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FORMULATION & EVALUATION OF LINAGLIPTIN LOADED ETHOSOMES FOR TREATMENT OF DIABETES

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ABSTRACT

Diabetes mellitus, one of the most prevalent chronic diseases, is an endocrine and metabolic condition characterised by hyperglycemia and a number of consequences. However, there is still no comprehensive treatment plan for managing diabetes mellitus due to inherent drug deficiencies and restrictions on delivery methods. Ethosomes are non-invasive delivery systems, to deep skin layers and/or the systemic circulation. This study attempts to investigate linagliptin entrapped ethosomes for treatment of diabetes. Ethosomes were prepared as per standard methods & evaluated for various parameters. Results showed that the entrapment efficiency for F4 formulation was found to be 79.85±0.41 and vesicle size was found to be 105.65±0.22nm. The zeta potential for F4 was observed to be -38.5. Commutative % drug release was also found to increase with time. Regression analysis data follows Peppa's plot. The initial burst release was due to the unbound drug being released from the ethosomes. The release profile of formulation F4 was much better than that of the other formulations tested Overall, the in vitro drug release data for optimized ethosomal formulation F4 showed a sustained release profile. This indicates that formulation F4 could be a suitable option for topical delivery of anti-diabetic drugs.

Keywords: Ethsosmes, Diabetes, Linagliptin, Anti-diabetic drugs, vesicular drug delivery system

INTRODUCTION

Nowadays, diabetes mellitus is one of the most deadly non-communicable diseases, causing a high death and morbidity rate alongside cardiovascular disease and cancer. Diabetes mellitus, one of the most prevalent chronic diseases, is an endocrine and metabolic condition characterised by hyperglycemia and a number of consequences. Genetic, environmental, microbial, immune system, and mental variables are the key contributors to diabetes mellitus, which results in inadequate insulin production and insulin resistance [1-3].

However, there is still no comprehensive treatment plan for managing diabetes mellitus due to inherent drug deficiencies and restrictions on delivery methods, such as the negative side effects of prolonged

subcutaneous injection and various difficulties with oral administration, such as enzymatic degradation, chemical instability, and subpar gastrointestinal absorption. As a result, it is crucial to create effective delivery methods and consider full treatment plans that take into account the characteristics of medications and diabetes mellitus [4,5].

Ethosomes are attractive options under vesicular drug delivery system. Drugs can be delivered using ethosomes, which are non-invasive delivery systems, to deep skin layers and/or the systemic circulation. These flexible, squishy vesicles are designed for improved active agent distribution. They contain a significant amount of ethanol, water, and phospholipids (phosphatidylcholine, phosphatidylserine, and phosphatidic acid) [6]. Ethosomes are able to encapsulate and transmit through the skin highly lipophilic substances like cannabis, testosterone, and minoxidil as well as cationic medications like propranolol, trihexyphenidil, Cyclosporine A, insulin, salbutamol, and others because to their special structural makeup. Ethosomes offer a number of significant advantages, such as improved patient comfort and compliance and lowering overall treatment costs [7,8]. This study attempts to investigate linagliptin entrapped ethosomes for treatment of diabetes.

Material and Methods

Preparation of Ethosomes of Linagliptin

Soya PC (0.5 to 1.5% w/v) was dissolved in ethanol (10-20% v/v) and heated up to 30 ± 1°C in a water bath in a closed vessel. Distilled water or drug solution in distilled water (0.1% w/v solution), which is previously heated up to 30 ± 1°C, was added slowly in a fine stream to the above ethanolic lipid solution with continuous mixing using a magnetic stirrer at 900 rpm. Mixing was continued for another 5 minutes and finally, the vesicular dispersions resulted was left to cool at room temperature (25 ± 1°C) for 45 minutes [9].

Table 1: Different Composition of ethosomes formulation

F. Code	Drug (mg)	Phospholipid (% w/v)	Ethanol (% w/v)	PEG (%w/v)	Water (%w/v)
F1	100	0.5	10	20	100
F2	100	0.5	20	20	100
F3	100	1.0	10	20	100
F4	100	1.0	20	20	100
F5	100	1.5	10	20	100
F6	100	1.5	20	20	100

Vesicle size and zeta potential

The size and zeta potential of linagliptin loaded ethosomes depends on the formulations used for the preparation of the ethosomes. Generally, the size of ethosomes range from 100 nm to 500 nm with a mean size of 200-300 nm. The zeta potential of ethosomes typically ranges from -20 to -60 mV, depending on the formulation and components used. In the case of linagliptin loaded ethosomes, the particle size and zeta potential may vary depending on the formulation used and the concentration of the drug. Vesicle size and zeta potential of the Ethosomes were measured by photon correlation spectroscopy[10] using a horiba scientific, nanoparticle analyzer instrument

Entrapment efficiency

Entrapment efficiency was determined by measuring the concentration of unentrapped free drug in aqueous medium. About 1 ml of the drug loaded ethosomes dispersion was placed in the eppendorf tubes and centrifuged at 10,000 rpm for 30 min. The ethosomes along with encapsulated drug were separated at the bottom of the tubes. Plain ethosomes without Linagliptin was used as blank sample and centrifuged in the same manner. In order to measure the free drug concentration, the UV absorbance of the supernatant was determined at 291nm [11].

In-vitro drug release studies using the semipermeable membrane

The semipermeable membrane approximately 25 cm x 2cm was taken and washed in the running water. It was then soaked in distilled water for 24 hours, before used for diffusion studies to remove glycerin present on it and was mounted on the diffusion cell for further studies. The prepared Ethosomes delivery system was evaluated for *in vitro* drug release. The drug release studies were carried out using modified franz diffusion cell. The dissolution study was carried out in 24 ml dissolution medium which was stirred at 50 rpm maintained at 37±0.2°C. Samples were withdrawn at different time interval and compensated with same amount of fresh dissolution medium. Volume of sample withdrawn was made up to 10ml by PBS (pH 7.4). The samples withdrawn were assayed spectrophotometrically at 291nm for Linagliptin and using UV visible spectrophotometer. The release of Linagliptin was calculated with the help of Standard curve of Linagliptin [12].

Release kinetics

In order to elucidate mode and mechanism of drug release, the *in vitro* data was transformed and interpreted at graphical interface constructed using various kinetic models. The zero-order release, first order release & Higuchi model.

RESULTS & DISCUSSION

The entrapment efficiency for F4 formulation was found to be 79.85±0.41 and vesicle size was found to be 105.65±0.22nm. The zeta potential for F4 was observed to be -38.5. Commutative % drug release was also found to increase with time. Regression analysis data follows peppas plot. The initial burst release was due to the unbound drug being released from the ethosomes. The release profile of formulation F4 was much better than that of the other formulations tested Overall, the in vitro drug release data for optimized ethosomal formulation F4 showed a sustained release profile. This indicates that formulation F4 could be a suitable option for topical delivery of anti-diabetic drugs.

Table 2: Result for Vesicle size and Entrapment efficiency of drug loaded Ethosomes

Formulation Code	Vesicle size (μ)	% Entrapment Efficiency
F1	145.65±0.25	72.23±0.35
F2	132.25±0.32	70.14±0.45
F3	125.45±0.15	74.46±0.62
F4	105.65±0.22	79.85±0.41
F5	120.23±0.18	68.85±0.30
F6	138.12±0.24	69.74±0.25

Table 3: Vesicle size and entrapment efficiency of optimized ethosomes

Formulation Code	Vesicle size (nm)	Entrapment Efficiency	Zeta potential
F4	105.65±0.22	79.85±0.41	-38.5

Table 4: Cumulative % drug release of Linagliptin from optimized ethosomes formulation F4

S. No.	Time (hrs)	% Cumulative drug release
1	0.5	23.25
2	1	36.65
3	2	49.98
4	4	68.85
5	6	76.65
6	8	89.98
8	10	98.74

Table 5: *In Vitro* Drug Release Data for optimized ethosomes formulation F4

S. No.	Time (H)	Square Root of Time	Log Time	Cumulative * Percentage Drug Release ± SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	0.5	0.707	-0.301	23.25	1.366	76.75	1.885
2	1	1	0	36.65	1.564	63.35	1.802
3	2	1.414	0.301	49.98	1.699	50.02	1.699
4	4	2	0.602	68.85	1.838	31.15	1.493
5	6	2.449	0.778	76.65	1.885	23.35	1.368
6	8	2.828	0.903	89.98	1.954	10.02	1.001
7	10	3.162	1	98.74	1.994	1.26	0.100

Table 6: Regression analysis data of ethosomal formulation

Formulation	Zero order	First order	Pappas plot
F4	R^2 = 0.945	R^2 = 0.880	R^2 = 0.990

CONCLUSION

Linagliptin ethosomes are an advanced drug delivery system that can be used to improve the solubility and bioavailability of lipophilic drugs. Research on linagliptin ethosomes aims to explore the potential of this novel delivery system for the efficient delivery of drugs, particularly those that are poorly soluble in water. Studies should focus on the formulation and characterization of linagliptin ethosomes, including their size and surface properties, as well as their drug loading and release profile. In vitro and in vivo studies should also be conducted to assess the efficacy of linagliptin ethosomes in delivering the drug to the target site and enhancing its bioavailability.

REFERENCES

1. Shikata K, Ninomiya T, Kiyohara Y. Diabetes mellitus and cancer risk: review of the epidemiological evidence. Cancer science. 2013 Jan;104(1):9-14.
2. Boles A, Kandimalla R, Reddy PH. Dynamics of diabetes and obesity: Epidemiological perspective. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2017 May 1;1863(5):1026-36.
3. Chaudhury A, Duvoor C, Reddy Dendi VS, Kraleti S, Chada A, Ravilla R, Marco A, Shekhawat NS, Montales MT, Kuriakose K, Sasapu A. Clinical review of antidiabetic drugs: implications for type 2 diabetes mellitus management. Frontiers in endocrinology. 2017 Jan 24;8:6.
4. Soewondo P, Ferrario A, Tahapary DL. Challenges in diabetes management in Indonesia: a literature review. Globalization and health. 2013 Dec;9(1):1-7.
5. Khursheed R, Singh SK, Wadhwa S, Kapoor B, Gulati M, Kumar R, Ramanunny AK, Awasthi A, Dua K. Treatment strategies against diabetes: Success so far and challenges ahead. European journal of pharmacology. 2019 Nov 5;862:172625.
6. Verma P, Pathak K. Therapeutic and cosmeceutical potential of ethosomes: An overview. Journal of advanced pharmaceutical technology & research. 2010 Jul;1(3):274.
7. Ainbinder D, Paolino D, Fresia M, Touitou E. Drug delivery applications with ethosomes. Journal of biomedical nanotechnology. 2010 Oct 1;6(5):558.
8. Satyam G, Shivani S, Garima G. Ethosomes: A novel tool for drug delivery through the skin. J Pharm Res. 2010 Apr;3(4):688-91.
9. Touitou E, Dayan N, Levi-Schaffer F, Pilipoponsky A. Novel lipid vesicular system for enhanced delivery. J. Lipid Res. 1998; 8:113-114
10. Bendas and Mina I. Tadros. Enhanced transdermal delivery of salbutamol sulphate via Ethosomes, AAPS PharmaSciTech. 2007; 8(4):E1-E8.
11. Touito E, Dayan N, Bergelson L, Godin B, Eliaz M. Ethosomes-novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. J Control Release. 2000; 65:403-418.
12. Ibrahim TM, Abdallah MH, El-Megrab NA, El- Nahas HM. Transdermal ethosomal gel nanocarriers; a promising strategy for enhancement of anti- hypertensive effect of carvedilol. J Liposome Res. 2019; 29(3):215-28.