EFFECT OF AEGLE MARMELOS GUM ON MODIFIED RELEASE OF GLIPIZIDE MUCOADHESIVE MICROCAPSULES

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ABSTRACT:

Extensive research over the years has led to significant advancements in drug delivery systems, particularly through microcapsules. However, the primary limitation of conventional microspheres is their short residence time at the site of absorption, reducing their effectiveness. Recently, mucoadhesive microcapsules have gained considerable attention due to their ability to enhance drug retention and improve therapeutic efficacy.

Glipizide, a second-generation sulfonylurea, is a commonly prescribed oral hypoglycemic agent for managing Type II diabetes mellitus. However, its short biological half-life necessitates frequent dosing, leading to poor patient compliance and fluctuations in blood glucose levels. Glipizide mucoadhesive microcapsules were formulated using the emulsification-gelation technique with varying concentrations of mucoadhesive polymer Aegle marmelos gum.

The prepared microcapsules were evaluated for various physicochemical parameters, including particle size, encapsulation efficiency, surface morphology (using scanning electron microscopy), and in vitro drug release kinetics. Drug release studies conducted in buffer media demonstrated a sustained release pattern, extending up to 8 hours. The release kinetics followed a zero-order model with a non-Fickian diffusion mechanism, indicating a controlled and prolonged drug release.

Among the different formulations, the microcapsules prepared using Aegle marmelos gum in a 5:1 polymer-to-drug ratio exhibited the most prolonged drug release and superior mucoadhesive properties compared to other ratios. The study confirmed that an increase in polymer concentration enhanced mucoadhesion and residence time, which is crucial for improving bioavailability.

In conclusion, the formulated Glipizide mucoadhesive microcapsules demonstrated promising potential as an effective controlled-release drug delivery system. The optimized formulation Aegle marmelos gum at a 5:1 ratio could be a viable alternative to conventional Glipizide therapy, reducing dosing frequency and improving patient adherence.

Key words: Glipizide, Aegle Marmelos gum, emulsification gelation technique, mucoadhesive polymer, microcapsules.

INTRODUCTION:

Diabetes mellitus is a prevalent metabolic disorder characterized by chronic hyperglycaemia, requiring long-term management. Among its types, non-insulin-dependent diabetes mellitus (Type II diabetes) is the most common, often treated with oral hypoglycaemic agents. Glipizide, a second-generation sulfonylurea, is widely used due to its insulinotropic effects. However, its short biological half-life (3.4 ± 0.7 hours) necessitates multiple daily doses (2.5–10 mg, 2 to 3 times a day), leading to poor patient compliance and fluctuating blood glucose levels. Controlled-release formulations are essential to provide sustained drug release, maintain stable plasma concentrations, and potentially enable once-daily dosing. The gastrointestinal (GI) tract is the preferred drug administration route, but conventional oral formulations face limitations such as rapid gastric emptying and poor bioavailability. Mucoadhesive drug delivery systems help overcome these challenges by prolonging the residence time of the dosage form at the absorption site, enhancing drug bioavailability, and ensuring a sustained release profile.
Microencapsulation is an effective technique for modifying drug release, improving stability, and enabling targeted delivery. Microparticles, which serve as efficient carriers, face challenges such as short GI residence time. To address this, incorporating mucoadhesive polymers enhances drug retention, leading to prolonged and controlled release. This study focuses on developing Glipizide mucoadhesive microcapsules using the emulsification-gelation technique with different mucoadhesive polymers. The objective was to create a controlled-release formulation sustaining drug release for 8–12 hours, reducing dosing frequency, and improving patient adherence. The microcapsules were evaluated for particle size, encapsulation efficiency, surface morphology, and in vitro drug release kinetics to assess their potential for sustained Glipizide delivery.

MATERIALS:

Glipizide was obtained as gift sample from madras pharmaceuticals, Sodium alginate and calcium chloride were procured from S.D Fine chemicals, India. All chemicals and reagents used were of analytical grade.

METHODS:

Preparation of Aegle Marmelos Gum

Fresh Aegle marmelos fruits were soaked in distilled water and heated in a water bath for 5 hours until a slurry was obtained. The slurry was then allowed to cool and stored in a refrigerator overnight to facilitate the settling of undissolved particles. The clear upper layer was carefully separated and subjected to centrifugation at 500 rpm for 20 minutes. The resulting supernatant was concentrated using a water bath until its volume was reduced to one-third of the initial amount.
Once cooled to room temperature, the concentrated solution was slowly added to acetone in a ratio of 1:3 with continuous stirring to induce precipitation. The obtained precipitate was thoroughly washed multiple times with acetone to remove impurities. Finally, the purified gum was dried under vacuum at 50°C, ground into a fine powder, and stored in an airtight container for future use.

Method of Preparation of mucoadhesive microcapsules by Emulsification Gelation process

In this process, sodium alginate (1 g) and Aegle marmelos gum (1 g) were dissolved in 32 mL of water. Glipizide (2 g) was then added and mixed thoroughly. The prepared polymer-drug dispersion was slowly added to 50 mL of heavy liquid paraffin in a 250 mL beaker while stirring at 500 rpm to form an emulsion. Next, 20 mL of 15% w/v calcium chloride solution was added to the emulsion while stirring continuously for 15 minutes, leading to the formation of spherical microcapsules. The microcapsules were collected by decantation, washed several times with petroleum ether, and air-dried to obtain discrete particles.
Different formulations were prepared using Aegle marmelos gum in varying ratios: MC1 (1:1), MC2 (2:1), MC3 (3:1), and MC4 (5:1).

EVALUATION OF MICROSPHERES:

Size distribution and size analysis

Particle sizes of different batches of microspheres were determined by optical microscopy. A minute quantity of microspheres was spread on a lean glass slide and average particle size was determined.

Determination of Micromeritic Properties

To measure the flow property angle of repose of the drug mixture and prepared microspheres was determined by fixed funnel method and bulk density and tapped density was measured by the tapping method.
The formulas were given below; $\theta=\tan^{-1}h/r$
Where, h- Height of the heap in cm, r- radius of the pile in cm
Bulk density=W/V_o, Tapped density=W/Vt
Where, W-Weight of the formulation, V_o-Bulk volume, Vt-Tapped volume
Carr's index= Tapped density - Bulk density × 100 Tapped density
Hausner's ratio=Tapped density/ Bulk density

FT-IR Studies
Fourier Transform Infrared Analysis (FT-IR) measurements of pure drug, carrier and drug loaded microspheres formulations were obtained using a (Perkin- Elmer system 200) FTIR spectrophotometer. The pellets were prepared on KBr-press under hydraulic pressure of 150kg/cm2, the spectra were scanned over the wave number range of 4000 to 400 cm-1 at the ambient temperature.

Drug content evaluation

Glipizide content in the microcapsules was estimated by a UV spectrophotometric method based on the measurement of absorbance at (220nm) in phosphate buffer (pH 7.4).

Scanning electron microscopy (SEM)

The samples for the SEM analysis were prepared by sprinkling the gel beads on one side of double adhesive stub. The stub was then coated with fine gold dust. The get beads were then observed with the scanning electron microscope.

Drug Encapsulation Efficiency

The assay of Glipizide was estimated by (UV/VIS) spectrometric method. Drug solution was prepared in phosphate buffer (pH- 7.4) and absorbance was measured on UV /Vis spectrometer at 220nm It is calculated by formula; [Actual drug content/Theoretical drug content] × 100 = % drug entrapped.

In vitro release studies

Dissolution studies of microcapsules were performed according to USP XXIII 6-station dissolution rate test apparatus in phosphate buffer. The temperature was maintained at 37±1°C and the rotation speed was 50 rpm. The samples were withdrawn at various time intervals and analysed spectrophotometrically.

Kinetic modelling

In order to understand the kinetics and mechanism of drug release, the result of in vitro drug release study of microcapsules was fitted with various kinetic equations like zero order (cumulative % release vs. time), first order (log % drug remaining Vs time), Higuchi's model (cumulative % drug release vs. square root of time), Peppas plot (log of cumulative % drug release Vs. log time). r2 and k values were calculated from the linear curve obtained by regression analysis of the above plots (Saparia B, 2002).

Permeability studies

Permeability constant was calculated by using
Pm = KVH/ACs
V is the volume of the dissolution medium; H is the wall thickness of the micro capsules; A is the surface area of the microcapsules. Cs is the solubility of the core material in the dissolution medium and K is the release rate constant.

Evaluation of swelling behaviour

Swelling behaviour was studied by measuring the percentage water uptake by the beads. About 100 mg of beads were accurately weighed and placed in 100 ml of phosphate buffer (pH 7.4) and 0.1 N HCl (pH 1.2). Beads were removed from their respective swelling media after 8 hours and weighed after drying the surface water using filter paper. The water uptake was calculated as the ratio of the increase in weight of beads after swelling to the dry weight.

Muco-adhesion testing by in vitro wash-off method

The mucoadhesive properties of various formulations were evaluated by the in vitro wash-off method. Freshly excised pieces of goat intestinal mucosa (1 cm × 1 cm collected from a slaughter house) were mounted on a glass slide (7.5 cm × 2.5 cm) using thread. About 50 beads were spread out on each piece of mucosa and then hung from the arm of the tablet disintegration test apparatus. The tissue specimen was given a regular up and down movement in a 1-l vessel containing 900 ml of 0.1 N HCl (pH 1.2) and phosphate buffer (pH 7.4) maintained at 37 ± 0.5 °C. The adherence of beads was regularly observed. The beads that remained adhered to the mucosa were counted at regular intervals for up to 8 hrs.

Ex vivo drug release study

The release of Glipizide from alginate- Aegle marmelos gum beads adhered to fresh goat intestinal mucosa were performed in acidic (0.1 N HCl) as well as alkaline phosphate buffer (pH 7.4) media. The Glipizide-loaded alginate Aegle marmelos gum beads were weighed accurately (100 mg) and spread out on the intestinal tissue specimen (goat intestinal mucosa) attached to a glass support. The beads were wetted by spraying the release medium. After hydration of the beads, the support was inserted in a 1-l beaker and kept inclined at an angle of 60° with the help of the beaker wall. The mucosa containing beads were washed with freshly prepared release medium maintained at 37 ± 0.5 °C with a flow rate of 0.5 mL/min. The concentration of Glipizide in the washings was determined using a UV-Vis spectrophotometer

Differential Scanning Calorimetry (DSC)

DSC was performed on Glipizide drug loaded microspheres using Differential scanning calorimeter (Seiko Japan. DSC model 220C). Samples were sealed in aluminium pans and the DSC thermo grams were reported at a heating rate of 10°C/min from 20°Cto 200°C.

RESULT AND DISSCUSSION:

Preparation of Natural gums

The study investigates the use of plant-based natural gums as a dehumidifier due to their unique properties, and uses cold/hot aqueous extraction and organic solvent precipitation for water-soluble components. The process was chosen based on literature to preserve components against degradation, recover organic solvents through fractional distillation, and be effective in selective preparation with good handling properties.

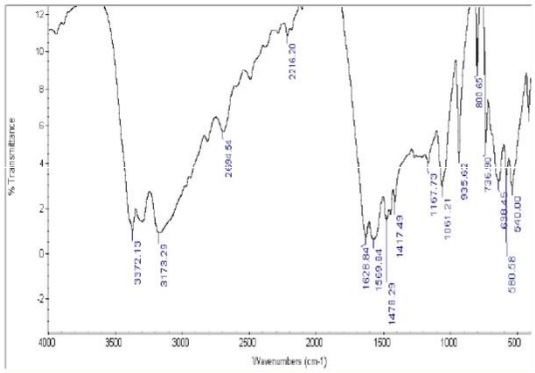

Figure 1: FTIR Spectrum of Glipizide

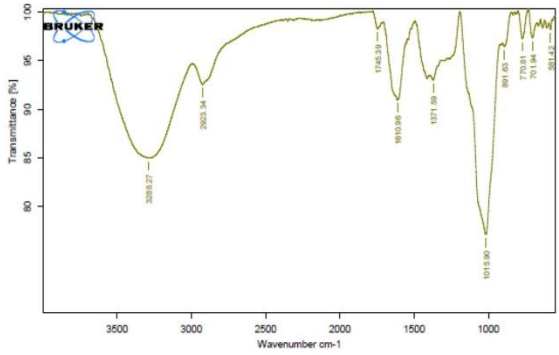

Figure 2: FTIR Spectrum of Aegle marmelos gum

FT-IR spectrum and DSC Study

The FT-IR spectrum and DSC thermogram showed no significant differences in onset and peak temperatures between the drug and polymers, indicating no chemical interaction.
The drug and polymer mixture did not exhibit any significant interaction, indicating no significant change in the drug's chemical integrity, as indicated by the absence of a characteristic peak.

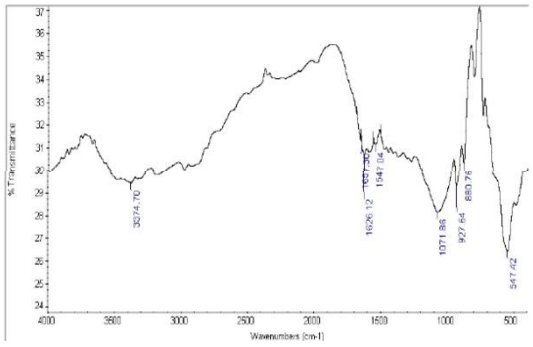

Figure 3: FTIR spectrum of Glipizide microcapsules prepared with Aegle marmelos gum

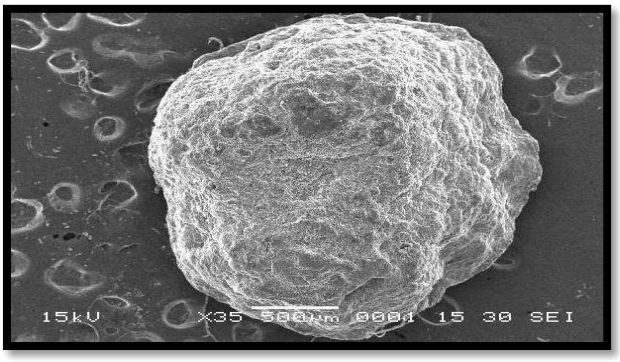

Figure 4: SEM photograph of glipizide microcapsules formulated with Aegle marmelos gum [5:1]by Emulsification Gelation technique

Formulation	Angle of repose	Bulk Density	Carr's Index	Hausner Ratio	Average particle size	%Encapsul-ation Efficiency	% Drug content
MC1	21.06±0.18	0.49±0.02	14.95±0.11	1.13±0.08	826.83	92.67±0.24	68.89
MC2	22.08±0.20	0.59±0.04	13.79±0.16	1.09±0.12	850.15	93.55±0.32	67.98
MC3	24.14±0.14	0.65±0.06	12.24±0.08	1.04±0.08	862.78	94.29±0.40	67.06
MC4	25.22±0.08	0.67±0.04	11.88±0.08	1.02±0.10	866.22	95.28±0.23	65.66

Table 1.1: Physicochemical properties of microcapsules prepared by Aegle marmelos gum

Glipizide microcapsules were found to be discrete, spherical, and free-flowing, with 90% falling within the 850µ size range. They showed good flow ability and varied release rate constants.

Formulation	Swelling Index	Wall Thickness	Release Rate Constant	Permeability Coefficient
MC1	57	26.08	2.52	66.80
MC2	98	37.22	1.60	60.08
MC3	124	48.22	1.15	55.92
MC4	135	59.88	0.98	50.08

Table 1.2: Permeability characteristics of Glipizide microcapsules prepared by Aegle marmelos gum

Formulation	Correlation Coefficient Values				n
	Zero Order	First Order	Higuchi model	Korsmeyer – Peppas mode	
MC 1	0.982	0.895	0.964	0.998	0.816
MC2	0.992	0.882	0.935	0.991	0.846
MC3	0.997	0.757	0.908	0.999	1.072
MC4	0.993	0.721	0.878	0.995	1.132

Table 1.3: Regression co-efficient (r^2) values of different kinetic models prepared with Aegle marmelos gum

Table 1.3 shows regression co-efficient values for all formulations, with R-value higher in Zero Order models, indicating drug release from microcapsules follows Zero Order Kinetics. The n-value, ranging from 0.816 to 1.132, indicates non-Fickian transport as the drug release mechanism.

Time (h)	Percent Glipizide Released			
	MC1	MC2	MC3	MC4
0	0	0	0	0
1	32.15 ± 0.22	21.11 ± 0.24	10.06 ± 0.12	8.22±0.14
2	54.78 ± 0.18	36.58 ± 0.20	22.20 ± 0.10	15.08±0.22
4	98.56 ± 0.36	61.48 ± 0.18	45.60 ± 0.16	32.56±0.16
4.5	99.92 ± 0.08	68.87 ± 0.18	49.98 ± 0.20	37.54±0.22
5	---	78.56 ± 0.08	56.24 ± 0.18	45.08±0.10
5.5	---	89.66 ± 0.12	62.44 ± 0.14	51.08±0.04
6	---	98.98 ± 0.08	68.89 ± 0.18	57.02±0.04
6.5	---	---	75.66 ± 0.22	62.02±0.18
7	---	---	82.66 ± 0.08	69.02±0.24
7.5	---	---	90.44 ± 0.10	74.98±0.16
8	---	---	97.32 ± 0.18	80.66±0.12
8.5	---	---	99.99 ± 0.10	85.44±0.14
9	---	---	----	90.04±0.22
9.5	---	---	----	95.22±0.18
10	---	---	----	99.99±0.12

Table 1.4: Release data of Glipizide microcapsules prepared with Aegle marmelos gum

CONCLUSION:

Glipizide mucoadhesive microcapsules formulated with the natural polymer Aegle marmelos gum demonstrated prolonged drug release. Among the different formulations, the microcapsules prepared with Aegle marmelos gum in a 5:1 ratio exhibited the most extended drug release compared to other ratios (5:1 > 3:1 > 2:1 > 1:1). Increased polymer concentration enhanced the *ex vivo* mucoadhesive residence time. Higher gum viscosity led to greater swelling, which in turn improved mucoadhesive strength. FTIR and DSC studies confirmed the absence of drug-polymer interactions.

All formulations followed zero-order drug release kinetics, with drug release governed by the Higuchi model. Glipizide mucoadhesive microcapsules, prepared using the emulsification-gelation method, exhibited mucoadhesive properties and controlled drug release over an extended period. The alginate-Aegle marmelos gum (5:1) formulation demonstrated a slow, diffusion-controlled release, making it a promising approach for oral sustained-release Glipizide delivery.

REFERENCE:

1. Cevik, A. G. S. (2000). Sustained release properties of alginate microspheres and tabletted microspheres of diclofenac sodium. *Journal of microencapsulation*, *17*(5), 565-575.
2. Gutcho, M. (1976). Microcapsules and Microencapsulation Techniques Noyes Data Corp.
3. Higuchi, T. J. J. O. P. S. (1963). Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *Journal of pharmaceutical sciences*, *52*(12), 1145-1149.
4. Jacob, S., Shirwaikar, A., Joseph, A., & Srinivasan, K. (2007). Novel co-processed excipients of mannitol and microcrystalline cellulose for preparing fast dissolving tablets of glipizide. *Indian Journal of Pharmaceutical Sciences*, *69*(5), 633-639.
5. Chowdary, K. P. R., & Rao, Y. S. (2003). Mucoadhesive microcapsules of glipizide: characterization, in vitro and in vivo evaluation. *Indian journal of pharmaceutical sciences*, *65*(3), 279-284.
6. Chowdary, K. P. R., & Rao, Y. S. (2004). Mucoadhesive microspheres for controlled drug delivery. *Biological and pharmaceutical Bulletin*, *27*(11), 1717-1724.
7. Korsmeyer, R. W., Gurny, R., Doelker, E., Buri, P., & Peppas, N. A. (1983). Mechanisms of solute release from porous hydrophilic polymers. *International journal of pharmaceutics*, *15*(1), 25-35.
8. Poncelet, D., Lencki, R., Beaulieu, C., Halle, J. P., Neufeld, R. J., & Fournier, A. (1992). Production of alginate beads by emulsification/internal gelation. I. Methodology. *Applied microbiology and biotechnology*, *38*, 39-45.
9. Ritger, P. L., & Peppas, N. A. (1987). A simple equation for description of solute release I. Fickian and non-fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. *Journal of controlled release*, *5*(1), 23-36.
10. Ritger, P. L., & Peppas, N. A. (1987). A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. *Journal of controlled release*, *5*(1), 37-42.
11. Bera, K., Mazumder, B., & Khanam, J. (2016). Study of the mucoadhesive potential of carbopol polymer in the preparation of microbeads containing the antidiabetic drug glipizide. *AAPS PharmSciTech*, *17*, 743-756..
12. Vinod, V. T. P., Sashidhar, R. B., Suresh, K. I., Rao, B. R., Saradhi, U. V., & Rao, T. P. (2008). Morphological, physico-chemical and structural characterization of gum kondagogu (Cochlospermum gossypium): A tree gum from India. *Food hydrocolloids*, *22*(5), 899-915.