EFFECT OF DIFFERENT NATURAL POLYMERS ON THE MODIFIED RELEASE OF MUCOADHESIVE MICROCAPSULES

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ABSTRACT:

Diabetes mellitus is a prevalent metabolic disorder that requires long-term management. Among various treatment options, 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, leading to poor patient compliance and fluctuating blood glucose levels. To overcome these limitations, the present study aimed to develop mucoadhesive microcapsules of Glipizide using natural polymers to provide a controlled-release formulation capable of sustaining drug release for 8–12 hours.

Mucoadhesive microcapsules were prepared using the emulsification-gelation technique, incorporating natural polymers such as Aegle marmelos gum and Gum Karaya in different ratios. Various formulations were developed and evaluated for particle size, encapsulation efficiency, surface morphology, in vitro drug release kinetics, permeability, swelling behaviour, and mucoadhesion properties. The prepared microcapsules were discrete, spherical, and free-flowing, with an average size of 850 µm. SEM analysis confirmed their spherical shape with a uniform polymer coating. FTIR and DSC studies demonstrated no drug-polymer interactions, ensuring formulation stability.

The in vitro drug release studies indicated a slow and prolonged release pattern, with formulations containing a 5:1 polymer-to-drug ratio exhibiting the most sustained release profile. Drug release kinetics followed the Higuchi model with zero-order kinetics, and the release mechanism was determined to be non-Fickian transport. The permeability coefficient analysis demonstrated significant differences among the formulations, with microcapsules containing Gum Karaya exhibiting superior permeability and mucoadhesive strength. The in vitro wash-off test confirmed that microcapsules prepared with Gum Karaya had better mucoadhesive properties compared to those made with Aegle marmelos gum, leading to prolonged gastrointestinal residence time.

Overall, the study successfully developed Glipizide mucoadhesive microcapsules with sustained drug release properties. Among all formulations, those containing a 5:1 ratio of Gum Karaya demonstrated the longest drug release duration and highest mucoadhesion. The combination of alginate and Gum Karaya effectively prolonged drug release while ensuring improved bioavailability. These findings suggest that the formulated mucoadhesive microcapsules are a promising approach for the sustained oral delivery of Glipizide, potentially improving patient adherence and therapeutic efficacy in diabetes management.

Key words: Glipizide, Aegle Marmelos gum, Gum Karaya emulsification gelation technique, mucoadhesive polymers, microcapsules

INTRODUCTION:

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycaemia, necessitating long-term management to prevent complications. Among its various forms, Type II diabetes mellitus (non-insulin-dependent diabetes mellitus) is the most prevalent, commonly treated with oral hypoglycaemic agents. Glipizide, a second-generation sulfonylurea, is widely used due to its insulinotropic effects, stimulating insulin secretion from pancreatic β-cells. However, its short biological half-life (3.4 ± 0.7 hours) requires frequent dosing (2.5–10 mg, 2–3 times daily), leading to poor patient compliance and fluctuations in blood glucose levels. To overcome these limitations, controlled-release formulations are essential to maintain stable plasma drug concentrations, reduce dosing frequency, and enhance therapeutic efficacy. While the gastrointestinal (GI) tract remains the preferred route for drug administration, conventional oral formulations often suffer from limitations such as rapid gastric emptying and poor bioavailability. Mucoadhesive drug delivery systems provide a viable solution by prolonging the residence time of the drug at the absorption site, ensuring sustained drug release and improved bioavailability. Microencapsulation is an effective strategy for modifying drug release, enhancing stability, and enabling targeted delivery. However, microparticles face challenges such as short GI residence time. To address this, mucoadhesive polymers can be incorporated to enhance retention at the absorption site, ensuring prolonged and controlled drug release. This study aims to develop and evaluate Glipizide mucoadhesive microcapsules using natural polymers via the emulsification-gelation technique. The formulations were assessed for particle size, encapsulation efficiency, surface morphology, drug release kinetics, permeability, and mucoadhesive properties to establish their potential for sustained Glipizide delivery.

MATERIALS:

Glipizide was obtained as gift sample from madras pharmaceuticals, Gum Karaya were
obtained from cooperative corporation ltd, Visakapatnam, 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 Aegle marmelos gum

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).

Method of Preparation of mucoadhesive microcapsules by Gum Karaya

The emulsification gelation process involves dissolving sodium alginate (1gm) and polymer (1gm) in water (32ml), adding a drug (2gm) and mixed properly. The polymer dispersion was then added in a thin stream to 50ml of heavy liquid paraffin in a 250m beaker, and stirring at 500rpm to emulsify the dispersion into fine droplets. Calcium chloride solution is then added to the emulsion, stirring at 500rpm for 15 minutes to create spherical microcapsules. These microcapsules are collected, washed with petroleum ether, and air dried to obtain discrete microcapsules. Different ratios of mucoadhesive microcapsules are prepared.
Different formulations were prepared using Gum Karaya in varying ratios: MC5 (1:1), MC6 (2:1), MC7 (3:1), and MC8 (5:1).

EVALUATION OF MICROCAPSULES:

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 and polymer 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 and polymer 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:

Mucoadhesive microcapsules of Glipizide were successfully prepared using different natural mucoadhesive polymers by emulsification-gelation process. The resulting microcapsules were discrete, spherical, and free-flowing, with an average size of 850µ, as shown in Table 1. SEM analysis (Fig. 6) confirmed their spherical shape and complete polymer coating. The low coefficient of variation (<2.0%) in drug content indicated uniform distribution across all batches. IR spectroscopy (Fig 1, 2, 3, 4, 5) confirmed the absence of chemical incompatibility between the drug and the polymer. The drug release (Table 5) from the microcapsules was slow and prolonged, with the release rate depending on the coat-to-core ratio. Microcapsules with a 5:1 coat-to-core ratio exhibited the most sustained drug release profile. Based on in-vitro studies, microcapsules prepared with a 5:1 ratio of different polymers were subjected to comparative analysis, revealing significant differences in permeability coefficients. An in-vitro wash-off test (Table 2) confirmed that microcapsules prepared with Gum karaya exhibited superior mucoadhesive properties compared to those made with Aegle marmelos gum. The drug release kinetics followed Zero Order, as indicated by a higher R-value in this model compared to others. Based on the n-value, the drug release mechanism was determined to follow non-Fickian transport.

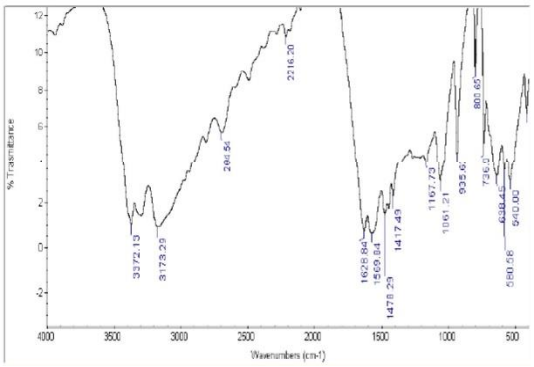

Figure 1: FTIR Spectrum of Glipizide

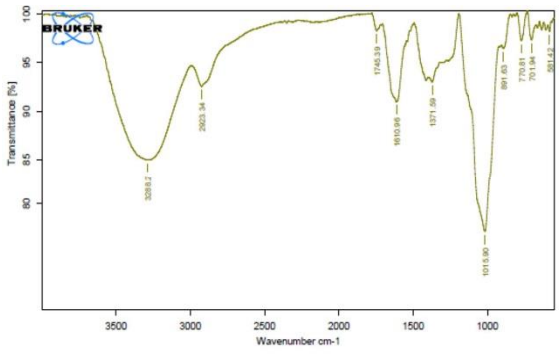

Figure 2: FTIR Spectrum of Aegle marmelos gum

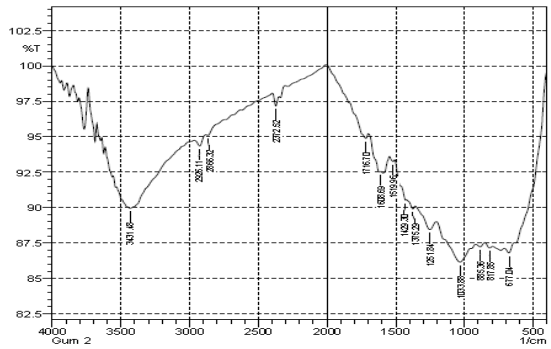

Figure 3: FTIR Spectrum of Gum Karaya

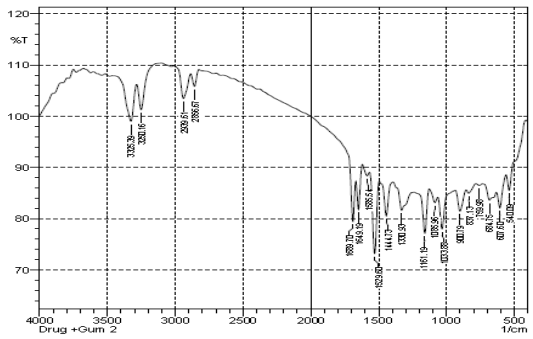

Figure 4: FTIR Spectrum of Glipizide + Gum Karaya

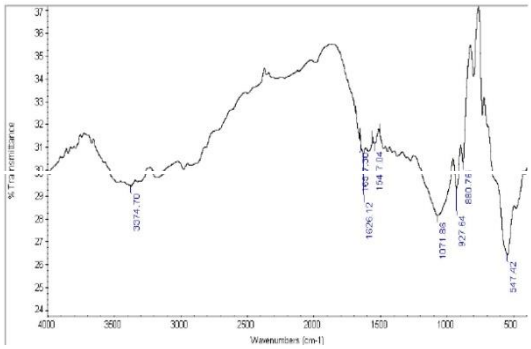

Figure 5: FTIR Spectrum of Glipizide + Aegle marmelos gum

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.

Formulation	Angle of repose	Bulk Density	Carr's Index	Hausner Ratio	Average particle size	%Encapsul-ation Efficiency	% Drug content
MC1	20.16	0.48	14.55	1.16	825.83	92.87	68.79
MC2	21.28	0.57	13.69	1.06	851.15	93.85	67.98
MC3	23.34	0.63	12.84	1.04	864.78	94.59	67.26
MC4	24.72	0.66	11.58	1.01	868.22	95.58	65.36
MC5	23.18	0.53	17.20	1.14	844	92.80	67.54
MC6	25.13	0.62	16.20	1.08	865	94.50	113.11
MC7	20.10	0.50	14.02	1.08	823	94.04	70.45
MC8`	21.99	0.54	12.43	1.09	844	93.89	96.34

Table 1.1: Physicochemical properties of Glipizide microcapsules

Formulation	Swelling Index	Wall Thickness	Release Rate Constant	Permeability Coefficient
MC1	55	25.08	2.57	66.60
MC2	96	36.22	1.63	60.18
MC3	127	49.22	1.16	55.62
MC4	138	58.88	0.96	50.28
MC5	54	26.44	2.33	62.22
MC6	94	36.66	1.54	58.28
MC7	128	51.44	1.02	52.90
MC8	139	60.44	0.90	26.22

Table 1.2: Permeability characteristics of Glipizide microcapsules

Formulation	Correlation Coefficient Values				n
	Zero Order	First Order	Higuchi model	Korsmeyer – Peppas mode	
MC 1	0.981	0.898	0.965	0.995	0.817
MC2	0.992	0.889	0.933	0.990	0.844
MC3	0.995	0.786	0.905	0.998	1.075
MC4	0.994	0.718	0.875	0.994	1.130
MC5	0.971	0.893	0.962	0.989	0.819
MC6	0.956	0.888	0.943	0.979	0.848
MC7	0.989	0.748	0.910	0.991	1.062
MC8	0.995	0.710	0.868	0.992	1.120

Table 1.3: Regression co-efficient (r^2) values of different kinetic models

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				Percent Glipizide Released			
	MC1	MC2	MC3	MC4	MC5	MC6	MC7	MC8
0	0	0	0	0	26.56 ± 0.26	20.67 ± 014	07.44 ± 0.10	06.10±0 .12
1	33.15 ± 0.22	22.11 ± 0.24	11.06 ± 0.12	8.52±0.1 4	50.89 ± 0.14	35.90 ± 0.10	17.22 ± 0.18	13.22±0 .08
2	53.78 ± 0.18	34.58 ± 0.20	23.20 ± 0.10	14.08±0. 22	85.65 ± 0.28	59.21 ± 0.16	35.28 ± 0.26	32.28±0 .24
4	97.56 ± 0.36	60.48 ± 0.18	44.60 ± 0.16	32.56±0. 16	89.92 ± 0.14	66.86 ± 0.18	41.08 ± 0.22	38.22±0 .18
4.5	99.95 ± 0.08	67.87 ± 0.18	47.98 ± 0.20	36.54±0. 22	92.88 ± 0.18	73.88 ± 0.08	46.98 ± 0.16	43.28±0 .22
5	---	75.56 ± 0.08	55.24 ± 0.18	44.08±0. 10	95.88 ± 0.10	79.98 ± 0.12	52.34 ± 0.13	49.12±0 .04
5.5	---	86.66 ± 0.12	61.44 ± 0.14	50.08±0. 04	99.08 ± 0.08	86.66 ± 0.18	58.17 ± 0.19	55.24±0 20
6	---	99.98 ± 0.08	67.89 ± 0.18	56.02±0. 04	---	89.98 ± 0.08	63.44 ± 0.20	60.22±0 .06
6.5	---	---	74.66 ± 0.22	63.02±0. 18	---	92.88 ± 0.08	68.98 ± 0.12	65.88±0 .22
7	---	---	83.66 ± 0.08	68.02±0. 24	---	96.04 ± 0.08	73.88 ± 0.12	71.32±0 .18
7.5	---	---	91.44 ± 0.10	73.98±0. 16	---	99.68 ± 0.08	79.56 ± 0.16	75.22±0 .08
8	---	---	96.32 ± 0.18	81.66±0. 12	---	---	84.54 ± 0.20	79.88±0 .12
8.5	---	---	99.95 ± 0.10	84.44±0. 1	---	---	89.04 ± 0.14	84.88±0 .12
9	---	---	----	89.04±0. 22	---	---	94.08 ± 0.14	86.88±0 .12
9.5	---	---	----	94.22±0. 18	---	---	99.42 ± 0.10	89.44±0 .10
10	---	---	----	99.95±0. 12	---	---	----	92.88±0 .14
10.5					---	---	----	95.88±0 .12
11					---	---	----	97.22±0 .18
12					---	---	----	99.99±0 .10

Table 1.4: Release data of Glipizide microcapsules prepared

CONCLUSION:

The study successfully developed Glipizide mucoadhesive microcapsules using natural polymers, Aegle marmelos gum and Gum Karaya, via the emulsification-gelation technique. The prepared microcapsules were discrete, spherical, and free-flowing, with an average size of 850 µm. SEM analysis confirmed uniform polymer coating, while FTIR and DSC studies demonstrated no chemical interactions between the drug and polymers, ensuring formulation stability. In vitro drug release studies indicated a slow and prolonged release pattern, with formulations containing a 5:1 polymer-to-drug ratio exhibiting the most sustained drug release. Drug release kinetics followed the Higuchi model with zero-order kinetics, and the mechanism was identified as non-Fickian transport. The in vitro wash-off test confirmed superior mucoadhesive properties for microcapsules prepared with Gum Karaya compared to Aegle marmelos gum, leading to prolonged gastrointestinal residence time. Additionally, swelling studies demonstrated that higher polymer concentrations contributed to increased hydration, enhancing mucoadhesive strength. Among all formulations, microcapsules prepared with a 5:1 ratio of Gum Karaya exhibited the longest drug release duration and the highest mucoadhesive strength, making them a promising candidate for sustained oral delivery of Glipizide. The combination of alginate and Gum Karaya effectively prolonged drug release while ensuring improved bioavailability and patient compliance. These findings suggest that the formulated mucoadhesive microcapsules could serve as an effective controlled-release system for Glipizide, potentially improving therapeutic outcomes in diabetes management.

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