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FORMULATION AND *IN-VITRO* EVALUATION OF MUCOADHESIVE MICROSPHERE FOR AN ALPHA GLUCOSIDASE INHIBITOR

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ABSTRACT

The aim of this study was to formulate and evaluate the release of Mucoadhesive Microsphere of Miglitol which is having the half life around 2 hours for the treatment of diabetes type 2 by combine the potential advantages of Mucoadhesive with controlled drug delivery using various ratio of different polymers. The results of this investigation indicate that ionic cross linking technique Ionotropic gelation method can be successfully employed to fabricate Miglitol microspheres. The technique provides characteristic advantage over conventional microsphere method, which involves an "all-aqueous" system, avoids residual solvents in microspheres. FT-IR spectra of the physical mixture revealed that the drug is compatible with the polymers and copolymers used. Micromeritic studies revealed that the mean particle size of the prepared microspheres was in the size range of 512-903µm and are suitable for bioadhesive microspheres for oral administration. Increase in the polymer concentration led to increase in % Yield, % Drug entrapment efficiency, Particle size, % swelling and % Mucoadhesion. The *in-vitro* mucoadhesive study demonstrated that microspheres of Miglitol using sodium alginate along with Carbopol934 as copolymer adhered to the mucus to a greater extent than the microspheres of Miglitol using sodium alginate along with Carbopol 971 and HPMC K4M as copolymers. Analysis of drug release mechanism showed that the drug release from the formulations followed non-Fickian diffusion and the best fit model was found to be Korsmeyer-Peppas. Based on the results of evaluation tests formulation coded T_4 was concluded as best formulation.

KEYWORDS: Miglitol. Mucoadhesive. Ionic gelation technique. Sodium alginate. Carbopol.

INTRODUCTION

Alpha-glucosidase inhibitors (Miglitol) are saccharides that act as competitive inhibitors of enzymes needed to digest carbohydrates: specifically alpha-glucosidase enzymes in the brush border of the small intestines. The membrane-bound intestinal alpha-glucosidases hydrolyze oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides in the small intestine.[1] Their mechanism of action being limited to the intestinal brush border membrane, and owing to their structural features, they have limited systemic bioavailability, due to which they have much reduced side-effect profile compared to contemporary antihyperglycemic drugs. A large section of people are diagnosed to be suffering from pre-diabetes condition (such as obesity) and to treat that condition alpha-glucosidase inhibitors is widely prescribed.[2]

Microspheres, in general have the potential to be used for targeted and controlled release drug delivery but coupling of mucoadhesive properties to Microspheres has additional advantages. Mucoadhesive and biodegradable polymers undergo selective uptake by the M cells of payer patches in gastrointestinal mucosa.[3,4]

Microspheres constitute an important part of novel drug delivery system by virtue of their small size and efficient carrier capacity. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers having a particle size ranging from 1-1000 μm. The range of Techniques for the preparation of microspheres offers a Variety of opportunities to control aspects of drug administration and enhance the therapeutic efficacy of a given drug.[5]

Mucoadhesive formulations orally would be to achieve a substantial increase in length of stay of the drug in the GI tract. Stability problem in the intestinal fluid can be overcome. Therapeutic effect of drugs insoluble in the intestinal fluids can be improved.[6] Mucoadhesive drug delivery systems utilize the property of bioadhesion of certain water-soluble polymers that become adhesive to mucous membranes on hydration[7] and hence can be used for targeting a drug to a particular mucus tissue (e.g. gastrointestinal. buccal, nasal, etc.) extended period of time.[8,9]

MATERIALS AND METHODS

Materials

Miglitol, carbopol 934, 971 were received from M/s Baris pharmaceuticals Pvt.Ltd. Sodium alginate was obtained from Sisco Research Laboratory Pvt. Ltd. All other reagents and solvents used were of pharmaceutical or analytical grade.

Formulation of Microspheres

Miglitol microspheres were prepared by Ionic gelation techniques.[10,11] Batches of microspheres were prepared by ionotropic gelation method which involved reaction between sodium alginate and polycationic ions like calcium to produce a hydrogel network of calcium alginate. Sodium alginate and the mucoadhesive polymer were dispersed in purified water (10 ml) to form a homogeneous polymer mixture. The API, Miglitol (100 mg) were added to the polymer premix and mixed thoroughly with a stirrer to form a viscous dispersion (Remi Equipments, Mumbai, India, model 2MIH).. The resulting dispersion was then added through a 22G needle into calcium chloride (4% w/v) solution. The addition was done with continuous stirring at 200rpm. The added droplets were retained in the calcium chloride solution for 30 minutes to complete the curing reaction and to produce rigid spherical microspheres. The microspheres were collected by decantation, and the product thus separated was washed repeatedly with purified water to remove excess calcium impurity deposited on the surface of microspheres and then air-dried. Five batches of microspheres were prepared and labeled as T1,T2,T3,T4,T5.

Fourier Transform Infrared Spectroscopy Studies (FT-IR)

In order to check the integrity (Compatibility) of drug in the formulation,FT-IR spectra of the formulations along with the drug and other excipients were obtained and compared using Shimadzu FT-IR 8400 spectrophotometer. In the present study, Potassium bromide(KBr) pellet method was employed. The samples were thoroughly blended with dry powdered potassium bromide crystals. The mixture was compressed to form a disc. The disc was placed in the spectrophotometer and the spectrum was recorded. The FT-IR spectra of the formulations were compared with the FT-IR spectra of the pure drug and the polymers.

CHARACTERIZATION OF MICROSPHERES

Drug entrapment Efficiency[12]

Microspheres equivalent to 15 mg of the drug Miglitol were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres. The powder was

transferred to a 100 ml volumetric flask and dissolved in 10ml of methanol and the volume was made up using simulated gastric fluid pH 1.2 . After 24 hours the solution was filtered through Whatmann filter paper and the absorbance was measured after suitable dilution spectrophotometrically at 269 nm. The amount of drug entrapped in the microspheres was calculated by the following formula,

$$\% \text{ Drug Entrapment Efficiency} = \frac{\text{Experimental Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

Particle Size Analysis[13]

Samples of the microparticles were analyzed for particle size by optical microscope. The instrument was calibrated and found that 1unit of eyepiece micrometer was equal to 12.5µm. Nearly about 100 Microparticles sizes were calculated under 45x magnification.

The average particle size was determined by using the Edmondson's equation:

$$D_{mean} = \frac{nd}{n}$$

Where,

n – Number of microspheres observed

d – Mean size range

Scanning Electron Microscopy[14]

Scanning Electron Microscopy was performed to characterize the surface morphology of the formed Microsphere and this was done by using a JSM 6100 JEOC scanning electron microscope at 20kV. Prior to examination samples were gold coated to render them electrically conductive and examined under the microscope.

Swelling study

Swelling ratio of different dried microspheres were determined gravimetrically in simulated gastric fluid pH 1.2 .The microspheres were removed periodically from the solution, blotted to remove excess surface liquid and weighed on balance. Swelling ratio (% w/v) was determined from the following relationship:

$$\text{Swelling ratio} = \frac{(Wt - W0)}{(W0)} \times 100$$

Where W0 & Wt are initial weight and Final weight of microspheres respectively.

Evaluation of mucoadhesive property[15]

The mucoadhesive property of microspheres was evaluated by an in vitro adhesion testing method known as wash-off method. Freshly excised pieces of goat stomach mucous were mounted on to glass slides with cotton thread. About 20 microspheres were spread on to each prepared glass slide and immediately thereafter the slides were hung to USP II tablet disintegration test, when the test apparatus was operated, the sample is subjected to slow up and down movement in simulated gastric fluid pH 1.2 at 37^0C contained in a 1-litre vessel of the apparatus. At an interval of 1 hour up to 8 hours the machine is stopped and number of microspheres still adhering to mucosal surface was counted.

$$\% \text{ Mucoadhesion} = \frac{\text{Number of microspheres adhered}}{\text{Number of microspheres applied}} \times 100$$

In vitro drug release study: The dissolution studies were performed in a fully calibrated eight station dissolution test apparatus (37 ± 0.5^0C, 50 rpm) using the USP type – I rotating basket method in simulated sodium phosphate buffer (900ml). A quantity of accurately weighed microspheres equivalent to 15mg Miglitol each formulation was employed in all dissolution studies. Aliquots of sample were withdrawn at predetermined intervals of time and analyzed for drug release by measuring the absorbance at 269nm. At the same time the volume withdrawn at each time intervals were replenished immediately with the same volume of fresh pre-warmed simulated sodium acetate buffer maintaining sink conditions throughout the experiment.

The release data obtained was fitted into various mathematical models. The parameters 'n' and time component 'k', the release rate constant and 'R', the regression coefficient were determined by Korsmeyer-peppas equation to understand the release mechanism.

To examine the release mechanism of Miglitol from the microspheres, the release data was fitted into Peppa's equation, $\mathbf{Mt / M\infty = Ktn}$

Where, $\mathbf{Mt / M\infty}$ is the fractional release of drug, 't' denotes the release time, 'K' repr-esents a constant incorporating structural and geometrical characteristics of the device, 'n' is the diffusional exponent and characterize the type of release mechanism during the release process.

RESULTS AND DISCUSSION

Preparation of Formulation

The resulting microspheres formulated by ionic gelation technique method was found to be spherical and free flowing in nature shown in fig.1. The formula for the formulation of microspheres given in the table 1.

Tab.1. Various Formulations of Miglitol Microspheres

S.No.	FORMULATION CODE	DRUG:POLYMER RATIO	POLYMER RATIO
1	T_1	1:2.5	Na alginate:Carbopol 934 (1.5:0.5)
2	T_2	1:3	Na alginate:Carbopol 934 (2:1)
3	T_3	1:4	Na alginate:Carbopol 934 (3:1)
4	T_4	1:4	Na alginate:Carbopol 971 (3:1)
5	T_5	1:4	Na alginate:HPMC K 4 M (3:1)

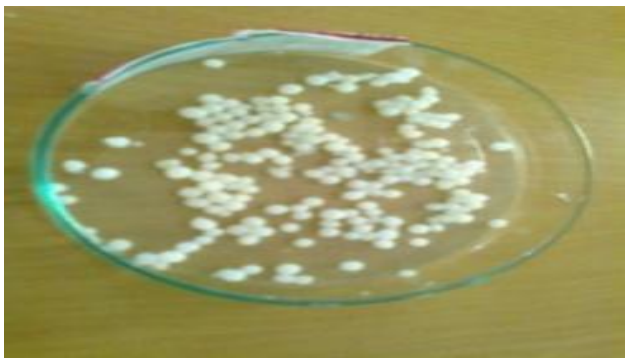

Fig.1. Miglitol Microspheres

FTIR studies: The FT-IR spectra of the formulations were compa- red with the FTIR spectra of the pure drug. The results indicated that the characteristic absorption peaks due to pure Miglitol have appeared in the formulated microspheres, without any significant change in their position after successful encapsulation, indicating no chemical interaction between Miglitol and Polymers.

Drug Entrapment Efficiency

Percentage Drug entrapment efficiency of Miglitol ranged from 82.66 to 88.66% for microspheres containing sodium alginate along with carbopol 934 as copolymer, 53.2 to 76.66% for microspheres containing sodium alginate along with carbopol 971 as copolymer and 66.73 to 79.2% for microspheres containing sodium alginate along with HPMC K 4 M as copolymer. The drug entrapment efficiency of the prepared microspheres increased progressively with an increase in proportion of the respective polymers. Increase in

the polymer concentration increases the viscosity of the dispersed phase. The particle size increases exponentially with viscosity. The % drug entrapment efficiency of the prepared microspheres is displayed in the table 2.

Particle Size

Microspheres containing sodium alginate along with carbopol 934 as copolymer had a size range of 512µm to 826µm, microspheres containing sodium alginate along with carbopol 971 as copolymer exhibited a size range between 517µm to 834µm and microspheres containing sodium alginate along with HPMC K 4 M as copolymer had a size range of 664 µm to 903µm. The particle size data is presented in Table 2. The particle size as well as % drug entrapment efficiency of the microspheres increased with increase in the polymer concentration.

Scanning Electron Microscopy

The SEM showed that the blend of sodium CMC and Carbopol 934 produced spherical with smooth surface microspheres due to their high solubility in water. While sodium alginate microspheres were of irregular shape with a rough morphology due to less water solubility and non uniform evaporation of water from the surface of microspheres. The SEM of microspheres of formulation are shown in figures 2,3.

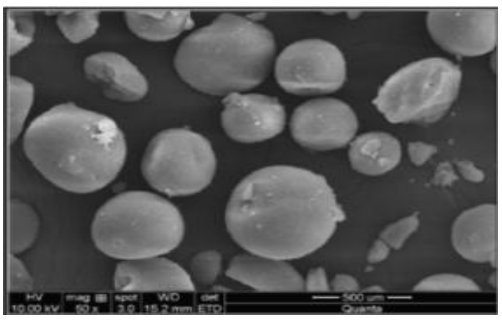

Fig. 2: SEM of T3 formulation

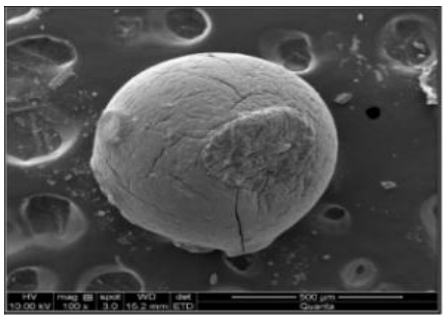

Fig.3: SEM of T4 formulation

Swelling Index

As the polymer to drug ratio increased, the percentage of swelling increased from 28 to 85% for microspheres containing sodium alginate along with carbopol 934 as copolymer, 24 to 64% for microspheres containing sodium alginate along with carbopol 971 as copolymer and 31 to 85 for microspheres containing sodium alginate along with HPMC K 4 M as copolymer. The percentage of swelling of the prepared microspheres is shown in Table 2.

Evaluation of mucoadhesivity of the formulations

Microspheres containing sodium alginate along with carbopol 934 as copolymer exhibited % mucoadhesion ranging from 65 to 85%, microspheres containing sodium alginate along with carbopol 971 as copolymer exhibited % mucoadhesion ranging from 60 to 75% and microspheres containing sodium alginate along with HPMC K 4 M as copolymer exhibited % mucoadhesion ranging from 60 to 80%. The results of in-vitro mucoadhesion test are compiled in Table 2.

Table.2. Comparative % drug entrapment efficiency, average particle size, swelling index, & percentage of mucoadhesion

S.No	Formulation	% Drug entrapment efficiency	Average Particle size (µm)	Percentage swelling	Percentage of Mucoadhesion
1	T1	82.66	512	28	65
2	T2	84.4	617	42	70
3	T3	88.66	826	85	85
4	T4	76.66	834	64	75
5	T5	79.2	903	85	80

Invitro Release

The formulations T_1, T_2 and T_3 containing Sodium alginate along with Carbopol 934 as copolymer showed a maximum release of 92.66% after 9 hours, 90.66% after 10 hours, 90.6% after 11 hours and 94.66% after 12 hours respectively.

The formulation T_4 containing Sodium alginate along with Carbopol 971 as copolymer showed a maximum release of 92.22% after 9 hours, 91.33% after 10 hours, 89.55% after 11 hours and 90.66% after 12 hours respectively.

The formulation T_5 containing Sodium alginate along with HPMC K 4 M as copolymer showed a maximum release of 92.6% after 9 hours, 91.3% after 10 hours, 90% after 11 hours and 92.44% after 12 hours respectively. The results of the in-vitro dissolution studies of formulations are shown in table no.3 & Fig. 4.

Table. 3. *In-Vitro* drug release data of Miglitol microspheres

TIME (h)	CUMULATIVE PRECENT OF DRUG RELEASED				
	T_1	T_2	T_3	T_4	T_5
0	0	0	0	0	0
1	24.88	21.11	15.88	17.11	16.44
2	31.55	31.55	24.22	26.44	27.11
3	42.44	39.77	32.66	37.55	36.44
4	53.55	47.77	39.33	46.88	45.55
5	62	56.66	47.55	55.77	55.33
6	74.66	62.44	55.77	63.55	63.11
7	83.55	69.55	61.77	71.33	71.55
8	89.33	75.33	69.55	75.77	76.44
9	92.66	84.66	77.55	79.77	80.66
10	85.55	90.66	85.55	82.44	85.55
11	80.22	84.22	90.66	86.88	89.55
12	78.88	80.88	94.66	90.66	92.44

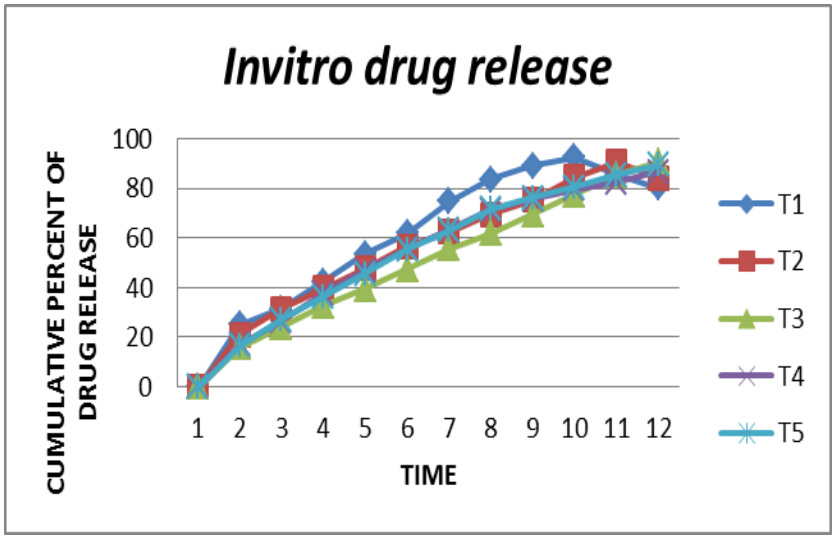

Fig.4. Invitro drug Release

The kinetic data analysis of all the formulations reached higher coefficient of determination with the Korsmeyer-Peppas model (R^2 = 0.914 to 0.996) whereas release exponent value (n) ranged from 0.498 to 0.743. From the coefficient of determination and release exponent values, it can be suggested that the mechanism of drug release follows Korsmeyer-Peppas model along with non-Fickian diffusion mechanism which leading to the conclusion that a release mechanism of drug followed combination of diffusion and spheres erosion. The values are compiled in Table 4.

Table. 4. Release Kinetics Studies of The Prepared Formulations

Formulation code	Release model								
	Zero order		First order		Higuchi matrix		Koresmeyer-peppas		
	K	R^2	K	R^2	K	R^2	n	K	R^2
T_1	21.6	0.797	1.923	0.720	-0.313	0.912	0.556	1.388	0.925
T_2	16.39	0.908	1.991	0.890	-3.945	0.970	0.595	1.326	0.983
T_3	7.434	0.990	2.118	0.914	-12.25	0.962	0.743	1.171	0.996
T_4	13.06	0.948	2.032	0.991	-7.587	0.984	0.690	1.241	0.991
T_5	11.94	0.959	2.061	0.982	-8.986	0.981	0.712	1.226	0.995

CONCLUSION

In the present work, bioadhesive microspheres of Miglitol using Sodium alginate along with Carbopol 934, Carbopol 971, HPMC K4M as copolymers were formulated to deliver Miglitol via oral route.The results of this investigation indicate that ionic cross linking technique Ionotropic gelation method can be successfully employed to fabricate Miglitol microspheres. The technique provides characteristic advantage over conventional microsphere method, which involves an "all-aqueous" system, avoids residual solvents in microspheres. Other methods utilize larger volume of organic solvents, which are costly and hazardous because of the possible explosion, air pollution, toxicity and difficult to remove traces of organic solvent completely. FT-IR spectra of the physical mixture revealed that the drug is compatible with the polymers and copolymers used. Micromeritic studies revealed that the mean particle size of the prepared microspheres was in the size range of 512-903µm and are suitable for bioadhesive microspheres for oral administration. Increase in the polymer concentration led to increase in % Yield, % Drug entrapment efficiency, Particle size, % swelling and % Mucoadhesion. The *in-vitro* mucoadhesive study demonstrated that microspheres of Miglitol using sodium alginate along with Carbopol934 as copolymer adhered to the mucus to a greater extent than the microspheres of Miglitol using sodium alginate along with Carbopol 971 and HPMC K4M as copolymers. The *invitro* drug release decreased with increase in the polymer and copolymer concentration. Analysis of drug release mechanism showed that the drug release from the formulations followed non-Fickian diffusion and the best fit model was found to be Korsmeyer-Peppas. Based on the results of evaluation tests formulation coded T_3 was concluded as best formulation.

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