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Formulation, Development and Characterization of Effective Niosomal Drug Delivery System for the Treatment of Diabetes Mellitus

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ABSTRACT

In the present study, gliclazide-loaded niosomes are formulated and evaluated for their in vitro as well as in vivo characteristic in an attempt to improve the oral bioavailability of the drug. Formulation of niosomes was optimized for highest percentage of drug entrapment. Microscopic observation confirmed that all particles were uniform in size and shape. The entrapment efficiency was determined by separating the unentrapped drug using dialysis. The *in vitro* release studies of drug from niosomes exhibited a prolonged drug release as observed over a period of 24 h. The positive values of zeta potential indicated that the gliclazide niosomes were stabilized by electrostatic repulsive forces. Results from stability study have shown that the drug leakage from the vesicles was least at 4ºC followed by 25 and 37ºC. The niosomes showing maximum entrapment and suitable release rate were selected for in vivo evaluation. In conclusion, the niosomal formulation could be a promising delivery system for gliclazide with improved bioavailability and prolonged drug release profile.

Key words: Heme Oxygenase Inhibitor; HO-1; 2D QSAR; 3D QSAR; kNN-MFA

1. INTRODUCTION

Diabetes mellitus (or Diabetes) is one of the chronic, lifelong metabolic disorders that affect individuals, families and society at large. It is caused due to disturbances in carbohydrate, fat and protein metabolism and also due to the defects in insulin secretion, insulin action or both. The disease condition may lead to short and long term complications like retinopathy, peripheral neuropathy, coronary heart disease, stroke and peripheral vascular diseases affecting normal life of people.[1-3] Since last twenty years, there has been an increase in the number of diabetes patients in many parts of the world and considered as one of the important health issues worldwide to be addressed to immediately. The death rate is increased, in case of diabetes patients, mainly due to diabetes related complications developed because of poor treatment methods to the patients. The global prevalence of diabetes in 1998 was estimated to be 143 million people based on the data published (Wild et al., 2004). A survey report shown in Table 1 represents the country having highest number of diabetic patients.[4-7]

Niosomes are non-ionic surfactant vesicles, which are obtained on admixture of non ionic surfactant of alkyl or dialkyl poly-glycerol ether class and cholesterol with subsequent hydration in aqueous media.[8] They are found to be more stable system than the liposomal drug delivery system because of higher chemical stability of surfactants than that of phospholipids, which are used in preparation of liposomes. The reason of phospholipids instability is their easy hydrolysis. They are non-ionic, so they are less toxic and improve the therapeutic index of drug by restricting its action to target cells. Besides Niosomes lie in nanometric scale, are osmotically active and stable. These are flexible in terms of structural characteristics (composition, fluidity and size) and thus can be designed according to the desired situation. [9-13]

Niosomes surfactants are biodegradable, biocompatible and non-immunogenic. Niosomes can be unilamellar or multilamellar depending upon the method used to prepare them. They possess an intra-structure consisting of hydrophilic, amphiphilic and lipophilic moieties together. As a result, they can accommodate drug molecules with a wide range of solubility, improves oral bioavailability of poorly absorbed drugs, enhance skin penetration of drugs, In addition, handling and storage of surfactants used in preparation of Niosomes do not need special conditions.[14-17]

2. MATERIALS AND METHODS

2.1 Material used

Metformin hydrochloride was obtained from Matrix laboratories, Hyderabad. Cholesterol was procured from Fisher Scientific, Mumbai.Sorbitan monostearate(span60) was obtained from Loba Chemie Pvt.Ltd Mmubai. Dicetylphosphate(DCP) was taken from Matrix laboratories ,Hyderabad. Lipid DOTAP also obtained from Fisher scientific,Mumbai. Chloroform was obtained from Merck specialties Pvt.Ltd Mumbai and diethyl ether also obtained from Matrix laboratories, Hyderabad.

2.2 Formulation development of metformin hydrochloride loaded niosomes

Reverse phase evaporation (REV) technique with slight modifications was used to prepare MH-loaded niosomes. MH niosomes was prepared from a total of 0.2 mM of film forming constituents consisting of Span 60, Chol with or without DOTAP or DCP in molar ratios. Blank niosomes without MH was prepared using Span 60 and Chol in a molar ratio 150:40.[18]

Lipid solution (Chol and Span 60 with or without charge inducing agents DOTAP or DCP dissolved in 5 ml chloroform) was emulsified with the aqueous phase containing drug (2 ml) using microson XL-2000 (Misonix Inc., Farmingdale, NY) probe sonicator at 4 ^{0}C for 5 min. The clear gel formed is further sonicated after the addition of a small amount (1 ml) of phosphate-buffered by swirling at room temperature to obtain thick gel. The gel was collapsed by the addition of 2 ml PBS with stimultaneous eddying and then evaporated in a rotary evaporator at 40 ^{0}C under low pressure for 10 min, then heated on a water bath at 60 ^{0}C for 10 min to yield niosomal vesicles. Metformin was characterised by partition coefficient, melting point,solubility,pH, and FTIR spectroscopy.[19-25]

Table 1: Optimization of niosomes by varying amount of lipid

Components	Formulation code					
	F1	F2	F3	F4	F5	F6
Drug (mg)	100	100	100	100	100	100
Span 60 (mg)	100	150	200	100	150	200
Cholesterol (ml)	20	30	40	20	30	40
Chloroform (ml)	20	10	10	10	10	10
PBS (7.4) (ml)	20	20	20	20	20	20

2.3 Stability Studies

The formulation investigated for physical stability studies showed the residual drug content in niosomes to be 77.61±0.22 at the end of three months. The results concluded that almost 99% of the drug was retained upto 1 month and at the end of the study 91.84% drug was retained by the formulation. There was no significant variation found in physical appearance, average particle size and % drug content of the niosomal formulation.

3. RESULT & DISCUSSION

3.1 Physiochemical Characterization of Drug

Table 2: Organoleptic property of metformin hydrochloride

S.No.	Sensory characters	Result
1.	Taste	Bitter
2.	Appearance	White
3.	Odor	Odorless
4.	Texture	Crystalline

Table 3: Solubility study of metformin hydrochloride

S. No.	Solvent	Solubility
1.	Water	Free Soluble (++)
2.	Alcohol	95% Soluble
3.	Acetone	Insoluble (+)
4.	Ether	Insoluble (+)
5.	Chloroform	Insoluble (+)
6.	HCL	Freely Soluble (++)

Table 4: Melting point of the metformin hydrochlorid

S.NO	Sample	Melting-point (^{0}C)
1.	1	220
2.	2	222
3.	3	225

Table 5: Partition coefficient determination of the Metformin Hydrochloride

S.NO	Solvent system	Partition coefficient
1.	n-Octanol/Distilled water	0.0622 ± 0.0021
2.	n-Octanol/PBS (Ph 7.4)	0.0541 ± 0.0016

The average partition coefficient is 0.0622

Table 6: Determination Of pH (1% W/V Solution In Water): pH

S.NO.	pH of the solution	Average pH of the solution
1.	6.67	6.68
2.	6.68	
3.	6.68	

Table 7: Loss of drying of drug sample

RAW MATERIAL	Observed LOD
Metformin	Not more than 0.5% determined on 1.0g by drying in an oven at 105^{0}C

Table 8: Drug-excipients compatibility study at room temperature for four weeks

Excipients	Caking	Discoloration	Odor/gas Formation	Aggregation
Metformin hydrochloride	No	No	No	No
Metformin hydochloride + all excipents	No	No	No	No

3.2. Formulation and Evaluation of Niosomes

3.2.1 Formulation Development of Metformin hydochloride loaded niosomes

Table 9: Optimization of niosomes by varying amount of lipid

Components	Formulation code					
	F1	F2	F3	F4	F5	F6
Drug (mg)	100	100	100	100	100	100
Span 60 (mg)	100	150	200	100	150	200
Cholesterol (ml)	20	30	40	20	30	40
Choloform (ml)	20	10	10	10	10	10
PBS (7.4) (ml)	20	20	20	20	20	20

Table: 10: Evaluations of niosomes for Particle size Zeta potential and entrapment efficiency

Batch code	Mean size (nm) (Z average)	Polydispersity index	Zeta Potential (mV)	Entrapment Efficiency %
Blank	291.3 ± 1.11	0.517 ± 0.8	-57.8 ± 7.7	-
MN1	298.7 ± 5.6	0.77 ± 0.6	-17.8 ± 1.6	89.75
MN2	388.8 ± 4.4	0.28 ± 0.5	-28.7 ± 2.0	94.60
MN3	225.7 ± 4.9	0.40 ± 0.3	+10.3 ± 3.1	85.34

Table 11: Stability study of metformin niosome formulation under refrige (28^{0}C) storage condition

Time (days)	Entrapment efficiency (%)	Drug remaining (%)
0	84.50±0.19	100.00±0.00
7	84.36±0.10	99.83±0.12
15	84.24±0.13	99.68±0.15
30	83.91±0.08	99.30±0.09
45	83.39±0.10	98.69±0.12
60	81.55±0.21	96.50±0.25
90	77.61±0.22	91.84±0.26

Table 12: *In vitro* drug release data for MN1

Time (h)	Square Root of Time $(h)^{1/2}$	Log Time	Cumulative % Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
1	0	1	0.983	0.995	0.855	0.577
2	0.414	1.301	0.983	0.997	0.859	0.574
3	032	1.477	0.963	0.098	0.819	0.551
4	1.000	1.602	0.947	0.978	0.789	0.512
6	1.449	1.778	0.964	0.985	0.834	0.521
8	1.828	1.903	0.966	0.098	0.831	0.600
12	2.464	2.079	0.937	0.094	0.770	0.484

Table 13: *In vitro* drug release data for MN2

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative % Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative %Drug Remaining
1	0	1	0.938	0.990	0.769	0.479
2	0.414	1.301	0.919	0.970	0.744	0.450
3	0.732	1.477	0.935	0.979	0.777	0.464
4	1.000	1.602	0.930	0.991	0.764	0.450
6	1.449	1.778	0.942	0.994	0.779	0.464
8	1.828	1.903	0.953	0.967	0.822	0.450
12	2.464	2.079	0.949	0.969	0.824	0.497

Table 14: *In vitro* drug release data for MN3

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative % Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
1	0	1	0.939	0.972	0.793	0.473
2	0.414	1.301	0.873	0.973	0.702	0.405
3	0.732	1.477	0.938	0.998	0.820	0.546
4	1.000	1.602	0.964	0.986	0.820	0.535
6	1.449	1.778	0.934	0.994	0.830	0.565
8	1.828	1.903	0.954	0.864	0.864	0.584
12	2.464	2.079	0.874	0.894	0.886	0.654

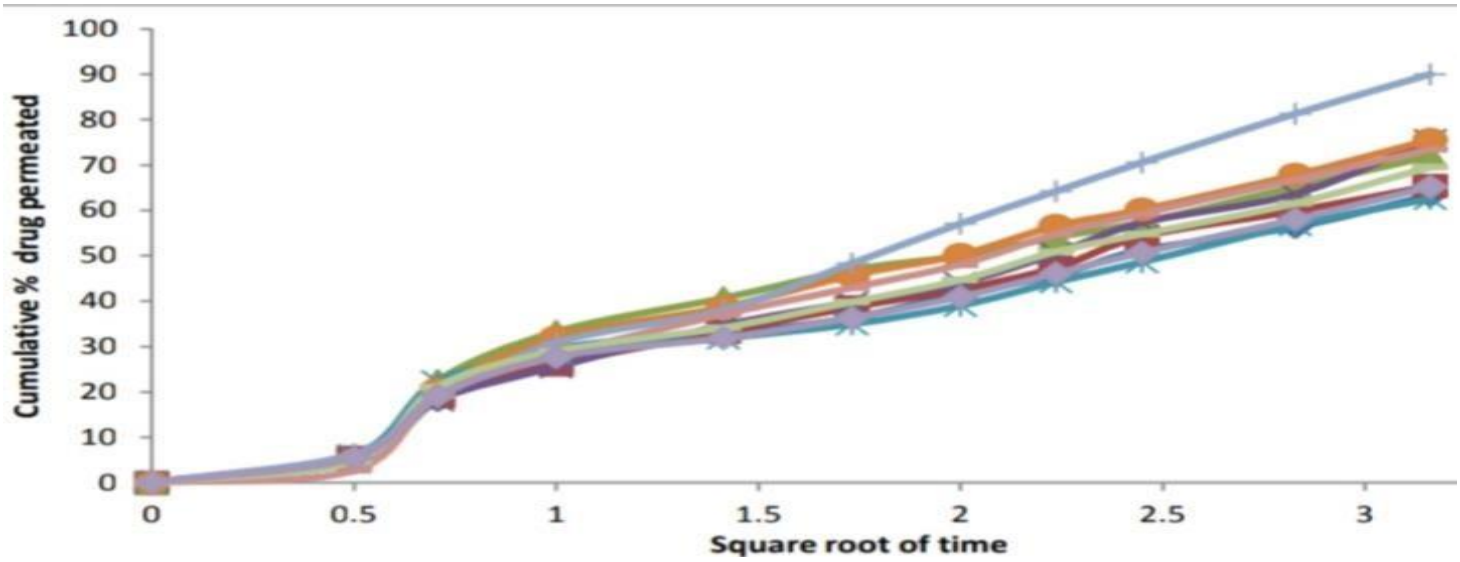

Figure 1: Cumulative % drug released Vs Time (Zero Order Kinetics)

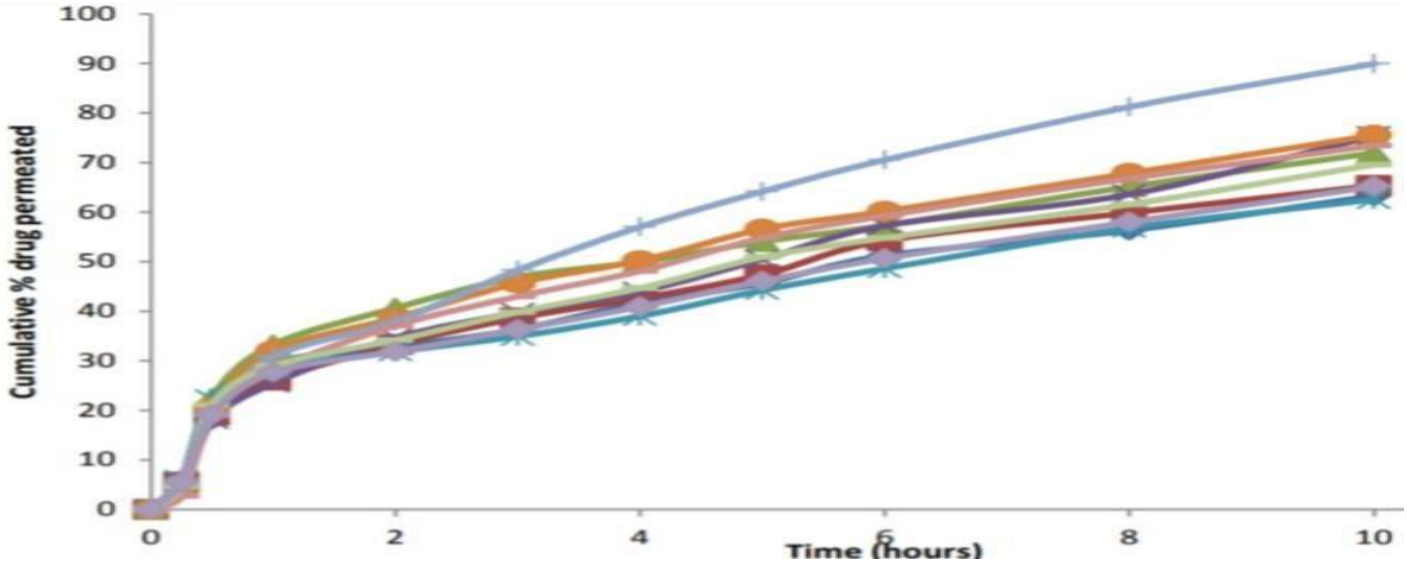

Figure 2: Drug Release Kinetics (First Order Kinetics)

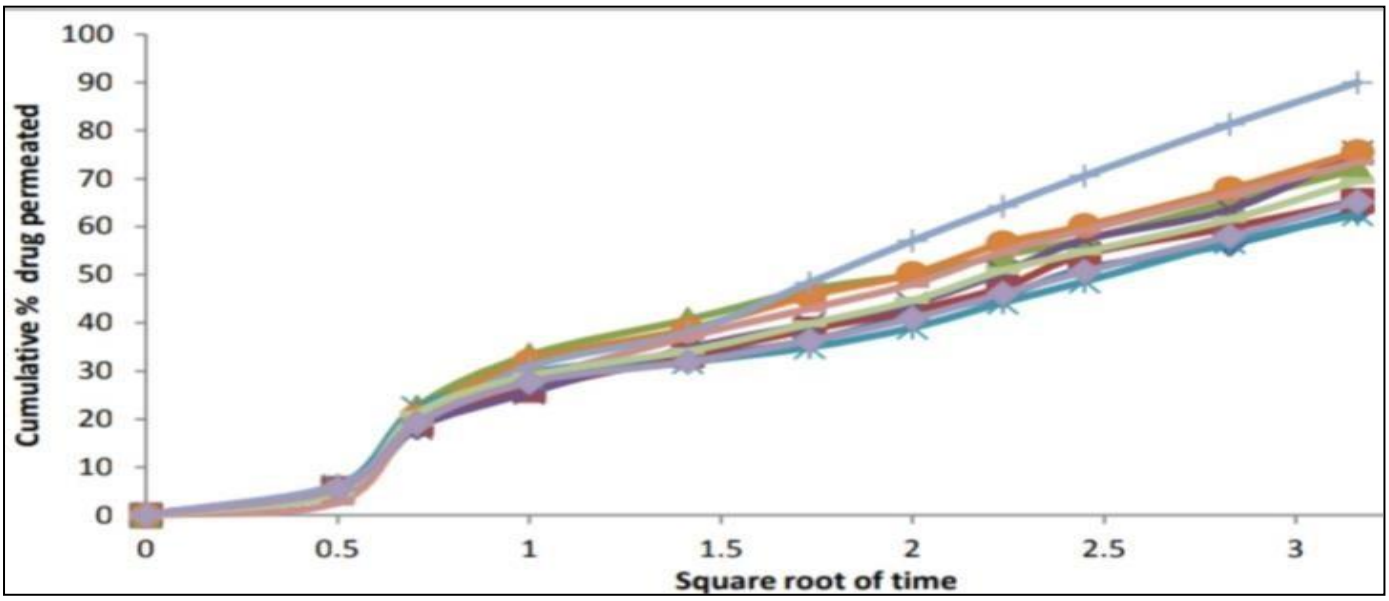

Figure 3: Drug Release Kinetics (Higuchi Model)

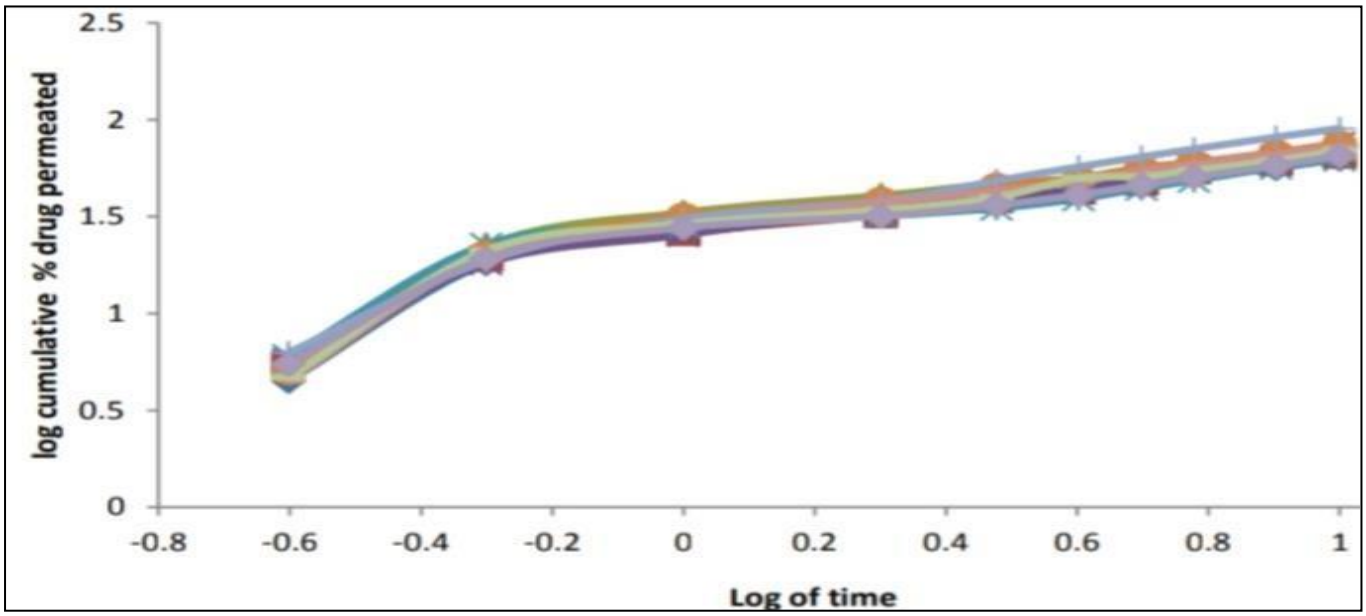

Figure 4: Drug Release Kinetics (Korsmeyer – Peppas Model)

4. CONCLUSION

It can be concluded that the administration of MH-loaded niosomes as a delivery system for oral purposes would be advantageous because a prolonged and improved hypoglycaemic effect can be obtained compared to free drug solution using the same dose. This leads to a reduction of the number of doses that should be given to the patients daily as well as expected minimizing the side effect of the drug. Hence, comfortable dosage form can be produced.

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