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Original Article

Preparation and evaluation of anti-hyperlipidaemic in topical preparation and characterization using vesicular drug delivery system

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ABSTRACT

Simvastatin is an HMG CoA reductase inhibitor used for the treatment of dyslipidemia, however the drug has two major problems; short biological half-life and extensive first pass effect. The aim of this work was to develop Simvastatin niosomal gel to prolong the residence time at the absorption site thereby increase bioavailability and avoid extensive first pass effect. Simvastatin niosomal gel were prepared by dispersing different ratios of carbopol 940, hydroxyl propyl methyl cellulose and sodium carboxy methyl cellulose (2:3: 4%) w/v into the alcoholic solution at room temperature. The 2^3 factorial design was used to develop Simvastatin niosomal gel, the independent factors used are polymer types (carbapol 940, HPMC H_{15} and Na CMC), polymer concentrations (2,3, 4% w/v) . The developed niosomal gel were characterized by clarity, pH determination, homogeneity, rheological characteristics, entrapment efficiency and *In vitro* diffusion studies. The results revealed that the Simvastatin noisomal gel were clear and homogenous at pH 6.8 , viscosity ranged from 1560 to1700 cn and the efficiency of entrapment ranged from 80 to 90%.It was found that the formula contains carbapol 940 and pellets of niosome which had the highest release rate and selected as optimized formula.

Key words: Simvastatin, niosomal gel, 2^3 factorial design and polymers

INTRODUCTION

Simvastatin is a 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG CoA reductase inhibitors) used in the treatment of dyslipidemia as well as to prevent atherosclerosis-related complications such as stroke and high risk heart attacks [1]. Simvastatin has low and incomplete absorption in the gastrointestinal tract but subjected to hepatic tissue binding and first-pass metabolism [2].

Transdermal drug delivery system can improve the therapeutic efficacy and safety of the drug, because it can be absorbed at a predetermined and controlled rate. Transdermal delivery of drugs from the skin to the systemic circulation provides a convenient route of administration for a variety of clinical indications. For transdermal delivery of drugs, stratum corneum is the main layer for permeation of drug. Different approaches of penetration enhancement are used to increase the flux through the skin , Drug-vehicle based enhancement methods such as liposomes, niosomes are used in transdermal research as better alternative methods to enhance permeation of drugs through skin [3].

Carbopol 940 P is a mucoadhesive polymer which has been investigated as a useful adjuvant for bioadhesive drug delivery system [4]. The main reasons for addition of mucoadhesive polymers in the system are the possibilities of prolongation of resident time in organ and increase of the contact time with absorbing mucosa, resulting in the enhancement of drug absorption.

Hydroxypropyl methylcellulose (HPMC H_{15}) is a mixed alkyl/ hydroxyalkyl cellulose ether containing methoxyl and hydroxypropyl groups, commonly used in hydrophilic matrix drug delivery systems and frequently as a gel base to provide

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sustained release for medications. It is available in a wide range of molecular weights and classified by the viscosity of the 2% (w/w) aqueous solution. HPMC H_{15}can be also used for the preparation of oral controlled drug delivery systems. [5]

Sodium carboxymethyl cellulose (Na CMC) is an anionic water soluble natural polymer derivative, which is biocompatible and non-toxic polysaccharides [6]. It formed hydrogel by the action of ionizing radiation at high concentration in aqueous solution [7]. It has been reported that a novel biodegradable hydrogel of Na CMC was synthesized without any additives from paste by the application of radiation [8]

MATERIALS AND METHODS

Materials: Simvastatin was kindly donated by Hikma Pharma S.A.E (6th of October City- Egypt), Na CMC, Carpobol 940 and HPMC H15 (Sigma Chemical Co., St. Louis), Ethanol, glycerin, phenol, camphor and triethanolamine were obtained from Merck, Darmstadt, Germany.

Methods

Calibration curve: Linear relationship was established between the concentration of Simvastatin and UV absorbance after proper dilution using spectrophotomter at 238 (Jasco V530, Japan).

The data was subjected to the best fitting line calculation and revealed high linearity coefficient value namely 0.9998. The procedural constant (K) was computed from the slope of the calibration curve and was found to be 0.0694. The calibration curve was plotted and depicted Therefore, the spectrophotometric assay within the used concentration range is valid and can be utilized to estimate Simvastatin in mixed solvent (40ml methanol:60ml phosphate buffer)

Experimental Design: Simvastatin loaded niosomal gel were prepared using 2^3 full factorial design. The design was applied to investigate the effect of the independent variables; polymers concentration (X1), the type of polymer (X2), on the physico-chemical properties of the prepared niosomal gel (Table 1).

Preparation of niosomal gel: The vehicle used in incorporation of niosomes for topical delivery gel were; carbopol 940, Na CMC and HPMC H15, and they were prepared by diffusion method. Pellet of niosomes was utilized for the formulation of topical gel. Gel polymer such as carbopol 940, Na CMC and HPMC H_{15} was used for the preparation of niosomal gel. 2 g of carbopol- 940 powder was dispersed into vigorously stirred (stirred by magnetic stirrer Remi 5MLH) with 100ml distilled water (taking care to avoid the formation of in dispersible lumps) which was and allowed to hydrate for 24 hrs. The dispersed system was neutralized with drop of triethanolamine to adjust the pH to [6.8] by using pH meter (Lab India Sab 5000).Appropriate amount of niosomes containing Simvastatin equivalent to 20mg were then incorporated into gel-base with continuous stirring until homogenous formulation was achieved.

Evaluation of Topical Gel [9]: Formulated gel was evaluated for their physico-chemical properties such as (clarity, homogeneity, pH) in-vitro release studies and drug entrapment efficiency.

Clarity: All formulations were observed for their clarity by visual inspection under black and white background and it was graded as follows; turbid: +, clear: ++, very clear (glassy): +++.

pH Determination: The pH of Simvastatin gel formulation was determined by using digtal pH meter standardized before with buffer of pH 4.0 and 7.0 . 1gram of gel was dissolved in 100ml of distilled water and then, average values of triplicate pH measurements were calculated.

Homogeneity: The homogeneity of all formulations was determined by visual inspection after the gels have been stored in the container for their appearance and presence of any aggregate.

Fourier transform infrared spectroscopy (FTIR): The FTIR spectrum of pure Simvastatin, pure polymers, and gel formulations are showen (figure 2). The spectra obtained from the drug and polymer combination showed band assignments at the same wavelength ranges indicating no interaction between the drug and the polymers.

Spreadability: The spreadability of the gel formulation was determined, by measuring diameter of 1 gm gel between horizontal plates (20×20 cm2) after 1 minute. The standardized weight tied on the upper plate was 125 gm [10] **.**

Extrudability study: A good gel extrude optimally from the gel with slight pressure applied. The extrudability of formulations from aluminium collapsible tubes was determined using universal tube filling machine. Aluminium collapsible tubes filled with 10g gels were held between two clamps. A tube was compressed and extrudibility of the formulation was determined in terms of weight in grams required to extrude a 0.5 cm. ribbon of gel in 10 seconds. If glassy +++this equal to excellent,

clear ++ this equal to good, turbid +this equal to satisfactory

Grittiness: All the formulations were evaluated microscopically for the presence of particles if any, no appreciable particulate matter was seen under light microscope. Hence obviously the gel preparation fulfils the requirement of freedom from particular matter and from grittiness as desired for any topical preparation.

Rheological Characteristics: The rheological studies of samples were carried out with Brookfield Digital viscometer (LV DV-E model) using S-18 spindle number. All developed formulations were poured into the small sample adaptor rotated with increased angular velocity up to 100 rpm.

Entrapment Efficiency: accurately weighed 0.5 g of niosomal gel was dissolved in 10 ml of phosphate buffer pH 6.8; the aqueous suspension was then sonicated. Niosomes containing Simvastatin were separated from un entrapped drug by centrifugation at 14000 rpm for 45 min at 4^{o}C. The supernatant was recovered and assayed spectrophotometrically at 238 nm wavelength [11]

In vitro diffusion studies: Accurately weighed 1 GM of niosomal gel was spread uniformly on the membrane and then, the donor compartment was kept in contact with a receptor compartment and the temperature was maintained at 37±0.5^{0}C. The solution on the receptor side were stirred by externally driven Teflon coated magnetic bars at predetermined time intervals, pipette out 2 ml of solution from the receptor compartment at specified time intervals for up to 24hrs and immediately replaced with the fresh 2 ml phosphate buffer. The cumulative % release of drug was calculated against time. [12]

RESULT AND DISCUSSION

Calibration curve: Linear relationship was established between the concentration of SIMVASTATIN and UV absorbance after proper dilution using spectrophotomer at 238 (Jasco V530, Japan). The data was subjected to the best fitting line calculation and revealed high linearity coefficient value namely 0.9998. The procedural constant (K) was computed from the slope of the calibration curve and was found to be 0.0694. The calibration curve was plotted and depicted Therefore, the spectrophotometric assay within the used concentration range is valid and can be utilized to estimate Simvastatin in mixed solvent (40ml methanol:60ml phosphate buffer).

Fourier transform infrared spectroscopy (FTIR): The spectra obtained from the drug and polymer combination showed band assignments at the same wavelength ranges indicating no interaction between the drug and the polymers

CONCLUSION

Niosomal system is atechnique for transdermal drug delivery because it decrease the toxicity and enhances penetration effect due to presence of surfactants. Also have a several advantages over the conventional vesicular systems. A wide variety of active agents of different therapeutic actions can also be given by niosomal drug delivery system in the form of tablets, beads or capsules. Optimized batch of niosome was used for the preparation of niosomal gel by incorporating hydrated niosomes to carbapol, HPMC H_{15} and Na CMC matrix.

All the gels were evaluated for their appearance, pH, rheological properties, drug entarppment efficiency and in-vitro release study. These work confirm that niosomes are a very promising carrier for the topical administration due to the enhanced delivery of drugs through the skin thus prompting various opportunities for the development of suitable therapeutic strategies through the topical route. The formulation is easy to scale up as it involve simple procedures and the use of pharmaceutically acceptable additives.

Table 1: **Composition of different coded values in 2^3 f ull factorial design**.

Independent variable	**Code value**		
	-1	**0**	**+1**
Polymer Concentration w/v % (X1)	2	3	4
Type of polymer(X2)	Carbapol	HPMC	NA CMC

Table 2: Relationship between concentration and absorbance of Simvastatin in methanol: Phosphate buffer at 238 nm.

Concentration of Simvastatin(Mcg /ml)	Absorbance
5	0.386
7.5	0.545
10	0.729
12.5	0.903
K	0.0694
R	0.998

Table 3: Values of evaluation parameters of developed gel

Formulation	X1	X2	Clarity	pH	Homogenity	Viscosity	Entrapment
N GR1	-1	-1	+++	6.8	Good	1560	87%
N GR2	0	-1	+++	6.7	Good	1570	90%
N GR3	+1	-1	++	6.8	Good	1550	81%
N GR4	-1	0	+++	6.8	Good	1557	86%
NGR5	0	0	+++	6.7	Good	1563	88%
N GR6	+1	0	+++	6.9	Good	1580	83%
N GR7	-1	+1	++	6.8	Good	1559	90%
N GR8	0	+1	+++	7	Good	1566	82%
N GR9	+1	+1	++	6.9	Good	1569	90%

Tablet 4 : The spreadability of formulations of niosomal gels

Formulations	Spreadability
N GR 1	11.75
N GR2	10.08
N GR3	10.75
N GR4	10.70
N GR5	10.25
N GR6	10.50
N GR7	12
N GR8	11.50
N GR9	10

Table 5 : The extrudability studies of formulations of niosomal gels

Formulations	Extrudibility
N GR1	+++
N GR2	++
N GR3	+++
N GR4	++
N GR5	+++
N GR6	++
N GR7	+++
N GR8	++
N GR9	++

Table 6 : The grittness of formulations of niosomal gels

Formulations	Grittiness
N GR 1	---
N GR 2	---
N GR 3	---
N GR 4	----
N GR 5	---
N GR 6	----
N GR 7	-----
N GR 8	------
N GR 9	---------

Table 7: *In-Vitro* drug release of niosomal gel formulations

Time Hr	N GR1	N GR2	N GR3	N GR4	N GR5	N GR6	N GR7	N GR8	N GR9
0	0	0	0	0	0	0	0	0	0
2	6	5	3	5	4	3	5	3	2
4	20	15	9	15	10	6	13	5	4
6	40	30	20	30	25	15	25	10	9
8	55	45	30	50	40	25	46	23	20
10	70	55	45	65	50	40	60	39	35
12	75	65	60	70	60	55	65	55	52
24	90	85	80	88	83	75	85	80	75

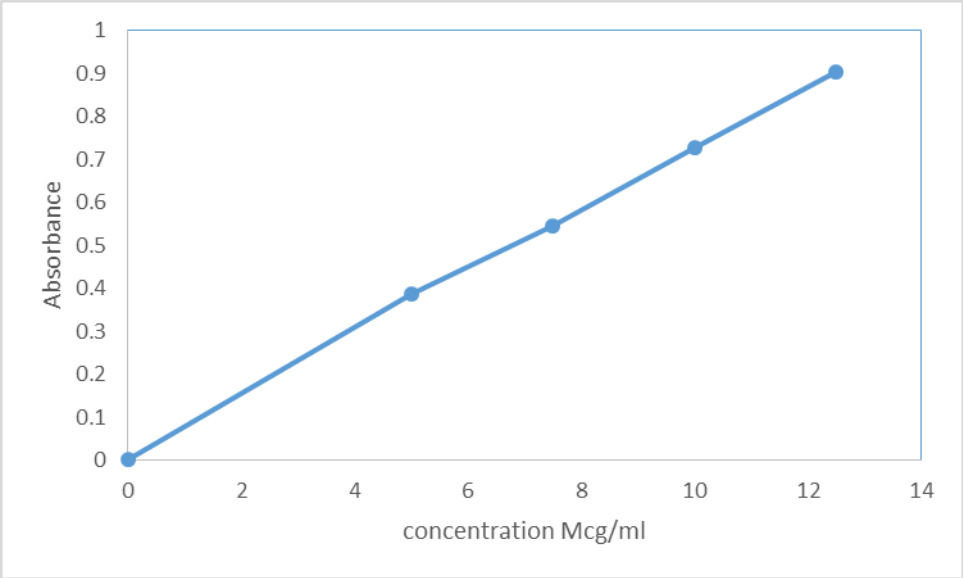

Figure 1: Calibration curve of Simvastatin

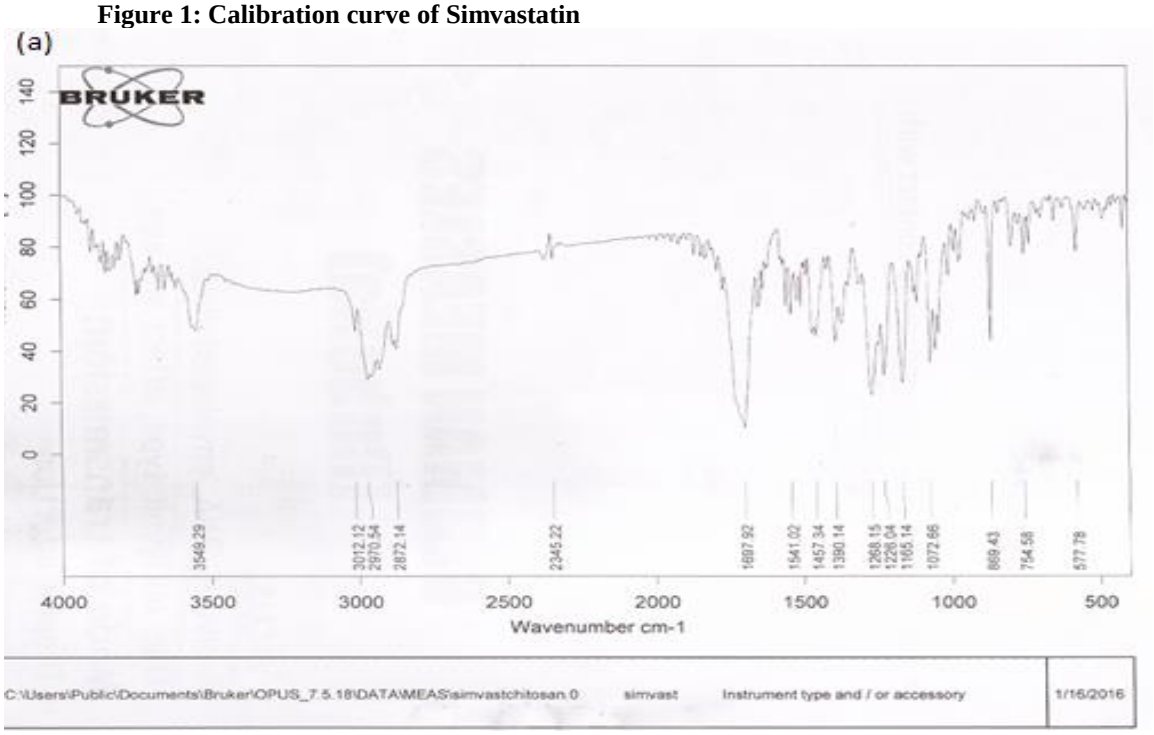

Figure (2): FT-IR Spectra of Simvastatin

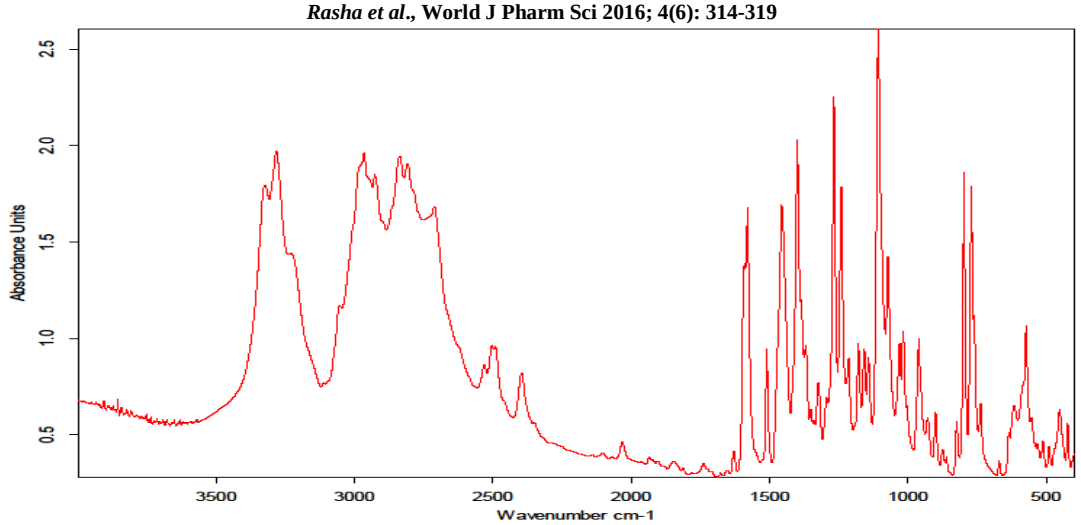

Figure (3): FT-IR Spectra of carpobol 940

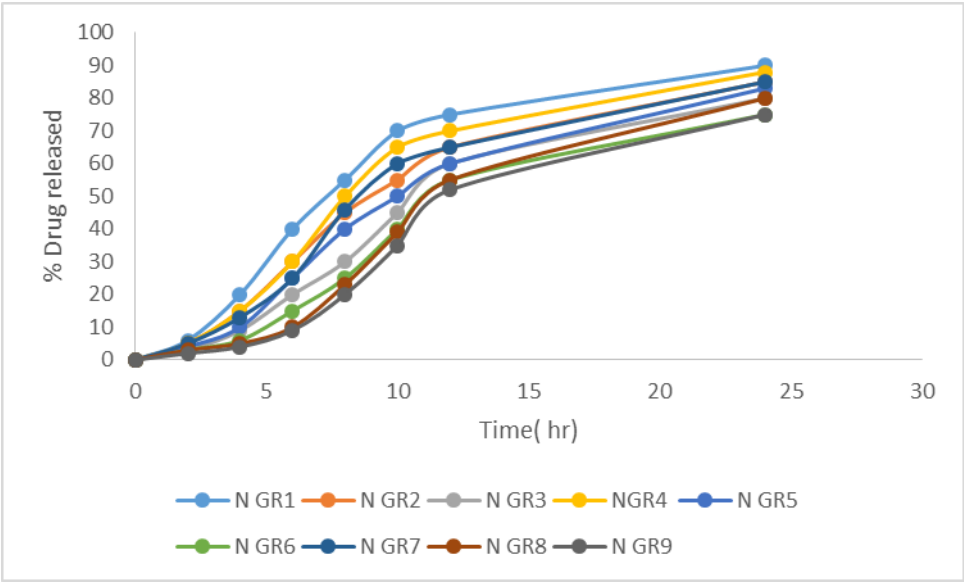

Figure (4) : Dissolution profile for niosomal gel formulations (F1-F9) [mean ± SD (n=3)]

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