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Development and Characterization of Glimepiride Mucoadhesive Microspheres

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ABSTRACT: The present study attempt is to prepare mucoadhesive microspheres of Glimepiride using Chitosan. The Glimepiride microspheres were prepared by emulsion solvent evaporation method. Prepared mucoadhesive microspheres were evaluated for Organoleptic characteristics and Solubility studies, Melting point, Partition coefficient, Determination of wavelength, Drug and polymer interaction studies, Entrapment efficiency, Drug loading, Production yield, Particle size analysis, Degree of swelling, In-vitro drug release study.

Keywords: Diabetes Mellitus, Glimepiride**,** Mucoadhesive Microspheres, Eudragit RS 100.

I. INTRODUCTION:

Diabetes Mellitus (DM) is a group of metabolic disorders which is characterized by increase blood sugar level, altered metabolism of lipids, carbohydrates, and proteins and increased risk of complications from vascular disease. This high blood sugar produces the symptoms of frequent urination, increased thirst, and increased hunger. Untreated, diabetes can cause many complications. The chronic hyperglycemic conditions are associated with dysfunction and failure of major organs like heart, eyes, nerves, blood vessels and kidneys. Variations in normal glucose homeostasis occur by numerous factors like impaired insulin secretion, hepatic gluconeogenesis and reduced uptake of glucose by skeletal muscle, adipose tissues and liver. Insulin is one of the most important hormones responsible for maintaining the homeostasis of glucose, triglycerides, amino acids, fatty acids, translocation of vital material, glycogen formation, and synthesis of biomolecules. Insulin is secreted into the blood stream by beta-cell of pancreas.[1] Diabetes is due to either the pancreas not producing enough insulin, or the cells of the body not responding properly to the insulin produced. There are three main types of diabetes mellitus:

- **Type-I diabetes mellitus:** Type-I diabetes is caused by the body's inability to contain insulin. Insulin-dependent diabetes mellitus (IDDM) or "juvenile diabetes" is the name given to this category. Diabetes Type-I is the most common type of diabetes.
- **Type-II diabetes mellitus:** Insulin tolerance, a disease in which cells refuse to utilize insulin correctly, causes Type-II diabetes mellitus, which may often be accompanied by an absolute insulin deficiency.
- **Gestational diabetes mellitus:** The third most common form, gestational diabetes, is a type of diabetes that affects certain women during pregnancy and is distinguished by elevated blood sugar levels.[2]
- **Symptoms of Diabetes Mellitus:** Blood sugar levels are high, and high glucose is excreted in the urine. High glucose levels in the urine might cause increased urine output and dehydration. As a consequence of dehydration, thirst and water consumption increases. Despite an increase in hunger, insulin insufficiency leads to weight reduction in the long run. Include fatigue, nausea, and vomiting. Intestinal, skin, and genital diseases are more probable.
- **Glimepiride** is also known as Amaryl. **IUPAC Name** -1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1carboxamido) ethyl]phenyl] sulfonyl]-3-(trans-4-methylcyclohexyl)urea. **Molecular formula-** $C_{24}H_{34}N_4O_5S$. It is white to yellowish or brownish solid state. The primary mechanism of action of glimepiride is lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. **Pharmacokinetics-**After oral administration, glimepiride is completely (100%) absorbed from the GI tract. Studies with single oral doses in normal subjects and with multiple oral doses in patients with Type 2 diabetes have shown significant absorption of glimepiride within 1 hour after administration and peak drug levels (Cmax) at 2 to 3 hours. **Metabolism-** Glimepiride is completely metabolized by oxidative biotransformation after either an IV or oral dose. The major metabolites are the cyclohexyl hydroxy

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methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 2C9 has been shown to be involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M1, but not M2, possesses about 1/3 of the pharmacological activity as compared to its parent in an animal model; however, whether the glucose-lowering effect of M1 is clinically meaningful is not clear.[3,4]

The pharmacokinetic parameters of glimepiride obtained from a single-dose, crossover, dose-proportionality (1, 2, 4, and 8 mg) study in normal subjects and from a single- and multiple-dose, parallel, dose-proportionality (4 and 8 mg) study in patients with Type 2 diabetes.

Due to its low biological half life (5 h), it requires frequent administration. To reduce the dosing frequency and to improve patient compliance prolonged release dosage forms are required. Hence, there is a scope for continued interest and need for developing controlled release formulations. In the present investigation solvent evaporation method was employed with an objective of developing micro particles for oral controlled release and for obtaining controlled release of Glimepiride.[5]

- **Mucoadhesive microspheres:** Drug action can be improved by developing new drug delivery system, such as the mucoadhesive microsphere drug delivery system. These systems remain in close contact with the absorption tissue, the mucous membrane, releasing the drug at the action site leading to enhance bioavailability and both local and systemic effects. The oral route of drug administration constitutes the most convenient and preferred means of drug delivery to systemic circulation of body. Microspheres (MS), which are emulsion cells or solid particles dispersed in a continuous phase, have been utilized in various industries such as foods, cosmetics and pharmaceuticals, etc. Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm). Microspheres are sometimes referred to as micro-particles dosage forms that can precisely control the release rate and target drugs to a specific body site have created enormous impact on the formulation and development of novel drug delivery system. The objective of controlled release drug delivery includes two important aspects namely spatial placement and temporal delivery of drug. Spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. Various mucoadhesive dosage forms such as discs, microspheres, and tablets have been prepared and reported by several research groups. Mucoadhesive drug delivery systems are used to enhance drug absorption in a site-specific manner. Mucoadhesion is defined as the interaction between a mucin and a synthetic or natural polymer. Mucoadhesion has been widely promoted as a way of achieving site-specific drug delivery through the incorporation of mucoadhesive hydrophilic polymers with in pharmaceutical formulations such as “microspheres” along with the active pharmaceutical ingredient (API). It is the reliable means to deliver the drug to the target site with specificity.[6,7]

II. MATERIALS:

Glimepiride, Chitosan and Analytical grade solvents and reagents were provided by Sigma Aldrich® Limited, Mumbai, India.

III. PRE-FORMULATION STUDIES:

Pre-formulation studies is the preliminary investigation of drug and other ingredient before developing any pharmaceutical product development in order to get stable, safe and effective dosage forms.The following pre-formulation studies are carried to get the initial information of the drug and excipients.

- **Organoleptic characteristics:**
- **Color:** Less quantity of pure Glimepiride is taken in butter paper and viewed in well illuminated place.
- **Odor:** very less quantity of Glimepiride as well as smelled place.
- **Taste:** very less quantity of Glimepiride is used to get taste with the help of tongue as well as smelled place.
- **Melting point:** little amount of the medicine taken in a capillary tube with one end closed, placed it in Thiele's melting point apparatus, and recorded the temperature at which the drug started to melts, the melting point of the drugs determined.
- **Solubility studies:** The solubility of drugs tested in distilled water, a number of buffer solutions and methanol. Three identical readings will be used to calculate the average.
- **Partition coefficient:** To calculate the partition coefficient of drugs, n-octanol and water will be utilised in equal parts in a separating funnel. A drug solution prepared, and 1 ml added to a 50/50 mixture of octanol and aqueous phase in a separating funnel. The mixture stirred for 10

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minutes, let to stand for an hour, and then continued for another 24 hours. Following this, the aqueous and octanol phases centrifuged for 10 minutes at 2000 rpm to separate them. Using a UV-Vis Spectrophotometer, the aqueous and octanol phases measured at their respective maximums before and after partition in order to estimate the partition coefficient.[8]

- **Determination of wavelength:** UV-Vis spectrophotometry is used to find drugs. The absorbance properties from 200 nm to 400 nm qualitatively match those of a standard solution that will be similarly prepared and tested at the same time. In terms of quantitative analysis, the absorbance of the equimolar sample and the standard solutions will be at their maximum.[9,10]
- **Drug and polymer interaction studies:** The drug and polymer compatibility study was conducted between Glimepiride and polymer Chitosan using a FT-IR spectrometer to check the suitability of polymer for the preparation of microsphere. The samples (drug, polymer, and physical mixture) were prepared into the KBr disks and scanning was performed in the range of 4000 to 500 cm^{-1} [11]

IV. PREPARATION OF MUCOADHESIVE MICROSPHERE:

Mucoadhesive microspheres was prepared by w/o emulsification cross-linking technique. The w/o emulsification cross-linking technique is one of the most prevalent preparation techniques used extensively for developing the therapeutic microspheres. Weighed amount of Glimepiride and polymer (Chitosan) in 1:1 ratio were dissolved in 10 ml of acetone. The organic solution was then slowly added to 100 ml of liquid paraffin containing 1% surfactant (span 80) with constant stirring for 1hr. The resulting microspheres were separated by centrifugation and washed with petroleum ether. The microspheres finally air dried over a period of 12 h and stored in a desiccator. In case of 1:1.5, 1:2 and 1:3 core:coat ratios, the corresponding polymer get varied respectively. The polymers possess good biocompatibility, are non-irritant, and non-toxic. Chitosan can prolong the residence time of drugs at the absorption site due to their desirable mucoadhesive property [12,13].

V. EVALUATION OF MUCOADHESIVE MICROSPHERES

5.1 Production yield The production yield of various microsphere formulation batches were determined by calculating the percentage of weight obtained after drying the final product (formulation) with respect to the initial weight of Glimepiride and Chitosan polymer [14].

5.2 Drug loading: The weighed amount of Glimepiride in the microsphere of each formulation was extracted in distilled water on a mechanical shaker for 24 hrs to extract the entrapped drug completely. The solution was filtered through Whatman filter paper. 1 ml of this solution was withdrawn and diluted to 10 mL with distilled water. This solution was assayed for the drug content by UV-Vis spectrophotometer at 228 nm [15].

5.3 Entrapment efficiency: The weighed amount of Glimepiride in the microsphere of each formulation was extracted in distilled water on a mechanical shaker for 24 hrs to extract the entrapped drug completely. The solution was filtered through Whatman filter paper. 1 ml of this solution was withdrawn and diluted to 10 mL with double distilled water. This solution was assayed for the drug content by UV-Vis spectrophotometer at 228 nm [16].
Where M actual is the actual drug content in a weighed quantity of powder of microspheres and theoretical amount of drug in microspheres calculated from the quantity added in the fabrication process is Theoretical.

5.4 Particle size analysis: For the determination of particle size, a microscopic image analysis technique was utilized by a digital microscope. The prepared microspheres were suitably dispersed on a microscope slide of standard dimension and the microscopic field was scanned by a video camera. The software analyzed the images that lie within the scanned field [17].

5.5 Degree of swelling: The swell ability of the Glimepiride microspheres in the physiological media was determined by allowing the formulations to swell in the phosphate buffer pH 6.8. An accurately weighed amount of microspheres was immersed in little excess of phosphate buffer pH 6.8 for 24 hr duration and washed thoroughly. The degree of swelling was calculated using the following formula [18]:

$$\alpha = (Ws - Wo) / Ws$$

$$I = \alpha \ 100$$

Where, α = degree of swelling; Ws = weight of microspheres after swelling; Wo = initial weight of microspheres; and I = % swelling index.

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5.6 Mucoadhesive Test: 10 mg of microspheres was dispersed in mucin solution having different concentration (100 µg/ml, 200 µg/ml. 300 µg/ml and 400 µg/ml), incubated at 37°C for specified time (30 min, 60 min. 120 min. and 180 min.) and centrifuged at 10,000 rpm for 30 min. The remaining free mucin in the supematant was determined at 228 nm by UV spectrophotometer. The % mucin binding efficiency of microspheres was calculated using the following formula.
Where, C_o is initial concentration of mucin and C_s is the concentration of free mucin in the supematant. [19]

5.7 Scanning electron microscopy (SEM): The microspheres were analyzed for their surface morphology under both 400x and 2000x magnifications under a scanning electron microscope. The surface morphology was determined by powdering the gold-coated (4A° thickness) microspheres over the double-sided tape placed on the aluminum stub of the SEM chamber system. The photomicrographs of the developed microspheres were taken at an operational accelerating voltage of 6 kV [20].

5.8 In-vitro drug release study: Glass-fabricated Franz diffusion cell was employed for the in vitro drug release study of the fabricated microspheres. The dialysis membrane was equilibrated by dispersing the fabricated mucoadhesive microspheres into the donor compartment. The phosphate buffer solution of pH 6.8 was filled into the receptor compartment. The donor compartment was kept in a way that it comes in contact with the receptor compartment containing the diffusion medium. The circulating water bath helped in maintaining the temperature of 37±2°C. From the receptor compartment, the samples were withdrawn periodically and the sink condition was maintained. The samples were analyzed at 228 nm in the UV spectrophotometer [21,22].

5.9. Drug release kinetics To study the release kinetics of Glimepiride oral mucoadhesive batches, the data obtained from In vitro drug release studies were plotted in a variety of kinetic models, where:
Zero-order is represented as the rate of the cumulative amount of drug released (Equation 1)

$$C = K_0 t \quad \text{..... (1)}$$

Where K_0 is the zero-order rate constant expressed in units of concentration/ time and t is the time in minutes. A graph of concentration vs. time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.[23]

First-order is presented as the rate of Log cumulative % of remaining drug (Equation 2)

$$\text{LogC} = \text{Log}C_0 - K_t/2.303 \quad \text{..... (2)}$$

Where C_0 is the initial concentration of the drug, K is the first order constant and t is the time.

Higuchi's model is depicted as the squared rate of cumulative % of drug released (Equation 3)

$$Q_t = K_t^{1/2} \quad \text{..... (3)}$$

Where Q_t is the amount of drug release in time t, K is the kinetic constant and t is the time in minutes.

Korsmeyer-Peppas exponential model is Log rate of Log cumulative percentage of drug released (Equation 4).

$$Mt = M1 ¼ Kt^n \quad \text{..... (4)}$$

The release exponent n and K value were calculated through the slope of the straight line. If the exponent n = 0.43 then the drug release mechanisms Fickian diffusion, if 0.43<n<0.85 then it is non-Fickian or anomalous diffusion, if n <0.85 mechanism is non-Fickian case-II diffusion [24].

VI. RESULTS AND DISCUSSION

6.1 Physical properties: Glimepiride exists as free-flowing white or almost white powder with no odor and having characteristic taste.
6.2 Melting point: The melting point of glimepiride was found to be in the range of 207-208°C.
6.3 Solubility profile The solubility profile of glimepiride showed highest solubility in petroleum ether, followed by ethyl acetate, thereby reflecting non-polar characteristics. Even, the solubility in water was quite limited reflecting slightly soluble nature.

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Table no.2. Solubility profile of glimepiride.

S. No.	SOLVENT	SOLUBILITY PROFILE	INTERPRETATION
•	Ethanol	++	Very slightly soluble
•	Methanol	++	Slightly soluble
•	Ethyl acetate	+++	Soluble
•	Distilled water	+	Slightly soluble
•	Petroleum ether	++++	Highly soluble
•	Acetone	++	Slightly soluble

6.4. Partition coefficient The partition coefficient was found to be 3.93, indicating lipophilic behavior.
6.5 λmax determination The λmax of glimepiride was found to be 228 nm (**Figure 9)**.

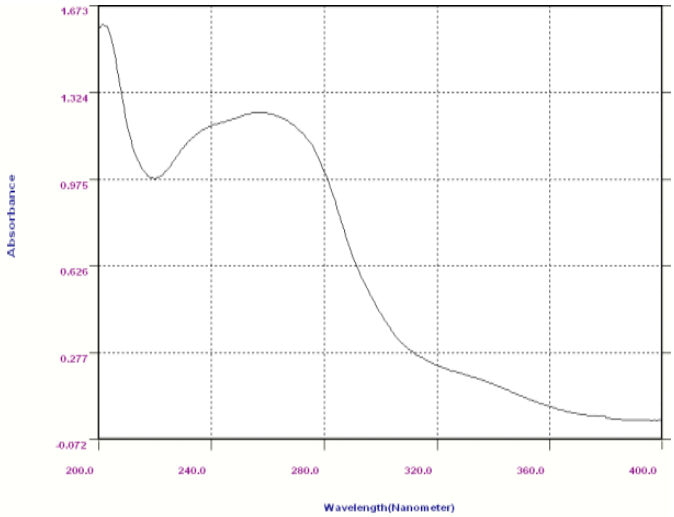

Fig.1**.** UV-Vis spectra of glimepiride.

6.5.1 Calibration curve The calibration curve of glimepiride was prepared in the range of 12 µg/ml - 75 µg/ml in stimulated gastric fluid which showed equation of 58278x - 66753 with R^2 of 0.998 (**Figure 10**).

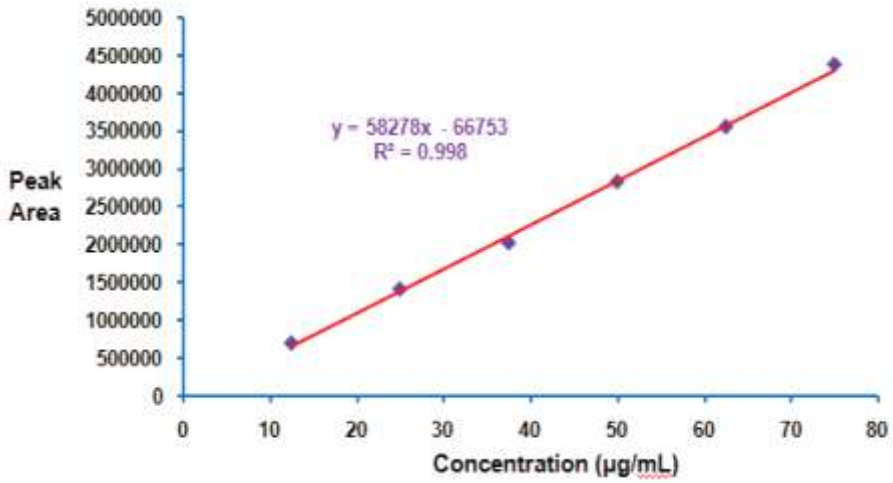

Fig.2. Calibration curve of glimepiride.

6.6 FT-IR spectroscopy The FT-IR spectra of glimepiride highlighted wavenumbers indicating carbonyl (-C=O, 1719 cm^{-1}), nitro (-NO_2, 1265 cm^{-1}), aromatic (-C_6H_5), hydroxyl (-OH, 3411 cm^{-1}), and amine (-NH_2, 2279 cm^{-1}) groups (**Figure 11**).

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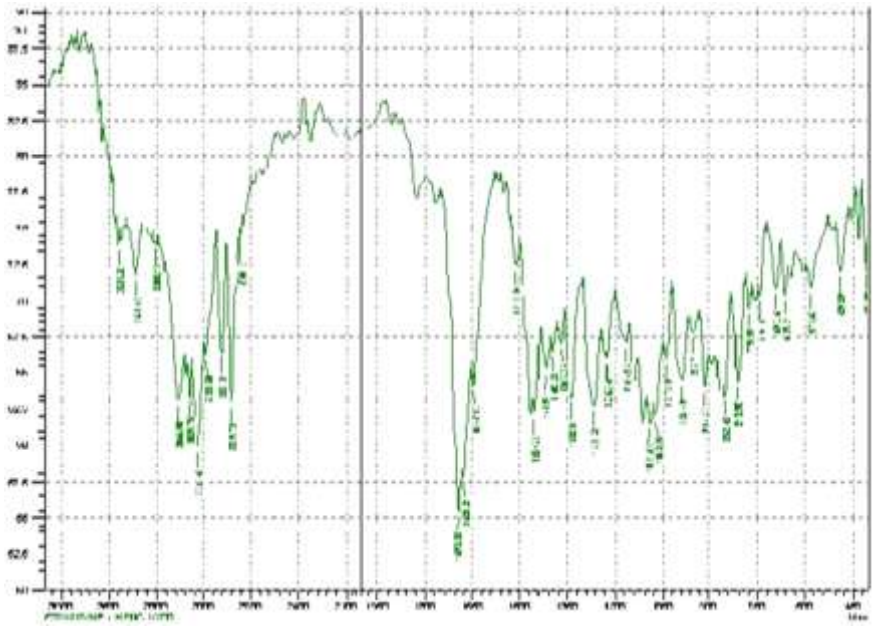

Fig.3. FT-IR spectra of glimepiride.

VII. FORMULATION EVALUATION

7.1. Drug-interaction studies

The FT-IR spectra of pure glimepiride drug (**Fig.12 A**), Chitosan (**Fig.13 B**), and mucoadhesive microspheres (**Fig.14 C**) were recorded which revealed no possible interactions between the drug and mucoadhesive polymers. There was no substantial modification in the positions of characteristic absorption bands and bonds of diverse functional groups present in the drug, indicating no such drug-excipients interactions. In the physical mixture and optimized formulation, the drug remained in pure, unchanged, and non-interactive state. The results stated that glimepiride was compatible with Chitosan.[25]

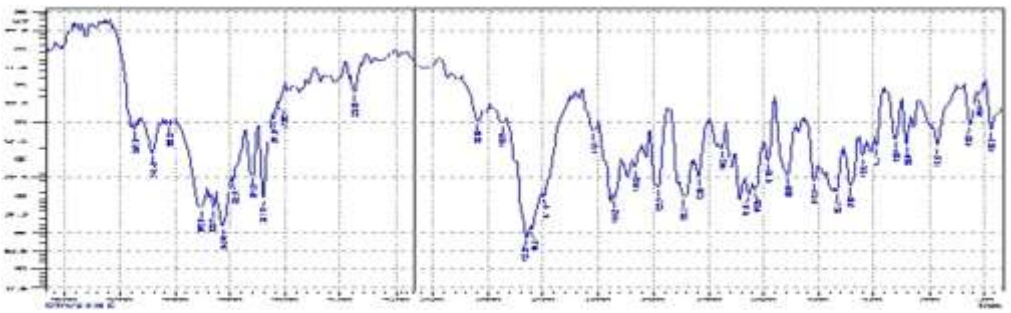

Fig 4 FT-IR spectra of (A) Drug.

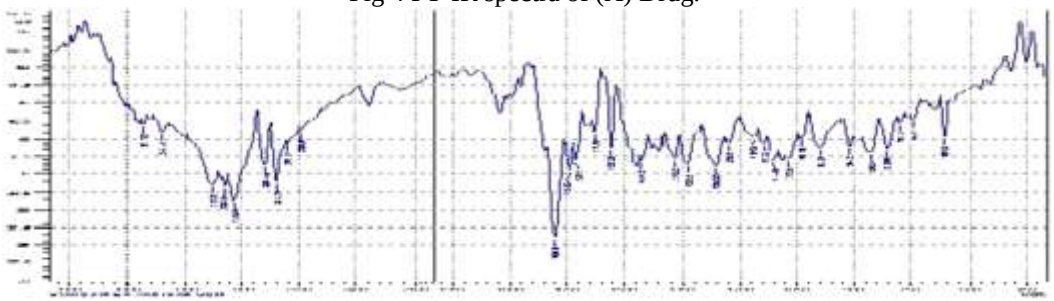

Fig.5. FT-IR spectra of (B) Polymer;

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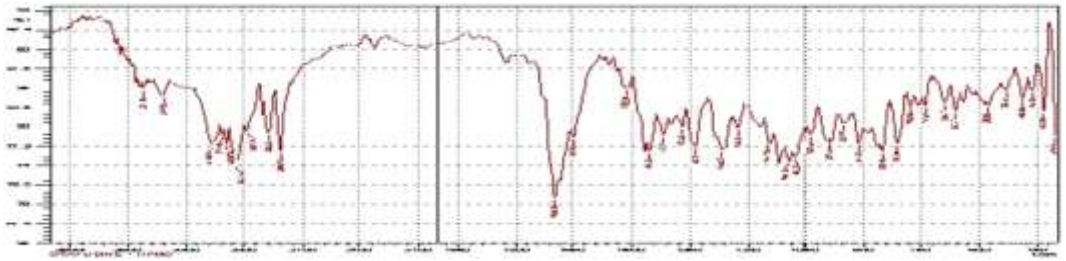

Fig.6. FT-IR spectra of (C) Formulation.

Post formulation study

7.2 Production yield (%) The production yield of microspheres was found to be in the range of 82.51-88.56% (**Table 03**). It was found that the production yield of the mucoadhesive microspheres was higher for Chitosan. The plausible cause following the difference in yield may be due to the high viscosity offered by the chitosan solution which may decrease its syringability resulting in the needle orifice blockade and leading to drug-polymer solution wastage, which eventually leads to decrease in the production yields. Another probable reason for that reduced yield may be the sticking and agglomeration of the polymeric contents to the wall of the beaker and the blades of the stirrer during the microsphere formation. [26]

7.3 Drug loading (%) and entrapment efficiency (%) The entrapment efficiency and drug content of the formulated glimepiride microspheres were found to be in the range of 73.53-80.67% and 74.81-79.97%, respectively (**Table 03**). The F1 batch has the highest drug loading and entrapment efficiency than other batches. It was scrutinized that with the increase in the concentration of mucoadhesive polymer, the entrapment efficiency increases simultaneously at higher and lower levels of stirring rate. Though, it was distinguished that Chitosan had higher influence over entrapment efficiency, owing to the higher molecular weight of chitosan which promotes the formation of more intact matrix network.[27]

7.4 Particle size analysis: The average size of the fabricated mucoadhesive microspheres were in the range of 17.9-29.12 µm. The rate of stirring had a key influence over the particle size. It was detected that with the increase in the stirring rate, the particle size decreases abruptly, irrelevant of the mucoadhesive polymer concentration (**Table 03**).

7.5 Swelling property: The swelling index of the mucoadhesive microsphere ranged from 0.72-0.91. In the study, chitosan microspheres exhibited higher degree of swelling which may be due to higher molecular weight of the former polymer. However, a clear cut conclusion was not produced. With the increase in the concentration of mucoadhesive polymer, a slight increase in swelling was observed.(**Table 03**).

7.6 Mucoadhesive test: The chitosan microspheres presented higher mucoadhesion attributes on account of higher molecular weight of Chitosan. It is also being known that the hydrophilic polymers have the characteristic to adhere with the mucosal surfaces, as a result of their ability to attract water molecules from the mucus gel layer. The studies also advocated that mucoadhesion increases with the enhancement in the mucoadhesive polymer concentration.

Table no 03. Evaluation parameters of Glimepiride microspheres.

F. code	Production yield (%)	Drug loading (%)	Entrapment efficiency (%)	Average particle size (µm ± SD)	Degree of swelling (µm ± SD)	Mucoadhesion (%)
F1	85.75	79.97±0.36	80.67±0.26	17.97±1.76	0.91±0.19	98.77±1.13
F2	88.13	75.46±0.54	78.87±0.19	20.13±0.84	0.85±0.11	98.23±0.97
F3	82.51	74.81±0.42	77.21±0.54	29.12±1.66	0.81±0.29	97.34±1.38
F4	88.56	76.99±0.46	73.53±0.37	19.34±1.69	0.72±0.15	98.78±0.71

* Values expressed as mean ± SD, n=3

7.7 Morphological studies

The optimized formulation was investigated by SEM for studying the morphology and surface characteristics of prepared mucoadhesive microspheres. The photomicrograph of the microspheres illustrated that the particles

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were well separated with spherical shape having attached drug particles this suggested that the entire drug was found uniformly over the surface of the separated microstructures.

7.8 In-vitro drug release study

The drug release profile of glimepiride from various batches of Chitosan microspheres at pH 6.8 phosphate buffer demonstrated significant drug release in the range of 77.53-82.67%. The selected optimized batch of formulation had highest cumulative release 82.67% as compared to other formulations (**Figure 07)**. The ratio of polymeric content, mucoadhesive polymers content, film forming polymer, particle size, and formulation technique had critical influence on drug release. The optimized formulation expressed best drug release attribute due to the lowest concentration of film former and mucoadhesive polymers content which promotes low entrapment of drug in the polymeric matrix and facilitates higher release.

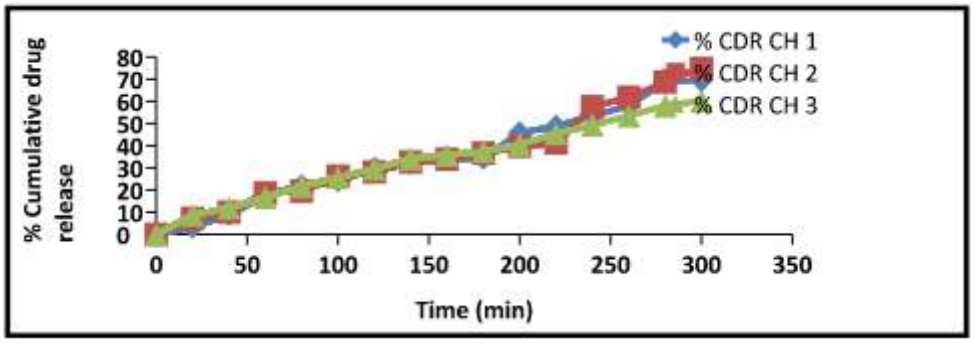

Fig. 07. Characterization of microspheres: in-vitro drug release study

7.9 Drug release kinetics

The analysis of in-vitro drug release data indicates that the glimepiride release from the microspheres followed zero order kinetics in most of the batches like F1, F2, F3, and F4 as the correlation coefficient 'r' values in the zero order model were higher than the other model. The overall kinetic study supported the diffusion mode as the primary phenomenon of drug release. [28] The results of kinetic treatment applied to release profile of formulation F1 to F4 are shown in **Table 04**

Table 04. Kinetic treatment of drug release profile of optimized formulations.

Formulation	Mathematical models				Best fit model
	Zero order	First order	Higuchi	Korsemeyer-Peppas	
F1	0.979	0.619	0.937	0.554	Zero order
F2	0.943	0.693	0.961	0.491	Zero order
F3	0.982	0.788	0.943	0.436	Zero order
F4	0.977	0.784	0.956	0.472	Zero order

VIII. CONCLUSION

The current research attempted at rationally formulating a mucoadhesive micro particulate system for the anti-diabetes drug Glimepiride for oral administration with a perspective of improving the bioavailability of the drug. The research suggested that solvent evaporation remained the most relevant procedure for the fabrication of mucoadhesive microspheres of Glimepiride based on mucoadhesive polymers. The particle size analysis indicated that all the fabricated formulations have particle size in the range of 17-29 µm which is most convenient for the oral administration of the prepared formulation for enhancing bioavailability. The SEM photomicrograph displayed spherical and smooth surface morphology of the formulations. From the studied parameters it can be concluded that Chitosan offered better mucoadhesive attributes for the formulating Glimepiride oral mucoadhesive microspheres. Thus, the formulated microspheres could be a potential carrier for elevating the bioavailability via oral route.

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