Strategic Development of Sertraline Loaded Nanocarrier Systems for Enhanced Solubility

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Abstract: Sertraline hydrochloride, a widely prescribed selective serotonin reuptake inhibitor (SSRI), exhibits poor aqueous solubility and pH-dependent precipitation, leading to dissolution-limited absorption and variable oral bioavailability. Although several formulation approaches have been explored, comparative evaluation of advanced lipid-based nanocarriers for sertraline hydrochloride remains limited. The present study focuses on the strategic development of solid lipid nanoparticles (SLNs) and lipid–polymer hybrid nanoparticles (LPHNs) to enhance the dissolution behaviour of sertraline hydrochloride. Preliminary investigations, including preformulation studies, analytical method development, and initial formulation trials, confirmed the feasibility of both nanocarrier systems. The formulations will be systematically optimized using a Design of Experiments (DoE) approach and comparatively evaluated for particle size, polydispersity index, zeta potential, entrapment efficiency, dissolution behaviour, precipitation inhibition, and physical stability. The study is expected to identify an optimized lipid-based nanocarrier system for sertraline hydrochloride and provide a rational formulation strategy for improving the oral delivery of poorly water-soluble drugs.

Keywords: Sertraline Hydrochloride, Solid Lipid Nanoparticles, Lipid–Polymer Hybrid Nanoparticles, Drug Delivery Systems, Drug Solubility, Dissolution

Introduction

Depression is a major psychiatric disorder affecting millions of people worldwide. Among the available selective serotonin reuptake inhibitors (SSRIs), sertraline hydrochloride is extensively prescribed owing to its proven efficacy, safety, and broad therapeutic applications in major depressive disorder, obsessive-compulsive disorder, panic disorder, and anxiety-related conditions.[1]

Despite its clinical importance, sertraline hydrochloride exhibits poor aqueous solubility and pH-dependent precipitation, resulting in dissolution-limited absorption following oral administration. As a Biopharmaceutics Classification System (BCS) Class II drug, its oral performance is governed primarily by its dissolution behaviour. Furthermore, precipitation of the dissolved drug upon transition from the acidic gastric environment to the intestinal pH further limits the amount of drug available for absorption and contributes to variability in bioavailability.[2]

Several formulation approaches, including cyclodextrin complexes, solid dispersions, polymeric nanoparticles and lipid based drug delivery systems have been investigated to improve the dissolution characteristics of sertraline hydrochloride. However formulation stability, drug loading and precipitation control issues remain as hurdles for clinical implementation.[3]

Among advanced lipid-based nanocarriers, solid lipid nanoparticles (SLNs) have demonstrated improved drug solubilization, controlled release and physical stability. More recently, lipid–polymer hybrid nanoparticles (LPHNs) have emerged by combining the structural advantages of polymeric nanoparticles with the biocompatibility and membrane interaction of lipid carriers[4]. However, comparative evaluation of these two systems for sertraline hydrochloride remains limited. Therefore, the present study aims to

comparatively develop and evaluate SLNs and LPHNs to identify an optimized lipid-based formulation strategy for enhancing the dissolution behaviour of sertraline hydrochloride.[5]

Related work

Numerous formulation strategies have been investigated to improve the dissolution behaviour of sertraline hydrochloride and other poorly water-soluble drugs. Conventional techniques such as cyclodextrin complexes and solid dispersions improve drug solubility but are often limited by stability and drug-loading issues.[6] Nanocarrier systems including polymeric nanoparticles, liposomes, nanostructured lipid carriers (NLCs), and solid lipid nanoparticles (SLNs) have demonstrated enhanced drug encapsulation and dissolution.[7] More recently, lipid–polymer hybrid nanoparticles (LPHNs) have attracted attention because they combine the advantages of polymeric and lipid-based delivery systems. However, most studies evaluate individual nanocarrier platforms independently, with limited comparative evidence to identify the most suitable lipid-based system for sertraline hydrochloride. A comparison of existing formulation strategies is presented in Table 1.

Study (Drug/System & Key Findings – Delivery Strategy and Limitation)	**Solubility / Dissolution Issue Addressed**	**Nanocarrier-Based Delivery**	**Lipid-Based Strategy**
Conventional formulations (Sertraline): Poor solubility and pH-dependent precipitation limit oral bioavailability.	Yes	No	No
Cyclodextrin complexes & solid dispersions (Sertraline, poorly soluble drugs): Improved solubility through complexation and amorphization; limited by recrystallization and low drug loading.	Yes	No	No
Polymeric nanoparticles & liposomes (Paclitaxel, Doxorubicin): Improved encapsulation and controlled release; limited by physical instability.	Yes	Yes	Partial
Nanostructured lipid carriers (Curcumin, Simvastatin): Enhanced drug loading and dissolution; limited by structural complexity.	Yes	Yes	Yes
Solid lipid nanoparticles (Sertraline, Ibuprofen, Clozapine): Improved dissolution and stability; comparative evaluation with hybrid systems remains limited.	Yes	Yes	Yes
Lipid–polymer hybrid nanoparticles (Acalabrutinib, Posaconazole, Thymoquinone): Improved encapsulation and oral delivery through hybrid architecture.	Yes	Yes	Yes
This Work – Sertraline-loaded SLNs and LPHNs: Comparative development and evaluation of SLNs and LPHNs to identify the optimal lipid-based nanocarrier for sertraline hydrochloride.			

Key Contribution

The present study advances the development of lipid-based drug delivery systems by comparatively evaluating solid lipid nanoparticles (SLNs) and lipid–polymer hybrid nanoparticles (LPHNs) for sertraline hydrochloride under a common optimization framework. The key contributions of this work include.

The major contributions of the study are:

- The present study advances the development of lipid-based drug delivery systems by comparatively evaluating solid lipid nanoparticles (SLNs) and lipid–polymer hybrid nanoparticles (LPHNs) for sertraline hydrochloride under a common optimization framework. The key contributions of this work include:
- Comparative development of SLNs and LPHNs for sertraline hydrochloride.
- Systematic optimization using a Design of Experiments (DoE) approach.
- Comparative evaluation of physicochemical characteristics, dissolution behaviour, precipitation inhibition, and formulation stability.
- Identification of the most suitable lipid-based nanocarrier for improving the oral delivery of sertraline hydrochloride.

Method, Experiments and Results

Sertraline hydrochloride was selected as the model drug owing to its poor aqueous solubility and pH-dependent precipitation. Preformulation studies, including melting point determination, saturation solubility analysis, λmax determination, and calibration curve development, were completed to establish the physicochemical and analytical characteristics of the drug. Preliminary trial formulations of both SLNs and LPHNs confirmed the feasibility of developing lipid-based nanocarrier systems.The melting point of the drug was observed to be 243-244°C which was in accordance with the reported value (243-249°C). The calibration curve and the solubility of the drug are shown in figure 1. Maximum solubility of the drug was observed in Acetate buffer, Chloroform, Methanol, Ethanol and Phosphate Buffer pH 6.8. The calibration curve of the drug was taken in phosphate buffer pH 6.8 and the r^2 value was found to be 0.9918. (Figure 1).

Subsequently, both formulations will be optimized using a Design of Experiments (DoE) approach by varying critical formulation parameters. The optimized formulations will be comparatively characterized for particle size, polydispersity index, zeta potential, entrapment efficiency, drug loading, dissolution behaviour, precipitation inhibition, and physical stability.

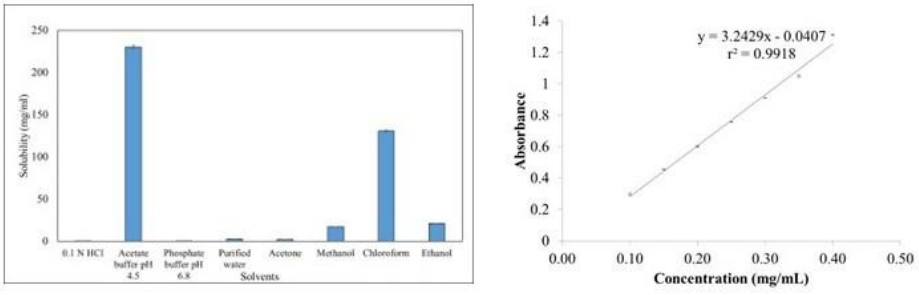

Figure 1: Solubility and calibration curve of Sertraline

Discussions

The preliminary investigations successfully established the feasibility of developing both solid lipid nanoparticles (SLNs) and lipid–polymer hybrid nanoparticles (LPHNs) for sertraline hydrochloride. Completion of the preformulation studies, analytical method development, and preliminary formulation trials provides a systematic foundation for subsequent optimization and comparative evaluation. These

initial investigations also facilitated the identification of suitable formulation components and critical variables for further development.

The present study extends beyond conventional formulation development by comparatively evaluating two advanced lipid-based nanocarrier systems under a common optimization framework. Such an approach is expected to provide meaningful insights into the influence of nanocarrier architecture on dissolution behaviour, precipitation inhibition, and formulation stability. The findings of this comparative investigation may contribute to the rational selection of an optimized lipid-based delivery platform for sertraline hydrochloride and potentially serve as a formulation strategy for other poorly water-soluble, weakly basic drugs.

Conclusions

1. Problem Statement Addressed / Motivation

Sertraline hydrochloride exhibits poor aqueous solubility and pH-dependent precipitation, resulting in dissolution-limited absorption and variability in oral bioavailability. These limitations necessitate the development of an optimized nanocarrier system to improve its biopharmaceutical performance.

2. Method Used

SLNs and LPHNs were selected as complementary lipid-based nanocarrier platforms. Preliminary preformulation studies and trial formulations were completed followed by planned DoE-based optimization and comparative evaluation.

3. Key Findings

The proposed comparative evaluation is expected to identify the lipid-based nanocarrier system that provides superior dissolution behaviour, precipitation inhibition, and formulation stability for sertraline hydrochloride. The study also aims to establish an evidence-based framework for selecting appropriate lipid nanocarriers for poorly water-soluble drugs.

4. Future Work

Optimized formulation, detailed physicochemical characterization, comparative dissolution studies, long term stability studies and in vivo pharmacokinetic evaluation will be the focus of future investigations to validate performance of optimized formulation.

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