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FORMULATION AND CHARACTERIZATION OF LINAGLIPTIN NIOSOMAL DRUG DELIVERY SYSTEM

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ABSTRACT

The need for the present study is to encapsulate the drug in the niosomes vesicle. Niosomes are non - ionic surfactant vesicles obtained on hydration with synthetic non - ionic surfactants with or without incorporation of cholesterol or other lipid. Niosomes prolong the circulation of many drugs and alter the distribution of drugs, we aimed at formulating linagliptin in niosomal drug delivery, thereby minimizing the dose and also used to achieve sustained release for a prolonged period of time. Preformulation studies were performed for the drug (linagliptin). Two formulations of F-1and F-2 of Linagliptin niosomes were prepared by modified ether injection techniques. Microscopic examination revealed that the vesicle diameter complies with in the range of 100 to 300nm. The entrapment efficiency of drug in F-2 containing span 60 was found to be 71.62% with showed that span 60 is the more suitable surfactant along with cholesterol for enhancing maximum entrapment for the drug linagliptin. F-2 showed 93.71% of drug release within 20 hours. These results showed that niosomes linagliptin has sustained release up to 20 hours.

KEYWORDS

Niosomes, Entrapment, Efficiency Ether injection technique and Linagliptin.

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INTRODUCTION

Drug targeting can be defined as the ability to direct a therapeutic agent specifically to designed site of action with little or no interaction with non - target tissue[1]. Advantages of targeted drug delivery system is to improve drug safety, minimize toxic effects caused by drug action at non target site, improve drug efficacy as the drug is concentrated at the site of action rather than being dispersed throughout the body and also improves patient compliance as increased safety, efficacy make therapy more

acceptable[2]. Carriers are one of the most important entities essentially required for successful transportation of loaded drugs such as niosomes, nanoparticle, released erythrocytes, microspheres, magnetic microspheres, monoclonal antibodies and liposomes. Niosomes are non - ionic surfactant vesicles obtained on hydration with synthetic non - ionic surfactants with or without incorporation of cholesterol or other lipids[3]. Niosomes are promising vesicles for drug delivery and beingnonionic, they are less toxic and improve the therapeutic index of drugs by restricted its action to the target cells[4].

MATERIAL

Linagliptin was procured from Mylan Laboratories, cholesterol was procured from RR Scientifics, span 40 and span 60 were purchased from Lobachemie and diethyl ether was procured from Pallav chemicals.

Preformulation studies

Identification of pure drug

Pure drug (Linagliptin) was identified using FTIR technique. IR spectra was taken for cholesterol, span 40 and span 60 and for mixture of drug, cholesterol and surfactants[5].

Solubility studies

The solubility analysis of drug was performed with water, organic solvents and buffer PSB 7.4 pH[6].

DSC Studies

The drug (Linagliptin), cholesterol, span 40, span 60 and mixture of drug and excipients was subjected to DSC studies for testing the compatability of the drug with the excipients used in the formulation[7].

OPTIMIZATION

Standard curve for linagliptin

100 mg of linagliptin pure drug was dissolved in 100ml of phosphate buffer (pH - 7.4). From this stock solution, 2.5ml pipette out and made upto 25ml with phosphate buffer. From this solution, serial dilutions were made to produce 5, 10, 15, 20, 30, 40, 50mg/ml concentrations. These samples were analyzed spectrometrically at 228nm using phosphate buffer (pH-7.4) as blank. The readings were analyzed spectrophotometrically at 228nm using phosphate buffer (pH– 7.4) as blank[8]. The readings are given in the Table No.4.

Optimization of temperature during niosomes preparation

Niosome preparation has been temperature-tuned so that vesicles with irregular shapes appear at temperatures below 60°C, spherical ones appear at 60°C ± 2°C and less irregular ones appear at temperatures above 80°C.

Optimization of rotating speed

During the optimization of rotating speed in the RPM below 80 there was a formation of clumped vesicles, in RPM 100±2 showed a spherical vesicles and above 100 there was observation of irregular shaped vesicles.

Optimization of temperature during ultrasonication

The temperature has been optimized during ultrasonication, the temperature below 10ºC showed a small sized vesicle, the temperature 10ºC showed a numerous vesicle of moderate size and at room temperature there was observation of large sized vesicles.

Optimization of ultrasonic time

In the preformulation studies of niosomes the ultrasonic time has been optimized in which the time at 10 mins observed an incomplete large sized vesicle, the time at 15 mins showed spherical vesicles and at 30 mins there was appearance of broken vesicles[9].

Selection of surfactant

In span 40 there was appearance of a smaller number of vesicles and in span 60 there was numerous vesicles[10].

PREPARATION OF LINAGLIPTIN NIOSOMES

Linagliptin was prepared by Modified ether injection technique. In this method, cholesterol and surfactant were dissolved in 8ml of diethyl ether mixed with 2ml methanol containing weighed quantity of Linagliptin. The resulting solution was slowly injected using a micro syringe at a rate of 1ml/min into 10ml of hydrating solution phosphate

buffer (pH-7.4). The solution was stirred continuously on magnetic stirrer and temperature was maintained at 60ºC - 65ºC. As the lipid solution was injected slowly into the aqueous phase, the difference in temperature between phases cause rapid vaporization of ether, resulting in spontaneous vesiculation and formulation of Niosomes. The suspension was sonicated to form unilamellar vesicles.

CHARACTERISATION OF NIOSOMES

Morphological studies

The Niosomes were subjected to microscopic examination by scanning electron microscopy for characterizing shape and surface morphology[11].

Optical microscopy

The niosomes was subjected to optical microscopy. Niosomes containing linagliptin was mounted on a slide and viewed through camera[12].

Scanning electron microscopy

Niosomes were characterized by SEM (TESCAN). Niosomes containing linagliptin was taken in a cover glass and transferred on a specimen stub. Dried samples were coated with platinum alloy to a thickness of 100 A using a sputter coater. After coating, scanning was done to examine the shape and size[13].

Determination of drug entrapment efficiency

1ml of the sample is taken and centrifuged at 13000RPM at 4°C for 90 minutes using Remi centrifuge. Using a micropipette, supernatant was separated without affecting the sediment layer. The supernatant layer (free drug) was diluted using phosphate buffer pH 7.4 and analyzed using UV spectrophotometer[14].

$$\text{Percentage of drug entrapment} = \frac{\text{Amount of drug entrapped}}{\text{Initial amount of drug}} \times 100$$

In-vitro drug release

The *in-vitro* release of niosomes were studied by using simple diffusion cell apparatus. A glass tube with an inner diameter of 2.5cm that is open at both ends and has a donor compartment linked to one end is the basis of the diffusion cell equipment. Niosomes equivalent to 5mg of linagliptin was taken in a dialysis tube and placed in 200ml of phosphate buffer (pH - 7.4). The medium was stirred by using the magnetic stirrer and the temperature was maintained at 37±2ºC. Periodically 5ml of samples were withdrawn and after each withdrawal same volume of medium replaced. Then the samples were assayed spectrophotometrically at 228nm using phosphate buffer as blank[15].

RESULTS AND DISCUSSION

Niosomes are promising vehicle for drug delivery and being non-ionic, it is less toxic and improve the therapeutic index of drug by restricting its action to target cells. Hence, in present study linagliptin was encapsulated in niosomes using non-ionic surfactants like span 40 and span 60. The preparation of niosomes was done by Modified Ether Injection technique. The formulated niosomes were characterized for optical microscopy, scanning electron microscopy, entrapment efficiency, *in vitro* drug release.

Solubility studies

The solubility analysis of drug was performed with water, organic solvents and buffer PBS 7.4pH. The results are given in Table No.3.

Identifiation of pure drug

Pure drug was identified using FTIR technique. These studies revealed that the drug is compatible with excipients used in formulations.

DSC studies

The DSC studies revealed that the drug linagliptin is compatible with the excipient used in the formulation.

Optical microscopy

The formulated niosomes were subjected to optical microscopy and the spherical vesicles were observed. The images of F1 and F2 are below.

Morphological studies

The formulated niosomes were subjected to microscopic examination by scanning electron microscopy for characterizing size and shape. Microscopic examination revealed spherical small unilamellar vesicles of 180nm for F-1 and 136nm for F-2 respectively. These results revealed that the vesicle diameter complies within the niosomal size range of 100 to 300nm. The SEM images of F-I and

F-II are given in Figure No.12 and Figure No.13 respectively.

Entrapment efficiency

The quantity of the drug entrapped in the niosomes is very essential to know before studying the behaviours of this entrapped drug in physical or biological system. The process and formulation variable (cholesterol and surfactant) were altered and optimized to obtain the niosomes with maximum drug entrapment. All the two formulation F-1 and F-2 were subjected to percentage drug entrapment.

The entrapment efficiency of drug in F-2 containing span 60 was found to be 71.62% which shown maximum percent drug entrapment whereas those containing span 40 was found to be 54.21% respectively. This showed that span 60 is the more suitable surfactant along with cholesterol for enhancing maximum entrapment for the drug linagliptin.

Further, the percent drug entrapment was increased by decreasing the sonication time. Therefore, the sonication time was optimized to 15 minutes and no attempt was made to reduce the size further by lengthening the sonication time. The results are tabulated in Table No.6.

***In-vitro* release studies**

***In-vitro* release of linagliptin niosomes**

The formulated Niosomes was subjected to *in-vitro* drug release using phosphate buffer (7.4) as the medium in sigma dialysis membrane. The amount of linagliptin diffused was estimated spectrophotometrically at 228nm. F-1 showed 87.97% of drug release within 19 hours. F-2 showed 93.71% of drug release within 20 hours. These results showed that niosomal linagliptin has sustained release upto 20 hours. This is because the drug was released slowly for a prolonged period in niosomal linagliptin. And also, it reveals that linagliptin niosomes prepared with span 60 showed better release than with span 40, the results are tabulated in Table No.7.

Table No.1: Preparation of linagliptin niosomes

FORMULATION CODE	AMOUNT OF LINAGLIPTIN	CHOLESTROL	SPAN 40	SPAN 60	DIETHYL ETHER	PHOSPHATE BUFFER SALINE OF pH -7.4	CHOLESTER-SURFACTANT RATIO
F - 1	110 mg	50mg	50mg	-	8ml	10ml	1:1
F - 2	110mg	50mg	-	50mg	8ml	10ml	1:1

Table No.2: Formulation code

S.No	Formulation code	Type of surfactant used
1	F – 1	Span 40
2	F – 2	Span 60

Table No.3: Solubility studies

S.No	Solvents	Solubility
1	Water	Slightly soluble
2	Chloroform	Freely soluble
3	Methanol	Freely soluble
4	Diethyl ether	Freely soluble
5	Acetone	Freely soluble
6	Phosphate buffer 7.4 pH	Slightly soluble

Standard curve

Table No.4: Standard curve for linagliptin

S.No	Concentration	Absorbance AT 228nm
1	5	0.069
2	10	0.177
3	15	0.292
4	20	0.411
5	30	0.660
6	40	0.915
7	50	1.147

r = 0.9998, a = -0.0644, b = 0.024

Table No.5: Vesicle diameter of niosomes

S.No	Type of formulation	Size (nm)
1	F – 1	180
2	F – 2	136

Table No.6: Percentage drug entrapment of the formulated niosomes

S.No	Formulation code	% Drug entrapment
1	F - 1 (Span 40)	54.21%
2	F -2 (Span 60)	71.62%

Table No.7: *In-vitro* drug release

Time (hrs)	Percentage of drug release of f1	Percentage of drug release of f2
1	14.46±0.60	13.29±1.17
2	15.08 ± 0.46	14.83±0.54
3	20.84 ± 0.86	17.95±0.19
4	26.17 ± 0.31	21.59±0.35
5	31.65 +0.19	24.40±0.34
6	35.16 ± 0.30	28.34±0.62
7	37.93 ± 0.34	30.83±0.11
8	40.02 0.34	33.60±0.22
9	41.72 ± 0.20	38.25± 0.15
10	46.15 0.28	42.77±0.27
11	49.50 ± 0.08	48.11±0.16
12	55.00 ± 0.19	55.51±0.15
13	59.76±0.23	60.86±0.10
14	62.97 ± 0.31	67.77±0.21
15	66.22±0.10	74.47±0.04
16	70.90 ± 0.17	78.98±0.20
17	76.34 ± 0.27	83.42±1.60
18	83.34 ± 0.24	90.04±0.25
19	87.97 ±0.08	91.49±0.22
20	87.40±0.20	93.71±0.23
21	85.45 ± 0.22	93.01±0.22

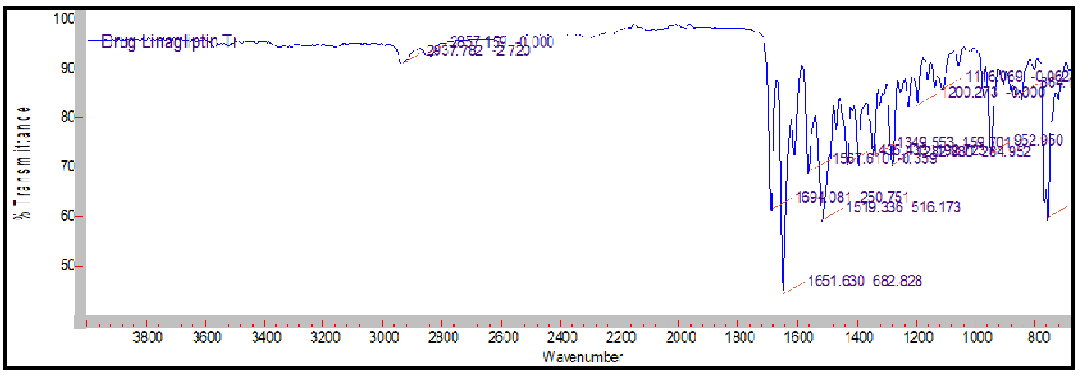

Figure No.1: IR spectra of pure drug

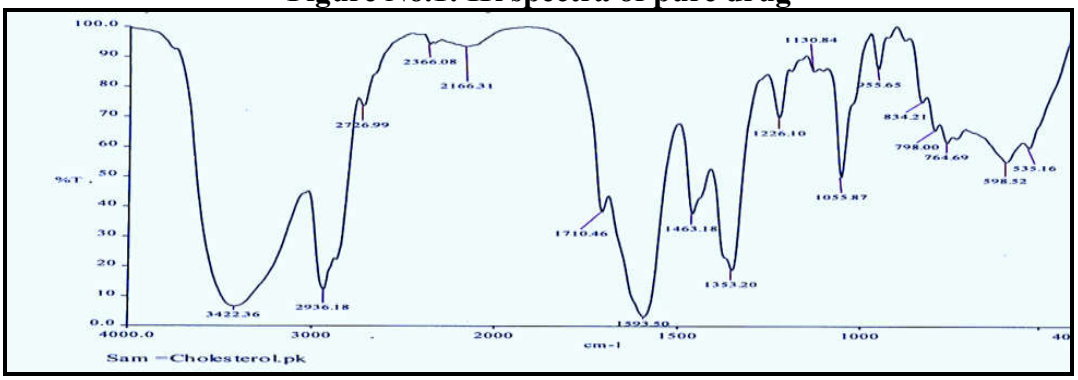

Figure No.2: IR spectra of cholesterol

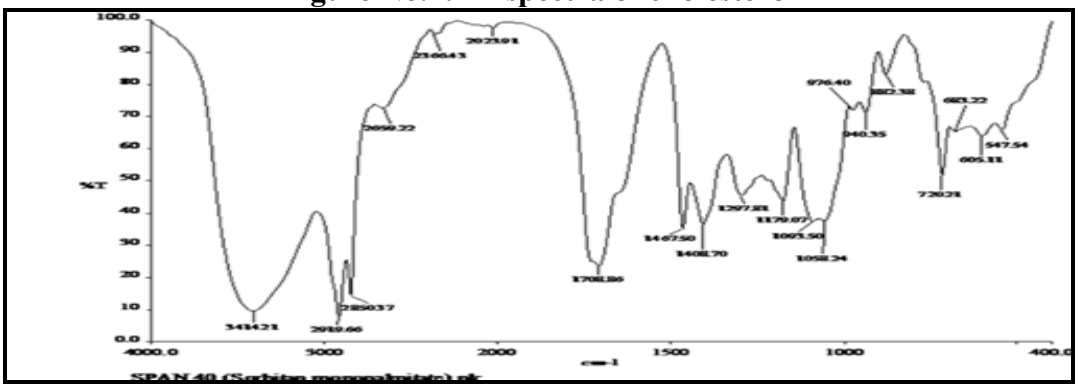

Figure No.3: IR spectra of span 4O

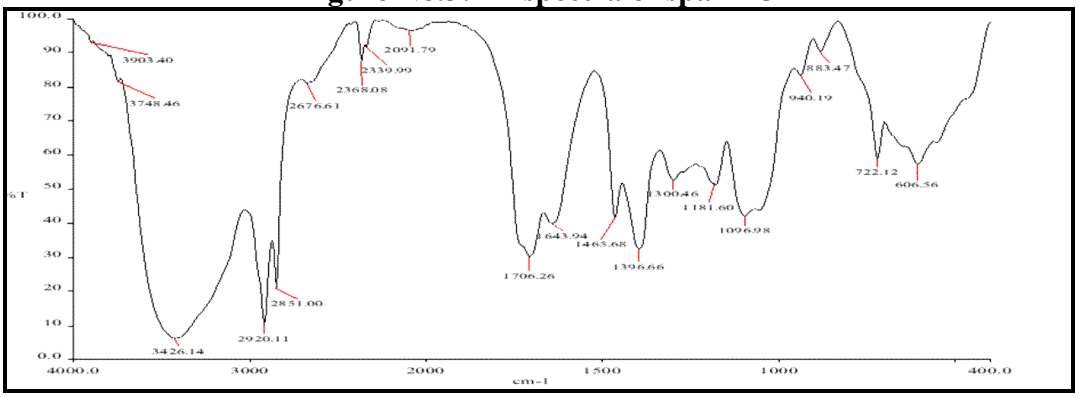

Figure No.4: IR spectra of span 60

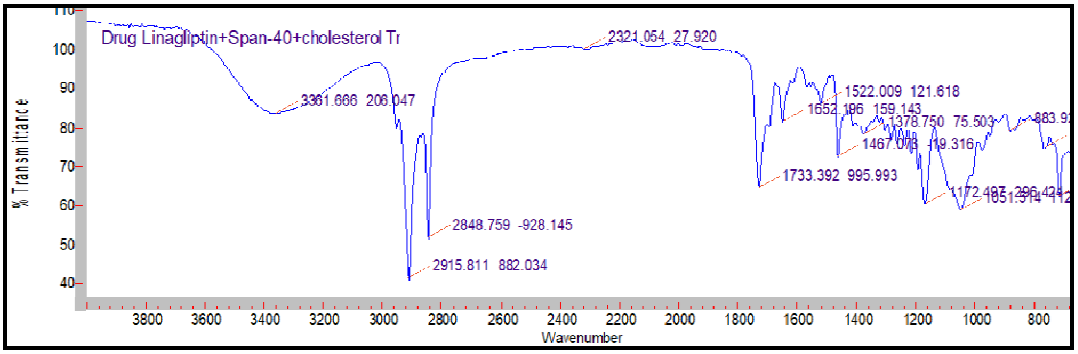

Figure No.5: IR spectra of drug + Cholestrol + Span 40

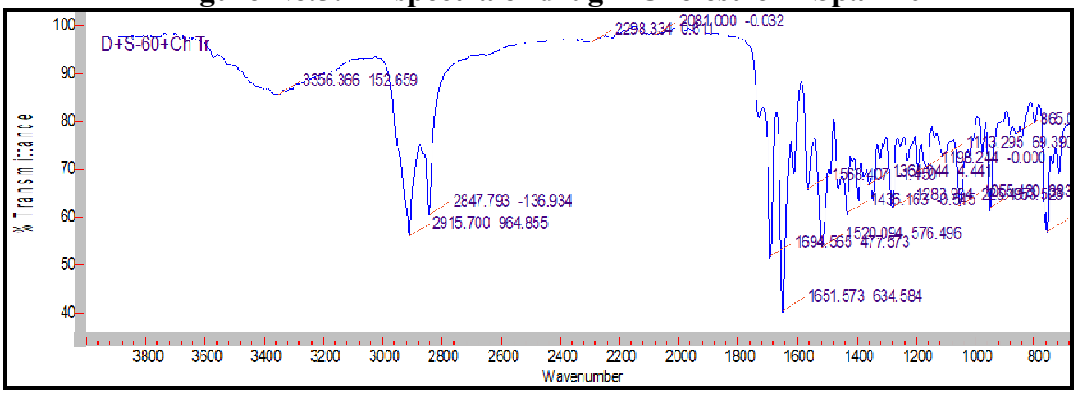

Figure No.6: IR spectra of drug + Cholestrol + Span 60

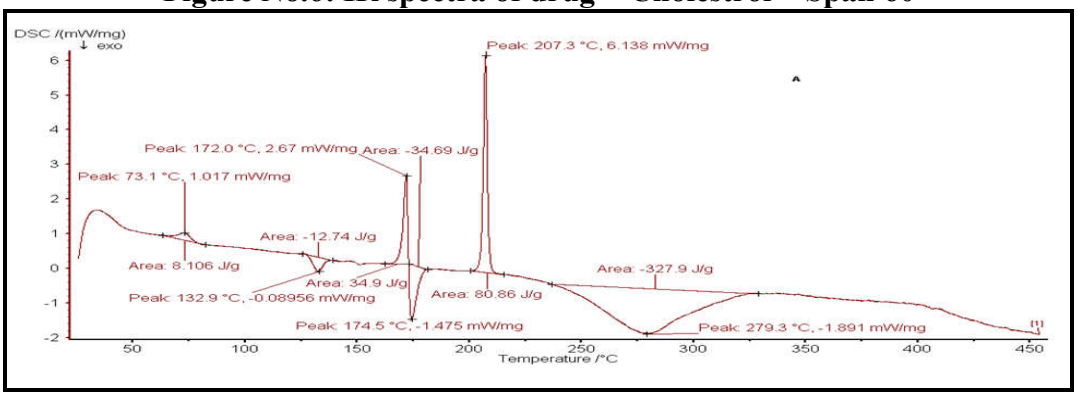

Figure No.7: DSC of pure drug linagliptin

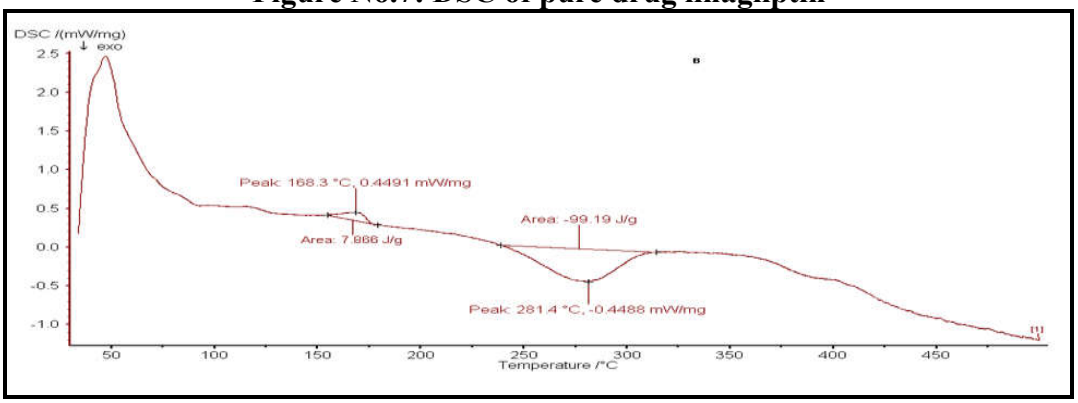

Figure No.8: DSC of drug + Cholestrol + Span 40

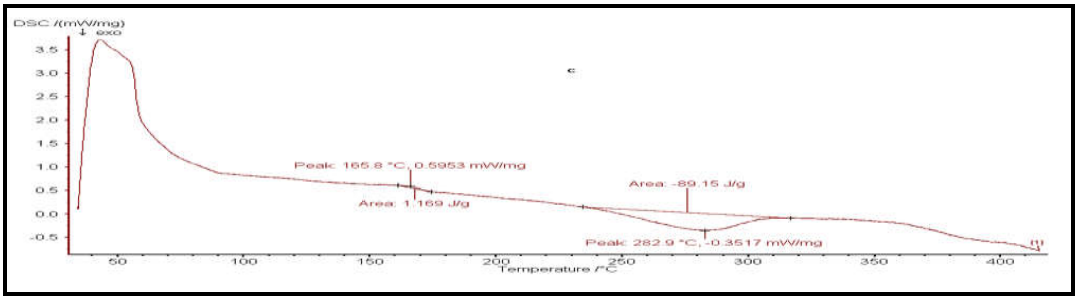

Figure No.9: DSC of drug + Cholestrol + Span 60

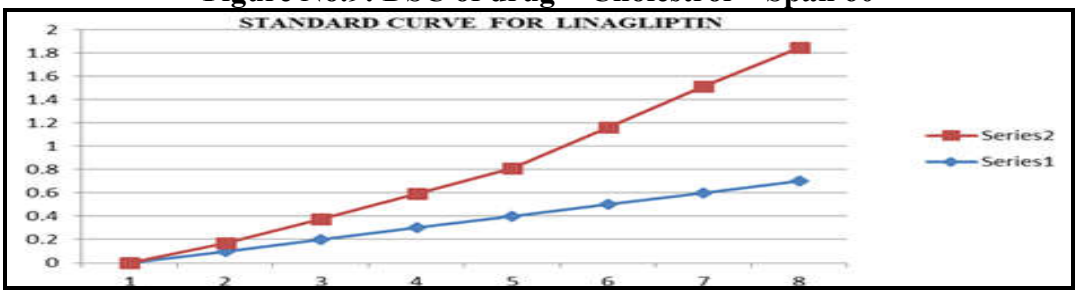

Figure No.10: Standard curve for linagliptin

Figure No.11: Optical microscopy of F1

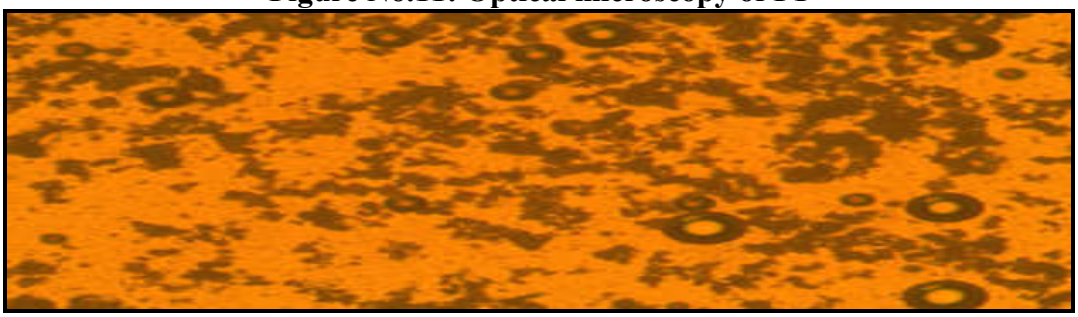

Figure No.12: Optical microscopy of F2

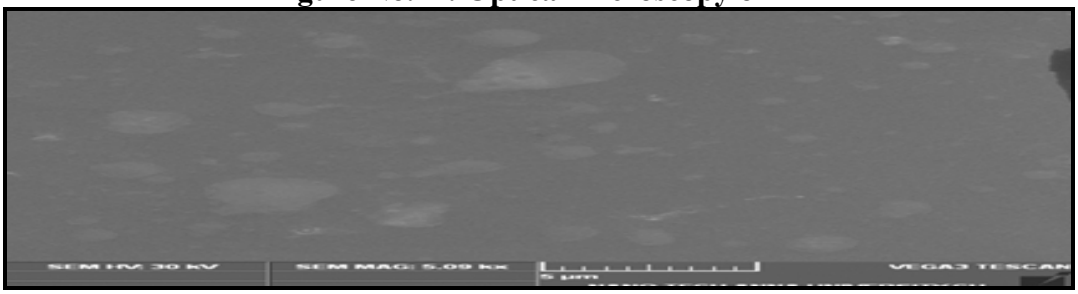

Figure No.13: SEM photography of F-I

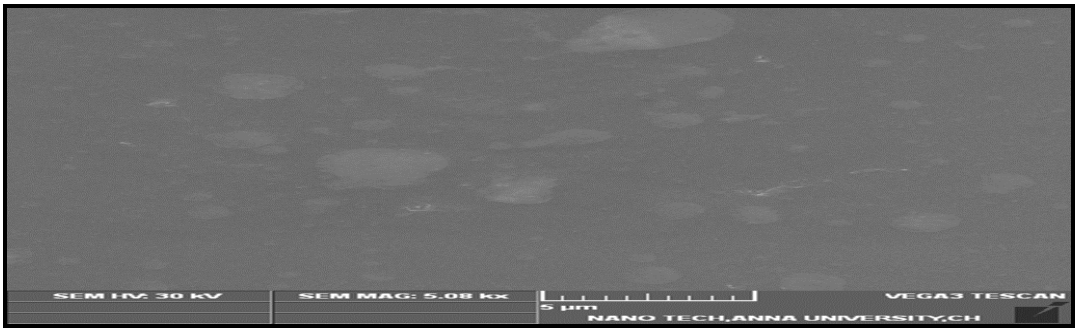

Figure No.14: SEM photography of F-II

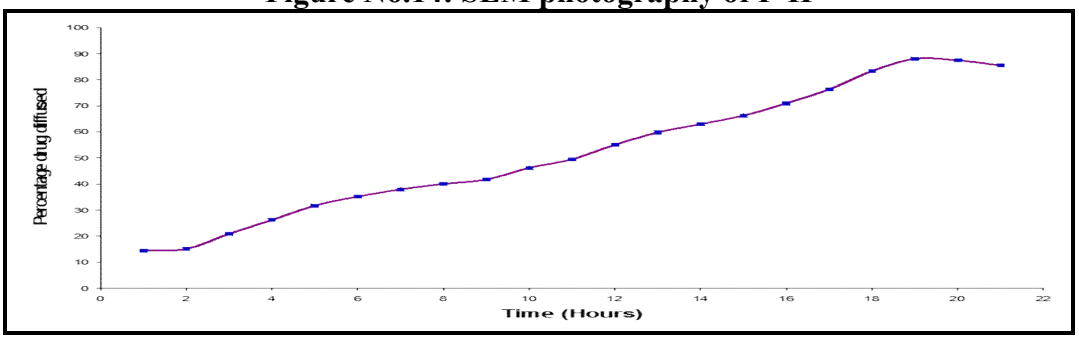

Figure No.15: *In-vitro* drug release of F1

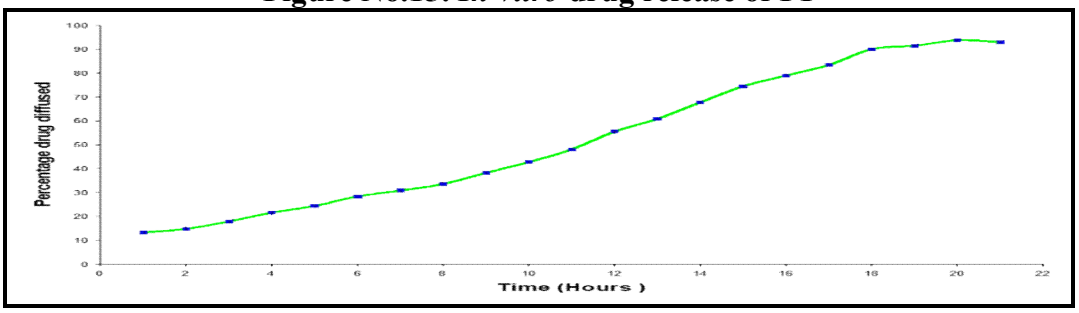

Figure No.16: *In-vitro* drug release of F2

CONCLUSION

Niosomes containing linagliptin was formulated using two surfactants such as span 40 and span 60 and evaluated for various parameters. The FTIR and DSC studied revealed that the drug linagliptin was compatible with all the excipients used in the formulation. The morphological studies revealed that the drug was entrapped into the vesicles of niosomes and particle size compiled with the limit range. From the studies it was concluded that linagliptin encapsulated in niosomes showed prolonged release and longer duration of action there by achieving sustained release. Thus, the objective of minimizing the dose of linagliptin was achieved with niosomal delivery system.

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CONFLICT OF INTEREST

We declare that we have no conflict of Interest.

REFERENCES

1. Gupta M, Sharma V. Targeted drug delivery system a review, *Research Journal of Chemical Sciences,* 1(2), 2011, 135-138.

2. Bae Y H, Park K. Targeted drug delivery to tumors: Myths, reality and possibility, *Journal of Controlled Release,* 153(3), 2011, 198-205.
3. Agnihotri J, Saraf S, Khale A. Targeting: New potential carriers for targeted drug delivery system, *International Journal of Pharmaceutical Sciences Review and Research,* 8(2), 2011, 117-123.
4. Bhaskaran S, Panigrahi L. Formulation and evaluation of niosomes using different non-ionic surfactants, *Indian Journal of Pharmaceutical Sciences,* 64(1), 2002, 63-65.
5. Onochie I T, Nwakile C D, Umeyor C E, Uronnachi E M, Osonwa U E, Attama A A, Esimone C O. Formulation and evaluation of niosomes of benzyl penicillin, *Journal of Applied Pharmaceutical Science,* 3(12), 2013, 66-71.
6. Salih O S, Samein L H, Ali W K. Formulation and *in vitro* evaluation of rosuvastatin calcium niosomes, *Int J Pharm Pharm Sci,* 5(4), 2013, 525-535.
7. Abdelkader H, Ismail S, Kamal A, Alany R G. Preparation of niosomes as an ocular delivery system for naltrexone hydrochloride: physicochemical characterization. Die Pharmazie, *An International Journal of Pharmaceutical Sciences,* 65(11), 2010, 811-817.
8. Sakthivel M, Kannan K, Manavalan R, Senthamarai R. Formulation and *in vivo* evaluation of niosomes containing oxcarabazepine, *Journal of Pharmaceutical Sciences and Research,* 5(1), 2013, 1-8.
9. Ruckmani K, Sankar V. Formulation and optimization of zidovudine niosomes, *Aaps Pharmscitech,* 11(3), 2010, 1119-1127.
10. Moghassemi S, Hadjizadeh A. Nano-niosomes as nanoscale drug delivery systems: An illustrated review, *Journal of Controlled Release,* 185, 2014, 22-36.
11. Abdelkader H, Wu Z, Al-Kassas R, Alany R G. Niosomes and discomes for ocular delivery of naltrexone hydrochloride: Morphological, rheological, spreading properties and photo-protective effects, *International Journal of Pharmaceutics,* 433(1-2), 2012, 142-148.
12. Srinivas S, Kumar Y A, Hemanth A, Anitha M. Preparation and evaluation of niosomes containing aceclofenac, *Dig J Nanomater Bios,* 5(1), 2010, 249-254.
13. Blazek-Welsh A I, Rhodes D G. SEM imaging predicts quality of niosomes from maltodextrin-based proniosomes, *Pharmaceutical Research,* 18(5), 2001, 656-661.
14. Pando D, Gutierrez G, Coca J, Pazos C. Preparation and characterization of niosomes containing resveratrol, *Journal of Food Engineering,* 117(2), 2013, 227-234.
15. Manconi M, Sinico C, Valenti D, Loy G, Fadda A M. Niosomes as carriers for tretinoin. I. Preparation and properties, *International Journal of Pharmaceutics,* 234(1-2), 2002, 237-248.

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