



Research Article

FORMULATION AND EVALUATION OF LINAGLIPTIN MUCOADHESIVE MICROSPHERES

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ABSTRACT

Linagliptin an anti-diabetic drug belonging to BCS class-III, inhibits the enzyme, dipeptidyl peptidase-4 (DPP-4). The aim of the present study is to enhance the permeability of linagliptin by increasing its residence time in the stomach. Mucoadhesive microspheres exhibit a prolonged residence time at the site of application and facilitate intimate contact with underlying absorption surface. Mucoadhesive microspheres of linagliptin were prepared by Ionotropic gelation method and single emulsion method. The mucoadhesive microspheres prepared were spherical in shape and were evaluated for various parameters. The microspheres prepared using carbopol by single emulsion method (LMS1) showed swelling index of 1.03, entrapment efficiency of $85 \pm 0.57\%$ and the particle size of $135 \pm 6 \mu\text{m}$. The microspheres showed good/excellent flow properties. SEM studies indicate the microspheres were having smooth surface. Mucoadhesion strength was found to be 87% in 7hrs. Drug release was found to be $98.2 \pm 0.63\%$ in 8 hrs and release kinetics of the drug was following anomalous transport mechanism. Radiographic studies were performed on rabbit and images indicated that these microspheres were retained successfully in stomach up to 7 hours. FTIR and DSC analysis revealed that there is no interaction between drug and the polymer. The microspheres were stable at accelerated stability conditions as per ICH guidelines. Single emulsion method was showing better results in all the above aspects compared to Ionotropic gelation method. This study concludes that the mucoadhesive microspheres could be one of the most appropriate drug delivery approaches for the successful delivery of linagliptin.

KEYWORDS: Mucoadhesive, microspheres, linagliptin, anti-diabetic.

INTRODUCTION

Delivery of a medication for an acute or chronic disease is carried out via various pharmaceutical dosage forms such as matrix tablets, capsules, suspensions, emulsions, micro beads, microspheres etc. Therapy with the conventional dosage formulation shows variation in the concentration of the drug in plasma. After administering first dose, the drug concentration declines due to the effect of metabolism. As the concentration gets decreased below the therapeutic range there is a need for the administration of the second dose to maintain concentration in plasma¹.

In order to avoid the frequency of administration and to maintain the steady state concentration of drug in plasma the controlled release formulations were used in which the medication is given once-a-day dose during which the concentration is maintained constant within therapeutic range for long period of time with minimum unwanted effects and with more patient compliance¹. A number of approaches have been developed to increase the residence time of the drug formulation. One of the approaches is the formulation of gastro retentive dosage forms in the form of mucoadhesive microspheres².

Microspheres carrier systems, made from natural polymers are attracting considerable attentions for several years, for sustained drug delivery. Microspheres are a part of such novel delivery systems³. Microspheres are defined as spherical particles having size less than $200 \mu\text{m}$ ⁴ (typically $1 \mu\text{m}$ to $1000 \mu\text{m}$) and made up of polymer matrix in which therapeutic substance is dispersed

throughout the matrix at the molecular or macroscopic level. The API will be released close to the site of action with a consequent enhancement of bioavailability. The microspheres can be made up of either natural or synthetic polymers^{3,5}.

Mucoadhesion has been a topic of interest in the design of drug delivery systems to prolong the residence time of the dosage form at the site of application or absorption and to facilitate intimate contact of the dosage form with the underlying absorption surface to improve and enhance the bioavailability of drugs⁶. Mucoadhesion or bioadhesion can be defined as the state in which two materials, at least one of which is biological in nature, are held together for a prolonged time period by means of interfacial forces⁷. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc can be termed as bioadhesion or mucoadhesion.

Linagliptin is a DPP-4 inhibitor for the treatment of type II diabetes. It is class-III drug which is highly soluble and low permeable. To increase its gastric retention time, mucoadhesive microspheres have been formulated. Mucoadhesive microspheres are carrier systems in sustained drug delivery; they are made from the biodegradable polymers. Mucoadhesive formulations are used orally to achieve a substantial increase in length of stay of the drug in the GI tract. Use of mucoadhesive polymers to develop microspheres is a novel approach to investigate their potential to control the drug delivery over a prolonged period of time. In the present study mucoadhesive microspheres of linagliptin were formulated using mucoadhesive polymers (carbopol 934P, guar

gum, sodium CMC, HPMC, sodium alginate) by two methods i.e., single emulsion method & ionotropic gelation method.

MATERIALS AND METHODS

Linagliptin was procured from Dr. Reddys's Laboratories, Hyderabad, India. Carbopol 934P from Moly Chem, HPMC K 100M, Guar Gum, Sodium Carboxy Methyl Cellulose from Yarrow chemicals products Mumbai.

Preparation of mucoadhesive microspheres: Mucoadhesive microspheres were prepared by single emulsion method and ionotropic gelation method.

Single emulsion method^{6,7}: Mucoadhesive microspheres were prepared using different polymers like HPMC K100, carbopol 934P, Guar gum, Sodium CMC, Sodium alginate and their combinations. Polymer solution was prepared by dissolving the polymers in 8ml of water. 5mg of drug was dissolved in 2ml of methanol and added to the polymer solution which gives a total volume of 10ml. The polymer solution was dispersed drop by drop in 50ml of heavy and 50ml of light liquid paraffin containing 0.5%w/v of span80 using mechanical stirrer with continuous stirring at 1500rpm. After complete mixing of aqueous solution to it add 25%v/v glutaraldehyde solution at different time intervals followed by continuous stirring at a constant speed of 1500rpm for 4hours. The obtained microspheres were filtered and washed with ethanol or Petroleum ether and then dried. Formulations LMS1 and LMS2 given in table 1 were prepared by single emulsion method.

Ionotropic gelation method^{6,7}: The linagliptin mucoadhesive microspheres are prepared by using sodium alginate as a gel forming polymer and by using natural bioadhesive polymers eg. Guar gum, carbopol 934P, Sodium CMC etc, in varying ratios with varying concentrations of calcium chloride solution. Sodium alginate was made into a solution and it was mixed with various concentrations of mucoadhesive polymers. The desired quantity of drug was added into polymeric solution and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added manually drop wise into calcium chloride solution through a syringe with a needle of size no. 21. The added droplets were kept dispersed in calcium chloride solution for 15 minutes to complete the curing reactions and to produce spherical rigid microspheres. The microspheres were collected by decantation, and the product thus separated, was washed with water and dried at 45°C for 12 hrs. Preliminary trails were performed by using different natural polymers in different ratios with varying concentrations of calcium chloride solution and the following are selected as optimized formulations. Formulations LMG1 to LMG8 given in table no.1 were prepared by ionotropic gelation method.

CHARACTERISATION OF MICROSPHERES

Drug-excipient compatibility studies by FTIR

The spectrum analysis of pure drug and physical mixture of drug with different excipients which are used for preparation of microspheres was studied by FTIR to find out the possible interactions between drug and excipients. FTIR spectra were recorded by preparing potassium bromide (KBr) disks using a shimadzu (Koyto, Japan) facility (model-8400S).

Differential scanning calorimetry

The physical nature of drug, polymer and optimized formulations were studied by DSC. DSC analysis was performed by using Q-

1000 TA Instruments, USA. The instrument was calibrated with indium standard.

Angle of repose

Angle of repose is the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The frictional forces in the loose powder can be measured by angle of repose. The angle of repose of the microspheres was determined by the funnel method. Accurately weighed quantity of microspheres were taken in a funnel and the height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the microspheres inside. The microspheres were allowed to flow through the funnel freely onto the surface. The diameter of the pile of the microspheres was measured and the angle of repose was calculated using the following equation⁸:

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} h/r$$

Where, θ = angle of repose, h = height of the heap (in cm) and r = radius of the base (in cm).

Drug entrapment efficiency⁹

A total of 50 mg microspheres were crushed and dispersed in 100 ml of 0.1 N HCl and sonicated for 20 min. Dispersion was stirred on magnetic stirrer for 6 hrs. After 24 hours, the solution was filtered and the filtrate was analyzed for the drug content, spectrophotometrically at 240nm.

The drug entrapment efficiency of the microspheres was calculated by using the following formula:

$$\text{Drug entrapment efficiency} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100$$

Particle size analysis

Particle size of the microspheres was determined by optical microscopy using stage micrometer¹⁰. Microspheres are suspended in distilled water and mounted on a glass slide. A minimum of 100 to 50 microspheres were counted for each formulation using calibration factor. Calibrate the stage micrometer with eye piece micrometer. Number of particles in each size, i.e., frequency was measured.

SEM (Scanning electron microscopy)

The surface and inner part of the microspheres were observed through the scanning electron microscopy (SEM). The physical characterization for SEM is performed for only optimized formulations.

Swelling index¹⁰

An accurately weighed amount of microspheres were placed in 0.1 N HCl and allowed to swell to a constant weight. The microspheres were removed, blotted with filter paper and the changes in their weight were measured at an interval period of 30 minutes and recorded. The degree of swelling was then calculated from the formula:

$$\text{Swelling index} = \frac{\text{Weight after swelling (Wf)} - \text{Initial Weight (W0)}}{\text{Initial Weight (W0)}} \times 100$$

In-vitro drug release studies

In-vitro drug release studies were carried out through dissolution using USP type-I (basket type) apparatus. The release of Linagliptin from the microspheres was studied using 0.1 N HCl in a dissolution apparatus with a rotating basket stirrer at a stirring speed of 50 rpm and a temperature of $37 \pm 1^\circ\text{C}$. 200mg of microspheres were used in each test and these were placed within each basket. Samples were withdrawn at different time intervals and replaced with 5ml of fresh dissolution medium. The withdrawn samples were assayed at 240 nm for linagliptin content using a UV visible spectrophotometer. Three trials were carried out for all the formulations^{11,12}. From this, percentage drug release was calculated and plotted against the function of time to study the pattern of the drug release.

In-vitro drug release kinetics

In order to understand the mechanism and kinetics of drug release from drug reservoir through rate controlling membrane, the *in-vitro* release data were fitted in to mathematical models. The release kinetic calculations were carried out. Regression coefficients (r^2) were calculated for all the formulations. Release compartment "n" was calculated from Korsmeyer-Peppas equation.

In-vitro wash-off test for microspheres (Mucoadhesion strength)⁸

The mucoadhesive properties of the microspheres were evaluated by *in-vitro* wash-off test. A 4cm x 4cm piece of goat intestinal mucosa was tied onto the paddle bottom of a USP dissolution test apparatus - II using a thread. A specified number of microspheres, i.e. 100 microspheres were spread onto the wet, rinsed tissue specimen. The dissolution test apparatus was operated such that the tissue specimen was rotated at a speed of 25 rpm in 0.1 N HCl. At the end of 1 hour, and at hourly intervals up to 8 hours, the number of microspheres still adhering onto the tissue was counted. The percentage mucoadhesion of the microspheres was determined using the following formula,

$$\text{Percentage Mucoadhesion} = \frac{\text{Number of microspheres still adhering}}{\text{Number of microspheres applied}} \times 100$$

Radiographic studies

The experimental protocol to carry out *in vivo* radiographic studies was reviewed and approved by the Institutional Animal Ethical Committee GPRCP/IAEC/20/16/02/PCE/AE-6. The *in vivo* radiographic studies were conducted in young & healthy male albino rabbits weighing 2.0 to 2.2 kg. The animals were kept under standard laboratory conditions (Temperature $25 \pm 2^\circ\text{C}$). Rabbits were kept one week in the animal house to acclimatize them and were fed a fixed standard diet. The 4 healthy male albino rabbits were used to monitor the *in vivo* transit behavior of the prepared mucoadhesive microspheres. None of the animals had symptoms or history of gastrointestinal (GI) disease. In order to standardize the conditions of GI motility, the animals were fasted for 12 hours prior to the commencement of each experiment. In each experiment, the first radiographic image of the animal subjects was taken to ensure the absence of radio opaque material in the GIT. One of each dosage form prepared for radiography was orally administered to rabbits with the sufficient amount of water. During the study, the rabbits were not allowed to eat, but water was available.

For radiographic imaging, the legs of the rabbit were tied over a piece of plywood (20 × 20 inch), and location of the formulation in the stomach was monitored by keeping the subjects in front of

X-ray machine (Allegers, Bharat Electrical, India, and model number E-080743). The distance between the source of X-rays and the object was kept the same during the imaging process. Gastric radiography was done at the intervals of 1hr and 7hr. In between the radiographic imaging, the animals were freed and allowed to move and carry out normal activities but were not allowed to take any food¹³.

Stability study

Mucoadhesive microspheres were tested for stability in ambered colored bottle containers. Optimized formulation were stored at accelerated stability conditions ($40^\circ\text{C} \pm 2^\circ\text{C}$ / $75\% \pm 5\% \text{RH}$) as per ICH guidelines over a period of 1month and in between were evaluated for drug entrapment efficiency, particle size analysis and swelling index properties every week.

RESULTS AND DISCUSSION

Drug-excipients compatibility studies: Drug excipient compatibility studies were performed by Fourier Transform Infrared spectroscopy and the results are presented in figure no. 1 and 2. The wave numbers of 1400 cm^{-1} , 1540 cm^{-1} , $1780\text{-}1540 \text{ cm}^{-1}$, $1275\text{-}1200 \text{ cm}^{-1}$, $950\text{-}675 \text{ cm}^{-1}$, $1500\text{-}1400 \text{ cm}^{-1}$ appeared as characteristic peaks in the IR graphs of the pure drug. The peaks were observed at the same wave numbers for the optimized formulation (physical mixture of drug and Carbopol 934P). This indicates that there is no interaction between drug and excipient and that the pure drug was not altered functionally¹⁴.

Differential scanning calorimetry: To study drug- excipient compatibility between linagliptin and carbopol 934P, DSC was conducted.

Thermal behavior of pure linagliptin, carbopol 934P and their physical mixture are depicted in figure no. 3 and 4. The pure linagliptin showed melting endothermic peak at 206°C . The endothermic peak for the drug in physical mixture did not show any changes in the melting endotherm of drug. Incompatibility between drug and carbopol 934P was not found¹⁴.

Angle of repose

Flow properties of prepared microspheres were determined. The angle of repose values are shown in table 2. All the formulations showed angle of repose within the range of 13-39. Results indicated that some formulations show excellent flow properties and some shows good flow properties¹⁵.

Drug entrapment efficiency

Table 2 shows drug entrapment of all the formulations using single emulsion method and ionotropic gelation method.

Effect of drug: polymer ratio: Entrapment of drug was increased with increasing in drug: polymer ratio. It occurred due to the increase in viscosity of aqueous phase with increase in the polymer concentration that stabilize droplets and which prevent out flow of drug during the hardening phase.

Effect of Glutaraldehyde: Here percentage entrapment was increased by increasing the volume of glutaraldehyde. It can be explained that higher degree of cross linking occurs by higher concentration of glutaraldehyde. Increase in amount of glutaraldehyde produces much denser matrix due to increased cross linking with chitosan that reduces the outflow of drug during stirring and increases the encapsulation efficiency¹⁶.

Particle size analysis

Particle size analysis of drug-loaded linagliptin microspheres was performed by optical microscopy using a compound microscope. A small amount of dry microspheres was suspended in purified water (10 ml). The suspension was ultrasonicated for 5 sec. A small drop of suspension thus obtained was placed on a clean glass slide. The slide containing linagliptin microspheres was mounted on the stage of the microscope and diameter of at least 100 particles was measured using a calibrated ocular micrometer. Maximum number of particles is found to be in size range of 61-80 μm . Thus, size analysis showed that they are almost uniform in size. The particle size of all the formulations was calculated and the results are shown in table 2.

From the above table 2, it indicates the average particle size of microsphere increased with increasing the polymer concentration, since higher concentration of polymer solution disperses into large droplets. At concentrations lower than the optimum, solution became less viscous and dispersed into numerous fine droplets that easily coalesced, resulting in large microspheres. We conclude that average diameter of microspheres is controlled by rotational speed¹⁷.

Swelling index

Swelling index study was performed and the results are given in the above table no 2 which indicated that the values were found to be within the range of 0.3 to 1.21. Using emulsification method we conclude that by increasing the concentration of cross linking agent, the swelling index predominantly decreases and by increasing the concentration of surfactant, swelling index increases due to relaxation of polymer network in high pH condition¹⁸.

Scanning electron microscopy for surface morphology

From SEM studies, the surface morphology was found to be smooth. The SEM photographs shown in figure 5 indicated that microspheres were spherical and completely covered with the coat polymer (carbopol 934P).

In-vitro drug release studies

Drug release studies for Single emulsion method: In-vitro drug release studies were performed and it can be concluded that the formulations prepared using LMS1 single emulsion method (SEM) are showing a good release of $98.2 \pm 0.63\%$ and LMS2 showing a release of $92.4 \pm 0.26\%$ in 8 hours as depicted in the figure 6. When compared with LMS2 formulation, LMS1 is having more mucoadhesiveness.

Drug release studies for Iontropic gelation method

Drug release studies were performed and it can be concluded that the formulation with a formulation code LMG4 prepared using carbopol as a polymer was showing better drug release of $98 \pm 0.52\%$ in 6 hrs when compared to the other polymers as shown in figure 7.

In-vitro drug release kinetic studies

The drug release data of linagliptin mucoadhesive microspheres was fitted to kinetics models, i.e., zero order, first order, Higuchi and korsmeyer peppas and the results are tabulated in table 3. For LMS1 formulation the regression coefficient of zero order and first order plots was observed to be 0.966 and 0.804 respectively, indicating zero order release kinetics. The 'r' value

of Higuchi kinetics was found to be 0.98. The Korsmeyer peppas exponent 'n' was found to be 0.533 indicating drug release by Anomalous transport. The release kinetic profile of optimized formulation LMG4 shows regression coefficient of zero order and first order plots 0.989 and 0.880 respectively, indicating zero order release kinetics. The 'r' value of Higuchi kinetics was found to be 0.94. The Korsmeyer peppas exponent 'n' was found to be 0.829 indicating drug release by Anomalous transport. This indicates that the drug release from microspheres follows zero order kinetics and anomalous transport mechanism based on 'n' value.

In-vitro wash off test (mucoadhesion strength): Mucoadhesive microspheres are evaluated by in-vitro wash off test.

In-vitro wash of test for LMS1 & LMS2 using single emulsion method: It was observed that mucoadhesive strength of formulation LMS1 was 87% which was better when compared with formulation LMS2 containing guar gum i.e., 64% and it was shown in figure 8.

In-vitro wash of test for LMG2, LMG4, LMG6 and LMG7 using ionotropic gelation method: It was observed that mucoadhesive strength of formulation containing Carbopol LMG4 was 76% when compared with the other polymers which are shown in figure 9.

Radiographic studies: The radiographic studies were conducted. The drug in all selected formulations was replaced with the same amount of barium sulphate while all other ingredients were kept constant. The microspheres were given orally to rabbit; radiographic images were taken in different intervals of 1hr and 7 hrs. The images are shown in below Figure 10 and 11. The microsphere containing BaSO_4 loaded mucoadhesive microspheres were clearly visible in figure 10 & figure 11 in the stomach after oral administration of dosage form. Dense images of microspheres were seen at initial hours but, as time passed on, the images of microspheres became lighter. It may be because of the distribution and scattering of microspheres within GI region. The radiographic images indicated that these mucoadhesive microspheres were retained successfully in the stomach up to seven hours.

Stability study²: Stability studies were carried out for optimized formulation (LMS1) at accelerated stability conditions ($40^\circ\text{C} \pm 2^\circ\text{C}$ / $75\% \pm 5\% \text{RH}$) as per ICH guidelines over a period of 1 month to various evaluation parameters like physical appearance, drug entrapment efficiency, particle size analysis, swelling index. The evaluation study results are given in table 4. After 1 month, it was found that there is no degradation of linagliptin drug. We conclude that the microspheres are stable¹⁹.

CONCLUSION

In the present study, an attempt was made to formulate and evaluate mucoadhesive microspheres of linagliptin using synthetic polymers i.e., Carbopol 934P, guar gum, HPMC K100M, Sodium CMC by two methods (single emulsion method, ionotropic gelation method). Spherical free flowing cross linked glutaraldehyde microspheres were successfully prepared by emulsification method. FTIR and DSC studies showed drug-excipient compatibility. Retainment of microspheres for 7hrs in stomach is seen in radiographic images and the formulation was found to be stable. This indicates that linagliptin residence time in stomach has increased, facilitating better absorption and bioavailability. So, it can be concluded that single emulsion method is better than that of ionotropic gelation method.

Table 1: Formulation table of mucoadhesive microspheres

Formulation code	Drug (mg)	Carbopol 934P (%)	Guar gum (%)	Solvent (Heavy and light liquid paraffin (ml))	Span 80 (%)	Glutaraldehyde 25%w/v (ml)	Sodium Alginate (%)	Sodium CMC (%)	HPMC K100M (%)	Calcium Chloride (%)	RPM
LMS1	5	2.5	-	100	0.5	25	-	-	-	-	1500
LMS2	5	-	2.5	100	0.5	20	-	-	-	-	1500
LMG1	5	-	0.1	-	-	-	0.1	-	-	10	100
LMG2	5	-	0.2	-	-	-	0.1	-	-	10	100
LMG3	5	0.1	-	-	-	-	0.1	-	-	10	100
LMG4	5	0.2	-	-	-	-	0.1	-	-	10	100
LMG5	5	-	-	-	-	-	0.1	0.1	-	10	100
LMG6	5	-	-	-	-	-	0.1	0.2	-	10	100
LMG7	5	-	-	-	-	-	0.2	-	-	10	100
LMG8	5	-	-	-	-	-	0.1	-	0.2	10	100

Table 2: Evaluation of linagliptin mucoadhesive microspheres

Formulation	Angle of repose (θ)	Drug entrapment efficiency (%)	Particle size(μ m)	Swelling index
LMS1	27.15	85 $\pm$ 0.57	135 $\pm$ 6	1.21
LMS2	34.17	91 $\pm$ 0.82	189 $\pm$ 3	1.03
LMG1	32.12	86.7 $\pm$ 1.23	67 $\pm$ 16	0.3
LMG2	28.64	92 $\pm$ 2.56	79 $\pm$ 8	0.56
LMG3	17.30	87 $\pm$ 2.39	96 $\pm$ 12	0.7
LMG4	24.21	76 $\pm$ 2.39	122 $\pm$ 23	0.58
LMG5	33.03	79.1 $\pm$ 1.81	76 $\pm$ 4	0.9
LMG6	39.23	85.5 $\pm$ 2.01	42 $\pm$ 6	0.6
LMG7	13.90	73 $\pm$ 1.45	105 $\pm$ 6	0.52
LMG8	22.26	87 $\pm$ 1.89	58 $\pm$ 25	0.81

Table 3: In-vitro drug release kinetic studies for linagliptin mucoadhesive microspheres

Batch	Zero order	First order	Higuchi	Korsemeyer- Peppas		Release mechanism
	R ²	R ²	R ²	R ²	n	
LMS1	0.966	0.804	0.987	0.991	0.533	Anomalous Transport
LMS2	0.975	0.772	0.99	0.99	0.557	Anomalous Transport
LMG1	0.983	0.875	0.984	0.974	0.474	Fickian diffusion
LMG2	0.976	0.782	0.977	0.990	0.621	Anomalous Transport
LMG3	0.933	0.724	0.978	0.980	0.629	Anomalous Transport
LMG4	0.989	0.880	0.940	0.972	0.829	Anomalous Transport
LMG5	0.979	0.848	0.948	0.977	0.580	Anomalous Transport
LMG6	0.956	0.846	0.982	0.980	0.389	Fickian diffusion
LMG7	0.965	0.748	0.978	0.987	0.649	Anomalous Transport
LMG8	0.969	0.871	0.901	0.974	0.815	Anomalous Transport

Table 4: Stability study of optimized formulation LMS1

Test	Initial	1 st week	2 nd week	1 month
Physical appearance	Colorless	colorless	colorless	colorless
Drug entrapment efficiency	85 $\pm$ 0.57	84.6 $\pm$ 0.59	84 $\pm$ 0.49	83 $\pm$ 0.55
Particle size analysis	135 $\pm$ 6	134 $\pm$ 6	132 $\pm$ 6	130 $\pm$ 6
Swelling index	1.21	1.20	1.20	1.19

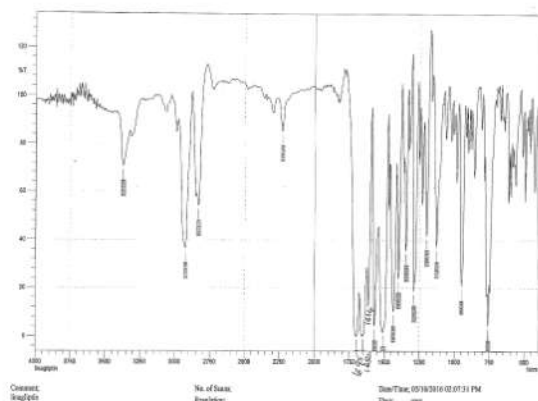


Figure 1: FTIR graph of pure drug (Linagliptin)

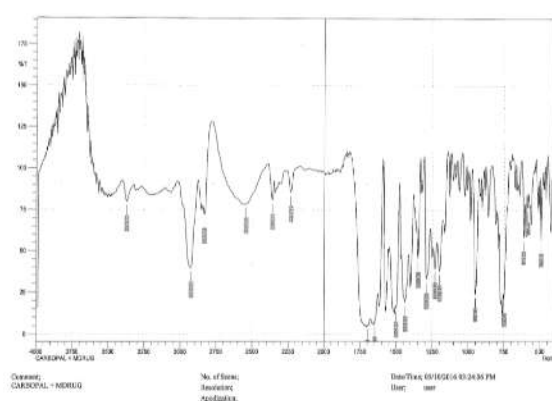


Figure 2: FTIR graph of pure drug (linagliptin) and Carbopol 934P Physical mixture

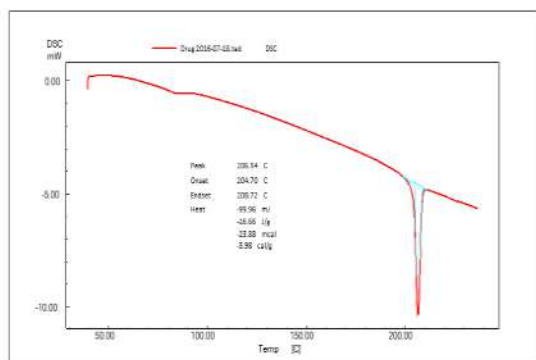


Figure 3: DSC thermogram of linagliptin

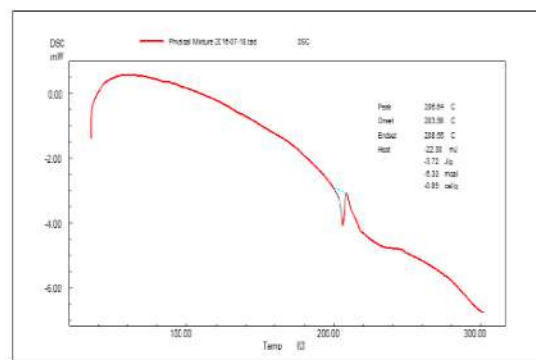


Figure 4: DSC thermogram of linagliptin and Carbopol 934 P

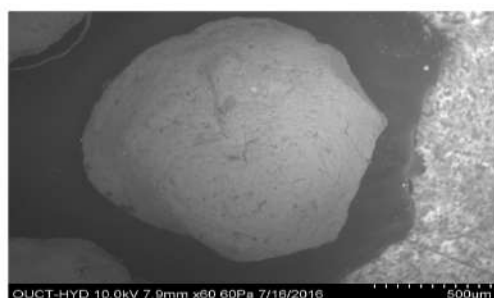


Figure 5: SEM analysis of LMS1 microspheres

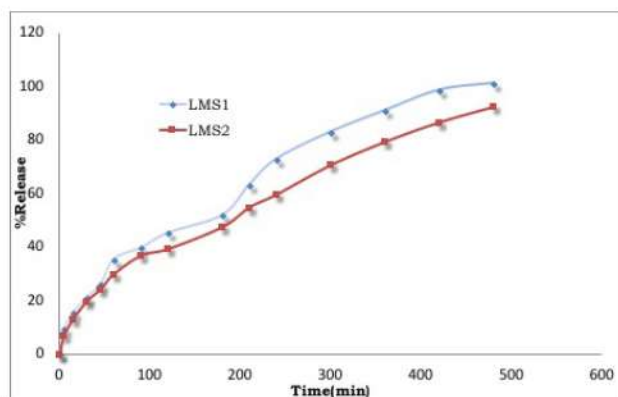


Figure 6: Comparative dissolution profiles of linagliptin mucoadhesive microspheres using Single emulsion method

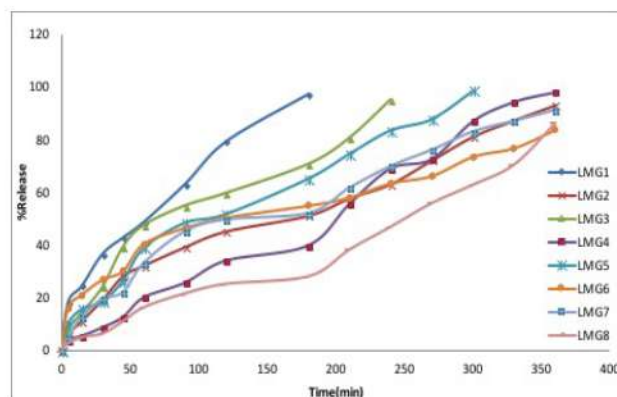


Figure 7: Comparative dissolution profiles of linagliptin mucoadhesive microspheres using Iontropic gelation method.



Figure 8: In-vitro wash off test for microspheres (LMS1)



Figure 9: In-vitro wash off test for microspheres.



Figure 10: Radiographic images showing the presence of BaSO₄ loaded mucoadhesive microspheres in the stomach at 1 hr

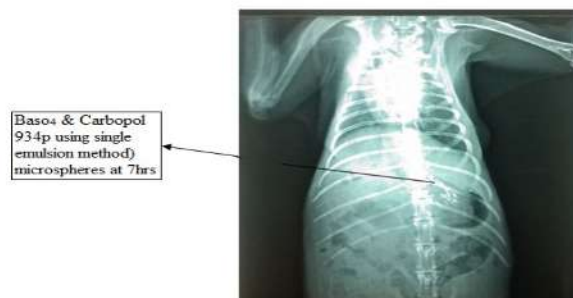


Figure 11: Radiographic images showing the presence of BaSO₄ loaded mucoadhesive microspheres in the stomach at 7 hrs.

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