Larix Publications

Journal of Pharma Research

https://jprinfo.com/

Vol. 9, Issue 12, 2020 ISSN: 2319-5622

USA CODEN: JPROK3

Original Article

FORMULATION AND EVALUATION OF LINAGLIPTIN TRANSFERSOMAL GEL

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Received on: 14-11-2020 **Revised and Accepted on: 31-12-2020**

ABSTRACT

Transferosomes are particularly optimized, ultrade formable (ultra flexible) lipid supramolecular aggregates, which are able to penetrate the mammalian skin intact. Transfersome is a type of carrier system which is capable of transdermal delivery of low as well as high molecular weight drugs. Transfersomes penetrate through the pores of stratum corneum which are smaller than its size and get into the underlying viable skin in intact form. Soya lecithin, Span 80. Methanol and all chemicals and reagents used were of analytical grade. Different formulation (F-1toF-8) of transfersomes was prepared and evaluated for vesicle size and entrapment efficiency. The vesicle size of all transfersomes varied between 465.2 and 314.3 nm where as entrapment efficiency was found between 66.35 to 79.76 %. Results showed that in formulation F4 which contain smallest vesicle size and increase in entrapment efficiency, Formulation F4 selected as optimized formulation and further incorporated into gel base (F4 1% Carbopol, F4 2% Carbopol and F4 3%Carbopol) and evaluated for Drug content, pH, Spreadability, Viscosity measurements and drug release study. Transfersomes gel released 81.71% drug in controlled release manner in 12hours. The developed Linagliptin as transfersomal gel has the ability to overcome the barrier properties of the skin and increase the drug release.

Keywords: *Linagliptin, Transfersomes, Soyalecithin, Span-80 and Tween-80.*

INTRODUCTION

Linagliptin is a medicine used to treat type 2 diabetes. Type 2 diabetes is an illness where the body does not make enough insulin, or the insulin that it makes does not work properly. This can cause high blood sugar levels (hyperglycaemia). It is a competitive, reversible DPP-4 inhibitor. Inhibition of this enzyme reduces the breakdown of glycogen in the liver and increase insulin release in response to glucose.

The oral bioavailability of linagliptin is low (29.5%) due to first pass metabolism in the intestine and liver and P-gpefflux.

Thus, the transdermal route of administration provides a non-invasive approach for avoiding first-pass metabolism and maintains plasma drug level for a prolonged period thus improving bioavailability. It allows very low dosed Formulations that retain a biological activity over a longer period of time without the subsequent systemic side effects .It is also suitable for people who cannot use drugs orally and gastrointestinal side effects can be also avoided.

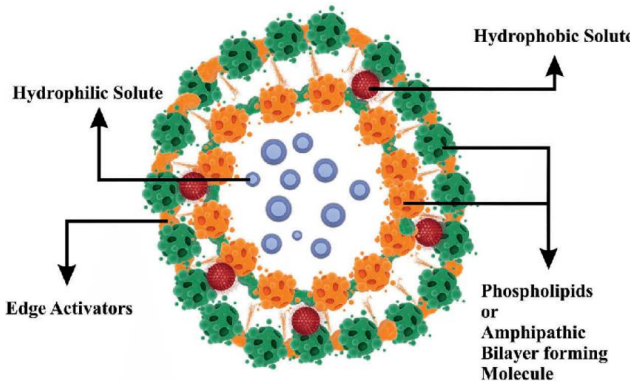

Figure 1: Structure of Transfersomes

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DOI: https://doi.org/10.5281/zenodo.14241847

Transfersomes are vesicular carrier systems that are specially designed to have at least one inner aqueous compartment that is enclosed by a lipid bilayer, together with an edge activator. These vesicular transfersomes are several orders of magnitudes more elastic than the standard. Vesicular carrier systems like liposomes and niosomes have both received lotof attention over the last decade as a means for the transdermal drug delivery. Initially the use of liposomes on the skin was reported, since then a wide range of agents loaded in liposomes have been tested on the skin, with differentrationalities in mind. In most cases transdermal drug penetration has not been achieved. To overcome all the problems mentioned above anew type of carrier system called a "transfersomes"was introduced recently for the effective Transdermal delivery of number of low and high molecular weight drugs.

Transfersomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipids of the stratum corneum. There is provision for this, because of the high vesicle deformability, which permits the entry due to the mechanical stress of surrounding, in aself-adapting manner.[1,2]

II.MATERIALS AND METHODMATERIALS

Linagliptin was provided by MSN Pharmachem pvt ltd, Telangana, Soya lecithin was procured from Himedia, Mumbai, India, Cholesterol and chloroform procured from Merck Limited, Mumbai (India), Span 80, Tween 80 and Methanol obtained from SD Fine-Chem Limited, Mumbai.

METHOD

Preparation of Linagliptin-Loaded Transfersomes By Rotary Evaporation – Sonication Method

First, a thin film is prepared, sonicated vesicles are homogenized by extrusion through a membrane filter. The mixture of vesicles forming ingredients, that is phospholipids and surfactant were dissolved in volatile organic solvent (chloroform-methanol), organic solvent evaporated above the lipid transition temperature using a rotary evaporator. Final traces of solvent were removed under vaccum for overnight. The deposited lipid films were hydrated with buffer (pH 6.4) by rotation at 60 rpm / min for 1hr at the corresponding temperature. The resulting vesicles were swollen for 2hr at room temperature .To prepare small vesicles; resulting LMVs were probe sonicated for 30 min at room temperature. The Syndicated vesicles were homogenized by manual extrusion through membranefilter.[1, 3, 5]

III. FORMULATION DESIGN

Table No 1– Formulation Design Of Linagliptin-Loaded Transfersomes

	F1	F2	F3	F4	F5	F6	F7	F8	F9
LINAGLIPTIN(mg)	10	10	10	10	10	10	10	10	10
SOYALECITHIN(mg)	15	30	45	15	30	45	15	30	45
CHLOROFORM:METHANOL	2:1	2:1	2:1	2:1	2:1	2:1	2:1	2:1	2:1
SODIUMDEOXYCHOLATE	6	12	18	-	-	-	-	-	-
TWEEN80	-	-	-	6	12	18	-	-	-
SPAN80	-	-	-	-	-	-	6	12	18
SODIUMBENZOATE	1	1	1	1	1	1	1	1	1
DISTILLEDWATER	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

IV. CHARACTERIZATION OF LINAGLIPTIN LOADED TRANSFERSOMES

Particle Sizes, PDI, Zeta Potential:

The mean particle length and poly dispersity index (PDI), that's a degree of the distribution of transfersomes, was decidedthe usage of dynamic light scattering (Delta Nano C, Beckman counter), and Zeta capability becomes anticipated on thepremise of electrophoretic mobility under an electric powered field, the use of zeta Sizer Nano ZS (Malvern Instruments,UK).6,7

ENTRAPMENT EFFICIENCY

The entrapment efficiency was determined by using direct method. Detergents are used to break the transfersomemembranes1 ml of 0.1% Triton X- 100(Triton X-100 dissolved in phosphate buffer) was added to 0.1 ml Transfersomes preparations and made up to 5 ml with phosphate buffer then it was incubated at 37oC for 1.5 hrs to complete breakup of the transfersome membrane and to release the entrapped material. The sample was filtered through a Millipore membrane filter (0.25) µm. and the filtrate was measured at 260 nm for Linagliptin. The amount of Linagliptin was derived from the calibration curve.[6, 8]

The entrapment efficiency is expressed as:

Amount trapped

---------- X100

Total Amount

IN VITRO DRUG RELEASE

Diffusion Study for Linagliptin Transfersomes

In Vitro Drug Release - Franz diffusion cell with cellulose membrane, Extrusion method

In brief, Franz diffusion cells are employed in the in vitro drug release study. A mixed cellulose ester membrane of an average pore size of 0.45 µm is used. The membranes are soaked in the release media (phosphate buffer) at room temperature overnight in order to allow the membrane pores to swell. The aliquots of 1mL of the receptor medium are withdrawn at appropriate time

intervals (such as 0, 0.5, 1, 2, 3, 4, 5 and 6 h), and simultaneously, the receptor medium is replaced by an equal volume of the fresh PBS to maintain the sink conditions. The obtained samples were analyzed for drug content using UV spectrophotometer at 230nm wavelength.[7]

V. PREPARATION OF TOPICAL TRANSFERSOMAL GEL FORMULATION

Prepared transfersomes were incorporated in to carbopol-934 (1%) gel base in a 1:1 ratio. The carbopol-934(1%) gel base prepared by soaking 30 min followed by continuous stirring with water. Transfersomes loaded with the drug were incorporated into the gel base by slow stirring until a homogeneous transfersomal gel was achieved. 1%carbopol-934 gel base has a good consistency (gelling characteristic). [6,7]

VI. CHARACTERIZATION OF LINAGLIPTIN TRANSFERSOMAL GEL

Physical appearance:

The prepared gels were also evaluated for the presence of any particles. Smears of gels were prepared on glass slide and observed under the microscope for the presence of any particle or grittiness.

PH of formulation:

pH measurement of the gel was carried out of the formulation was measured by using a digital pH meter (LabIndiaSAB5000.8

Determination of viscosity

Viscosities of the gels were determined by using Brookfield Viscometer (model- RVTP).Spindle type, RV-7 at 100 rpm.100gm of the gel was taken in a beaker and the spindle was dipped in it and rotated for about 5 minutes and then reading was taken.

Extrudability

It is useful empirical test to measure the force required to extrude the material from the tube. The formulations were filled in a collapsible metal tubes with a nasal tip of 5mm opening tube extrudability was then determined by measuring the amount of gel, extruded the tip when a pressure was applied on tube gel. The extrudability of the formulation was checked and the results were tabulated.[9,10,12]

Spreadability: For the determination of spreadability, excess of sample was applied in between two glass slides and was compressed to uniform thickness by placing 1kg weight for 5 min. weight (50 g) was added to the pan. The time in which the upper glass slide moves over to the lower plate was taken as measure of spreadability.

S=M.L/T

M- Weight tied to the upper slideL-Length movedontheglass.

T-TimeTaken

Homogeneity:

The homogeneity of Linagliptin Transfersomal gels were checked by visual inspection. In this regard the gels were filled into narrow transparent glass tubes and were checked in light for the presence of any particulate or lump.[10,11,12]

Drug Content Determination

A specific quantity of developed gels was taken and dissolved in 100ml of respective media. The volumetric flaskcontaining gel solution was shaken for 2hr on a mechanical shaker in order to get complete solubility of the drug. This solution was filtered. After suitable dilution drug absorbance was recorder by using UV[13,1]

VII. RESULTSANDDISCUSSIONS

FORMULATION	ParticleSizes(nm)	PDI	EntrapmentEfficiency(%)
F1	465.2	0.668	75.91
F2	425.8	1.268	67.35
F3	432.6	1.153	77.17
F4	314.3	0.168	79.76
F5	404.1	0.277	78.42
F6	387.3	0.309	67.30
F7	329.8	0.698	72.91
F8	505.4	0.385	66.35

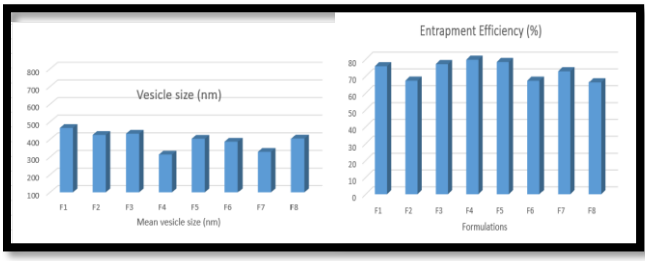

Figure No 2: Graphical representation of mean vesicle size and of % EE

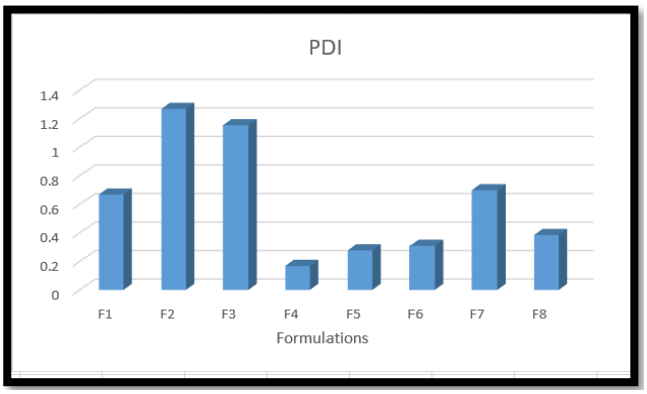

Figure No 3: Graphical representation of PDI

Determination of In-vitro diffusion of Linagliptin Transfersomes

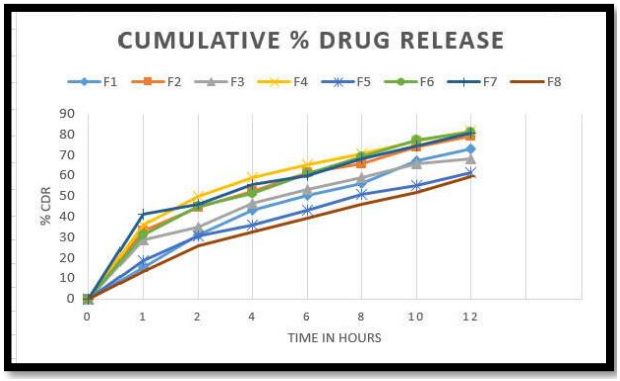

Figure No 4: Graphical representation of % CDR of transfersomes

In vitro drug release study of the selected Transfersomes (F1, F2, F3, F4, F5, F6, F7 and F8) was carried out. The Transfersomes exhibited 12 hours sustained release pattern. Fifty percent of the incorporated amount of drugs was foundto be released during the first 2hours, followed by a slowed release of 81.71% of the drug up to 12 hours. The Linagliptin Transfersomes F4 showed a better release profile of 81.71 % by 12 hours. The prolonged release at 12 hours can be attributed to slow diffusion of drug from lipid matrix. The results of in vitro drug release are depicted in above Table.

CHARACTERISATIONOFOPTIMISEDFORMULATION

Vesicle shape and morphology

The transferosomes were subjected to microscopic examination (S.E.M) for characterizing size and shape of the transfersomes. Microscopic examination revealed, spherical small uni-lamellar vesicles size.

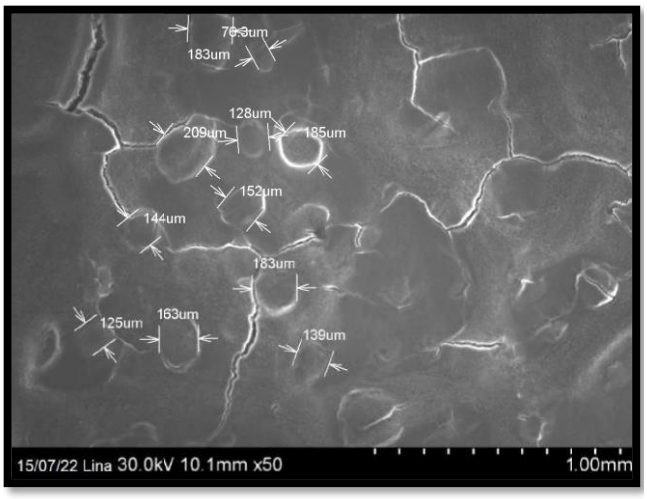

Fig 5: SEM Photograph of Linagliptin Transfersomes (Formulation-4)

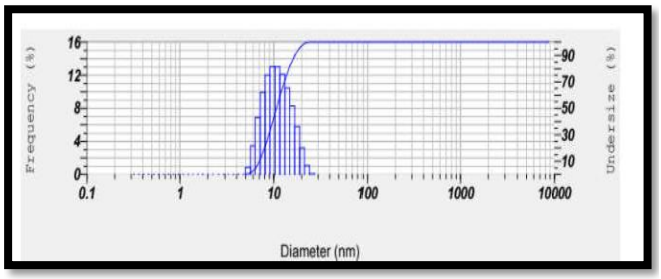

Fig 6: Particle Size of optimised formulation F4

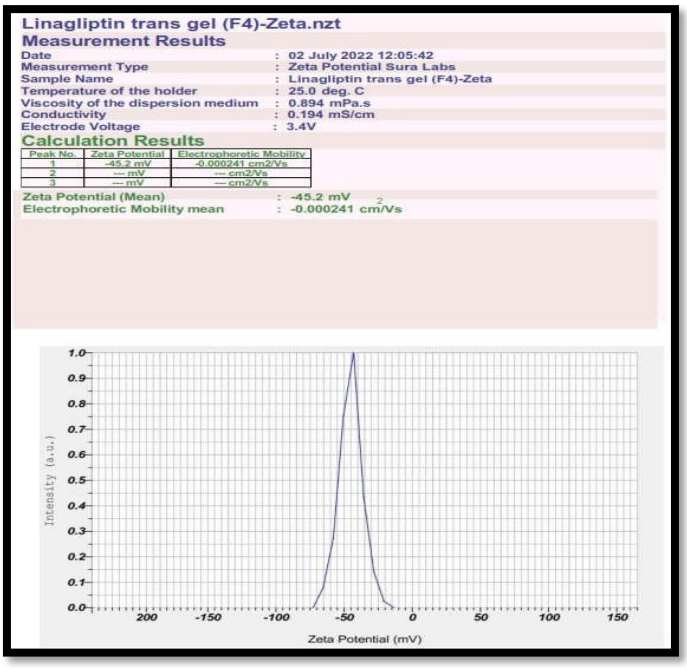

Fig 7: Zeta Potential of optimised formulation F4

CHARACTERIZATIONOF LINAGLIPTIN TRANSFERSOMAL GEL

Table no 2: Physical evaluation of Linagliptin Pharmacosomal gel

Formulation	pH	Viscosity(cp)	Extrudability	Homogeneity	Drug Content(%)
F4optimized1%carbopolgel	6.11	65154	+	Satisfactory	76.54
F4optimized2%carbopolgel	6.07	71797	++	Excellent	85.19
F4optimized3%carbopolgel	6.02	70560	+	Satisfactory	77.67

Formulation	Colour	Spreadability(g.cm/sec)
F4optimized1%carbopolgel	Whitetooffwhite	0.521±0.90
F4optimized2%carbopolgel	Whitetooffwhite	0.413±0.29
F4optimized3%carbopolgel	Whitetooffwhite	0.603±0.19

All values are expressed as mean ± SD,(n=3)

Immediately after the formulations were prepared their physical characteristics of formulations were studied and the data was shown in Table. Thus all the formulations exhibited good characteristics like homogeneity in colour, and appearance.

IN-VITRODRUGRELEASE

TableNo: 3 In-Vitro Drug release of Transfersomal gels

Time(hrs)	F4optimized 1%carbopolgel	F4optimized 2%carbopolgel	F4 optimized 3%carbopolgel
0	0	0	0
1	38.18±0.11	37.82±0.65	27.11±0.41
2	49.06±0.72	46.53±0.36	35.48±0.39
4	57.67±0.88	56.12±0.46	46.57±0.32
6	61.96±0.02	63.02±0.93	57.98±0.42
8	70.10±0.55	71.10±0.58	60.84±0.16
10	74.29±0.57	75.63±0.21	68.93±0.03
12	79.07±0.67	82.24±0.76	73.65±0.25

All values are expressed as mean±SD,(n=3)

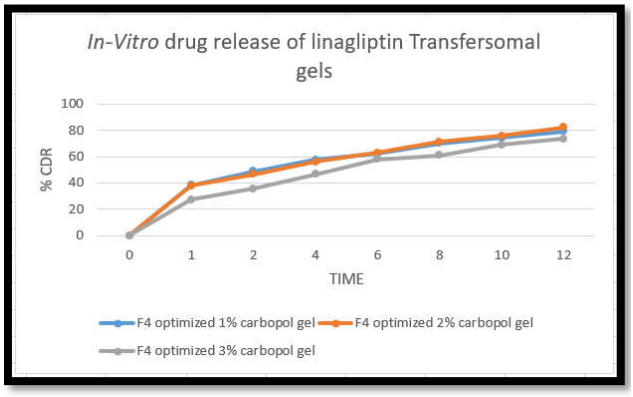

Figure No 8: Graphical representation of In-vitro drug release of transfersomal gels

VIII. CONCLUSION

Total Eight formulations were prepared using varying amount of Soya-phosphatidylcholine, Cholesterol and drug and evaluated for Vesicle size and Entrapment efficiency. Formulation F4 which contain smallest vesicle size and increase in entrapment efficiency, Formulation F4 Sleeted as optimized formulation for further evaluation. The optimized batch of Transfersomes was further incorporated into gel base and evaluated for pH, Spreadability, Measurement of viscosity, Drug content and In-vitro diffusion study. From this study, it was concluded that the optimized batch of Linagliptin, with high EE% and small particle size. Also, the preparation of Linagliptin as transfersomal gel has the ability to overcome the barrier properties of the skin and increase the drug release.

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How to cite this article:
Dr. G. Nagaraju *, FORMULATION AND EVALUATION OF LINAGLIPTIN TRANSFERSOMAL GEL Pharma Res, 2020; 09(12): 162-167. DOI: https://doi.org/10.5281/zenodo.14241847

Conflict of interest: The authors have declared that no conflict of interest exists.
Source of support: Nil

