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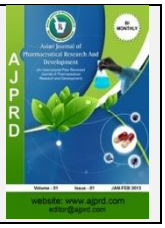

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Research Article

Formulation and Evaluation of Polymeric Micells Loaded With Antidiabetic Drug

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A B S T R A C T

Polymeric micelles have gained significant attention as nanocarriers for antidiabetic drug delivery, addressing challenges such as poor solubility and rapid clearance associated with conventional therapies.This research focuses on the formulation and evaluation of polymeric micelles encapsulating an antidiabetic agent, aiming to enhance its bioavailability and therapeutic efficacy.Micelles were prepared using amphiphilic block copolymers by thin film hydration method, with parameters such as polymer concentration, drug loading, and micelle size optimized to achieve desired characteristics.The formulations were characterized for particle size, zeta potential, drug entrapment efficiency, drug loading and in vitro release profile.The results revealed that this method is reproducible, more feasible and led to the entrapment of drug with an expected sustained release. The nanoparticle precipitated was with particle size of 192.7 nm, zeta potential of −21.72 mV. The entrapment efficiency noted was 36.12. In vitro release was about 11.33 % release in 6 h. When the regression coefficient values were compared, it was observed that 'R2' values of first order was maximum i.e. 0.9806 hence indicating drug release from formulation was found to follow first order release kinetics. Antidiabetic drug-loaded polymeric micells may be a good choice for the improvement of solubility, bioavailability and reduction in toxicity. This research underscores the efficacy of polymeric micelles as a viable strategy for the controlled delivery of antidiabetic drugs, offering a promising approach to improve patient compliance and therapeutic outcomes.

Keywords: Polymeric Micells , bioavailability, ampiphillic block copolymers, diabeties

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INTRODUCTION

In recent years, nanotechnology-based drug delivery systems have garnered considerable attention for their potential to improve the therapeutic performance of pharmaceutical agents, particularly those with poor water solubility. Among these, polymeric micelles have emerged as promising nanocarriers due to their unique structural features and favorable physicochemical properties. Polymeric micelles are nano-sized colloidal dispersions typically formed by the self-assembly of amphiphilic block copolymers in aqueous media. These micelles consist of a hydrophobic core, which can encapsulate poorly water-soluble drugs, and a hydrophilic shell that stabilizes the structure and enhances solubility in biological fluids.[1]The nanoscale size, high drug-loading capacity, and ability to passively target tissues through the enhanced permeability and retention (EPR) effect make polymeric micelles highly suitable for delivering a wide range of therapeutic agents. Additionally, polymeric micelles offer controlled and sustained drug release, improved pharmacokinetics, and reduced systemic toxicity. Among the various methods used for the preparation of polymeric micelles, the thin-film hydration method stands out due to its simplicity, scalability, and suitability for encapsulating hydrophobic drugs. This method involves the formation of a thin polymeric film followed by hydration with an aqueous phase, resulting in the spontaneous formation of micelles.[2]

Diabetes mellitus is a complex and chronic metabolic disorder characterized by sustained elevation in blood glucose levels. It results from defects in insulin secretion, insulin action, or both, and is associated with serious long-term complications affecting the eyes, kidneys, nerves, and cardiovascular system. Type 2 diabetes mellitus (T2DM), the most prevalent form, is commonly managed with oral

hypoglycemic agents, among which DPP-4 inhibitors play a crucial role. These agents enhance the body's natural ability to regulate blood glucose by prolonging the activity of incretin hormones.[3]

Linagliptin, a DPP-4 inhibitor, is effective in improving glycemic control in patients with T2DM. However, its clinical application is limited by poor aqueous solubility and variable bioavailability, which can affect therapeutic outcomes. To address these limitations, the use of nanocarrier systems such as polymeric micellesoffers a viable strategy to enhance the solubility, stability, and delivery of linagliptin.[4]

Linagliptin-loaded polymeric micelles represent a significant advancement in the targeted delivery of antidiabetic drugs, offering enhanced therapeutic efficacy and reduced side effects. Polymeric micelles, formed by the self-assembly of amphiphilic block copolymers, provide a nanocarrier system that improves the solubility, stability, and bioavailability of linagliptin, a DPP-4 inhibitor commonly used in type 2 diabetes management. The nanoscale size of micelles allows for better penetration and retention in target tissues, potentially enabling controlled and sustained drug release.[5] This results in improved glycemic control with reduced dosing frequency, enhancing patient compliance. Furthermore, linagliptin-loaded polymeric micelles minimize systemic toxicity and protect the drug from enzymatic degradation, making them a promising platform for oral and possibly alternative routes of administration in diabetes therapy. The ability to modify surface characteristics of these micelles also opens avenues for targeted delivery, reducing off-target effects and maximizing drug efficacy.[6]

The present study focuses on the formulation and evaluation of polymeric micelles loaded with linagliptin, prepared using the thin-film hydration technique. The objective is to improve the drug's solubility and bioavailability, and to explore its potential for sustained drug release. The study involves optimizing formulation parameters, characterizing the micelles for particle size, zeta potential, drug loading, entrapment efficiency, critical micellar concentration and in vitro drug release, thereby contributing to the development of an efficient nanocarrier-based delivery system for antidiabetic therapy.[7]

MATERIAL AND METHODS

Materials:

Linagliptin and polaxomer188 was gifted by alvita pharma pvt. Ltd. Mumbai, Maharashtra, india. Polaxomer 407 was purchased from SM pharma& chemicals Mumbai, Maharashtra,india. Distilled water was purchased from unique car exclusives,Amravati. Methanol was supplied by Lobachemiepvt. ltd. Mumbai.

Method of preparation for antidiabetic drug loaded polymeric micells:

Polymeric micells loaded with linagliptin was prepared by thin film hydration method. In brief, 1-10 mg of linagliptin was used for the different ratios of millimolar concentration of both the ampiphillic polymers such as 1:0, 0:1, 1:1, 1:2, 1:3, 1:4. The milimoles of the polymer concentration was calculated according to 400 mg of polymer.[8]10ml of methanol was measured and transferred to the round bottom flask. required amount of both the polymers was weighed and transferred in the round bottom flask containing methanol it, both the polymers were allow to dissolve in the methanol to form the diblock for the entrapment of drug in it. After the dissolution of both the polymer in methanol the required amount of Linagliptin was weighed and transferred in the round bottom flask. The round bottom flask then connected to the rotary vaccum evaporator after the dissolution of drug then the RBF was rotated for 1hr at 42^{o}C. The thin film was formed at the bottom of the RBF. The film was then hydrated with 10ml double distilled water. The clear solution was formed which was then filtered through whatmann filter paper and collected in closed container. The collected solution was then kept for the selfassembly of micells and then the formulation was evaluated.[9]

Characterization of polymeric micells loaded with linagliptin:

Particle Size: Size of polymeric micellswas determined using Malvern Zetasizer

Zeta Potential Determination: Surface charge of drug loaded micells was determined using Malvern Zetasizer.

Drug Entrapment Efficiency:0.1 ml of formulation was pippet out and transferred to the 10ml volumetric flask then volume was makeupto the mark with ethanolic buffer then the diluted formulation was scanned on UV spectrophotometer and the absorbance was recorded. % Entrapment efficiency was then calculated by using the following formula.

$$\% \text{ Entapment Efficiency} = \frac{\text{weight of drug in micells}}{\text{Weight of feeding drug}} \times 100$$

Drug Loading: 0.1 ml of formulation was pippet out and transferred to the 10ml volumetric flask then volume was makeupto the mark with ethanolic buffer then the diluted formulation was scanned on UV spectrophotometer and the absorbance was recorded. % Drug Loading was then calculated by using the following formula.[10]

$$\% \text{ Drug Loading} = \frac{\text{weight of drug in Micells}}{\text{Weight of feeding drug + polymer}} \times 100$$

Critical micellar concentration determination: Critical Micellar Concentration was determined by iodine probe method. CMC was determined to check the complexation of both the polymer. In these method 0.5 gm of Iodine (I2) and 1gm of Potassium Iodide (KI) was weighed accurately and dissolved in 50ml distilled water. 1ml of formulation was transferred to the test tubes and 0.2ml of iodine solution was added to it Then the test tubes were sealed. These solutions was then kept in dark room for 12 hrs then after 12 hrs the two layers was appeared From which the 1ml of supernatant was taken and diluted to10ml with ethanolic buffer. These solutions were then scanned on UV Spectrophotometer in range of 800nm –200nm by taking baseline of Ethanolic buffer. The Sharp peak was observed and the absorbance of each formulation was measured at 366nm. The graph was plotted as absorbance vs. log polymer mass of selected batch, the sharp peak was observed at which the CMC was determined.[11]

In vitro drug release study: In vitro release of drug is perform to test the release of drug in certain time to observe

the release rate of the formulation. The in vitro release of the batches was performed on franz diffusion cell for 6hrs, against the dialysis membrane. The receptor chamber of franz diffusion cell was filled with ethanolic buffer solution and 1milimolar Equivalent formulation was filled in the donor chamber of franz diffusion cell and the In vitro release was performed for 6 hrs. After the each time intervals of 1,2,3,4,5, and 6 hrs the 1ml aliquots was removed and replaced with the same release media the 1ml aliquots then transferred to 10ml volumetric flask and diluted with ethanolic buffer and the absorbance was measured on UV spectroscopy for each hr. From the absorption the concentration of drug was found and the cumulative amount of drug diffuse was calculated.[12]

The release kinetics was modeled using various mathematical models such as zero-order, first order, Higuchi, or Korsmeyer–Peppas model to elucidate the mechanism of drug release.[13]

RESULT AND DISCUSSION:

Antidiabetic drug loaded Polymeric Micells were prepared by thin film hydration method. Particle size was measured using malvernzetasizer having a size of 192.7nm, and the zeta potential was measured to be −21.72 mV [Figures 1 and 2]. The polymeric micellsshows percentage entrapment of 0.366% and this may be due to the low solubility of drug. The critical micellar concentration was determined by iodine probe method and was found to be 28.3ug/ml, which is indicating the formation of micells at the determined concentration of polymer mixture as shown in fig 3. From the In vitro drug Release study polymeric micellsrelease around 11.33 % of drug at the end of 6 hours the polymeric micells releases more than 80% of drug release after 72 hrs for a sustained release. Drug release of polymeric micells was shown in fig 4.

Consequently, the mechanisms of diffusion and biodegradation are key determinants in the drug release process. Drug release study shows that the release of drug from the polymeric micells by first order (0.9806) followed by koresmayerpeppas model (0.9681), zero order model (0.8964) and Higuchi model (0.8228) as shown in table No. 1

Particle Size:

Figure 1: Particle Size of Polymeric Micells

Zeta Potential:

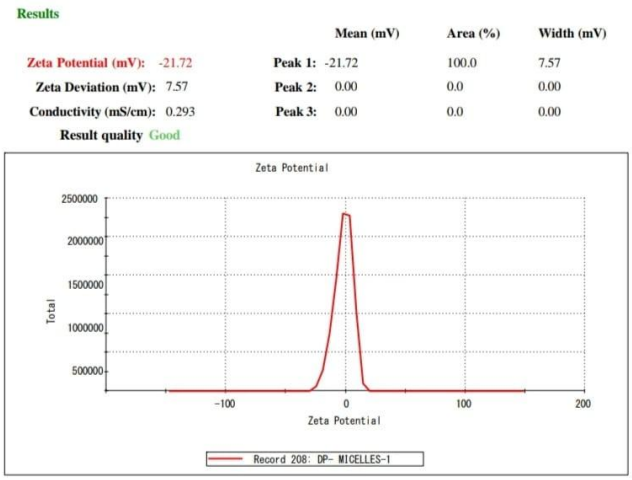

Figure 2: Zeta Potential of Polymeric Micells

Drug Entrapment Efficiency: Drug entrapment of the polymeric micells was calculated using given formula and was found to be 0.366 %.

Drug Loading: Drug loading of the polymeric micells was calculated using given formula and was found to be 13.26 %.

CMC Determination:

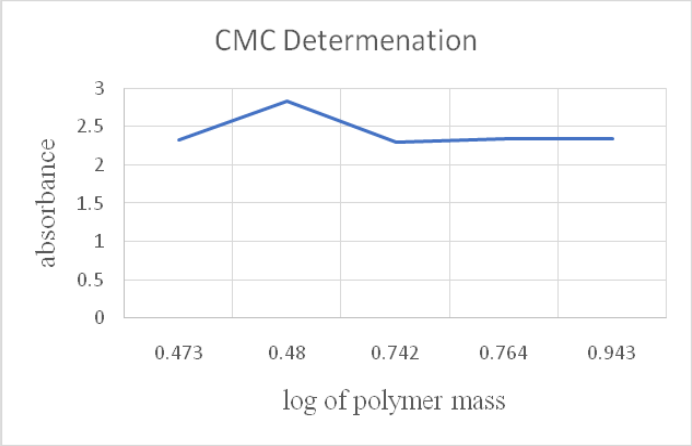

Figure 3: CMC determination of polymer mixture

In vitro Drug Release:

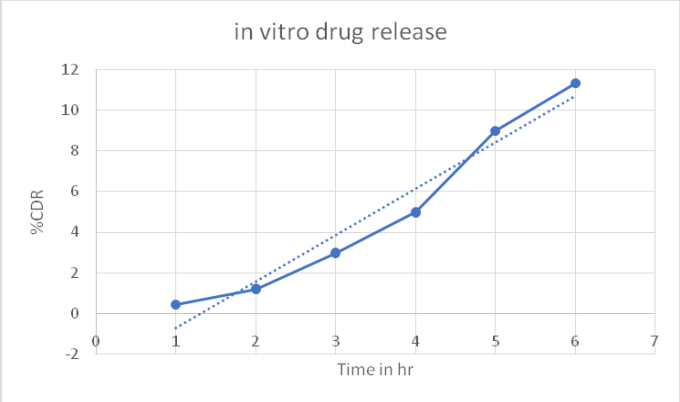

Table 1: Regression coefficient of polymeric micells

Sr. No.	Release Kinetic Model	R^2 Value
1	Zero Order	0.8964
2	First Order	0.9806
3	Higuchi Model	0.8228
4	KoresmayerPeppas Model	0.9681

CONCLUSION:

Antidiabetic drug-loaded polymeric micells were prepared by thin film hydration method. The formulated polymeric micells shows the particle size of 192.6nm. Zeta potential of solid lipid nanoparticles was -21.72mV indicating presence of optimum charge on the surface of formulations to prevent aggregation during their shelf life. The polymeric micells shows percentage entrapment efficiency of 0.366%, drug loading of 13.26%. critical micellar concentration of polymeric micells was found to be 28.3ug/ml which shows the formation of micelles at the determined concentration. In vitro drug release were performed in Franz diffusion cell apparatus and cumulative drug release was found to be 11.33% in 6hrs which shows optimum sustained release of drug. Drug release kinetic study shows that the release of drug from the polymeric micells by first order (0.9806) followed by koresmayerpeppas model (0.9681) and zero order (0.8964). The results demonstrated the effective use of Linagliptin-loaded polymeric micells as a sustained release preparation for the treatment of diabetes.

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