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DEVELOPMENT AND INVITRO EVALUATION OF MIGLITOL *INSITU* GEL FOR MANAGEMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS.

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Abstract:
The objective of the present investigation was to develop an effective insitu proliposomal gel formulations for treatment of Non-insulin dependent diabetes.The proliposomes containing Miglitol was prepared by film deposition on carrier method using vacuum rotary evaporator. The optimization of Miglitol proliposomes was done by preparing the different formulations by varying the concentration of mannitol, phosphatidyl choline and cholesterol. Formulation prepared by using 50mg of miglitol, 1g mannitol, Phosphatidyl choline 150mg, Cholesterol 100 mg, chloroform 6ml and methanol 4ml was selected as optimized formulation. The cumulative amount of drug release of various proliposomal formulations and conventional Miglitol gel in 7.4 pH after 16hrs showed 80.5% and 95.1% for conventional gel. The drug release followed Peppas model.which confirms that release of proliposomal formulation was Fickian diffusion.

Key Words: ***Miglitol proliposomal gel, Mannitol, cholesterol, phosphatidyl choline***

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INTRODUCTION:

Proliposomes are defined as dry, free flowing powder formulations containing water soluble carrier particles coated with phospholipids that immediately form a liposomal dispersion on contact with water in the body.They act as a sustained release dosage form of the loaded drugs.Because of the solid properties of proliposomes the stability problems of liposome can be resolved without influencing their intrinsic characteristics. Transdermal drug delivery system has significant drawbacks namely poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient.To overcome these difficulties there is a need for the development of new drug delivery system; which will improve the therapeutic efficacy and safety of drugs by more precise (i.e., site specific), spatial and temporal placement within the body thereby reducing both size and number of doses. Alpha-glucosidase inhibitors are oral anti-diabetic drugs used for diabetes mellitus type 2 that work by preventing the digestion of carbohydrates. Miglitol is fairly well absorbed by the body so it was used in the present investigation.

MATERIALS AND METHODS:

Miglitol was a gift sample from Dr.Reddy's laboratories, Phosphotidyl choline was obtained from Dr. Reddy's laboratories and all other chemicals used were of pharmaceutical grade.

Preparation of Proliposomal gel:

Preparation of Miglitol loaded proliposomes- The proliposomes containing Miglitol was prepared by film deposition on carrier method using vacuum rotary evaporator.Miglitol (50 mg), phosphotidyl choline and cholesterol were dissolved in mixture of organic solvents (chloroform:methanol, 6:4,v/v) and 5ml of aliquot of organic solution was slowly introduced into the flask via the solvent inlet tube. After complete drying second aliquot (5ml) was introduced. After complete dying, the vacuum was released and proliposomes were placed in a desiccator over night and then sieved with 100 mesh.The collected powder was transferred into a glass bottle and stored at the freeze temperature.

The optimization of Miglitol proliposomes was done by preparing the different formulations by varying the concentration of mannitol, phosphatidyl choline and cholesterol, Mannitol (1 g, sieved with 100 mesh) was placed in 100ml round bottom flask which was held at 60-70^{0}C temperature and the flask rotated at 80-90 rpm for 30 min under vacuum.

Table No.1: Composition of proliposomal formulations (F1 to F9)

Excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Miglitol(mg)	50	50	50	50	50	50	50	50	50
Mannitol(g)	1	1	1	1	1	1	1	1	1
Phosphatidyl choline(mg)	100	100	150	150	50	150	100	50	50
Cholesterol(mg)	150	100	50	100	100	150	50	50	150
Chloroform(ml)	6	6	6	6	6	6	6	6	6
Methanol (ml)	4	4	4	4	4	4	4	4	4

Table No.2: Composition of proliposomal formulations (F10 to F18)

Excipients	F10	F11	F12	F13	F14	F15	F16	F17	F18
Miglitol(mg)	50	50	50	50	50	50	50	50	50
Mannitol (g)	2	2	2	2	2	2	2	2	2
Phosphatidyl choline(mg)	150	100	150	100	50	50	100	50	150
Cholesterol(mg)	50	100	100	50	100	150	150	50	150
Chloroform (ml)	6	6	6	6	6	6	6	6	6
Methanol (ml)	4	4	4	4	4	4	4	4	4

Preparation of Carbopol gel base:
1gm of carbopol 934 was weighed and dispersed in distilled water. Then, propylene glycol was added and the mixture was neutralised by drop wise addition of 1% triethanolamine. Mixing was continued until the transparent gel was obtained and allowed to swell for 24 hours. Similarly 2% and 3% carbopol gels were prepared.

Preparation of proliposomal gels:
Proliposomes containing Miglitol (separated from the unentrapped drug) were mixed into the 1% carbopol gel by using mortar and pestle, the concentration of proliposomes in the gel being 1%. All optimized formulations were incorporated into different carbopol gels (1%,2% and 3%).

Fourier Transform Infrared study: The analytical technique used for drug excipient compatibility study was FTIR with Attenuated Total Reflectance (ATR) technique. A small portion of a sample was placed on the zinc selenide crystal and spectrum was taken.

Characterization of Proliposomes:
Vesicle size and count:
Average size and size distribution proliposomes were determined using optical microscope (Metzer 5000DTM). A drop of distilled water was added to proliposome granules on a glass slide without a cover slip, and the process of liposome formulation was observed using optical microscope with 100X magnification. Size of liposomal vesicles was measured at different locations on the slide. From the obtained results size distribution and average size of liposome vesicles was determined.

Surface morphology:
The surface morphology of proliposomes and plain mannitol particles were examined by scanning electron microscopy (SEM) after coating with gold. After gold coating of proliposome and plain mannitol particles, their surface morphology was viewed and photographed.

Drug content:
Miglitol content in proliposomes was assayed by an UV-visible spectrophotometer. Proliposomes (100mg) were dissolved in 10ml methanol by shaking the mixture for 5 mins. One ml of the resultant solution was taken and diluted to 10ml with methanol. Then, aliquots were withdrawn and absorbance was recorded at 270nm using UV-visible spectrophotometer (Lab India 3200).
Entrapment efficiency:
Separation of unentrapped drug from the liposomal suspension was done by centrifugation method. The entrapment efficiency of proliposomes was determined after hydration with distilled water. 10ml of phosphate buffer (PH 7.4) was added to proliposomes granules and then subjected to sonicate for 10 mins using ultra sonicator (Citizen, India). The liposomal suspension was subjected to centrifugation on a cooling centrifuge (REMI TR-01) at 15000rpm for 30 mins for the separation of unentrapped drug. The clear supernatant (1ml) was taken and diluted to 10ml with buffer and absorbance was recorded at 270nm using UV-visible spectrophotometer (Lab India 3200). Then calculate the percentage drug in the each formulation.

$$\text{Entrapment efficiency (\%)} = \frac{Ct - Cf}{Ct} \times 100$$

Ct – concentration of total drug
Cf – concentratin of free drug

Surface charge:
The optimized proliposomal formulation was dissolved in phosphate buffer (pH 7.4) and made the serial dilutions until the clear solution was obtained. Then the sample was analyzed for surface charge using zeta sizer (Malvern).

Yield of proliposomes:
After complete drying the proliposome powders were collected and weighed accurately. The yield of proliposomes was calculated using the formula

$$Percentage yield = \frac{Total weight of proliposomes}{\text{total weight of drug} + \text{weight of added materials}} \times 100$$

Characterization of Gel:
Physical appearance:
All prepared gel formulations have been observed for their visual appearance, such as transparency, colour, texture, grittiness, greasiness, stickiness, smoothness, stiffness and tackiness. The prepared gels were also evaluated for the presence of any particles. Smears of gels were prepared on glass slide and observed under the microscope for the presence of any particle or grittiness.

pH of formulation: pH measurement of the gel was carried out of the formulation was measured by using a digital pH meter (Lab India SAB 5000), dipping the glass electrode completely into the gel system. The observed pH values were recorded for all formulations (F1-F9) in triplicates

Rheological properties:
The rheological properties of prepared gels was estimated using a Brookfield viscometer pro D II apparatus, equipped with standard spindle LV1 with 61 marking. Sample holder of the Brookfield viscometer was filled with the gel sample, and then spindle was inserted into sample holder. The spindle was rotated at 100 rpm.

All the rheological studies were carried out at room temperature. A viscosity measurement was done in triplicate[50]. Viscosity of 1, 2 and 3% carbopol gel was determined and selects the optimized formulation.

Homogeneity:
The homogeneity of Miglitol proliposomal gels were checked by visual inspection. In this regard the gels were filled into narrow transparent glass tubes and were checked in light for the presence of any particulate or lump.

Drug Content
For determination of drug content, accurately weighed quantity (1 gm) of gel equivalent to 50 mg of Miglitol was dissolved in phosphate buffer (PH 7.4) and analyzed by UV-Vis Spectrophotometer (Lab India 3200) at 270 nm for drug content.

***In vitro* studies:**
Percent amount of drug release from semi permeable membrane:
Franz diffusion cell was used for the in vitro drug release studies. Semi permeable membrane was placed between donar and receptor chamber of diffusion cell. Receptor chamber was filled with freshly prepared 30ml 7.4 PH phosphate buffer. Proliposomal gel equivalent to 1gm was placed on semi permeable membrane. The Franz diffusion cell was placed over magnetic stirrer (REMI 1ML) with 500rpm and temperature was maintained at 37 ± 1^0C. 5ml of samples were withdrawn periodically and replaced with fresh buffer. The withdrawn samples were periodically diluted and analysed for drug content using UV visible spectrophotometer (Lab India 3200) at 270nm.
Stability studies: Stability studies were carried out by storing the prepared gels in tightly sealed amber colour glass bottles at various temperature conditions like refrigeration temperature ($2\text{-}8^0$c), room temperature (25 ± 0.5^0c) and elevated temperature (45 ± 0.5^0c) from a period of one month to three months. Drug content and variation in colour, morphology and consistency were periodically monitored.

Drug release kinetics: Drug release data was plotted in kinetics models to determine drug release kinetics.

RESULTS AND DISCUSSION:

The proliposomes containing Miglitol was prepared by film deposition on carrier method using vacuum rotary evaporator.Proliposomes containing Miglitol (separated from the unentrapped drug) were mixed into the 1% carbopol gel by using mortar and pestle. All optimized formulations were incorporated into different carbopol gels (1%,2% and 3%).

Fourier Transform Infrared analysis: There was no significant interaction of encapsulated drug with the phospholipid and water soluble solid support (mannitol) with formulations.

Characterization proliposomes and proliposomal gel:

Determination of vesicle size: With increase in the concentration of phospholipid and cholesterol vesicle size was found to be increased.

Surface morphology: From SEM photographs it was clear that, the surface of mannitol crystals becomes illegible due to deposition of phospholipid on mannitol surface.

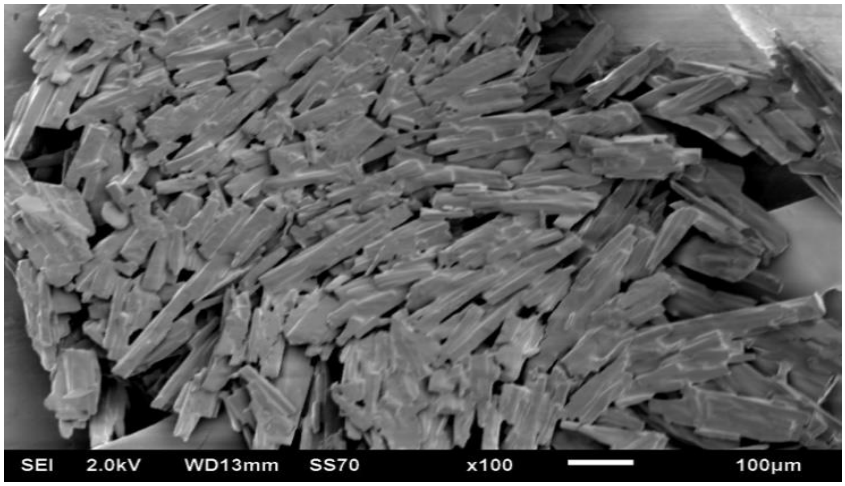

Fig.No:1 SEM Image of Miglitol proliposomes

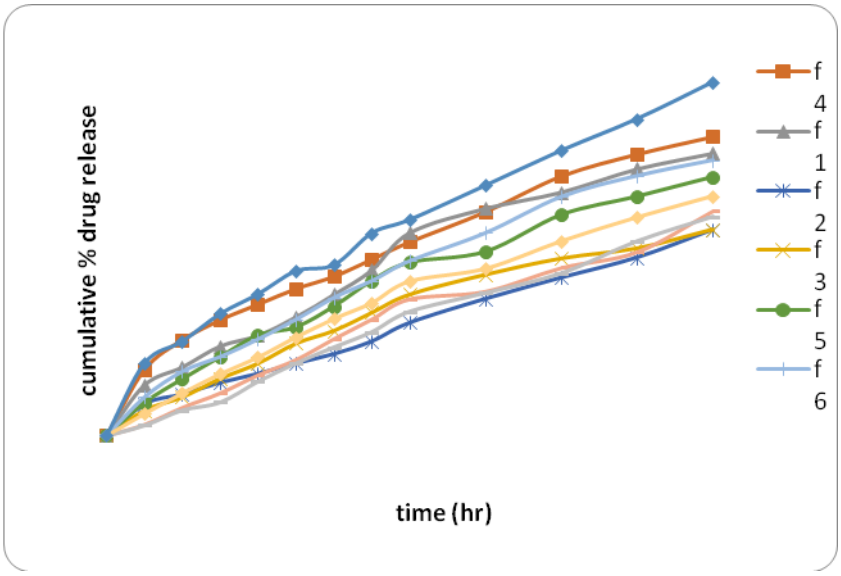

Fig.No:2 Diffusion data of various proliposomal formulations and conventional gel

Drug content estimation: The Miglitol content in the proliposomes were observed in the range of 86.4% to 96.8% at various drug to phospholipid ratios. From the above results it is concluded that F4, F1, F5 and F6 formulations showed maximum drug content when compare to other formulations.

Determination of entrapment efficiency: In the present study, the observed entrapment efficiency for all batches of Miglitol proliposome formulation in the range of 72 to 90%.

Percentage yield of proliposomes: Percentage yield for F1 – F9 formulations was found to be with increase in the phospholipid concentration.

Viscosity measurement: Viscosity of proliposomal gel showed 1156cps at 100rpm using Brookfield viscometer.

pH measurement: The pH of the developed formulation was in accordance with human skin pH andgel was suitable for topical application.

***In – vitro* studies:** The percentage cumulative drug release of optimized formulation was found to be 80.5%.

Drug Release kinetics:

The drug release follow peppas model in the range of 0.1 to 0.5 which confirms that release of proliposomal formulation was fickian diffusion.

Stability studies:

The drug leakage of <1% of the initial load at refrigeration conditions is well within the limits and sgood for topical application.

CONCLUSION:

A sustained delivery of Miglitol can be achieved by proliposomal drug delivery system. Phospholipids, being the major component of liposomal system, can easily get integrated with the skin lipids and maintain the desired hydration conditions to improve drug permeation.The free flowing properties of the proliposomes granules will be beneficial in formulating the proliposomes as a solid dosage form. In-vitro studies concluded that enhance skin permeation and retention of Miglitol was observed and was due to lipo-solubilized state of drugs within proliposomes which helped to produce the depot effect.Ex-vivo studies concluded that the proliposomal formulation showed higher permeation and residence within skin than the marketed gel indicating sustain release of drug at site which prevents further inflammation.

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