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Short Communication Article

Preparation and evaluation of metformin hydrochloride loaded Niosomes for enhancement of oral Bio-availability

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ABSTRACT

The purpose of this study was to develop metformin hydrochloride loaded niosomes as controlled release drug delivery system for the treatment of diabetes mellitus. The aim of the present work was to develop metformin hydrochloride loaded niosomes by centrifuge technique using various type of surfactants and cholesterol. Surfactants used were (Span 40, Tween 80) and cholesterol was added. The prepared neosomes were evaluated by determination of particle size using photon correlation spectroscopy (Zetasizer Nano ZS, Malvern), determination of entrapment efficiency (E.E %) and in-vitro drug release study usingdialysis bag technique at phosphate buffer 6.8. The particle size of prepared niosome range between found to be 974.1 nm indicating that these vesicles were all of a small size. The poly-dispersity index(PDI) of the investigated vesicles showed values in the range of 0.141.The data obtained from the 8 hours release study of F2 formulation was found to be 84.60% and was considered to be the best formulation as it shows better linearity as compared to F1 and F3 formulations. The present study suggested that niosome formulations provide sustain and prolong delivery of drug with enhance Bio-availability.

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1. Introduction

Metformin hydrochloride has become the standard of care for type II diabetes, particularly in overweight and it has been shown to reduce the cardiovascular disease within the population. Metformin hydrochloride is a small molecule with 50% oral bioavailability (Rao et al., 2011). It does not undergo hepatic metabolism and the main route of elimination is renal tubular secretion. Metformin impairs lactate clearance of the liver through the inhibition of complex I of the mitrochondrial respiratory chain. So, lactic acidosis associated with the use of metformin hydrochloride is predominantly due to lack of lactate's clearance rather than to an increased production (Carafa et al., 1998).

Nanotechnology appears as one of the most promising areas in the field of pharmaceutics. Many varieties of nanoparticles are available such as different polymeric and liposomes, niosomes, micelles, microcapsules (Rao et al., 2011). Niosomes are vesicles composed of non-ionic surfactants which are biodergradable, relatively nontoxic, more stable than liposomes and inexpensive. It is an alterna-tive way to liposomes. Niosomal vesicles can be small unilamellar, multilamellar or large unilamellar. Niosomes are capable of encapsulating large quantities of material in a relatively small volume of vesicles (Corti et al., 2008).

Recently, niosomes have been studied as drug delivery system to provide a better oral bioavailability considering stability and high penetration property through biological membrane. Niosome formation requires the presence of a particular class of charge inducing agents to prevent vesicle aggregation hence improves stability (Fang et al., 2001). In addition, charged vesicles may achieve more therapeutic efficiency than neutral vesicles, due to its ability to target certain cells. For example, cationic niosomes are used successfully as drug delivery systems for improving potency of oligonucleotides *in vivo* (Chakilam et al., 2007). The aim of this study is to produce more effective form of MH preparation with more prolonged effect by formulation of MH-loaded niosomes targeting for maintaining effective plasma drug concentrations.

2. Material and Methods

2.1. Materials

Metformin hydrochloride was supplied by Saudi Pharmaceutical Industries & Medical Appliances Corporation (SPIMACO), Al-Qassim City, KSA; Span 40, Tween 80, Diethyl ether and chloroform and Cholesterol were obtained from Merck Specialist Pvt. Ltd., Mumbai-18. All other chemicals used were of analytical grade.

2.2. Methodology

2.2.1. Drug excipient compatibility study

FTIR: The drug-excipient compatibility of samples, accomplished by KBr pellet method, was tested by FTIR spectroscope (Bruker Alpha-E, modedl no- 10059736) in a fixed wavelength region between 400- 4000 cm−1 (Pardakhty et al., 2007)

2.2.2. Preparation of standard calibration curve of Metformin hydrochloride pH 6.8

100mg of drug was weighed and transferred to a 100mL volumetric flask. The volume was made up to the mark with pH 6.8 phosphate buffer to obtain stock solution (A) having concentration of 1000 μg/mL.1mL of stock solution (A) was further diluted to 100mL with pH 6.8 phosphate buffer to obtain stock solution (B) having concentration 10 μg/mL. Aliquots of stock solution (B) was serially diluted to obtain solutions in concentration of 2 to 10 μg/mL of drug with pH 6.8 phosphate buffer (Devalapally et al., 2007; Khandare et al., 1994). The absorbance of the final solutions was measured at 232 nm as shown in **Figure 1**.

2.2.3. Particle size determination

Niosomal size distribution was determined using photon correlation spectroscopy (Zetasizer Nano ZS, Malvern). The size distribution analysis was performed at a scattering angle of 90ºC and at a temperature of 25ºC (Guinedi et al., 2005; Omaima et al., 1997).

2.2.4. Drug entrapment efficiency

To determine the entrapment efficiency, an aliquot of niosomal suspension was taken in a centrifuge tube and was centrifuged for 1 hour at 2500 rpm (Omaima et al., 1997; Owen et al., 2000). The supernatant was collected and diluted with required amounts of methanol. The absorbance of the samples was determined using a UV- spectrophotometer at a λmax of 232 nm. The percent drug entrapment efficiency was determined using the formula:

$$\textbf{Drug entrapment}\ (\%) = \frac{\textbf{Amount encapsulated in the niosomes}}{\textbf{Amount of the lipid and surfactant taken}} \times \mathbf{100}$$

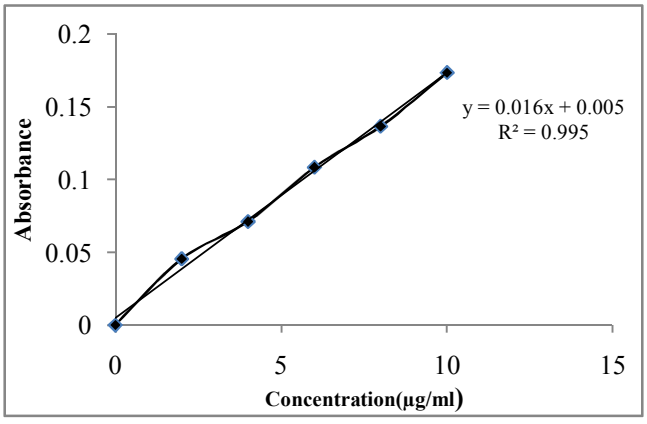

Figure 1: Calibration curve of Metformin Hydrochloride

2.2.5. In vitro drug release studies

In vitro drug release studies from the prepared niosomal formulation were carried out at PH 6.8 using a dialysis bag. An amount of niosomes equivalent to 100mgof metformin hydrochloride was weighed and filled in the bag which was placed into a beaker containing 100ml of phosphate buffer PH 6.8 (Namdeo et al., 1999). The beaker was placed over a magnetic stirrer (50 rpm). The temperature was maintained at 37±1ºC. Aliquots were withdrawn periodically and equal volumes of fresh medium equilibrated at 37±1ºC were replaced. The withdrawn samples were then analysed for drug content spectrophotometrically at 232 nm (Popli et al., 1996).

3. Result and Discussion

3.1. Compatibility study with FTIR

Figures 5-6 show that all standard peaks for functional group are at their place indicating compatibility of drug with all other excipients. Drug and/or excipients were crushed in 1:1 ratio and compressed with KBr to form pallets, which were used to analyze.

3.2. Particle size

The particle size of the MH loaded niosomes were evaluated by photon electron microscopy. The particle size analysis showed that the average diameter of metformin hydrochloride loaded niosomes was found to be 974.1 nm indicating that these vesicles were all of a small size (Van Hal et al., 1996) and was shown in **Figure 2**.

3.3. Drug entrapment efficiency

Entrapment efficiency of MH in different niosomal preparations is presented in **Table 1**. Entrapment efficiency was high in all the formulations which may be attributed to the use of REV technique to prepare niosomes. This technique resulted in high uptake of MH due to the large encapsulated volume in unilamellar vesicles of REV (Namdeo et al., 1999; Guinedi et al., 2005), which leads to more entrapped MH as a hydrophilic drug within the aqueous core. The drug entrapment efficiency of metformin loaded niosomes was found to be 40.17.

3.4. In vitro drug release studies

In vitro drug release studies from the prepared niosomal formulation were carried out at PH 6.8 using a dialysis bag. The data obtained from **Table 2** for 8 hours release study of F2 formulation was found to be 84.60% and was considered to be the best formulation as it shows better linearity as compared to F1 and F3 formulation. This release pattern of the water soluble drugs seems to be characteristic of the bilayer vesicles. Similar reports exist in the case of liposomes (Betageri et al., 1992) and in niosomes (Popli et al., 1996). The drug release study curve was shown in **Figure 4**.

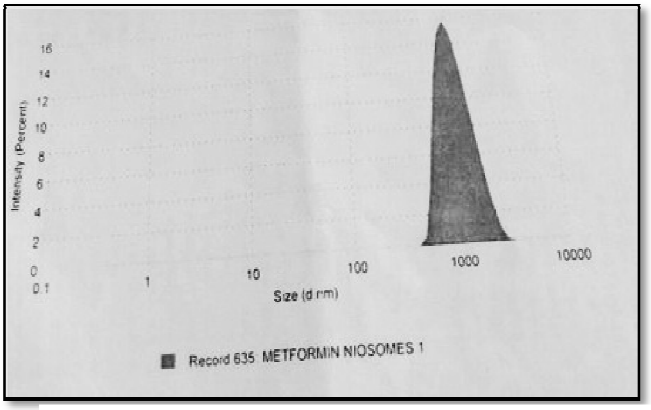

Figure 2: Particle size distribution of metformin hydrochloride loaded niosomes

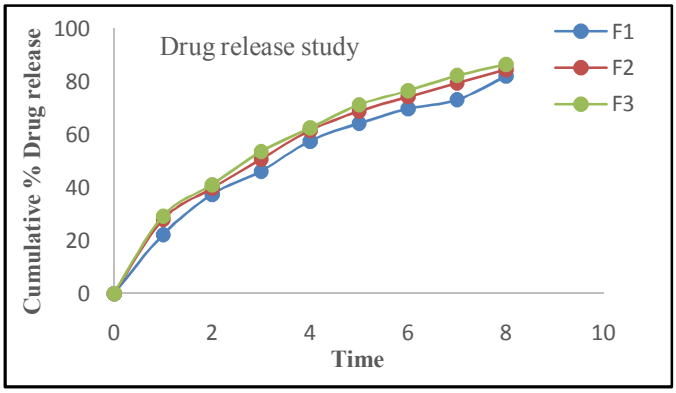

Figure 4: Comparative release profile of metformin hydrochloride loaded noisome

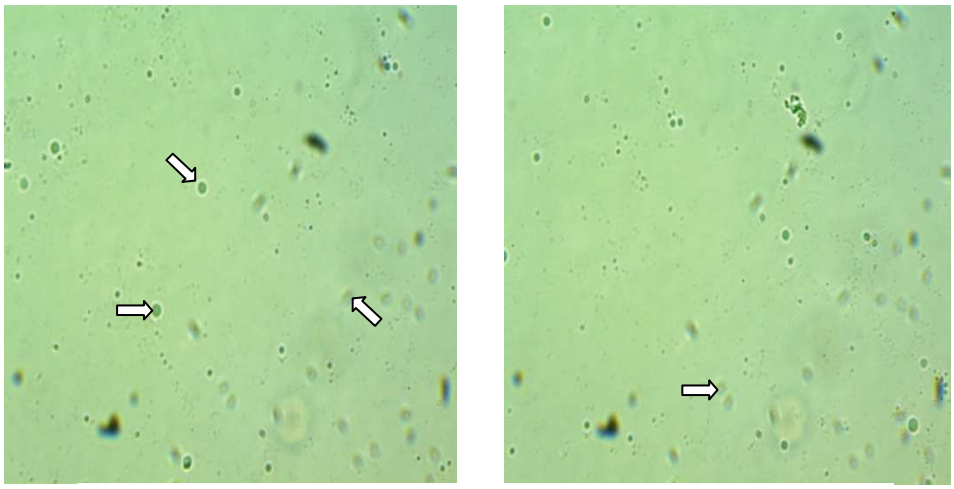

Figure 3: Optical microscopy of metformin hydrochloride loaded niosomes

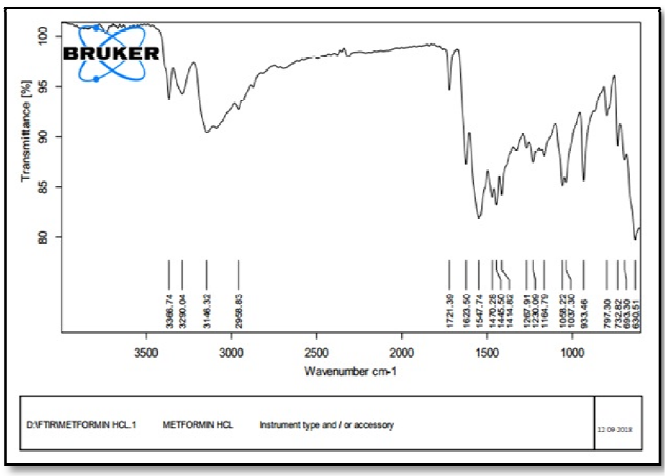

Figure 5: FTIR spectra of Metformin Hydrochloride

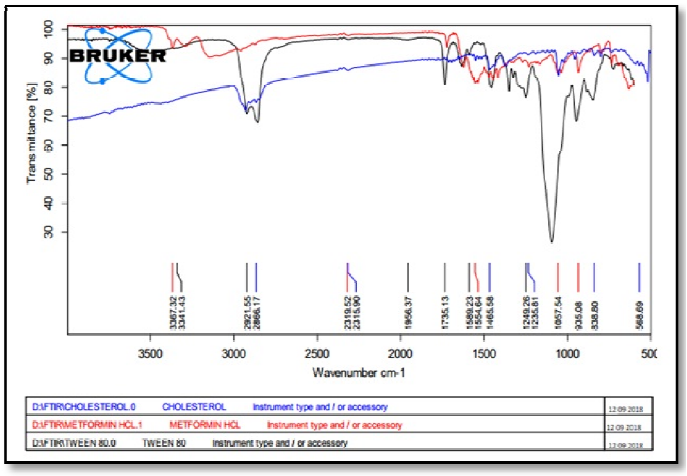

Figure 6: FTIR spectra of metformin HCl + Tween80 + Cholesterol

Table 1: Table for drug entrapment efficiency

Absorbance	Concentration (µg/ml)	Total conc. (mg)	Drug entrapment (%)
0.8323	45.02	45.02	40.17

Table 2: Table for drug release profile of metformin hydrochloride loaded niosomes.

Time(hr)	Cumulative % Drug release		
	F1	F2	F3
0	0	0	0
1	22.21	27.98	29.24
2	37.45	39.8	41.11
3	46.23	50.8	53.63
4	57.61	61.6	62.56
5	64.34	68.9	71.34
6	69.87	74.31	76.55
7	73.21	79.53	82.32
8	82.22	84.6	86.53

Conclusion:

It can be concluded that the administration of MH loaded niosomes as a delivery system for oral purposes could be advantageous because a prolong and improved hypoglycemia effect can be obtain compare to free drug solution using the same dose. This leads to a reduction of the no. of doses that should be given to the patient daily as well as expected minimizing the side effects of the drug and the F2 formulation shows better drug release and enhance bioavailability. Lyophillization of MH niosomal nanosuspension and incorporating it in the tablet form is recommended for further investigation as promising sustained release oral preparation using the same tablet dose on the market.

Conflict of Interest

No conflict of interest.

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