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Research Article

FORMULATION AND *INVITRO* EVALUATION OF GLIMEPIRIDE MUCOADHESIVE MICROSPHERES

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A B S T R A C T

Microspheres are free-flowing spherical particles made up of either proteins or synthetic polymers that are having sizes between 1 and 1000 µm. Microspheres are manufactured to obtain extended or controlled drug delivery to increase bioavailability and activity at the targeted site to a predetermined rate. By encouraging the production of insulin granules from the pancreatic islet beta cells, Glimepiride decreases blood sugar levels. Mucoadhesive drug delivery systems retain in the stomach for a longer period and avoid the first-pass effect. The current study's objectives are to increase gastrointestinal resident time and provide controlled oral release of Glimepiride. To achieve these goals, Glimepiride mucoadhesive microspheres were created using the ionic gelation process. The formulation of microspheres includes Glimepiride, Carbopol 934, Tragacanth, Sodium alginate, and Calcium chloride. Preformulation studies were conducted to evaluate drug excipient compatibility studies by FTIR. Formulated microspheres were evaluated for particle size, percentage yield, entrapment efficiency, swelling index, and % drug release. Among all GP3 formulation has shown the best % drug release, so selected as optimized formula. These *invitro* drug release results are subjected to kinetic studies of different models. It followed Peppas model indicates the mechanism of drug release i.e., release of drug from the formulation is by diffusion, erosion, swelling and may by the combination of diffusion and swelling.

INTRODUCTION

Microspheres are solid sphere-shaped particles with a diameter ranging from 1-1000 micrometers. They are freely moving spherical particles made up of proteins or artificial biodegradable polymers. (Sarlesh Rajput *et al*., 2015 and T. Virmani *et al*., 2017).

These drug delivery systems make use of the bioadhesion properties of particular polymers, where they become adhesive upon hydration and may thus be used for targeting specific area. The Adhesion that takes place between a biological substrate and an artificial membrane, for example adhesion between a polymer & a biological membrane. The "mucoadhesion" word is used to explain the attachment of a polymer to that of the mucosal tissue containing the mucin layer. Various approaches can be used to deliver mucoadhesive drug delivery systems such as buccal, oral, rectal, ocular, vaginal, nasal drug delivery systems. (B. SreeGiri Prasad, *et al* 2014, and D. Srinivasa Rao, *et al*., 2014).

METHODS AND MATERIALS

Glimepiride was obtained as a Gift sample from Hetero labs, Hyderabad. Carbopol 934, Tragacanth, Sodium alginate, and Calcium chloride were procured from SD Fine Chemicals Ltd.

Preformulation studies

Identification of drug and excipient compatibility study

The Spectral analysis of pure drugs and physical mixtures of drugs and various excipients used to create microspheres was investigated by FTIR (BRUKER).The sample was placed on aappropriate holder in an IR spectrometer and the spectrum was measured from 4000- 400 cm^{-1}. FTIR study was carried on the Glimepiride, polymers, physical mixture of Glimepiride and polymers individually. It was compared to look for any spectral alterations in the final spectrum.They were noticed when the corresponding functional groups in the test compounds had the expected peaks (S. Sivaprasad *et al*., 2022 and R. Saisree *et al*., 2019)

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Standard Graph of Glimepiride in 0.1N HCL with 0.5% w/v SLS

A stock solution was created by dissolving 50 mg of glimepiride in 100 ml of methanol.10ml of this stock solution was taken out and diluted with 0.1N HCL and 0.5 percent w/v SLS to make 100ml. Different concentrations (5 g/ml to 25 g/ml) of the stock solution were used to create the calibration curve. At 230nm, the absorbance was measured (J. Satyanarayan *et al*., 2011).

Formulation of Glimepiride mucoadhesive microspheres

Table 1 Formulation trials (Composition) of Glimepiride mucoadhesive microspheres

Formulation code	Drug Glimepiride, mg	Carbopol, mg	Tragacanth, mg	Sodium alginate, %	Calcium chloride, %
GP1	4	10	10	0.7	10
GP2	4	50	10	0.7	5
GP3	4	50	10	0.7	10
GP4	4	10	10	0.7	5

METHODOLOGY

Glimepiride mucoadhesive alginate beads were made by using ionic gelation technique. To make a homogenous polymer dispersion, sodium alginate, Carbopol and tragacanth are dissolved in filtered water. Glimepiride, the core ingredient, was poured into polymer dispersion and well mixed to make a smooth viscous dispersion. For the ionic gelation step, the resultant dispersion was dropped into a 100 mL calcium chloride solution drop by drop. The beads were then separated and dried for 12 hours at 45 ℃ (J. Satyanarayan *et al*., 2011).

Evaluation of Glimepiride mucoadhesive microspheres
Particle Size

Using optical microscopy, the particle size of various batches of the microspheres was assessed. Using an ocular and stage micrometres with an optical microscope, the projected diameter from each batch of 100 microspheres was calculated. Under a microscope, the slide containing the microspheres was examined to perform the analysis. The diameter of the microspheres served as a measure of their typical particle size (Walia S *et al*., 2011).

Drug Entrapment Efficiency

50 mg of microspheres were crushed, and the crushed microspheres was then dissolved in 50 ml of 0.1 N HCL. The magnetic stirrer was used to shake the final mixture for 24 hours. The solution was then filtered, and a UV spectrophotometer operating at 230 nm examined the filtrate to determine its drug content. (Sarath C Irisappan *et al*., 2014) The following formula was used to compute the drug entrapment efficiency:

% Entrapment efficiency = Actual drug content/Theoretical drug content x 100

Percentage yield

The microspheres yield was determined by weighing microspheres that had been dried at room temperature. The following formula was used to calculate preparation (PooviGanesan *et al*., 2014).

%Yield = [(Weight of dried microsphere) ÷ (Total weight of medication & excipient)] ×100

Swelling Index

Microspheres dynamic swelling characteristics in the dissolution liquid were identified. A centrifuge was used to obtain the swollen microspheres after they had been placed in a dissolution solution for eight hours. The moisture weight of the swollen microspheres was then calculated by firstly blotting the microparticles with the help of filter paper for removing the water that had been absorbed on the surface and immediately measuring them on an analytical balance (KatariaSahil *et al*., 2014).

Swelling index = [(Swollen microsphere size – Dry microsphere size) ÷ Dry microsphere size]× 100

In vitro Dissolution Studies

The rate of release of medication from microparticles was investigated utilizing a Dissolution Test Apparatus with the use of a paddle stirrer running at 50 rpm & 37 ± 0.5 ℃ in buffer (900 ml). Each test employed a sample of microparticles and measured by using UV spectrophotometer at 230 nm after samples were withdrawn and filtered at various time intervals. The drug release tests were carried out three times (ParomaArefin *et al*., 2020).

In-vitro wash off test

An *in-vitro* adhesion test approach known as *invitro* wash off method was used to assess the microspheres mucoadhesive properties. Freshly removed goat stomach mucosa was mounted onto glass slides. Each wet-washed tissue specimen received around 50 microspheres, and was immediately attachedonto the tablet disintegrating machine arm. The specimen's tissue was provided by a regular up & down, slow movements in the test liquid at 37 ℃ held in a 1L basket of the disintegration test machine while it was run. The machine was stopped after 30 mins, one hour, and at hourly intervals until 8 hours, and the number of microspheres remaining sticking to the tissue was then examined. The test was carried out at 0.1NHClsolution (Kadam N.*et al*., 2015).

RESULTS AND DISCUSSION

Calibration curve

The absorbance at 230 nm for various concentrations measured are as follows

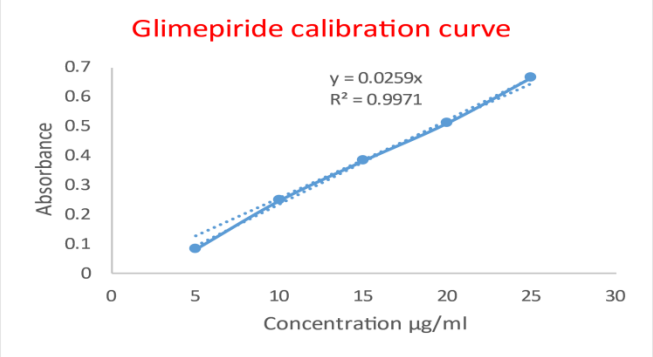


Fig 1 Standard Graph of Glimepiride in 0.1N HCL with 0.5% w/v SLS

Drug -Excipient Compatibility by FTIR

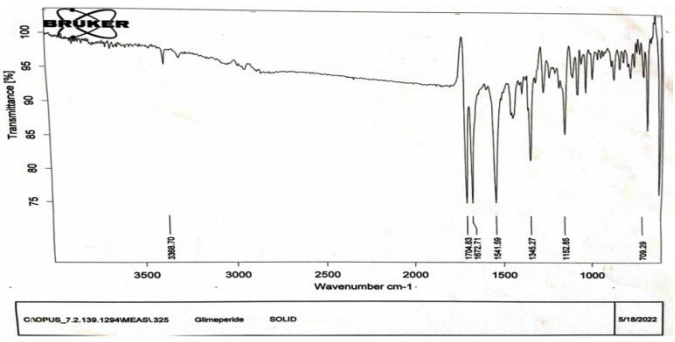


Fig 2 FTIR spectrum of Glimepiride

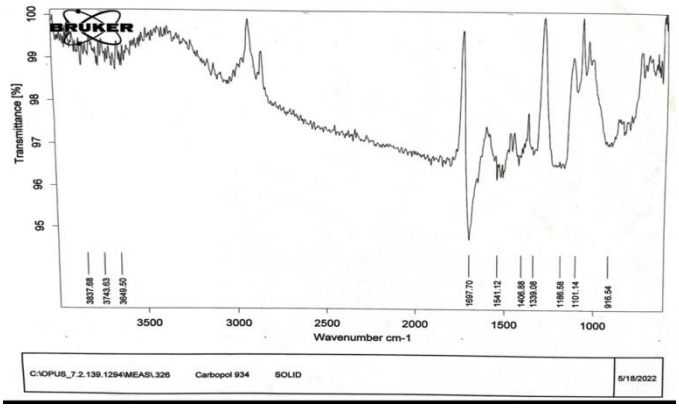


Fig 3 FTIR spectrum of Carbopol

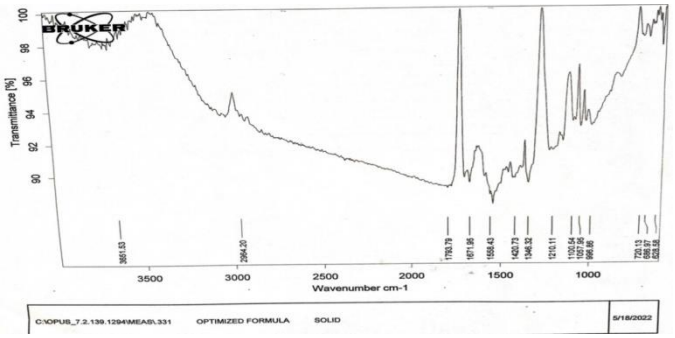


Fig 4 FTIR spectrum of the optimized formulation

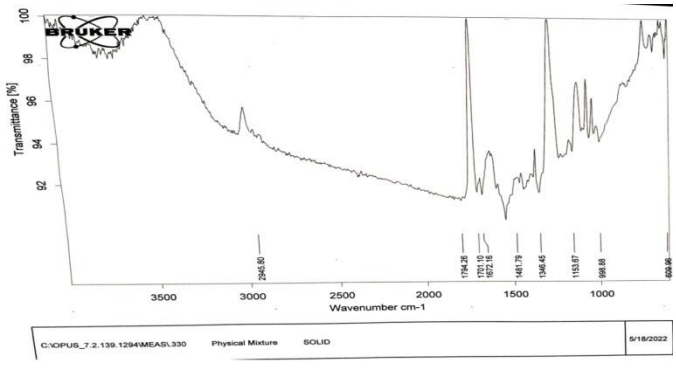


Fig 5 FTIR spectrum of physical mixture

Interpretation of FTIR

Drug Excipient interactions are effectively analysed by FTIR spectroscopy (Shimadzu). FTIR spectra of pure drug, Glimepiride, Sodium alginate, Carbopol, Tragacanth, Physical mixture, & final optimized formulation are observed. FTIR spectra of optimized formulation show bands for specific functional group in Glimepiride. All peaks of physical mixture and optimized formulation are almost matching with functional group peaks of pure drug. so, drug is compatible with polymer

Table 3 FTIR spectra of Glimepiride pure drug display principal bands at a wave number as follows

Functional groups	Wave number (cm^{-1})
N-Hgroup	3300 – 3500cm^{-1}
SO2 group	1300-1400cm^{-1}
C=O (carbonyl group)	1650-1800cm^{-1}
C-N group	1400cm^{-1}
C-H group	2850-3100cm^{-1}

Invitro drug release studies

Invitro dissolution studies of various formulations and marketed sample are observed. The dissolution profile of various formulations GP1 to GP4 and marketed product are as mentioned below in Table 7 as depicted in Figure.6 respectively**.**

Table 4 In vitro drug release profile data of various formulation

Time(hrs)	GP1	GP2	GP3	GP4	Marketed Product
0	0	0	0	0	0
1	7.3±1.23	7.92±1.34	11.47±1.32	8.2± 1.23	9.45± 1.34
2	16.26±1.43	14.53±1.23	19.95±1.23	14.87± 1.43	18.56± 1.23
3	22.31±1.34	22.03±1.34	27.17±1.34	23.28± 1.22	26.69± 1.23
4	30.23±1.43	30.23±1.12	36.49±1.56	31.41± 1.67	36.21± 1.65
5	36.35±1.76	38.71±1.45	47.54±1.87	41.77± 1.87	46.01± 1.54
6	42.53±1.67	45.03±1.23	56.43±1.56	51.64± 1.22	55.39± 1.67
7	50.8±1.23	54.83±1.21	67± 1.43	60.12± 1.87	64.77 ± 1.87
8	56.5±1.98	60.6±1.89	76.59±1.23	67.62± 1.23	73.81 ± 1.67
10	67.97±1.00	72.21± 1.67	85.34±1.23	75.82± 1.45	82.84 ±1.65
12	75.54±1.23	81.38± 1.56	96.32±1.45	86.66± 1.34	91.32±1.62

In all formulations 75 to 97% of release was observedup to 12 hours.

As the drug release is maximum in GP3 this is concluded as optimized formula.

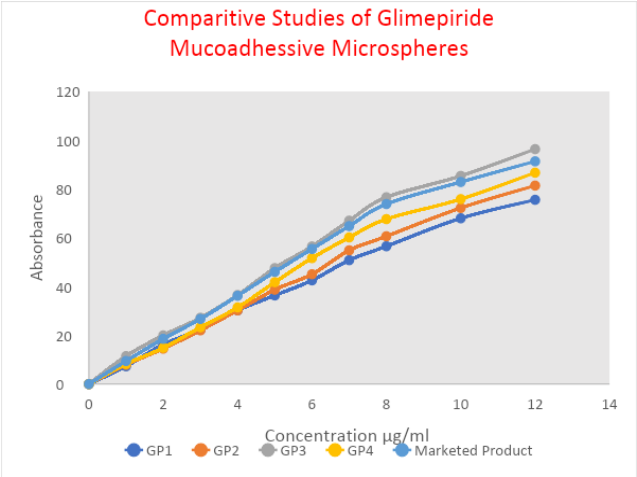


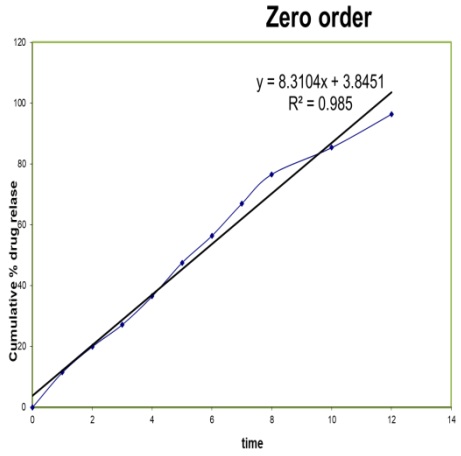
Fig 6 In vitro drug release profile data of various formulations

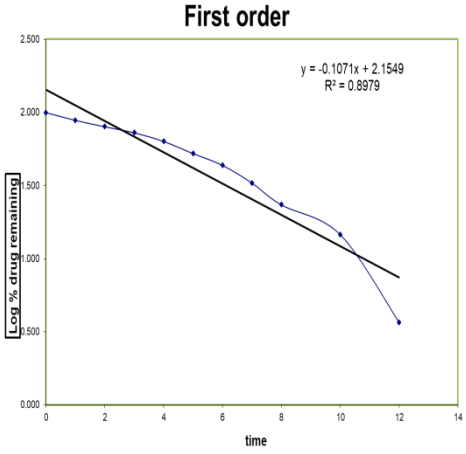
Table 5 Mean particle size, % Drug entrapment efficiency, swelling index %, percentage yield, mucoadhesion %

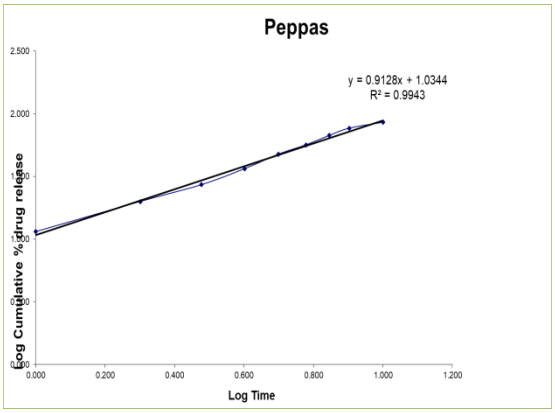
S.NO	Particle size µm	Drug Entrapment Efficiency, %	Swelling Index, %	% Yield	Mucoadhession, %
GP1	74 ± 1.32	77.22 ± 1.34	62.33 ± 1.45	84.55±1.01	76 ±1.44
GP2	80 ±1.45	84.94 ± 1.45	74.66 ±1.98	88.62 ±1.00	84±1.76
GP3	84 ±1.45	92.66 ± 1.87	78.33 ±1.89	91.24 ±1.21	90±1.78
GP4	62±1.55	69.49 ± 1.76	59 ± 1.98	80.55±1.56	64±1.67

Mean particle size of microspheres was found to be minimum in GP4 that is 62µm and maximum in GP3 that is 84 µm.

Drug entrapment efficiency of microspheres was found to be minimum in GP4 and maximum in GP3 ranging 69.50 %and 84.94 Swelling index of microspheres was found to be minimum in GP4 and maximum in GP3 ranging 59.00 and 78.33%. Percentage yield of microspheres was found to be minimum in formulation GP4 that is 80.55% and maximum in GP3 that is 91.24%. Mucoadhesion % of microspheres was found to be minimum in GP4 that is 64 % and maximum in GP3 that is 90%.Release order Kinetics given in Figure.7**.** It follows Zero order drug release and mechanism of drug release is diffusion.







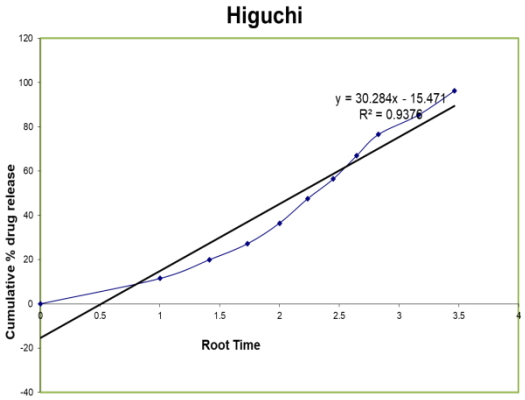


Fig 7 Release order Kinetics

CONCLUSION

The process of medication absorption in the GIT varies. This study's objective is to develop and evaluate novel delivery systems –the mucoadhesive microspheres. This system helps toobtain extended or controlled drug delivery to increase bioavailability and activity at the targeted site to a predetermined rate. In this study, the mucoadhesive microspheres of Glimepiride were prepared and evaluated. They were prepared by using polymers, Carbopol, and tragacanth employing the ionic gelation method. Formulated microspheres were evaluated for particle size determination, percentage yield, entrapment efficiency, swelling index, *invitro* wash-off test, *invitro* dissolution studies and drug excipient compatibility studies by FTIR. Different formulations GP1, GP2, GP3, and GP4 were evaluated where they have shown results for entrapment efficiency ranging from 69.49 ± 1.76% to 92.66 ± 1.87%, swelling index of 59 ± 1.98% to 78.33 ±1.89%, % Mucoadhesion ranging from 64±1.67 to 90±1.78, invitro % drug release ranging from 75.54±1.23 to 96.32±1.45. As the drug release was maximum in GP3 of 96.32%, this was concluded as optimized formula. It follows Zero order drug release and mechanism of drug release is diffusion.

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