

DEVELOPMENT AND OPTIMIZATION OF PRNIOSOMES FOR ORAL DELIVERY OF GLIPIZIDE

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ABSTRACT

Approaches to stabilize niosomal drug delivery system without affecting its properties of merits have resulted in the development of the promising drug carrier "Proniosomes". Proniosomes is a dry formulation using suitable carrier coated with non-ionic surfactants and can be converted into niosomes immediately before use by hydration. These proniosome-derived niosomes are as good as or even better than conventional niosomes. Glipizide loaded Sorbitol, Maltodextrin and Mannitol based proniosomes were prepared by slurry method with different surfactant to cholesterol ratio. The proniosome formulations were evaluated for FT-IR study, angle of repose and scanning electron microscopy. The niosomal suspensions were further evaluated for entrapment efficiency, *In-vitro* release study, Kinetic data analysis, Stability study. The result from SEM analyses has confirmed the coating of surfactant on the surface of carrier. The formulation based maltodextrin showed higher entrapment efficiency of 82.64 ± 1.25 and *in-vitro* release of 98% at the end of 24hr was found to be best among the various formulations. The proniosome formulations were evaluated for FT-IR study, angle of repose and scanning electron microscopy and the result showed that the maltodextrin based formulation was best suited. Release was best explained by the zero order kinetics. Kinetic analysis shows that the drug release follows super case II transport diffusion. Maltodextrin based Proniosome formulation has showed appropriate stability for 90 days when compared with other carriers reconstituted niosomes by storing the formulation at refrigerator condition.

Keywords: Glipizide, Proniosome, Maltodextrin, Sorbitol, Mannitol, Span-60, FT-IR, SEM.

INTRODUCTION

A number of novel drug delivery systems have emerged encompassing various routes of administration, to achieve controlled and targeted drug delivery. Encapsulation of the drug in vesicular structures is one such system, which can be expected to prolong the duration of the drug in systemic circulation, and to reduce the toxicity by selective up taking. Consequently a number of vesicular drug delivery systems such as liposomes, niosomes, transferosomes and pharmacosomes and provesicular systems like proliposomes and proniosomes have been developed.¹

Vesicular systems like liposomes or niosomes have specific advantages while avoiding demerits associated with conventional dosage forms because these particles can act as drug reservoirs. These carriers play an increasingly important role in drug delivery because by slowing drug release rate, it is possible to reduce the toxicity of drug. Whereas provesicular system like proniosomes have advantage of minimizing the problems of physical stability related to niosomes such as aggregation, fusion and leaking and provided additional convenience in transportation, distribution, storage and dosing.²

Proniosomes

Proniosomes are dry formulations of surfactant-coated carrier, which can be measured out as needed and rehydrated by brief agitation in hot water. These "proniosomes" minimize problems of niosomes physical stability such as aggregation, fusion and leaking and provided additional convenience in transportation, distribution, storage and dosing.

Proniosome-derived niosomes are superior to conventional niosomes in convenience of storage, transport and dosing. Stability of dry proniosomes is expected to be more stable than a pre-manufactured niosomal formulation. In release studies proniosomes appear to be equivalent to conventional niosomes. Size distributions of proniosome-derived niosomes are somewhat better than those of conventional niosomes so the release performance in more critical cases turns out to be superior. Proniosomes are dry powder, which makes further processing and packaging possible. The powder form provides optimal flexibility, unit dosing, in which the proniosome powder is provided in capsule could be beneficial. A proniosome formulation based on maltodextrin was recently developed that has potential applications in delivery of hydrophobic or amphiphilic drugs. The

better of these formulations used a hollow particle with exceptionally high surface area. The principal advantage with this formulation was the amount of carrier required to support the surfactant could be easily adjusted and proniosomes with very high mass ratios of surfactant to carrier could be prepared. Because of the ease of production of proniosomes using the maltodextrin by slurry method, hydration of surfactant from proniosomes of a wide range of compositions can be studied.^{3, 4, 5, 6, 7}

Advantages of proniosomes over the niosomes:

- Avoiding problem of physical stability like aggregation, fusion, leaking.
- Avoiding hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion.

Brief review of various carriers used in the research work

Maltodextrin

It is a mixture of glucose, disaccharides and polysaccharides, obtained by the partial hydrolysis of starch. Maltodextrin is a flavorless, easily digested carbohydrate made from cornstarch. A maltodextrin is a short chain of molecularly linked dextrose (glucose) molecules, and is manufactured by regulating the hydrolysis of starch. A white or almost white, slightly hygroscopic powder or granules, freely soluble in water.

Sorbitol

It is also known as glucitol, Sorbogem and Sorbo, is a sugar alcohol that the human body metabolizes slowly. It can be obtained by reduction of glucose, changing the aldehyde group to a hydroxyl group. Sorbitol is found in apples, pears, peaches, and prunes. It is synthesized by sorbitol-6-phosphate dehydrogenase, and converted to fructose by succinate dehydrogenase and sorbitol dehydrogenase. Succinate dehydrogenase is an enzyme complex that participates in the citric acid cycle. Sorbitol is a sugar substitute.

Mannitol

It is a white, crystalline organic compound. This polyol is used as an osmotic diuretic agent and a weak renal vasodilator. It was originally isolated from the secretions of the flowering ash, called manna after their resemblance to the Biblical food, and is also referred to as mannite and manna sugar.¹⁸

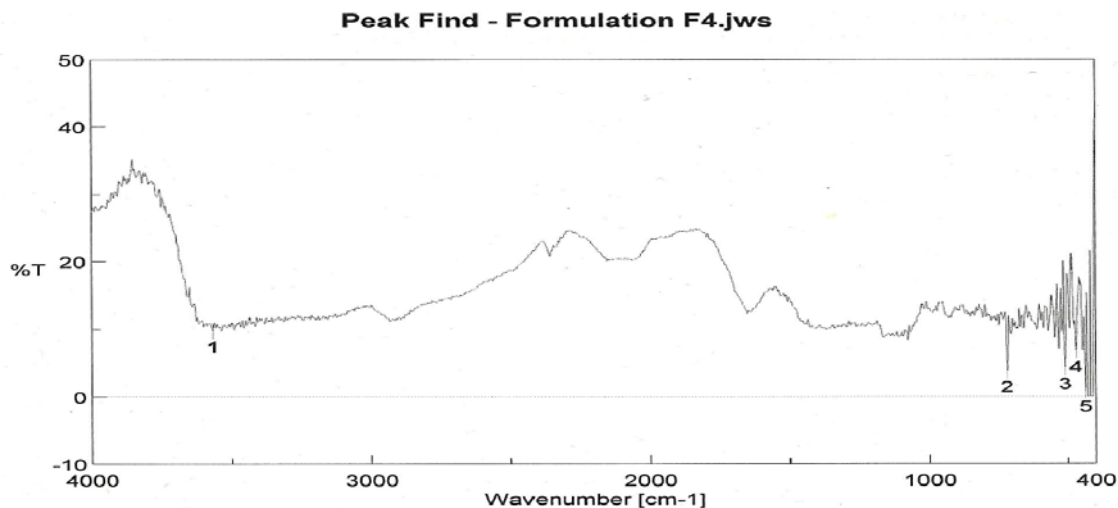
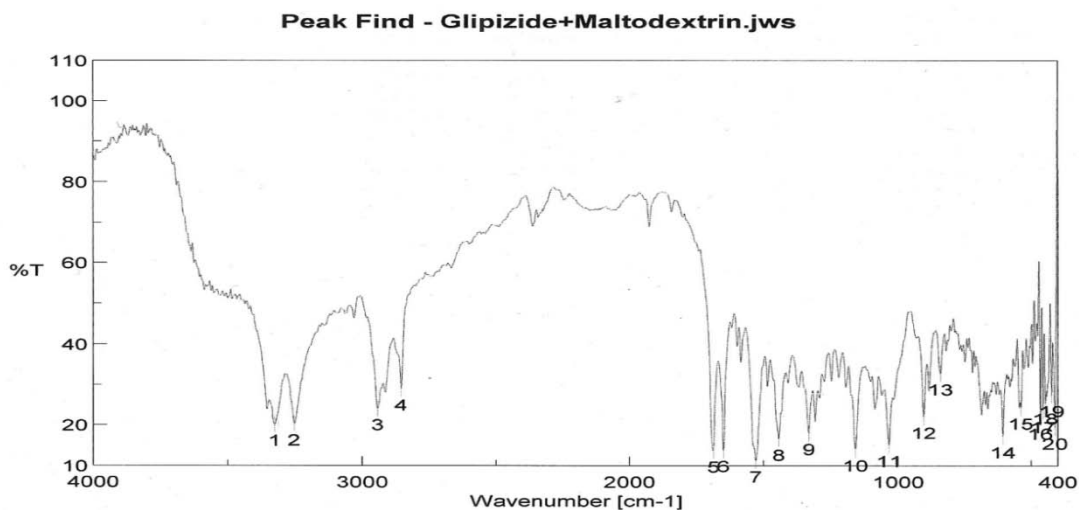
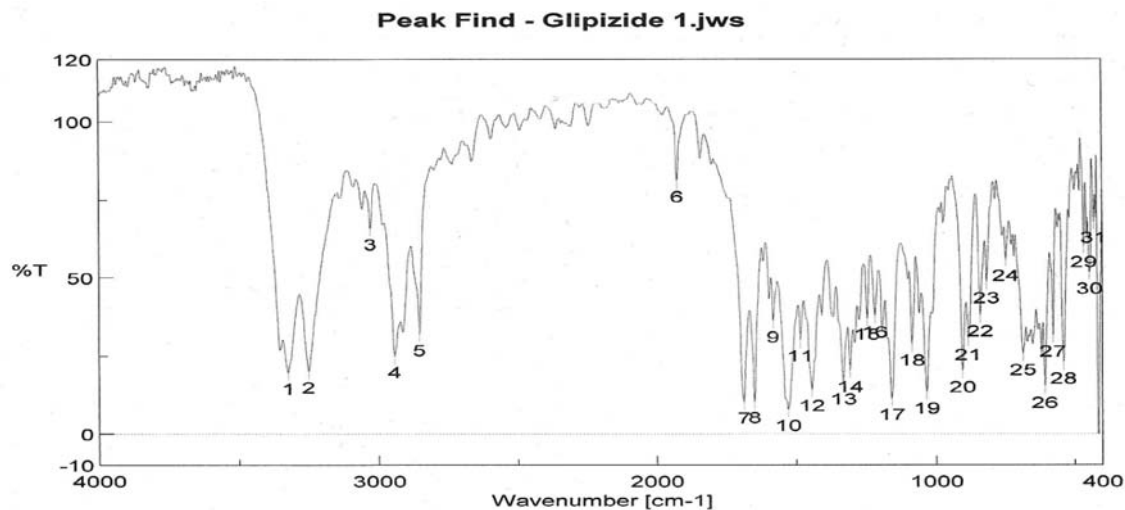
MATERIALS AND METHOD

Chemical and reagents

Glipizide (Cadila pharmaceuticals), Cholesterol (Loba chem., Mumbai), Span 60 (Loba chem., Mumbai), Chloroform (Loba chem., Mumbai), Methanol (S. D. Fine Chem. Mumbai), Maltodextrin (S. D. Fine Chem., Mumbai), Sorbitol (S. D. Fine Chem., Mumbai), Mannitol (S. D. Fine Chem., Mumbai). All other ingredients used for the study were of analytical grade.

Preformulation Studies

FT-IR Spectra of Glipizide, maltodextrin, Sorbitol, Mannitol, physical mixture of drug carrier and F4 formulation were recorded. The Glipizide present in the formulation F4 was confirmed by FTIR spectra. The characteristic peaks due to pure Glipizide at 3250.16, 2943.47, 1689.70, 1651.12, 1373.36, 159.26, 686.68 for N-H stretching, C-H Stretching, C=O Stretching, -CONH Stretching, C-H bending, S=O Stretching, C-H bending respectively. All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Glipizide and carriers. It also confirmed that the stability of drug during formulation.



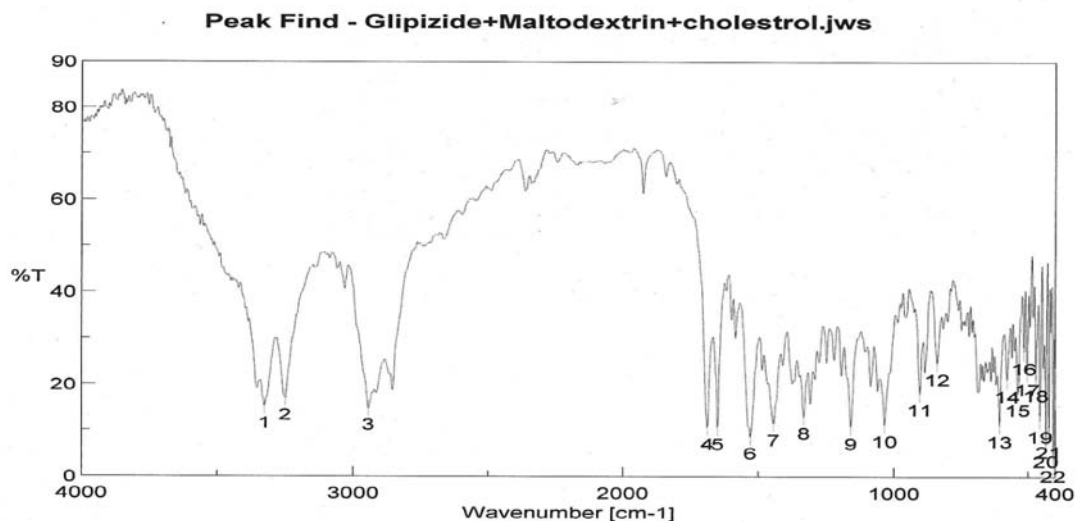


Fig. 1: IR Spectra, IR spectra of Glipizide drug, IR spectra of Glipizide drug with maltodextrin, IR spectra of Glipizide drug with maltodextrin and cholesterol, IR spectra of proniosome formulation F4

Formulation of proniosomes

Preparation of proniosomes with Maltodextrin/Sorbitol/Mannitol carrier

Proniosomes were prepared by the slurry method. For ease of preparation, a 250µmol stock solution of span-60 and cholesterol was prepared in chloroform:methanol (2:1) solution. The required volume of span-60, cholesterol stock solution and drug dissolved in chloroform:methanol (2:1) solution was added to a 100ml round bottom flask containing the maltodextrin/Sorbitol/Mannitol carrier. Additional chloroform:methanol solution added to form slurry in the case of lower surfactant loading. The flask was attached to a rotary flash evaporator to evaporate solvent at 60to70 rpm, a temperature

of 45 ± 2°C, and a reduced pressure of 600mmHg until the mass in the flask had become a dry, free flowing product. These materials were further dried overnight in a desiccator under vacuum at room temperature. This dry preparation is referred to as 'proniosomes' and was used for preparations and for further study on powder properties. These proniosomes were stored in a tightly closed container at refrigerator temperature until further evaluated. ⁵

Preparation of niosomes from proniosomes

Proniosomes were transformed to niosomes by hydrating with hot water 80°C and by gentle mixing. The niosomes were sonicated twice for 30sec using sonicator and then evaluated for further studies. ⁷

Table 1: Compositions of proniosome batches of Glipizide with Maltodextrin, Sorbitol and Mannitol:

Formulation	Ratio(SF:CH)	Surfactant	Cholesterol	MD/SL/ML
F1	225:25	96.75	9.66	225
F2	200:50	86.12	19.33	200
F3	175:75	75.35	29.01	175
F4	150:100	64.59	38.67	150
F5	125:125	58.82	48.33	125
F6	100:125	43.06	58.00	100
F7	75:175	32.29	68.67	75
F8	50:200	21.53	77.34	50

Abbreviations-SF-Surfactant(mg),CH-Cholesterol(mg),Ratio(µmol),MD-Maltodextrin,SL-Sorbitol,ML- Mannitol.

1 g of Carrier per 1 m mole of surfactant; Drug content used 25 mg per batch

Evaluation of proniosomes:^{14,15,17,18}

Measurement of Angle of repose

The angle of repose of dry proniosomes powder and maltodextrin powder was measured by a funnel method (Lieberman et al 1990).The maltodextrin powder or proniosomes powder was poured into a funnel which was fixed at a position so that the 13m outlet orifice of the funnel is 2.5cm above a level black surface. The powder flows down from the funnel to form a cone on the surface

and the angle of repose was then calculated by measuring the height of the cone and the diameter of its base.

Microscopy

The vesicle formation by the particular procedure was confirmed by optical microscopy in 1200x resolution. The niosome suspension placed over a glass slide and fixed over by drying at room temperature, the dry thin film of niosome suspension observed for the formation of vesicles. The photomicrograph of the preparation also obtained from the microscope by using a digital SLR camera.

Table 2: Angle of Repose of Maltodextrin Based Proniosome Formulation

Preparations	Angle of repose*
Proniosome F ₁	36°.22' ± 0.19
Proniosome F ₄	35°.91' ± 0.15
Proniosome F ₇	33°.37' ± 0.25
Maltodextrin powder	35°.15' ± 0.42

* Average of three Preparation

Table 3: Angle of Repose of Sorbitol Based Proniosome Formulation

Preparations	Angle of repose*
Proniosome F ₁	30°:22' ± 0.19
Proniosome F ₄	31°:91' ± 0.15
Proniosome F ₇	29°:37' ± 0.25
Sorbitol powder	30°:15' ± 0.42

* Average of three Preparation

Preparation	Angle of repose*
ProniosomeF ₁	22°:22' ± 0.19
ProniosomesF ₄	20°:91' ± 0.15
ProniosomesF ₇	21°:37' ± 0.2
Mannitol powder	23°:15' ± 0.42

* Average of three Preparation

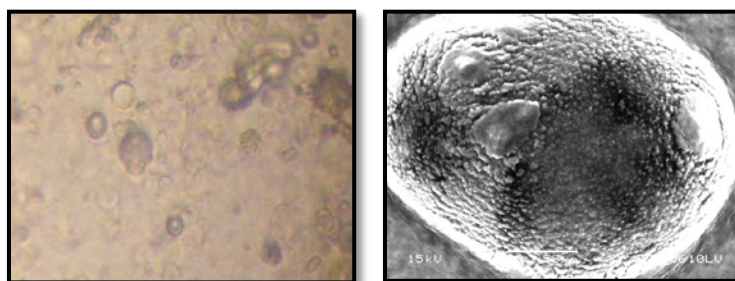


Fig. 1

Microscopy and SEM

Entrapment efficiency

Niosome entrapped glipizide was estimated by dialysis method. The prepared niosomes were placed in the dialysis bag 50 (presoaked for 24 hrs). Free glipizide was dialyzed for 30 minutes each time in 100 ml of phosphate buffer saline pH 7.4. The dialysis of free Glipizide always completed after 12-15 changes, when no Glipizide was detectable in the recipient solution. The dialyzed Glipizide was

determined by finding out the concentration of bulk of solution by UV spectrophotometer at 276 nm. The samples from the bulk of solution diluted appropriately before going for absorbance measurement. The free Glipizide in the bulk of solution gives us the total amount of un-entrapped drug. Encapsulation efficiency is expressed as the percent of drug trapped.

$$\% \text{ Entrapment} = \frac{\text{Total drug} - \text{Unentrapped drug}}{\text{Total drug}} \times 100$$

Table 5:

Formulation Code	Ratio(SF:CH)	Entrapment efficiency % (MD/SL/ML)
F1	225:25	55.21, 50.8, 45.8
F2	200:50	65.21, 55.12, 43.92
F3	175:75	73.22, 60.72, 40.00
F4	150:100	82.64, 65.12, 45.6
F5	125:125	62.61, 50.82, 41.76
F6	100:125	54.52, 40.8, 33.76
F7	75:175	42.81, 33.12, 22.08
F8	50:20	30.16, 20.96, 17.72

Entrapment Efficiency

In-vitro release study

In-vitro release pattern of niosomal suspension was carried out in dialysis bag method. 10 mg equivalent of Glipizide niosomal suspension was taken in dialysis bag (Hi media) and the bag was placed in a beaker containing 75 ml of 0.1 N HCl. The beaker was placed over magnetic stirrer having stirring speed of 100 rpm and the temperature was maintained at 37±1°C. 5 ml samples were

withdrawn periodically and were replaced by fresh buffer. After two hours, 25 ml of 0.2 M tri-basic sodium phosphate was added to change the pH of test medium to 7.4, and the test was continued for a further 24 hours.

The sink condition was maintained throughout the experiment. The withdrawn samples were appropriately diluted and analyzed for drug content using U.V. spectrophotometer at 276 nm keeping phosphate buffer pH 7.4 as blank. All the determinations were made in triplicate.

Table 6: In- vitro release profile of all formulations

Time	2hr	4hr	6hr	8hr	10hr	12hr	14hr	16hr	18hr	20hr	22hr	24hr
Formulation	% Cumulative Drug Release											
F1	18	24	33	41	50	61	73	85	91	98	-	-
F2	20	28	36	44	52	60	69	76	85	93	98	-
F3	15	25	32	41	49	56	72	78	87	87	94	97
F4	14	21	30	37	47	54	64	74	81	87	94	98
F5	13	21	31	37	47	54	64	74	81	88	94	97
F6	15	24	31	41	47	58	64	71	75	80	83	95
F7	13	24	30	36	43	47	52	58	65	76	82	89
F8	11	23	28	36	41	47	55	59	66	74	81	88

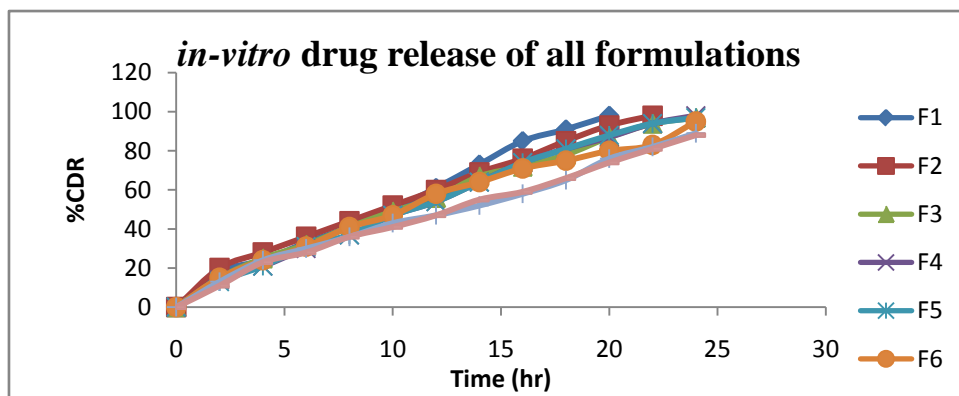


Fig. 2: In-vitro release profile for all 8 formulations

Drug release kinetic data analysis

The release data obtained from various formulations were studied further for their fitness of data in different kinetic models like Zero order, Higuchi's and Peppa's.

In order to understand the kinetic and mechanism of drug release, the result of *in-vitro* drug release study of niosome were fitted with various kinetic equation like zero order (equation 1) as cumulative % release vs. time, Higuchi's model (equation 2) as cumulative % drug release vs. square root of time. r^2 and k values were calculated for the linear curve obtained by regression analysis of the above plots.

$$C = k_0 t \dots\dots\dots (1)$$

Where k_0 is the zero order rate constant expressed in units of concentration / time and t is time in hours.

$$Q = k_H t^{1/2} \dots\dots\dots (2)$$

Where, k_H is Higuchi's square root of time kinetic drug release constant

To understand the release mechanism *in vitro* data was analyzed by Peppa's model (equation 3) as log cumulative % drug release vs. log

time and the exponent n was calculated through the slope of the straight line.

$$M_t / M_\infty = bt^n \dots\dots\dots (3)$$

Where M_t is amount of drug release at time t , M_∞ is the overall amount of the drug, b is constant, and n is the release exponent indicative of the drug release mechanism. If the exponent $n = 0.5$ or near, then the drug release mechanism is fickian diffusion, and if n have value near 1.0 then it is non-fickian diffusion.

Physical stability

Physical stability study was carried out to investigate the degradation of drug from proniosome during storage. Best three (F_3 , F_4 , F_7) of the optimized Glipizide proniosome formulation composed of span-60 and cholesterol sealed in glass vials and stored in refrigerated temperature (2-8°C) for a period of 3 months. Protection from effect of change in the relative humidity was provided by keeping the formulation in the stability chamber. Samples from each batch were withdrawn after the definite time intervals and converted into niosome and the residual amount of drug in the vesicles was determined. Stability data of three formulations were further analyzed for significant difference by paired t-test.¹²

Table 7: Slope and correlation values for each formulation

Formulation	Zero order		Higuchi's		Peppa's	
	Slope	Correlation	Slope	Correlation	Slope	Correlation
F1	4.840	0.993	22.75	0.934	1.254	0.860
F2	4.225	0.989	21.44	0.964	1.173	0.829
F3	3.964	0.993	21.16	0.961	1.172	0.868
F4	4.109	0.989	21.74	0.947	1.197	0.890
F5	4.109	0.992	21.77	0.947	1.204	0.895
F6	3.689	0.980	19.85	0.968	1.153	0.862
F7	3.420	0.988	18.13	0.946	1.129	0.866
F8	3.450	0.992	18.30	0.951	1.156	0.888

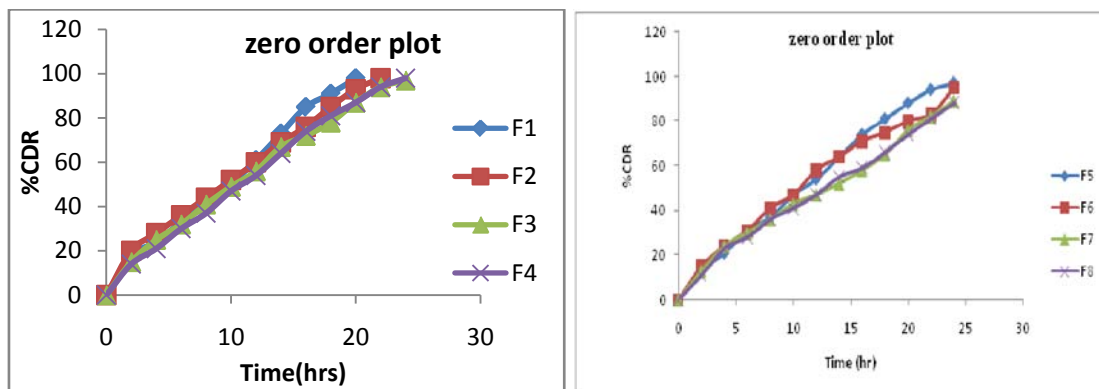


Fig. 2: Zero order plot for formulation F1, F2, F3, F4, F5, F6, F7, F8

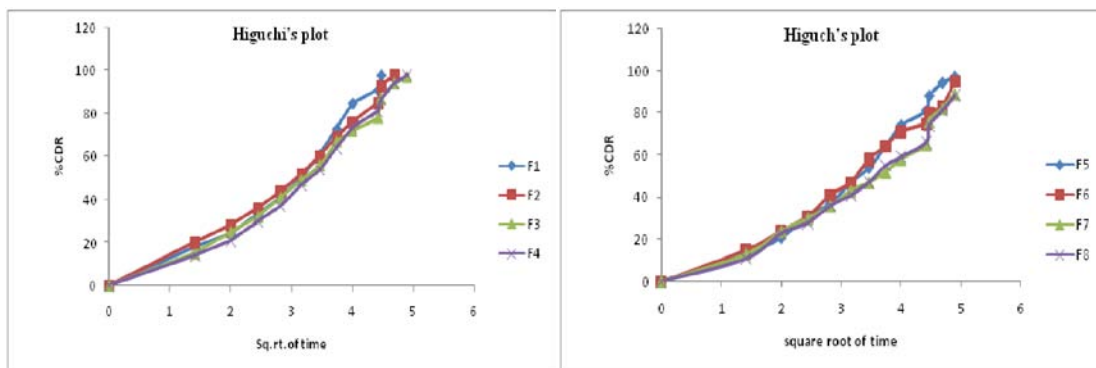


Fig. 3: Higuchi's plot for formulation F₁, F₂, F₃, F₄, F₅, F₆, F₇, F₈

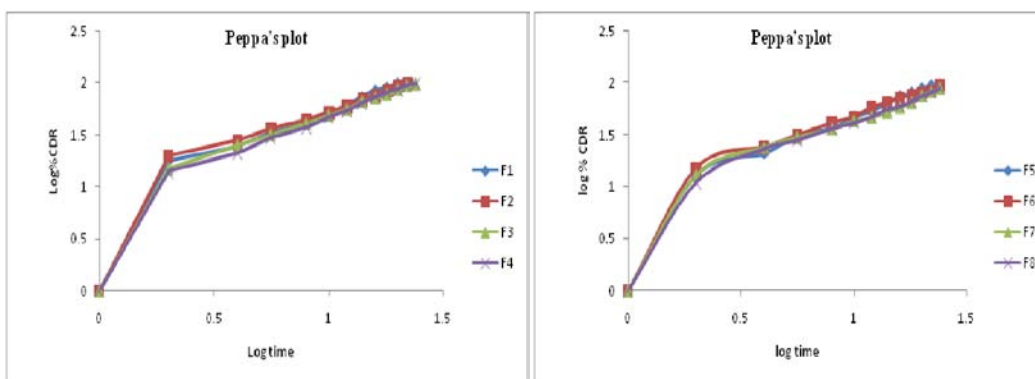


Fig. 4: Peppas's plot for formulation F₁, F₂, F₃, F₄, F₅, F₆, F₇, F₈

Table 8: Percentage of Glipizide from proniosome retained at refrigerated storage

Day's	Percent drug retained		
	F3	F4	F5
0	100	100	100
15	96	99	99
30	97	99	98
45	95	98	98
60	95	98	97
90	95	97	98

Zeta potential analysis

Zeta potential was analyzed to measure the stability of niosome by studying its colloidal property. The study was conducted using zeta potential probe (model DT-300). The formulation F₄ which was found to have a better physical stability was further analyzed by this method for its vesicular stability.⁹

RESULT AND DISCUSSION

FT-IR Spectra of Glipizide, maltodextrin, Sorbitol, Mannitol, physical mixture of drug carrier and F₄ formulation were recorded. The Glipizide present in the formulation F₄ was confirmed by FTIR spectra. The characteristic peaks due to pure Glipizide at 3250.16, 2943.47, 1689.70, 1651.12, 1373.36, 159.26, 686.68 for N-H stretching, C-H Stretching, C=O Stretching, -CONH Stretching, C-H bending, S=O Stretching, C-H bending respectively. All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Glipizide and carriers. It also confirmed that the stability of drug during formulation.

Angle of repose of maltodextrin, Sorbitol and Mannitol powders compared with proniosome formulation by fixed funnel method. Results indicate that the angle of repose of dry proniosome powder is nearly equal to that of pure maltodextrin, but slightly differentiate with other carriers. This shows that the prepared proniosome formulations have appreciable flow properties.

Shape and surface characteristic of proniosome was examined by Scanning Electron Microscopy analysis. Pure maltodextrin and Glipizide loaded maltodextrin, Sorbitol and Mannitol Proniosome (F₄ formulation) are evaluated for surface morphology. Surface morphology confirms the coating of surfactant in carrier. The prepared vesicles were studied under 400x magnifications to observe the formation of vesicles. Some unevenness of vesicles that observed under the study may be due to drying process under normal environment condition. The particles found to be uniform in size and shape. Entrapment efficiency was studied for all the 8 formulations to find the best, in terms of entrapment efficiency. Higher entrapment efficiency of the vesicles of span 60 is predictable because of its higher alkyl chain length. The entrapment efficiency was found to be higher with the formulation no. F₄ (82.64%) with Maltodextrin, (72.64%) with sorbitol and (65.64%) with Mannitol which may have an optimum surfactant cholesterol ratio to provide a high entrapment of Glipizide. The niosomal formulations having high surfactant concentration (F₂, F₃, F₄ and F₅) have the higher entrapment efficiency which might be due to the high fluidity of the vesicles. Very low cholesterol content (F₁) was also found to cause low entrapment efficiency (55.21%), which might be because of leakage of the vesicles. The higher entrapment may be explained by high cholesterol content (~50% of the total lipid).

There are reports that entrapment efficiency was increased, with increasing cholesterol content and by the usage of span-60 which

has higher phase transition temperature. It was also observed that very high cholesterol content (F7, F8) had a lowering effect on drug entrapment to the vesicles (42.81%, 30.16%). This could be due to the fact that cholesterol beyond a certain level starts disrupting the regular bi-layered structure leading to loss of drug entrapment. The larger vesicle size may also contribute to the higher entrapment efficiency. The carrier Also Plays a vital role as we can see directly from data, there is high entrapment efficiency with Maltodextrin as compare to sorbitol and Mannitol.

The release study was conducted for all the 8 formulations. Most of the formulations were found to have a linear release and the formulations were found to provide approximately 88-98% release within a period of 24 hours. The formulations which have high cholesterol ratio (F7, F8) were found to sustain the drug release. Cholesterol, which has a property to abolish the gel to liquid transition of niosomes, this found to prevent the leakage of drug from the niosomal formulation. The slower release of drug from

multilamellar vesicles may be attributed to the fact that multilamellar vesicles consist of several concentric sphere of bilayer separated by aqueous compartment. The three best formulations F3, F4, and F5 were found to give a cumulative release of 97.49 %, 98.31 % and 97.69 % respectively over a period of 24 hrs, the higher release from the formulation F3 may be because of its low cholesterol content. Formulations F7 and F8 having the highest cholesterol content showed the slow release over 24 hours, they provide a release of 89.57% and 87.73% respectively.

The zero order plots showed the zero order release characteristics of the formulation, which was confirmed by the correlation value which found to be nearer to one. Correlation value of Higuchi's plot revealed that the mechanism of drug release is diffusion. The *in vitro* kinetic data subjected to log time log drug release transformation plot (peppas's model) revealed the fact that the drug release follows a super case II transport diffusion. We have Conducted the release study only with the Maltodextrin carrier formulation.

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ZETA POTENTIAL ANALYSIS RESULT

INSTUMENT: - ZETA POTENTIAL PROBE

MODEL: - MODEL DT- 300

SAMPLE DESCRIPTION: -

1. SAMPLE NO 1: - WHITE MILKY

SAMPLE CODE	VALUES RECORDED
SAMPLE NO 1	+ 26

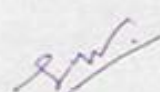

Head of Dept.

Fig. 6: Zeta Potential

Physical stability was carried out to investigate degradation effect of the Glipizide from proniosomes at refrigerated temperature. The percentage of Glipizide retained in the reconstituted vesicles after a period of three months were 88.72%, 96.83% and 97.67% respectively for formulations F3, F4 and F7. Also the results indicate

that more than 95% of Glipizide was retained in the proniosomal formulation for a period of 90 days. From this it can be concluded that proniosomes are stable to store under refrigeration temperature with least leakage. The leakage of drug from F6 may be due to its lower surfactant content and higher cholesterol which formed a leaking vesicle.

Proniosomes are prepared with non-ionic surfactant (span 60) and cholesterol by coating maltodextrin powder as carrier, and for comparing the result, proniosomes are prepared with sorbitol and mannitol, which upon reconstitution gives niosomes. Glipizide, an anti-diabetic drug is encapsulated in these formulations for the sustained action of drug. On using different ratios, 150:100 μ mol ratios of the surfactants to cholesterol preparation shows the highest entrapment efficiency and good release characteristics. In this study it is found that entrapment efficiency of drug is depend upon the cholesterol surfactant ratio and maltodextrin as carrier.

Maltodextrin-based proniosomes are a potentially scalable method for producing niosomes for delivery of hydrophobic or amphiphilic drugs. The method of preparation is very easy when compared to conventional niosomes. Proniosomes minimizes the problems of niosome physical stability, such as aggregation, fusion, and leaking and provide additional convenience in transportation, distribution, storage and dosing. The optimized formulation developed using the desirability approach produced high drug encapsulation efficiency.

CONCLUSION

On conclusion, this novel drug delivery system i. e. proniosome as compared to liposome or niosome represent a significant improvement by eliminating physical stability problems, such as aggregation or fusion of vesicles and leaking of entrapped drugs during long-term storage. Proniosomes derived niosomes are found to be superior in their convenience of storage, transport, and dosing as compare to niosomes and liposomes prepared by conventional method. By these facts of the study it is concluded that glipizide will be successfully entrapped within the bilayer of the vesicles with high entrapment efficiency and said that proniosomes based niosomes formed from span 60, cholesterol using maltodextrin as a carrier is a promising approach to sustain the drug release for an extended period of time and by that reducing the side effects related to GI irritation. The slurry method was found to be simple and suitable for laboratory scale preparation of glipizide proniosomes.

Maltodextrin-based proniosomes is a potentially scalable method for producing niosomes for delivery of hydrophobic or amphiphilic drugs. The method is simple and overcomes several problems encountered in previous studies. The niosomes produced using this method are effective carriers for amphiphilic drugs.

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