International Journal of Pharmacy and Natural Medicines

Journal Home Page: www.pharmaresearchlibrary.com/ijpnm

RESEARCH ARTICLE

Formulation and Characterization of Mucoadhesive Microcapsules of Gliclazide by Ionic Gelation Technique

B. Lakshmi Aasritha*[1], Bharghava Bhushan Rao P[2]

[1]*VJ'S College of Pharmacy, Rajahmundry, Andhra Pradesh, India*
[2]*V. V. Institute of Pharmaceutical Sciences, Gudlavalleru, A.P, India*

ABSTRACT

The objective of the present research was to develop the controlled release mucoadhesive microcapsules of Gliclazide using various natural and synthetic mucoadhesive polymers such as Guar gum, Xanthum gum , Sodium CMC and Carbopol by Ionic gelation technique. Gliclazide and polymer compatibility studies were performed using Fourier transform infrared spectroscopy(FT-IR) and Differential scanning calorimetry (DSC). The microcapsules were prepared by Ionic gelation method. The prepared microcapsules were evaluated for Product yield, Drug loading and drug entrapment efficiency, particle size, Morphological study using SEM, Micrometric Studies and Mucoadhesion Testing by *In Vitro* wash-off Test. The effect of concentration and type of polymers, on in - vitro drug release and release kinetics was studied extensively. FT-IR and DSC studies revealed no interaction between Gliclazide and polymers. Product yield of the prepared beads was in the range of 68.2 - 89.1%. Drug entrapment efficiency of Gliclazide microcapsules ranged from 63.31-83.4%. Mean particle size of the prepared beads was in the size range of 321-622µm and suitable for bioadhesive microcapsules for oral administration. The results obtained confirm that the flow properties of microcapsule of all the formulations except F6, F9, F12 and F15 exhibited good flow properties. The formulations F6, F9, F12 and F15 were found to be poor because of their irregular shape. The *in vitro* mucoadhesive study demonstrated that microcapsules of Gliclazide with polymer Carbopol adhered to the mucus to a greater extent. In -vitro drug release studies exhibited that the drug release was not sustained up to 12 h for Gliclazide microcapsules prepared with Guar gum and Sodium CMC but the In-vitro drug release studies exhibited that the drug release was sustained up to 12h for Gliclazide microcapsules prepared with Xanthum gum and Carbopol but Carbopol showed better sustained action with high entrapment efficiency, good percent drug release and high mucoadhesion when compared with Xanthum gum.

Key words: Guar gum, Xanthum gum, Sodium Alginate, Carbopol, Sodium CMC, *In-vitro* drug release.

ARTICLE INFO

Corresponding Author
B. Lakshmi Aasritha
VJ'S College of Pharmacy,
Rajahmundry, Andhra Pradesh, India
MS-ID: IJPNM4410

PAPER QR-CODE

ARTICLE HISTORY: Received 12 May 2019, **Accepted** 18 Oct 2019, **Available Online** 15 December 2019

Citation: *B. Lakshmi Aasritha, et al.* Formulation and Characterization of Mucoadhesive Microcapsules of Gliclazide by Ionic Gelation Technique. *Int. J. Pharm. Natural Med.,* 2019, 7(2): 124-129.

CONTENTS

1. Introduction

Development of controlled release oral dosage forms is beneficial for optimal therapy regarding efficacy, safety and patient compliance. Frequently used approaches to achieve adequate control of drug release include microencapsulation. Microencapsulation [1] is a useful method to prolong the drug release from dosage forms and reduces adverse affects. Microparticles are defined as spherical polymeric particles. These microparticles constitute an important part of these novel drug delivery systems, by virtue of their small size and efficient carrier characteristics. However, the success of these novel microparticles is limited due to their short residence time at the site of absorption. If these drug delivery systems provide an intimate contact with the absorbing membranes then they will become an effective drug delivery. It can be achieved by coupling bioadhesion characteristics to microparticles and developing novel delivery systems referred to as "bioadhesive microparticles". Bioadhesive microparticles [2-4] include microcapsules (having a core of the drug) of 1- 1000 um in diameter and consisting either entirely of a bioadhesive polymer or having an outer coating of it. Bioadhesive microparticles have advantages such as efficient absorption and enhanced bioavailability of drugs owing to their high surface to volume ratio, a much more intimate contact with the mucus layer, and specific targeting of drugs to the absorption site. Gliclazide[5] is an oral hypoglycaemic second generation sulfonyl urea drug which is useful for a long-term treatment of non-insulin dependent diabetes mellitus (NIDDM). For an oral hypoglycaemic drug, rapid absorption from the GIT is required for an effective pharmacological activity but the absorption rate of Gliclazide from the GIT is slow and varied among the subjects. The slow absorption is due to either poor dissolution of Gliclazide owing to its hydrophobic nature or poor permeability of the drug across the GI membrane. Incorporation of Gliclazide in controlled release dosage forms may regulate its absorption from the GIT and overcome the variability problems. Therefore, it is evident that bioadhesive microcapsules will best suit the purpose of dosage form design**.** The modified-release preparation demonstrates very high bioavailability and allows reduction in the effective dose. Hence, the main aim of the present work is to develop the controlled release mucoadhesive microcapsules of Gliclazide using various natural and synthetic mucoadhesive polymers such as Guar gum, Xanthum gum, Sodium CMC and Carbopol by Ionic gelation technique.

2. Materials and Methods

Materials

Gliclazide was obtained as gift sample from Aurobindo Pharma Ltd., Hyderabad, India. Sodium alginate was a gift sample from FMC, Norway. Guar Gum, Calcium Chloride and Sodium CMC were gift samples from Loba Chemicals, Mumbai. Xanthum gum was a gift sample from Keshav chem Pvt Ltd, New Delhi. Carbopol was a gift sample from Zenita Life Sciences Pvt Ltd, Mumbai. All other reagents of analytical grade were used.

Preparation of Gliclazide microcapsules:

The Gliclazide loaded calcium alginate beads were prepared by employing Ionic gelation technique. The accurately weighed Gliclazide was dispersed in 10ml of sodium alginate solution (2%w/v) and agitated thoroughly on hot plate to form a viscous homogenous dispersion which was sonicated for 3 min to remove any air bubbles. Then the dispersion was dropped through the 24G needle into the 100 ml of 5% calcium chloride solution, stirred up to 2 min, allowed to retain in calcium chloride solution for curing up to 15 minutes. The obtained microcapsules were then separated by decantation, washed three times with deionized water and dried at 45^0 C for 8hrs. The composition for the preparation of the microcapsules was showed in Tables 1.l and 1.2.

Characterization of Prepared Mirocapsules

Product yield

The total amount of dried microcapsules was weighed and the percentage yield was calculated by taking into consideration the total weight of the drug and polymer used for preparation of microcapsules. It is expressed as a percentage and calculated from the following equation:

$$\text{Product Yield} = \frac{\text{Practical mass (microcapsules)}}{\text{Theoretical mass (drug + polymers)}} \times 100$$

Drug loading and drug entrapment efficiency

Microcapsules containing equivalent to 10mg of Gliclazide were weighed and crushed to fine powder in a mortar. The drug was extracted with 10 ml of methanol. It was filtered, suitably diluted with phosphate buffer pH 7.4. The drug content was determined from the absorbance measured at 226nm. Based on the absorbance entrapment efficiency of different formulations were calculated. The amount of drug entrapped in microcapsules was calculated by following formula:

$$\% \text{ Drug entrapment} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

Analysis of particle size [6]

A random sample of dried Microcapsules was placed on glass slide with drop of liquid paraffin, and the size was measured using an optical microscope. The mean of 100 microcapsules was noted as particle size. All the studies were carried out in triplicate.

Morphological study using SEM:

The shape and surface morphologies of the drug loaded microcapsules were investigated using the scanning electron microscopy [7] (SEM Jeol, JSM- 6390 LV, Japan). Prior to examinations, samples were mounted onto stubs using double-sided dried carbon tape and vacuum coated with gold palladium film using coater, to render them electrically conductive. The scanning electron microscope photomicrographs were taken at 15 kV in various magnifications appropriate to each formulation.

Mucoadhesion Testing by *In Vitro* wash-off Test [8]

The mucoadhesive properties of the microcapsules were evaluated by *in-vitro* wash-off test. A 2 cm wide and 2 cm

long (2×2) piece of rat intestinal mucosa was tied onto a glass slide using thread. About fifty microcapsules were spread onto the wet, rinsed, tissue specimen, and allowed to hydrate for 30s. The prepared slide was hung onto one of the grooves of a tablet disintegrating test apparatus. The disintegrating test apparatus was operated such that the tissue specimen was given regular up and down movements in the test fluid at 37 °C contained in one litre vessel of the machine. At the end of 6 h, the machine was stopped and the number of microcapsules still adhering to the tissue was counted. The test was performed in intestinal pH (phosphate buffer, pH 7.4).All the trials were conducted in triplicate and the average (± SD) reading was noted.

***In vitro* Release Study**

The *in-vitro* release studies of microcapsules were carried out in USP type I (basket) dissolution test apparatus (Labindia dissolution apparatus. India) at 37± 2^0C and 100 rpm speed. Microcapsules containing equivalent to 60 mg of Gliclazide were subjected to *in- vitro* drug release studies. Release of Gliclazide from the beads was studied in 0.1N Hcl solution (1.2pH) for 2 hours and then transferred to 7.4 pH phosphate buffer for 10 hours. Samples were withdrawn at regular intervals up to 12 hrs and each sample withdrawn was replaced with an equal volume of fresh dissolution medium, to maintain sink conditions. After suitable dilution, the samples were analyzed for drug concentration at a λmax 226 nm using Elico UV-VIS spectrophotometer. The dissolution studies were conducted in triplicate.

Data Analysis

Release data were analyzed as per zero order, first order, Higuchi equation and Peppas equation models to assess the drug release kinetics and mechanism of release from the microcapsules.

Table 1.1: Composition of Gliclazide Mucoadhesive Microcapsules Prepared Using Sodium alginate alone and in combination with Natural polymers.

Ingredients (mg)	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	60	60	60	60	60	60	60	60	60
Sodium alginate	60	120	180	60	60	60	60	60	60
Guar gum	-	-	-	60	120	180	-	-	-
Xanthum gum	-	-	-	-	-	-	60	120	180
$CaCl_2$ (w/v)	5%	5%	5%	5%	5%	5%	5%	5%	5%

Table 1.2: Composition of Gliclazide Mucoadhesive Microcapsules Prepared using sodium alginate in combination with Synthetic polymers.

Ingredients (mg)	Formulations					
	F10	F11	F12	F13	F14	F15
Drug	60	60	60	60	60	60
Sodium alginate	60	60	60	60	60	60
Sodium CMC	60	120	180	-	-	-
Carbopol	-	-	-	60	120	180
$CaCl_2$ (w/v)	5%	5%	5%	5%	5%	5%

3. Results and Discussion

Mucoadhesive microcapsules of Gliclazide prepared by Ionic gelation method using 2%w/v sodium alginate alone and in combination with mucoadhesive polymers like Guar gum, Xanthum gum, NaCMC and Carbopol, were evaluated for particle size, surface morphology, flow properties, product yield, entrapment efficiency and *in-vitro* mucoadhesion test. Product yield of the prepared beads was in the range of 68.2 - 89.1%. It was observed that as the polymer ratio increases, the product yield slightly decreases. The reason behind this might be the high viscosity of the solution which decreased its syringeability resulting in blocking of needle and wastage of the drug-polymer solution due to the adhesion of drug-polymer solution to the stirrer and container in which it was prepared which ultimately decreased the production yields of microcapsules. The order of Product Yield of Gliclazide microcapsules was found to be: Formulations of sodium alginate alone < sodium alginate - Guar gum < sodium alginate- NaCMC < sodium alginate - Carbopol < sodium alginate - Xanthum gum. Drug entrapment efficiency of

Gliclazide microcapsules ranged from 63.31-83.4%. The higher drug polymer ratio tended to restrict migration of the drug and the rapid precipitation of the polymer in the droplets; it resulted in the enhancement of encapsulation efficiency. The order of Entrapment Efficiency of Gliclazide microcapsules was found to be formulations of sodium alginate alone < sodium alginate - NaCMC < sodium alginate-Guar gum < sodium alginate-Xanthum gum < sodium alginate-Carbopol. Mean particle size of the prepared beads was in the size range of 321-622µm and suitable for bioadhesive microcapsules for oral administration. The mean particle size increased with the increasing polymer concentration due to a significant increase in the viscosity, thus leading to an increased droplet size and finally a higher microcapsule size. All the microcapsules except F6, F9, F12 and F15 formulations were found to be spherical in shape. The reason behind the irregularity of F6, F9, F12 and F15 formulations were due to high polymer concentration on the surface of microcapsule leading to the distortion of the shape.SEM analysis revealed that optimized Formulation F14 microcapsules were discrete and had satisfactory surface morphology.

Flow property of all the formulations were determined by calculating bulk density, tapped density, Carr's Index and Hausner's Ratio and angle of repose. Bulk density and tapped density for the formulations were within the range of 0.554 - 0.668 gm/ml and 0.745- 0.962 gm/ml respectively. Compressibility index, Hausner's Ratio and angle of repose were found to be in the range of 11.26 -16.9, 1.04-1.20 and 18.39 to 29.3 respectively for all the formulations except F6, F9, F12 and F15. The results obtained confirm that the flow properties of microcapsule of all the formulations except F6, F9, F12 and F15 exhibited good flow properties. The formulations F6, F9, F12 and F15 were found to be poor because of their irregular shape.

The *in vitro* mucoadhesive study demonstrated that microcapsules of Gliclazide with polymer Carbopol adhered to the mucus to a greater extent than the microcapsules of Gliclazide using sodium alginate alone also microcapsules of Gliclazide using Guar gum, Xanthum gum and Sodium CMC .The rank of order of degree of mucoadhesion of Gliclazide microcapsules was found to be: Formulations of sodium alginate alone < sodium alginate - Guar gum < sodium alginate- Xanthum gum < sodium alginate -Sodium CMC < sodium alginate-Carbopol.

All the formulations were subjected to *in-vitro* dissolution studies in 900 ml of 0.1N HCl (1.2 pH buffer) for initial 2 hr and later in 7.4 pH buffer for next 10 hr as dissolution medium, in order to assess drug release profiles including release kinetics and drug release mechanisms from microcapsules. The Formulations F1, F2 and F3 containing drug and Sodium alginate in the ratio of 1:1, 1:2 and 1:3 could not provide controlled release of the drug as sodium alginate is hydrophilic in nature. Formulations F4, F5 and F6 containing drug , Sodium alginate and Guar gum prepared at a ratio of 1:1:1, 1:1: 2 and 1:1:3. The microcapsules in case of F4, F5 and F6 showed drug release of 96.54%, 86.69% and 75.49% respectively at the end of 10 hrs.This shows that more sustained release was observed with the increase in the percentage of Guar gum but it could not extend the release upto 12 hrs because of its less swelling and gelling tendency. Formulations F7, F8, and F9 containing drug and Sodium alginate and Xanthum gum prepared at a ratio of 1:1:1, 1:1:2 and 1:1:3 showed release of 95.16% within 10hrs, 87.20% and 74.39% release of Gliclazide upto 12 hrs respectively. This shows that more sustained release was observed with the increase in percentage of Xanthum gum. Formulations F10, F11 and F12 containing drug and Sodium alginate and Sodium CMC prepared at a ratio of 1:1:1, 1:1:2 and 1:1:3 . The microcapsules in case of F10, F11 and F12 showed a release of 93.73%, 87.34%, 74.02% for 8, 10 and 10hrs respectively. This shows that more sustained release was observed with the increase in percentage of Sodium CMC. Formulations F13, F14, and F15 containing drug and Sodium alginate and Carbopol prepared at a ratio of 1:1:1, 1:1:2 and 1:1:3. The microcapsules in case of F13 showed release of 95.7% at the end of 10hrs , whereas in case of F14 , F15 showed 88.94% and 80.08% release of Gliclazide upto 12 hrs respectively

All the formulations followed first order kinetics. Analysis of drug release mechanism showed that the drug release followed Fickian diffusion and the best fit model was found to be the Peppas plot.

From the above results it is evident formulations F8, F9 , F14 and F15 showed controlled release upto 12 hrs. Although the formulations F9 and F15 showed sustained action upto 12 hrs, beads of these formulations were irregular in shape with poor flow properties.

The order of release retarding capacity was found to be:
F9<F15 <F12 <F8 <F14 <F6 <F5 <F11 <F13 <F7 <F4 <F10 <F3 <F2 <F1.

Table 1.3: Estimation of Product yield and Entrapment efficiency for formulations F1-F15

Formulation	Product yield (%)	Entrapment efficiency (%)
F1	74.43	66.33 ± 0.34
F2	71.87	72.87 ± 0.99
F3	68.92	78.50 ± 0.45
F4	81.27	67.34 ± 0.17
F5	79.19	74.04 ± 0.41
F6	75.44	80.96 ± 0.32

F7	89.7	70.55 ± 0.35
F8	81.56	76.79 ± 0.81
F9	72.14	83.20 ± 0.32
F10	82.93	66.31 ± 0.43
F11	81.57	73.59 ± 0.18
F12	74.64	78.84 ± 0.53
F13	84.13	70.09 ± 0.37
F14	80.53	79.66 ± 0.12
F15	71.09	83.34 ± 0.58

Table 1.4: Mean particle size and shape of formulations F1-F15

Formulation	Mean diameter (µm)	Shape
F1	321 ± 14.34	Spherical
F2	396± 05.87	Spherical
F3	435±11.35	Spherical
F4	371±15.68	Spherical
F5	448±12.43	Spherical
F6	492±09.45	Slightly irregular
F7	330±07.62	Spherical
F8	420±14.67	Spherical
F9	468±12.34	Slightly irregular
F10	438±16.14	Spherical
F11	474±13.78	Spherical
F12	511±20.19	Slightly irregular
F13	560±19.10	Spherical
F14	602±15.43	Spherical
F15	622±23.10	Slightly irregular

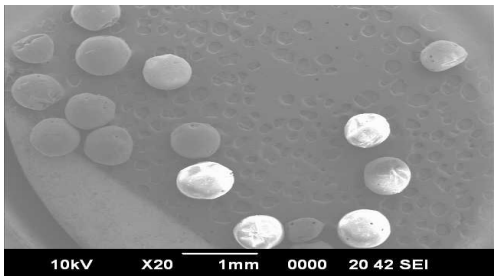

Fig 1.1: Blank Microcapsules

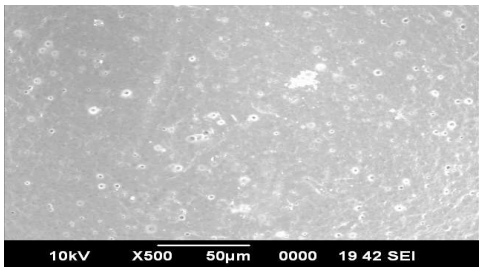

Fig 1.2 Presence of drug particles on surface of drug loaded microcapsules

Table 1.5: Percent Mucoadhesion data of the formulations

Formulation	% Mucoadhesion
F1	70.00 ± 0.066
F2	73.64 ± 0.564
F3	76.65 ± 0.378
F4	75.54 ± 0.431
F5	76.21 ± 0.987
F6	79.76 ± 0.987
F7	77.84 ± 0.565
F8	81.55 ± 0.148
F9	82.09 ± 0.432
F10	78.43 ± 0.321
F11	80.32 ± 0.654
F12	84.69 ± 0.240
F13	81.07 ± 0.318
F14	88.43 ± 0.662
F15	89.01 ± 0.458

4. Conclusion

Formulation F14 containing drug: sodium alginate: Carbopol in 1:1:2 ratio was found to be the optimized formulation based upon the high entrapment efficiency (79.6%) , better sustained release (88.94%) , percent mucoadhesion and good flow properties. Regarding all properties evaluated in order to achieve objective of this study the novel formulation design facilitated the optimization and successful development of Gliclazide microcapsules. Gliclazide release from the mucoadhesive microcapsules was slow and extended over longer periods depending on composition of the coat material. Drug release followed diffusion controlled with first-order kinetics. These mucoadhesive microcapsules are thus, suitable for oral controlled release of Gliclazide. Thus this research work successfully developed an anti-diabetic formulation with mucoadhesive approach to maintain the desired blood glucose levels in the diabetic population.

5. References

[1] Venkatesan P, Manavalan R, Valliappan K. Microencapsulation: A vital technique in novel drug delivery system. Journal of Pharmaceutical Sciences and Research. 2009; 1(4):26-35.

[2] Edith Mathiowitz. Encyclopedia of controlled Drug Delivery, Bioadhesive drug delivery systems. A Wiley-Interscience Publication, John Wiley & Sons, 2001; 1:14-17.

[3] Kharenko EA, Larionova NI and Demina NB. Mucoadhesive Drug Delivery Systems (Review). Pharma Chemistry Journal. 2009; 43 (4):21 - 29.

[4] Chang HS, Park H, Kelly P. Robinson JR. Bioadhesive polymers as platforms for oral controlled drug delivery, II: synthesis and evaluation of some swelling water insoluble bioadhesive polymers. Journal of Pharmaceutical Sciences. 1985; 74:399-40.

[5] Tripathi KD. Essentials of Medical Pharmacology. Jitendar P Vij Jaypee Brothers Medical Publishers, New Delhi. 2008; (6):175-192.

[6] Patrick.J, Sinko. Martins's Physical Pharmacy and Pharmaceutical Sciences. 5th edition, Lippincott Williams & Wilkins; North America.2000; 540-548.

[7] Aulton ME. Pharmaceutics: The Science of Dosage form Design, 2nd edition. Churchill Livingston, Philadelphia, USA. 2002; 133- 134.

[8] Lehr CM, Bowstra JA, Tukker JJ and Junginger HE. Intestinal transit of bioadhesive microspheres in an *in-situ* loop in the rat. Controlled Release Drug Delivery. 1990; 13:51–62.