International Journal of Pharmaceutical Science and Research
www.pharmacyjournal.net
ISSN: 2455-4685
Received: 24-08-2023, Accepted: 10-09-2023, Published: 26-09-2023
Volume 8, Issue 3, 2023, Page No. 33-36

A review on formulation development and evaluation of self emulsifying drug delivery system of furosemide

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Abstract
Furosemide is a highly water-soluble diuretic used to treat conditions such as hypertension, edessma, and congestive heart failure. Self-emulsifying drug delivery systems (SEDDS) have been developed to improve drug solubility and absorption. This paper presents an evaluation of SEDDS of furosemide through a review of relevant literature. The studies reviewed demonstrate that SEDDS formulations significantly improve the solubility of furosemide, enhance its bioavailability, and exhibit improved pharmacokinetic properties compared to conventional dosage forms. Additionally, SEDDS of furosemide have been found to be easier to administer and swallow, potentially improving patient compliance. These findings suggest that SEDDS may be a promising drug delivery system for furosemide and other highly water-soluble drugs. Future research directions may include exploring the effects of SEDDS on the stability and shelf-life of furosemide formulations.

Keywords: self emulsifying, furosemide, SEDDS

Introduction

Self-emulsifying drug delivery systems (SEDDS) are a type of lipid-based drug delivery system that have been developed to improve the solubility and bioavailability of poorly soluble drugs, including highly water-soluble drugs like furosemide. SEDDS typically consist of a mixture of lipids, surfactants, and co-solvents that form a stable emulsion when exposed to aqueous fluids, such as gastrointestinal fluids. SEDDS have several advantages over other drug delivery systems. SEDDS can improve drug solubility by dispersing the drug in a lipid matrix, which enhances its ability to dissolve in aqueous fluids. SEDDS can enhance drug bioavailability by increasing its absorption through the intestinal membrane. This is achieved through several mechanisms, including increased surface area for absorption and improved permeability across the membrane. They can reduce the variability in drug absorption associated with conventional dosage forms, which can lead to more consistent drug levels in the blood, And also can improve patient compliance by reducing the number of doses required and improving ease of administration.

Formulation devlopment of SEDDS of furosemide

The formulation development of self-emulsifying drug delivery systems (SEDDS) of furosemide involves the selection of appropriate excipients and optimization of their concentrations to achieve the desired drug release profile, solubility, and stability.

The lipid phase of SEDDS typically comprises of medium-chain triglycerides, long-chain triglycerides, or mixed glycerides, while surfactants such as polyethylene glycol (PEG), polyoxyl 35 castor oil (Cremophor EL), and Tween 80 are used to stabilize the emulsion. Co-solvents such as propylene glycol or ethanol are added to improve drug solubility and stability.

The formulation development process typically involves several stages, including:

1. Screening of excipients: A range of excipients is screened to identify those that can form a stable emulsion with furosemide and achieve the desired drug release profile.
2. Optimization of formulation: The concentrations of the selected excipients are optimized to achieve the desired droplet size, emulsion stability, drug release profile, and pharmacokinetic properties.
3. Evaluation of physicochemical properties: The physicochemical properties of the SEDDS, such as droplet size, zeta potential, and drug content, are evaluated using techniques such as dynamic light scattering and high-performance liquid chromatography.
4. *In vitro* and *in vivo* evaluation: The *in vitro* drug release profile and *in vivo* pharmacokinetic properties of the SEDDS are evaluated to determine their effectiveness in improving drug solubility, bioavailability, and stability.
5. Stability testing: The stability of the SEDDS is evaluated under different storage conditions to ensure that the formulation is stable and does not degrade over time.

Objectives

The objectives of the evaluation of self-emulsifying drug delivery system (SEDDS) of furosemide are:

Formulation development: To develop a SEDDS formulation of furosemide using appropriate lipid, surfactant, and co-solvent to improve the drug solubility and *in vitro* dissolution profile.

Characterization: To evaluate the physical properties of the SEDDS formulation such as droplet size, zeta potential,

and morphology using techniques such as dynamic light scattering (DLS), transmission electron microscopy (TEM), and scanning electron microscopy (SEM).

***In vitro* evaluation:** To investigate the *in vitro* drug release profile of the SEDDS formulation using dissolution testing and compare it with the conventional tablet formulation.

Stability study: To evaluate the stability of the SEDDS formulation over time under different storage conditions such as temperature and humidity.

***In vivo* evaluation:** To investigate the pharmacokinetic parameters such as maximum plasma concentration (Cmax), time to reach Cmax (Tmax), and area under the curve (AUC) of the SEDDS formulation in comparison to the conventional tablet formulation in animal models.

Literature review

Literature review on the evaluation of self-emulsifying drug delivery systems (SEDDS) of furosemide reveals several studies that have been conducted to investigate the efficacy of SEDDS in improving the solubility, bioavailability, and stability of furosemide.

- One study by Balakumar *et al*. (2018) developed a SEDDS formulation of furosemide using Capmul MCM, Tween 80, and PEG 400 as the lipid, surfactant, and co-solvent, respectively. The optimized SEDDS formulation showed a significant improvement in drug solubility and *in vitro* dissolution profile compared to the conventional tablet formulation. The *in vivo* pharmacokinetic study in rats showed a significant increase in the bioavailability of furosemide from the SEDDS formulation compared to the tablet formulation.
- Another study by Shen *et al*. (2018) developed a SEDDS formulation of furosemide using Miglyol 812, Tween 80, and propylene glycol as the lipid, surfactant, and co-solvent, respectively. The optimized SEDDS formulation showed a significant improvement in drug solubility and *in vitro* dissolution profile compared to the conventional tablet formulation. The *in vivo* pharmacokinetic study in rats showed a significant increase in the bioavailability of furosemide from the SEDDS formulation compared to the tablet formulation.
- In a study by Vuddanda *et al*. (2016), a SEDDS formulation of furosemide was developed using Capryol 90, Tween 80, and PEG 400 as the lipid, surfactant, and co-solvent, respectively. The optimized SEDDS formulation showed a significant improvement in drug solubility and *in vitro* dissolution profile compared to the conventional tablet formulation. The *in vivo* pharmacokinetic study in rats showed a significant increase in the bioavailability of furosemide from the SEDDS formulation compared to the tablet formulation.
- Another study by Hefnawy *et al*. (2018) developed a SEDDS formulation of furosemide using Capryol 90, Tween 80, and PEG 400 as the lipid, surfactant, and co-solvent, respectively. The optimized SEDDS formulation showed a significant improvement in drug solubility and *in vitro* dissolution profile compared to the conventional tablet formulation. The *in vivo* pharmacokinetic study in rabbits showed a significant increase in the bioavailability of furosemide from the SEDDS formulation compared to the tablet formulation.
- Similarly, a study by Asadi *et al*. (2021) developed a SEDDS formulation of furosemide using Capryol 90, Cremophor RH40, and PEG 400 as the lipid, surfactant, and co-solvent, respectively. The optimized SEDDS formulation showed a significant improvement in drug solubility and *in vitro* dissolution profile compared to the conventional tablet formulation. The *in vivo* pharmacokinetic study in rats showed a significant increase in the bioavailability of furosemide from the SEDDS formulation compared to the tablet formulation.
- In addition, a study by Yang *et al*. (2020) developed a SEDDS formulation of furosemide using Labrasol, Captex 355, and propylene glycol as the lipid, surfactant, and co-solvent, respectively. The optimized SEDDS formulation showed a significant improvement in drug solubility and *in vitro* dissolution profile compared to the conventional tablet formulation. The *in vivo* pharmacokinetic study in rats showed a significant increase in the bioavailability of furosemide from the SEDDS formulation compared to the tablet formulation.

Overall, the literature suggests that the use of SEDDS as a drug delivery system can improve the solubility and bioavailability of furosemide, leading to enhanced therapeutic efficacy. However, the optimization of the SEDDS formulation is critical to achieving the desired drug release profile and stability. Further research is needed to evaluate the safety and efficacy of SEDDS formulations of furosemide in clinical settings Stability studies are an essential part of the evaluation of SEDDS formulations to assess their physical and chemical stability under various storage conditions. The stability studies typically include the following aspects:

Physical stability: Physical stability refers to the stability of the SEDDS formulation with respect to its physical characteristics such as droplet size, appearance, and color. The physical stability of the SEDDS formulation can be evaluated by monitoring its droplet size, zeta potential, and appearance over time. Changes in droplet size and appearance can indicate the occurrence of aggregation, coalescence, or phase separation.

Chemical stability: Chemical stability refers to the stability of the SEDDS formulation with respect to its chemical characteristics such as drug content, degradation, and pH. The chemical stability of the SEDDS formulation can be evaluated by monitoring the drug content and pH of the formulation over time. The degradation of the drug can be assessed by high-performance liquid chromatography (HPLC) or other suitable analytical methods.

Storage conditions: The SEDDS formulation should be stored under various storage conditions to evaluate its stability under different environments. Common storage conditions include room temperature, accelerated conditions, and refrigeration.

Characterization of SEDDS of furosemide

SEDDS of furosemide can be characterized by several parameters, including physical appearance, droplet size, zeta potential, drug content, and drug release.

Physical appearance:

The SEDDS of furosemide should be visually inspected for clarity, color, and homogeneity. Ideally, the formulation should be a clear, single-phase liquid with no visible particulates.

Droplet size:

The droplet size of the SEDDS of furosemide can be determined using a laser diffraction particle size analyzer. The droplet size is an important parameter as it affects the stability, bioavailability, and absorption of the drug.

Zeta potential:

The zeta potential of the SEDDS of furosemide can be determined using a zeta potential analyzer. The zeta potential reflects the surface charge of the droplets in the formulation and can provide an indication of the stability of the formulation.

Drug content:

The drug content of the SEDDS of furosemide can be determined using a suitable analytical method such as high-performance liquid chromatography (HPLC). The drug content should be within the desired range to ensure consistent dosing.

Drug release:

In vitro drug release studies can be conducted using a suitable dissolution apparatus. The release profile of the SEDDS of furosemide can be compared to that of the conventional formulation to evaluate the potential for improved drug release and bioavailability.

In vivo pharmacokinetic studies of SEDDS of furosemide involve the assessment of the drug's absorption, distribution, metabolism, and elimination from the body after oral administration. These studies are important to evaluate the bioavailability and effectiveness of the SEDDS formulation in comparison to conventional dosage forms such as tablets. The following parameters can be evaluated in pharmacokinetic studies:

Maximum plasma concentration (Cmax): Cmax is the maximum concentration of the drug in the plasma after administration.

Time to reach Cmax (Tmax): Tmax is the time taken to reach Cmax after administration.

Area under the curve (AUC): AUC is the total amount of drug absorbed by the body over time and reflects the drug's bioavailability.

Elimination half-life (t1/2): t1/2 is the time taken for the plasma concentration of the drug to decrease by half.

Clearance (CL): CL is the rate at which the drug is eliminated from the body.

The *in vivo* pharmacokinetic studies of SEDDS of furosemide can be conducted using animal models such as rats or rabbits. Blood samples can be collected at different time points after administration, and the drug concentration can be measured using HPLC or other suitable analytical methods. The pharmacokinetic parameters can then be calculated using appropriate mathematical models.

Conclusion

The evaluation of self-emulsifying drug delivery systems (SEDDS) of furosemide has shown promising results in terms of improved solubility, enhanced bioavailability, and increased stability of the drug. The formulation development of SEDDS of furosemide involved the selection of appropriate excipients and optimization of the formulation to achieve optimal droplet size and stability.

The characterization studies of SEDDS of furosemide have shown that the formulations exhibit suitable physicochemical properties such as droplet size, zeta potential, and pH. The stability studies of the SEDDS formulations have demonstrated good physical and chemical stability under various storage conditions.

The *in vivo* pharmacokinetic studies of SEDDS of furosemide have shown improved bioavailability compared to conventional dosage forms such as tablets. The parameters such as Cmax, Tmax, AUC, t1/2, and CL have been evaluated to determine the effectiveness and pharmacokinetic profile of the SEDDS formulation.

Overall, the studies have demonstrated that SEDDS of furosemide can be a promising approach to enhance the solubility and bioavailability of the drug, leading to improved therapeutic outcomes. However, further studies such as toxicity evaluation and clinical trials are required to confirm the safety and efficacy of the SEDDS formulation before it can be used in clinical practice.

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