Research Article

Formulation and Evaluation of Metformin Based Niosomes

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ABSTRACT

Many active compounds have limited aqueous solubility, so there is great need for delivery systems suitable for hydrophobic and amphiphilic drugs. One approach to this problem has been to use lipid-based vesicles as drug carriers. The history, properties, and applications of niosomes have been recently reviewed. Niosomes have been investigated for drug delivery through the most common routes of administration, such as intramuscular, intravenous, subcutaneous, ocular, oral, and transdermal. Niosomes appear to be multilamellar surfactant structures, and are thus best suited for hydrophobic or amphiphilic drugs. Niosomes are promising vehicle for drug delivery and being non-ionic; it is less toxic and improves the therapeutic index of drug by restricting its action to target cells. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. Recently, niosomes have been studied by many researchers as a choice of oral drug delivery system to provide better oral bioavailability consideration, high penetration property of the niosome encapsulated agents through biological membrane and their stability. The present formulation study on metformin is an attempt to prepare niosomal drug delivery system and evaluate its in-vitro Performance. The formulations were prepared with different types of surfactant. The study is based on formulation of metformin niosome which provide most promising oral bioavailability of metformin.

Keywords: Bioavailability, hypoglycemia, metabolism, niosome

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INTRODUCTION

Metformin activates AMP-activated protein kinase (AMPK), an enzyme that plays an important role in insulin signaling, whole body energy balance, and the metabolism of glucose and fats; activation of AMPK is required for metformin's inhibitory effect on the production of glucose by liver cells. In addition to suppressing hepatic glucose production, metformin increases insulin sensitivity, enhances peripheral glucose uptake (by phosphorylating GLUT-4 enhancer factor), increases fatty acid oxidation, and decreases absorption of glucose from the gastrointestinal tract. Metformin is used with a proper diet and exercise program and possibly with other medications to control high blood sugar. It is used in patients with type 2 diabetes (non-insulin-dependent diabetes). Proper control of diabetes may also lessen your risk of a heart attack or stroke. It is also used in women with a certain disease of the ovaries (polycystic ovarian syndrome). Metformin may make menstrual cycles more regular and increase fertility. Freely soluble in water, slightly soluble in acetone & chloroform. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. PKa value is 12.8. It is White crystalline powder Half life is 2 hours. Metformin is not metabolized. It is cleared from the body by

tubular secretion and excreted unchanged in the urine.

Niosomes are unilamellar or multilamellar vesicles that are made up of non-ionic surfactant and can entrap amphiphilic and hydrophobic solutes [1,2]. Niosomes have shown advantages as drug carriers, such as being a cheap and chemically stable alternative to liposome's, but they are associated with problems related to physical stability, such as fusion, aggregation, sedimentation, and leakage on storage [3]. The proniosomes which is more stable during sterilization and storage minimizes these problems by using dry, free-flowing particles that immediately form noisome dispersion when in contact with water. Proniosomes are suitable for administration by oral or other routes [4]. Preliminary studies indicate that noisome may increase the absorption of certain drugs from the gastrointestinal tract following oral ingestion and prolong the existence of the drug in systemic circulation [5]. The encapsulation of metformin in lipophilic vesicular structure may be expected to enhance the oral absorption and prolong the existence of the drug in systemic circulation of the drug due to the slow release of the encapsulated drug. Accordingly, the objective of this study is to prepare metformin proniosomes and evaluate the influence of proniosomal formulation on its oral bioavailability.

MATERIALS AND METHODS

MATERIALS

Metformin was a gift sample from Aurobindo pharmaceuticals, Vijayawada. Span 20, span 80, tween 40, tween 80 was obtained from Tiny pharmaceuticals. All other materials used were of pharmacopeia grade.

METHODS

Preparation of proniosomal gel

Proniosome was prepared by slurry method. This method involves formation of slurry by addition of the carrier and the entire surfactant solution in a round bottomed flask. This is fitted to a rotary flash evaporator and vacuum was applied to form a dry and free flowing powder. Then the flask was removed and kept under vacuum over night. The obtained powder was collected in a sealed container and kept at 4°C. The time required for proniosome production is independent of the ratio of surfactant solution to carrier material and appears to be sealable [5-8]. This dry product, referred to as proniosomes, was stored in a tightly closed container and was used for preparation of proniosome derived niosomes and for further evaluation.

Table 1: Composition of surfactant for Preparation of proniosomal gel

DRUG (100 mg)	SPAN	TWEEN	CHOLESTEROL
SPAN 20	400 mg	-	200 mg
SPAN 80	400 mg	-	200 mg
TWEEN 40	-	400 mg	200 mg
TWEEN 80	-	400 mg	200 mg

Table 2: Optimized formula for Preparation of proniosomal gel

S.NO	INGREDIENTS	QUANTITY REQUIRED
1	CHOLESTEROL	200 mg
2	SPAN 20	400 mg
3	SPAN 80	400 mg
4	TWEEN 80	400 mg
5	TWEEN 40	400 mg
6	ETHANOL	2 ml
7	GLYCEROL	1 ml

Preparation of niosomes gel from proniosomal gel

Preparation of noisome was carried out by ether injection method. This method includes slowly introducing a solution of surfactant dissolved in diethyl ether into warm water maintained at 60°C. The surfactant mixture in ether is injected

through 14-gauge needle into an aqueous solution of material. Vaporization of ether leads to formation of single layered vesicles [9]

INVITRO-STUDIES

Encapsulation efficiency

Each preliminary proniosomal formulation was centrifuged at 25°C for 30min to separate entrapped drug.supernant was separated, filtered and sufficiently diluted with methanol to determine the concentration of entrapped drug spectrophotometrically. The percentage of drug encapsulation was calculated by equation [10-13]

EE % = ED/ TD × 100

- Where EE% is the entrapment efficiency percent,
- ED is the entrapped drug concentration and
- TD is the theoretical drug concentration.

PH determination

The proniosomal gel was made into niosomal formulation. The pH of niosomal suspension was determined using pH meter. The electrode first calibrated with ph 4.0 and 7.0 solution then readings were recorded on ph meter.

Vesicle shape & size

A drop of niosomal dispersion prepared from proniosomal gel was spread on a glass slide and examined for the vesicle structure .The proniosomal gel (100mg) was hydrated with phosphate buffer solution (10ml) in a test tube by manual shaking or by sonication for 5min and the resulting niosomes were observed under optical microscope at 100X magnification. The size of vesicle was measured using calibrated ocular and stage micrometer in the microscope [14].

Drug content

The drug content was determined by 2gm proniosomal gel sample was withdrawn from container and dissolved in 100ml ethanol .From that solution 1ml solution was diluted up to 10ml with ethanol. The absorbance was measured by U.V spectrophotometer against blank at λmax 241 and the drug content was calculated [15].

In-vitro dissolution study

In-vitro release pattern of niosomal suspension prepared from proniosomes was carried out using dialysis bag as a donor compartment. An accurately measured amount of metformin niosomes, equivalent to 400 mg metformin, were taken in the dialysis membrane and placed in a beaker containing 75 ml of phosphate buffer solution, which acted as a receptor compartment [16]. Previously the sealed with closure clips after adding the niosomal preparation. The beaker was placed over a magnetic stirrer (100 rpm) and maintained at 37+1˚C. At predetermined time intervals during 24 hrs; aliquot samples (5 ml) were withdrawn and replaced with fresh buffer. The sink condition is maintained throughout the experiment. The withdrawn samples were appropriately diluted and analyzed for drug content spectrophotometrically at 233 nm using PBS as blank.

Dissolution medium

6.8 PH phosphate buffer:

44.8ml of 0.1M NaOH, 100ml of potassium dihydrogen phosphate in sufficient amount of distil water and then finally make up the volume to 1000ml of volumetric flask .If necessary adjust the ph to 6.8.

RESULTS AND DISCUSSION

Table 3: Encapsulation efficiency

FORMULATIONS	% ENTRAPMENT EFFICIENCY
SPAN20	72.6 %
TWEEN80	65.52 %
SPAN80	57.2 %
TWEEN40	45 %

Table 4: PH determination

Formulation	Span20	Tween80	Span80	Tween40
pH	5.8	6.5	6.2	5.85

Table 5: Vesicle size

No. of particles	Span-20	Tween-80	Span-80	Tween-40
1	0.2*9=1.8	0.1*8.3=0.83	0.2*9.5=1.9	0.2*9=1.8
2	0.1*9=0.9	0.4*8.3=3.32	0.4*9.5=3.8	0.3*9=2.7
3	0.2*9=1.8	0.5*8.3=4.15	0.5*9.5=4.7	0.3*9=2.7
4	0.2*9=1.8	0.5*8.3=4.15	0.4*9.5=3.8	0.4*9=3.6
5	0.3*9=2.7	0.6*8.3=4.98	0.5*9.5=4.7	0.2*9=1.8
6	0.4*9=3.6	0.3*8.3=2.49	0.2*9.5=1.9	0.4*9=3.6
7	0.3*9=2.7	0.2*8.3=1.66	0.3*9.5=2.85	0.2*9=1.8
8	0.1*9=0.9	0.4*8.3=3.32	0.5*9.5=4.7	0.3*9=2.7
9	0.3*9=2.7	0.7*8.3=5.81	0.3*9.5=2.85	0.3*9=2.7
10	0.3*9=2.7	0.5*8.3=4.15	0.4*9.5=3.8	0.4*9=3.6
	Avg=2.16µm	Avg=2.26µm	Avg=3.5µm	Avg=2.7µm

Here the least count values are 9, 8.3, 9.5, 2.7 of span-20, tween-80, span-80, tween-40 respectively.

Table 6: Drug content

FORMULATION	ABSORBANCE	CONC.	Drug content
SPAN20	2.196	0.272	18.19
TWEEN80	1.972	0.244	16.38
SPAN80	1.714	0.014	14.30
TWEEN40	1.335	0.0415	11.25

Table 7: Standard curve

S.NO	Drug content in µg/ml	Absorbs at 233nm	x-x	y-y	$(x-x)^2$	$(y-y)^2$	(x-x)(y-y)
1	0	0	-4	-0.443	16	0.196249	1.772
2	1	0.080	-3	-0.363	9	0.131769	1.082
3	2	0.197	-2	-0.246	4	0.060516	0.492
4	3	0.327	-1	-0.116	1	0.013456	0.116
5	4	0.420	0	-0.023	0	0.000529	0
6	5	0.537	1	0.094	1	0.008836	0.094
7	6	0.650	2	0.207	4	0.042849	0.414
8	7	0.830	3	0.387	9	0.149769	1.161
9	8	0.948	4	0.505	16	0.255025	2.02

Σy=3.989, Σx=36

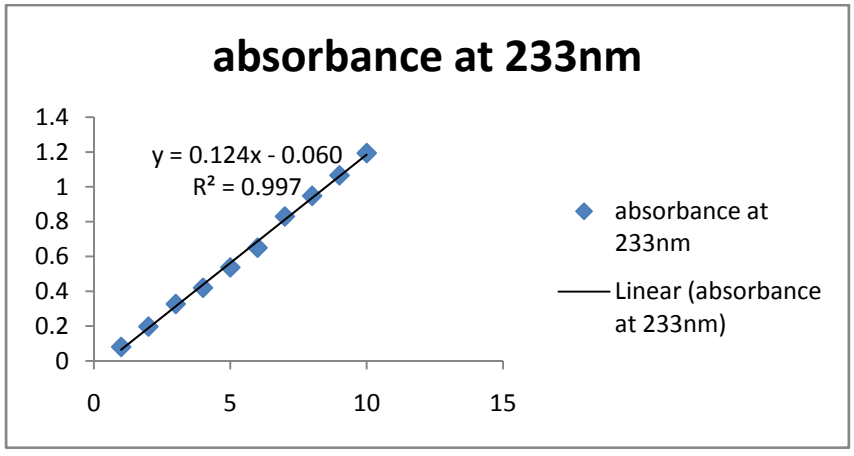

Fig. 1

DISSOLUTION OF NIOSOMES:

Table 8: Dissolution of niosomes using span-20

s.no	Time in min	Absorbance	%drug release
1	0	0.23	7
2	60	0.256	37
3	120	0.289	52
4	240	0.312	64
5	360	0.48	78
6	480	0.68	85
7	720	0.73	92
8	960	0.84	93.7
9	1440	0.96	98.2

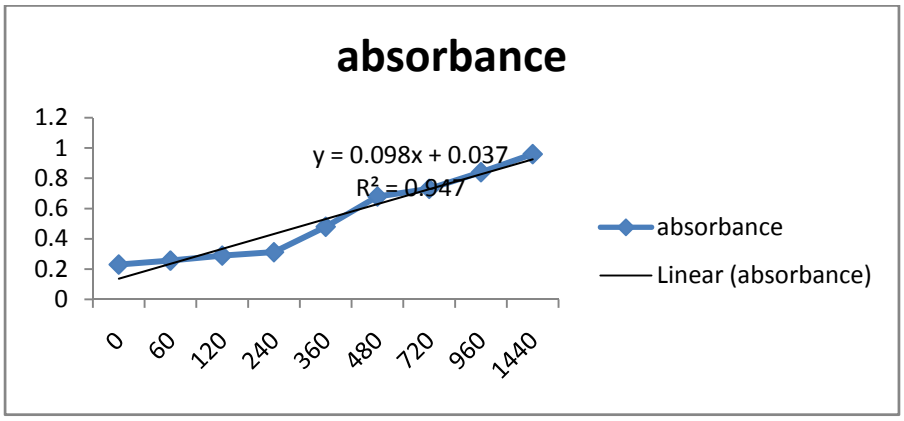

Fig. 2

Table 9: Dissolution of niosomes using tween-80

s.no	Time in min	Absorbance	%drug release
1	0	0.245	3.3
2	60	0.26	39
3	120	0.302	48
4	240	0.42	62
5	360	0.59	77
6	480	0.61	88
7	720	0.72	93
8	960	0.81	97
9	1440	0.92	97.7

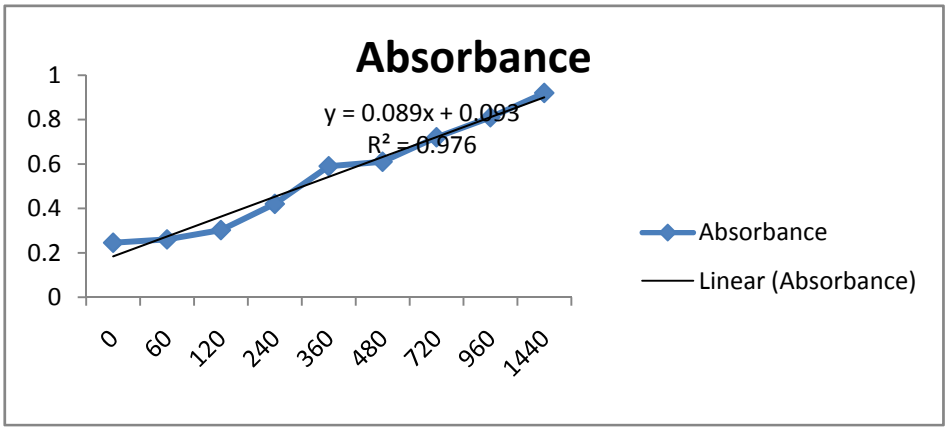

Fig-3

Table 10: Dissolution of niosomes using span 80

S.NO	Time in min	Absorbance at 233nm	%drug release
1	0	0.234	4
2	60	0.252	46
3	120	0.312	53
4	240	0.347	68
5	360	0.57	73
6	480	0.62	84
7	720	0.74	91.1
8	960	0.83	94.8
9	1440	0.94	97.4

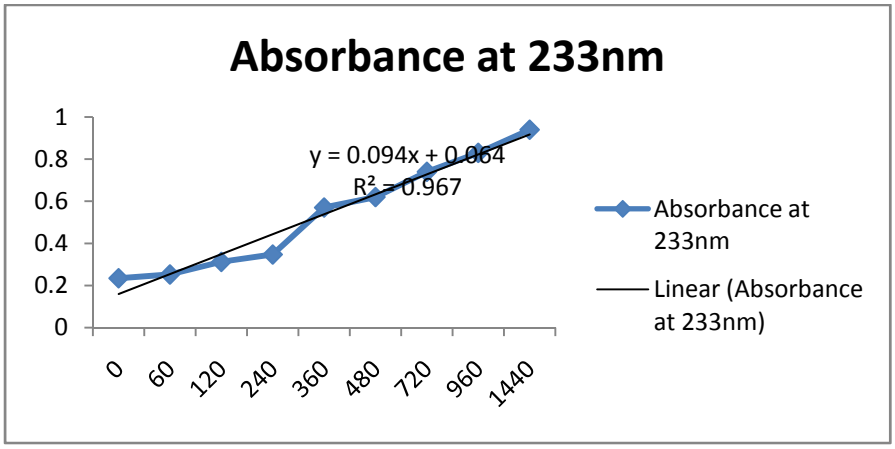

Fig. 4

Table 11: Dissolution of niosomes using tween-40

S.No	Time in min	Absorbance at 233nm	% drug release
1	0	0.281	3
2	60	0.294	14
3	120	0.338	28
4	240	0.473	31.5
5	360	0.691	42
6	480	0.767	61
7	720	0.812	72
8	960	0.88	87.5
9	1440	0.95	92.4

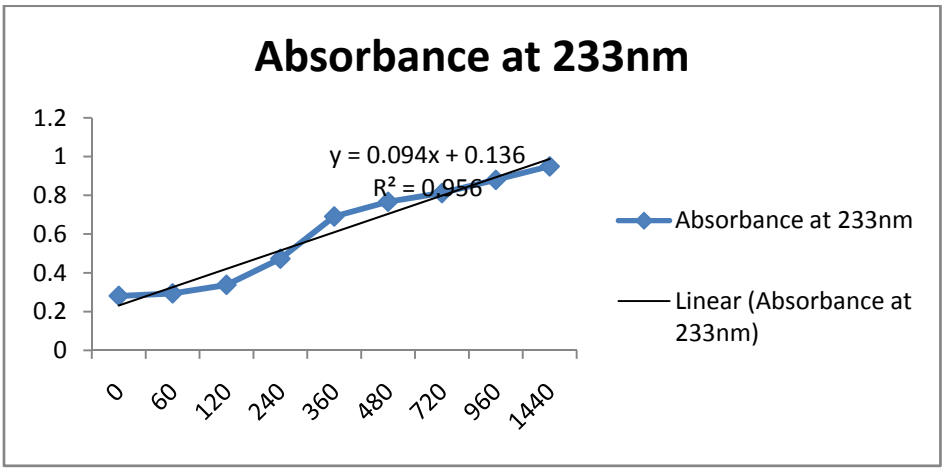

Fig. 5

CONCLUSION

An ideal or best formulation of niosome is said to be one that gives high entrapment efficiency i.e., SPAN20. In this study, entrapment efficiency was found to be cholesterol: surfactant ratio dependent. Formulations were found to ensure a good oral bioavailability of the drug in vitro. On the basis of these facts, it can be concluded that niosomes may be a promising approach to improve the oral bioavailability of metformin.

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