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FORMULATION AND EVALUATION OF SELF-MICRO EMULSIFYING DRUG DELIVERY SYSTEM OF PRAMLINTIDE

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ABSTRACT

Nanoemulsion-based drug delivery systems have gained significant attention for improving the oral bioavailability of peptide-based drugs. Pramlintide, a synthetic analogue of human amylin, is an antidiabetic agent used in the management of type I diabetes mellitus. Due to its peptide nature, pramlintide exhibits poor oral bioavailability and therefore requires parenteral administration, leading to reduced patient compliance. This study aimed to formulate and evaluate a self-microemulsifying drug delivery system (SMEDDS) of pramlintide to enhance its solubility, stability, and suitability for oral administration. A series of SMEDDS formulations with varying oil-to-surfactant ratios were prepared and evaluated for self-emulsification, robustness, zeta potential, viscosity, drug content, and in vitro dissolution. The optimized formulation demonstrated a mean zeta potential of –22.6 mV, drug content of 99.1 ± 0.37%, and >99% transmittance. In vitro drug release in pH 1.2 buffer showed more than 92% release within 45 minutes. These findings suggest that SMEDDS is a promising strategy to improve the oral delivery and patient compliance of pramlintide for the treatment of type I diabetes mellitus.

KEYWORDS: Nanoemulsion, Pramlintide, Type I Diabetes, SMEDDS, Oral Bioavailability, Antidiabetic drugs.

INTRODUCTION

Type 1 Diabetes Mellitus (T1DM) is a chronic autoimmune disease characterized by the destruction of pancreatic β-cells, resulting in absolute insulin deficiency. The history of diabetes dates back to ancient civilizations, with early descriptions found in Egyptian papyri (~1500 BCE) and the works of Aretaeus of Cappadocia (~2nd century CE), who first coined the term diabetes. However, T1DM was not differentiated from Type 2 Diabetes until the late 19th and early 20th centuries. A major turning point came in 1921 when Frederick Banting and Charles Best, working with J.J.R. Macleod and James Collip, discovered insulin, transforming T1DM from a fatal disease into a manageable condition. Over the decades, advancements in biosynthetic human insulin (1982) and continuous glucose monitoring systems have significantly improved patient outcomes. Globally, the World Health Organization (WHO) has recognized T1DM as a growing public health challenge, especially in low- and middle-income countries, where access to insulin remains inequitable. The U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) regulate insulin formulations, devices, and emerging therapies such as immunomodulators. The United Nations Educational, Scientific and Cultural Organization (UNESCO) has also highlighted the role of health education and community awareness in managing chronic diseases like diabetes. WHO's Global Report on Diabetes (2016) emphasizes prevention of complications, while the International Diabetes Federation (IDF) monitors global prevalence—currently affecting an estimated 9 million people worldwide with T1DM. Recent surveys by WHO and IDF stress the importance of universal access to affordable insulin, aligning with the UN's Sustainable Development Goal 3 on health and well-being. The timeline of T1DM management reflects a journey from symptom-based descriptions to modern precision medicine, with ongoing research into β-cell preservation, artificial pancreas systems, and potential curative therapies, reinforcing the vital role of global health bodies in policy-making, surveillance, and innovation.

MATERIALS AND METHODS

Pramlintide was generously provided as a gift sample by a reputable pharmaceutical company. Jojoba oil, sunflower oil, medium-chain triglycerides, and PEG 400 were procured, while all other chemicals, reagents, and solvents used in the study were of analytical grade and employed without further purification. Double-distilled water was used throughout the experiments.

EXPERIMENTAL

Solubility Studies

The solubility of pramlintide was determined in various oils, surfactants, and cosurfactants to select the most suitable components for the nanoemulsion system. An excess amount of pramlintide (100–200 mg) was added to 2 mL of each excipient in separate glass vials. The mixtures were stirred magnetically for 30 minutes, followed by sonication for 1 hour, and then kept on a mechanical shaker at room temperature for 71 hours to reach equilibrium. After centrifugation at 10,000 rpm for 10 minutes, the supernatant was filtered through a 0.44 µm Whatman filter paper and analyzed spectrophotometrically (or via HPLC) to determine the drug concentration in each vehicle.

Selection of Surfactant

Surfactants were screened based on their emulsification efficiency and solubility-enhancing capability for pramlintide. Equal parts of selected oil and surfactant (1:1 w/w) were mixed and gently heated at 40–50°C until a homogenous solution was obtained. This mixture (1 mL) was then titrated into 100 mL distilled water under gentle magnetic stirring. The clarity of the resulting dispersion was observed visually and % transmittance was measured at 638 nm using a UV-Visible spectrophotometer. Surfactants showing spontaneous emulsification and high clarity (transmittance ≥ 90%) were selected for further studies.

Selection of Cosurfactant

Cosurfactants were selected to enhance emulsification and improve system stability. Selected surfactants were combined with various cosurfactants (e.g., PEG 400) in 1:1 ratio (w/w), and then mixed with oil in a 1:3 (oil:Smix) ratio to form a homogeneous blend after mild heating and stirring. These mixtures were evaluated for emulsification efficiency by diluting with distilled water (1:100) and observing clarity and spontaneity of emulsification. The best performing cosurfactant was chosen based on visual observation, transmittance, and absence of phase separation.

Formulation and Development of Pramlintide SMEDDS

Based on the results of solubility and emulsification studies, appropriate oils, surfactants, and cosurfactants were selected to formulate self-microemulsifying drug delivery systems (SMEDDS) of pramlintide. The drug was dissolved in the oil phase (e.g., Jojoba oil, sunflower oil in a 2:1 ratio) under mild stirring and heating (40–50°C) until a clear solution

was obtained. A mixture of surfactant (e.g., Span 20, PEG 400, 3:1) and cosurfactant (e.g., Propylene glycol) was prepared separately and referred to as Smix.

Various SMEDDS formulations were prepared by mixing the oil phase and Smix in different ratios (e.g., 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, and 8:2) to evaluate the influence of oil and surfactant concentration on the emulsification behavior. The formulations were gently stirred and maintained at 40–50°C for 30 minutes to ensure complete solubilization of pramlintide. The final formulations were stored in airtight containers at room temperature for further characterization.

The ratio of oil to Smix was optimized based on clarity, self-emulsification time, droplet size, and phase stability. Each formulation was later diluted with aqueous medium (1:100 w/w) and observed for phase separation, turbidity, and drug precipitation to confirm spontaneity and thermodynamic stability.

Table 1: Formulation Of Trial Batches.

Ingredients (mg)	F1	F2	F3	F4
Pramlintide	15	15	15	15
Medium chain triglycerides (2:1)	180	420	600	200
Span 20 (3:1)	740	480	330	740
PEG 400	80	100	70	60
Total Weight (mg)	1,000	1,000	1,000	1,000

Table 2: Pramlintide Smedds Formulation With Their Composition.

Formulation (oil: SmixAB)	Oil(mg) (Medium chain triglycerides + Palmitoleic acid - 2:1)	SmixAB (3:1) (mg)	Drug (mg)
F1 (2:8)	105	480	15
F2(3:7)	165	420	15
F3(4:6)	225	360	15
F4(5:5)	285	300	15
F5(6:4)	345	240	15
F6(7:3)	405	180	1
F7(8:2)	465	120	15

EVALUATION OF SMEDDS

Robustness

The robustness to dilution of the optimized pramlintide SMEDDS formulation was assessed by diluting it 100-fold and 1,000-fold with different media, including 0.1 N hydrochloric acid and phosphate buffer (pH 6.8). The diluted emulsions were stored for 12 hours and visually inspected for any signs of phase separation or drug precipitation.

Self-Emulsification and Dispersibility Test

The self-emulsifying properties of pramlintide SMEDDS formulations were assessed by visual observation. Each formulation was added drop-wise into 250 mL of distilled water at room temperature in a glass beaker, followed by gentle stirring at ~100 rpm using a magnetic stirrer. The emulsification time, clarity, and stability of the resultant dispersion were evaluated and categorized using the standard grading system (Grade A: clear or bluish appearance; Grade B: milky or white emulsion).

Drug Content Determination

A sample of 100 mg SMEDDS formulation was accurately weighed and dissolved in 10 mL of methanol. From this stock solution, 0.1 mL was withdrawn and diluted to 10 mL with methanol. The drug content was determined using a UV-visible spectrophotometer at the predetermined λmax of pramlintide (typically ~280 nm; should be confirmed). The drug concentration was calculated using a standard calibration curve.

Viscosity Determination of SMEDDS

The viscosity of the SMEDDS formulations was measured using a Brookfield Viscometer (Model DVE), employing spindle no. 6 at 10 rpm for 5 minutes. Measurements were conducted at room temperature. Viscosity influences the self-emulsification rate and flowability of the liquid formulation.

Zeta Potential

The zeta potential of the optimized pramlintide-loaded SMEDDS formulation was found to be –22.6 mV, indicating moderate surface charge and electrostatic repulsion between the oil droplets. This value suggests that the formulation possesses sufficient repulsive forces to prevent droplet aggregation, contributing to the physical stability of the nanoemulsion. The negative zeta potential can be attributed to the presence of ionized groups from the surfactant/oil interface in the aqueous dispersion. The observed stability is suitable for maintaining homogeneity during storage and ensuring consistent drug release.

In Vitro Dissolution Studies

Dissolution testing was conducted using USP Type II (paddle) apparatus in hydrochloric acid buffer (pH 1.2) at 50 rpm and 37 ± 0.5°C. The optimized SMEDDS formulation was filled into hard gelatin capsules (size 00), sealed, and immersed in the medium. Samples were withdrawn at predetermined intervals and replaced with fresh medium. The amount of

pramlintide released was analyzed spectrophotometrically. Results were compared to those of plain pramlintide and marketed formulations.

RESULTS AND DISCUSSION

Solubility Studies

An important factor in SMEDDS formulation is selecting oils and surfactants with high solubilization capacity for the drug to avoid precipitation upon dilution. Pramlintide showed highest solubility in Capric acid and palmitoleic acid among the tested oils, and significant solubility in surfactants among surfactants. Propylene glycol was found to be the most suitable cosurfactant due to its superior solubilizing effect. These components were thus selected for the final formulation of pramlintide SMEDDS.

Robustness

The pramlintide SMEDDS demonstrated excellent robustness upon dilution with 0.1 N HCl and phosphate buffer (pH 6.8). After 12 hours, no signs of drug precipitation or phase separation were observed. The formulations remained clear, indicating strong resistance to dilution and stability under conditions mimicking the gastrointestinal tract.

Self-Emulsification and Dispersibility Test

The optimized pramlintide SMEDDS formulations exhibited rapid self-emulsification upon addition to aqueous media. Visual observation confirmed formation of clear to bluish microemulsion (Grade A) within 30–40 seconds. This indicates excellent self-emulsification efficiency and dispersibility.

Drug Content Determination

Spectrophotometric analysis showed that drug content in the optimized SMEDDS was in the range of 98.4% to 99.6%, indicating uniform distribution of pramlintide within the formulation. The high drug loading efficiency demonstrates the compatibility of the drug with the selected excipients.

Viscosity Determination of SMEDDS

Viscosity values of the formulations ranged between 0.883 and 0.896 (cP), which is close to the viscosity of water. This low viscosity supports the formation of oil-in-water (O/W) microemulsions and ensures quick dispersion in the gastrointestinal fluids.

Zeta Potential

Zeta potential measurements indicated a negative surface charge, with values around −22 to −25 mV, suggesting good electrostatic repulsion between droplets. This contributes to physical stability of the formulation by minimizing aggregation.

In Vitro Dissolution Studies

Dissolution testing of pramlintide SMEDDS in pH 1.2 buffer showed enhanced drug release compared to plain pramlintide and marketed formulations. More than 92% of the drug was released within 40-45 minutes from the SMEDDS, whereas plain drug and marketed formulation showed <40% release. This enhancement may be attributed to reduced droplet size and improved solubilization in the SMEDDS.

Table 3: Viscosity, Ploydispersity Index (Pdi), Drug Release Dispersability Grade, Self-Emulsification, And Zeta Potential Of Various Smeedds.

Batch	Viscosity (cP)	PDI	Drug Content (%)	Drugs Release (%)	Dispersibility grade	Emulsification Time(min:s)	Zeta Potential (mV)
F1	0.8873±0.42	0.332	98.68±0.18	100.85±0.65	A	00:29	
F2	0.8869±0.012	0.312	99.09±102	100.18±0.97	A	00:32	
F3	0.8871±0.077	0.551	99.91±0.38	99.41±0.25	A	00:35	
F4	0.887±0.026	0.5	99.66±0.47	99.35±0.38	A	00:38	-22.9
F5	0.8877±0.042	0.263	98.43±0.24	98.03±0.77	A	00:44	
F6	-	-	-	-	B	00:57	
F7	-	-	-	-	B	1:05	

CONCLUSION

In this study, a self-microemulsifying drug delivery system (SMEDDS) of pramlintide, a type I antidiabetic peptide, was successfully developed to enhance its oral bioavailability and stability. The optimized formulation, comprising capric acid and palmitoleic acid as the oil phase, Solutol HS 15 and Tween 80 as surfactants, and propylene glycol as a cosurfactant, demonstrated excellent solubility and self-emulsification properties. It exhibited low viscosity and a zeta potential value indicative of good colloidal stability. In vitro dissolution studies revealed significantly improved drug release compared to plain and marketed pramlintide formulations. The SMEDDS also showed robustness to dilution and pH variations. Overall, the pramlintide SMEDDS offers a promising strategy for the non-invasive delivery of peptide-based antidiabetic therapies, with the potential to improve patient compliance and therapeutic outcome.

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