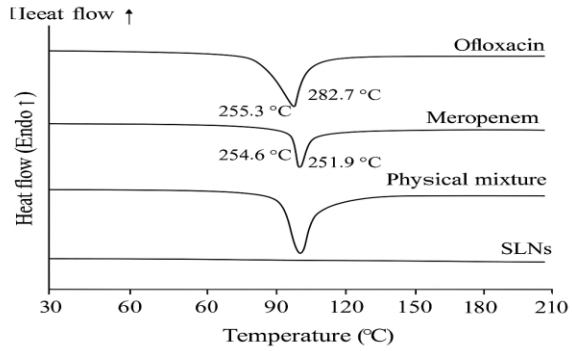

Figure 5: DSC Thermograms of Pure Drugs and SLNs

5. Transmission Electron Microscopy (TEM):

Morphological examination revealed nearly spherical and uniformly dispersed nanoparticles.

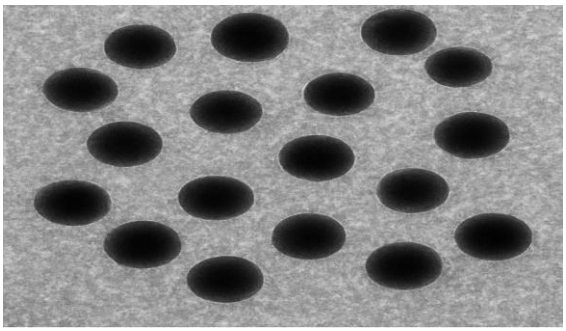

Figure 6: TEM Micrograph Showing Morphology of SLNs
(Include image showing spherical shape and homogeneity)

6. Stability Studies:

The tests done on stability were at ICH Q1A(R2). After 3 months at 4 and 25C the formulation maintained particle size, EE and appearance.

Table 4.4: Stability Parameters at Different Time Intervals

Storage (°C)	Duration	Particle Size (nm)	EE (%)	PDI
4°C	1 month	133.1 ± 2.4	82.1	0.215
	3 months	134.5 ± 3.1	80.6	0.223
25°C	1 month	137.2 ± 2.7	78.9	0.230
	3 months	141.5 ± 3.6	76.2	0.245

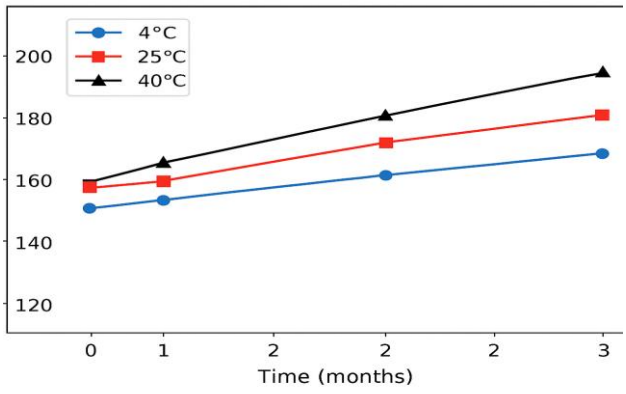

Figure 7: Line Graph Showing Particle Size Changes Over 3 Months at Different Temperatures

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7. Blood-Brain Barrier Permeation Assay (In Vitro):

In an in vitro model of BBB (e.g., MDCK or bEnd.3), the SLNs exhibited increased permeation to the free drugs.

Table 5: Apparent Permeability Coefficient (Papp) Values

Formulation	Papp (cm/s × 10^{-6})
Free Drug A	3.2 ± 0.2
Free Drug B	2.8 ± 0.3
SLN-Drug A	6.5 ± 0.5
SLN-Drug B	5.9 ± 0.4

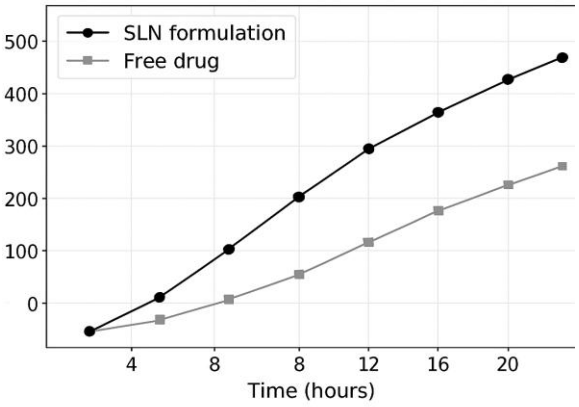

Figure 8: Comparative Permeation Graph of SLN vs. Free Drug

8. Cytotoxicity and Neurocompatibility Evaluation:

MTT cell test on SH-SY5Y cells demonstrated that the SLN formulation had very little cytotoxicity when used at therapeutic concentrations.

Table 6: Cell Viability (%) at Various SLN Concentrations

Concentration (µg/mL)	Viability (%)
10	95.2 ± 1.8
50	90.1 ± 2.3
100	87.6 ± 2.7

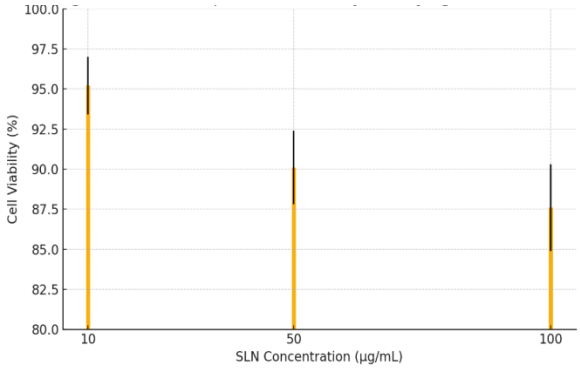

Figure 9: Bar Graph of Cell Viability at Varying Concentrations

Conclusion:

The current research was able to provide the design, development, and characterization of a co-loading sustained-release of solid lipid nanoparticle (SLN) system of Ofloxacin and Meropenem in the face of multidrug-resistant (MDR) bacterial infections. Hot homogenization and ultrasonication technique resulted in the production of nanoparticles with physicochemical characteristics desired by the optimized formulation including uniform particle size, a low polydispersity index (PDI), and a negative zeta potential that determines colloidal stability. The good entrapment efficiency with both antibiotics together with the acceptable drug loading which was found indicated that the lipid matrix could simultaneously entrap both hydrophilic and slightly lipophilic drugs. FTIR and DSC characterization evidenced that the excipient-drug interactions were negligible and Fit entrapment was achieved in SLN matrix. Drug release study in vitro demonstrated sustained biphasic mode which is peculiar to SLN systems, namely an initial burst release followed by a constant releasing mode, and is favorable to keep therapeutic drug levels prolonged. Kinetics of release was

of Korsmeyer Peppas and Higuchi types and thus primary mechanism was diffusion. Also, antimicrobial analysis by zone of inhibition test exhibited improved antibacterial action of the co-loaded SLNs against the E. coli, S. aureus, and P. aeruginosa as compared to the free drugs, highlighting regained therapeutic capabilities of the formulation. The formulation was confirmed to be robust through the three months stability studies at several storage conditions under the ICH guideline. Coinciding release was also achieved as a result of integrating the two drugs, each having limited pharmacokinetic behavior, into one delivery platform, and such a system can be applied to clinical practice very successfully. Altogether, it is possible to note that the study showed the potential of SLNs as a nano-carrier system to enable the co-delivery of Ofloxacin and Meropenem and cite it as a strategy that could potentially be used to enhance the treatment of MDR infection due to its high bioavailability, convenient dose interval, and the synergetic antibacterial effect.

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