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Development and in vitro evaluation of Sitagliptin Phosphate mucoadhesive tablets for NIDDM

Badri Nagarani*[1], Santhosh Kumar Chinnaiyan[2], Venkata Radha Gadela[3]

Abstract

The objective of the present work was to develop an oral mucoadhesive Sitagliptin Phosphate tablet for the sustained-release. The tablets were prepared by the wet Granulation method, using biodegradable mucoadhesive polymer Methocel-K4M at different concentrations. After examining the flow properties of the powder blends the results were found to be within prescribed limits and indicated good flowing property, hence it was subjected to compression. The tablets were evaluated for post-compression parameters like weight variation, hardness, thickness, friability, drug content uniformity, surface pH, in-vitro studies like swelling, mucoadhesive strength, residence time and drug release. Formulation (F3) showed good muco-adhesive strength (17.15g) and maximum drug release of 100 % in 12 h and residence time (6.1 h). The drug content shown 95.43%, surface pH was found to be 6.5. The Sitagliptin Phosphate release effectively controlled for 12 h with Methocel, thus, can be successfully employed for formulating mucoadhesive tablets. Fitting the data to the Zero order and Higuchi equation indicated the mechanism of drug release.

Keywords: Sitagliptin Phosphate, Methocel-K4M, Mucoadhesive tablets.

Author Affiliation: [1] Department of Pharmaceutics, Srikrupa Institute of Pharmaceutical Sciences, Vill: Velikatta, Mdl: Kondapak, Dist: Siddipet, Telangana state-502277, India.
[2] Faculty of pharmacy, Karpagam academy of higher education, Eachaanari, Coimbatore-641021, Tamil nadu, India.
[3] Department of Pharmaceutics, GITAM (deemed to be) University, Rushikonda, Visakapatnam-530045, Andhra Pradesh, India.
Corresponding Author: Badri Nagarani. Department of Pharmaceutics, Srikrupa Institute of Pharmaceutical Sciences, Vill: Velikatta, Mdl: Kondapak, Dist: Siddipet, Telangana state-502277, India.
Email: badri.naga33@gmail.com
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1. Introduction

Controlled release formulation describes sustained action along with its predictability of release of drug ingredients from the drug delivery system (Kiniwa et al., 2019). Out of drug delivery systems, the mucoadhesive drug delivery is more reliable than traditional drug delivery systems (Abu et al., 2020). Mucoadhesion is an Interfacial phenomenon based on two materials, one of which is mucosal layer of mucosal tissue to which drug is held together by means of interfacial forces for prolonged period of time (Anders and Merkle 1989). Trans-mucosal drug delivery bypass first pass effect in gastrointestinal tract and avoid Gastro intestinal side effects (Koirala et al., 2021). Mucoadhesive drug delivery systems utilises the property of bioadhesion of certain polymers. Bioadhesion defined as ability of a material to adhere a particular region of body for extended period of time (Tunpanich et al., 2019).

Mucoadhesion is also defined as the interaction between mucin and synthetic/natural Polymer (Gennari et al., 2019 and Abruzzo et al., 2015). The principle of mucoadhesive preparation offers a simple practical approach and it's practically useful to prolong the retention time of dosage form in the stomach, thereby improving oral bioavailability of drug (Silva Favacho et al., 2020). Most of the mucoadhesive materials are either synthetic or natural or hydrophilic or water insoluble polymers and are capable of forming numerous hydrogen bonds because of presence of hydroxyl, carboxyl or sulphate functional groups (Kurcubic et al., 2020, and Al-Ani et al., 2020).

Diabetes mellitus is a condition in which a person has a high blood sugar level, either because a body does not produce enough insulin or body cells don't properly respond to insulin that is produced. To treat this diabetes, medications/Insulin therapy were used. Under this diabetes, Type-II was most

commonly occurred and only ant diabetic drugs are used. Among those ant diabetic drugs Sitagliptin was more acceptable. Sitagliptin is a Dipeptidyl Peptidase-4 (DPP-4) Inhibitor. It inhibits the enzyme Dipeptidyl peptidase which breaks the incretions GLP- and GIP, gastrointestinalhormones released in response to a meal. By preventing GLP-1 and GIP inactivation, they are able to increase secretion of insulin and suppress the release of glucagon by pancreas.

2. MATERIALS AND METHODS:

Materials

Sitagliptin Phosphate, and Methocel™-K4M Premium (Methoxy Substitution 22%, Hydroxypropoxyl substitution 8%) gift sample provided by Caplin Point Laboratories Ltd Chennai, India. Gelzan™ CM (CAS Number: 71010-52-1) and Avicel PH 101 was purchased from Sigma Aldrich Bangalore, India. Magnesium stearate and Talc was purchased from S.D fine chemicals Mumbai, India.

3. Methodology

Standard plot of Sitagliptin Phosphate in 6.8 pH

Sitagliptin Phosphate dissolved in 50 ml of phosphate buffer to produce primary stock solution having a concentration of 1 mg/ml. 10 ml of primary stock further diluted to 100 ml to produce secondary stock solution having concentration of 100 µg/ml. 0.1-1 ml aliquots of the secondary stock were further diluted to 10 ml to produce standard solutions having concentrations of 0-10 µg/ml. The absorbance of the solutions was measured at 235 nm using double beam UV-Visible spectrophotometer (ELICO-164, India). The plot of absorbance vs. concentration (µg/ml) was plotted and data was subjected to linear regression analysis.

Preparation of tablets

Sitagliptin phosphate mucoadhesive tablets were prepared by wet granulation method using various concentrations Methocel K4M as polymer. Mucoadhesive matrix tablet each containing 50 mg Sitagliptin phosphate were prepared by Non-aqueous granulation method using Isopropyl alcohol. All the ingredients except drug and lubricants were weighed and blended, drug was added to this mixture and triturated for two min for uniform mixing. The powdered blend then subjected to granulation by using isopropyl alcohol as granulating agent. The wet powder mass was passed through sieve no. 12 and the granules obtained were dried at 45 ºC for 30 min. the dried granules were passed through sieve no. 16 and lubricated with magnesium stearate and talc. The blended granules were finally compressed in to tablets of desired weight (200 mg) and hardness by 8 mm flat faced punch on 10 stages rotary tablet compress machine (CTX-8, Cadmach Machinery, Ahmadabad, India). Formulations composition of the prepared mucoadhesive tablets of Sitagliptin phosphate is given in Table 1.

Preformulation studies

Angle of repose

A funnel was kept vertically in stand at a specified height above a paper placed on horizontal surface. The bottom was closed and 10 gm of sample powder was filled in funnel. The funnel was opened to release the powder on paper to form a smooth conical heap. The height of heap was measured using the scale. A border of heap was marked circularly and its diameter was measured at four points. The angle of repose was calculated using following formula: The flow property of granules was determined by measuring Angle of repose.

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

Where, θ = Angle of repose, h = Height of heap, r = Radius of pile.

Bulk density

It is the ratio of mass to bulk volume. It is required to decide appropriate packing of dosage forms. An accurately 10 gm of sample was weighed and transferred to a 50 ml measuring cylinder. The volume was noted. The Bulk density was obtained by dividing weight of the sample in grams by final volume in cm3 and it was determined by equation given below Bulk density was measured by taking the ratio of Mass of powder to its bulk volume.

Bulk density = M / V0

M = Mass of the powder, V0 = Bulk volume of powder.

Tapped density

Accurately weighed quantity of powder was carefully poured in to graduated 50 ml measuring cylinder through large funnel. The cylinder was then tapped 100 times from a constant height and the tapped volume was read. This is expressed in gm / ml and determined by the following formula: True density was determined by taking ratio of mass of powder to its true volume.

Tapped density = M / Vr

M= Mass of powder, Vr = final tapping volume of powder.

Compressibility Index and Hausner Ratio

To measure the unsettled apparent volume, (V0) and the final tapped volume, (Vf) of the powder after tapping the material until no further volume changes occur .given by the expression as follows.

Compressibility Index= (1-Bulk Density)/ Tapped density ×100

A small index like percentage compressibility index has been defined by Hausner. Values less than <1.25 indicates good flow, where as greater than 1.25 indicates poor flow. Added glidant normally improves flow of the material under study. Hausner's ratio can be calculated by

Hausners Ratio = Tapped density/Bulk Den

Post compression Parameters

Hardness

The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The degree of hardness varies with the different manufactures and with the different types of tablets. The hardness was tested by using Monsanto hardness tester.

Thickness

Six tablets from each batch of formulation were collected and the thickness of the tablets was measured with the help of venires caliper. The average thickness was calculated.

Friability

Roche friability test apparatus was used to determine the friability of the tablets. Twenty pre-weighed tablets were placed in the apparatus and operated for 100 revolutions and then the tablets were reweighed. The percentage friability was calculated according to the following formula:

% Friability = Initial weight - final weight/ Initial weight×100

Weight Variation

The weight of tablet is measured to ensure that a tablet contain the proper amount of drug. Randomly selected twenty tablets form each batch were subjected to weight variation test as per Indian Pharmacopoeia 2007. Not more than two individual weight deviate from the average weight by more than 5% percentage deviation.

Uniformity of Content

Drug content uniformity was determined by dissolving the tablets in ethyl alcohol and filtering with whattman filter paper. The filtrate was evaporated and drug residue dissolved in 100 ml phosphate buffer pH 6.8. The 5 ml solution was then diluted with phosphate buffer pH 6.8 to 20 ml, filtered through whattman filter paper, and analyzed at 235 nm using UV double beam spectrophotometer.

Swelling studies

The swelling property of bio adhesive polymer plays an important role in bio adhesion (Manwar et al., 2016). Swelling studies were conducted by placing the tablet in a petri dish containing 5mL phosphate buffer pH 6.8 for 6 hours. After 6 hours the tablets were taken out from buffer and excess water was removed with filter paper and swelling index calculated.

Swelling index = Wt. – Wo / Wo x 100

Wt. = weight of swollen tablet at each time interval

Wo = weight of initial tablet

Surface pH

To protect the mucosal layer from irritation by acidic or basic pH this surface pH studies were conducted. The tablet was placed in 1 ml distilled water for 2 hours. After 2 hours the pH was determined.

Measurement of adhesion force

Measurement of adhesion force was determined by using bovine intestinal mucosa, which was obtained, from slaughterhouse. The underlying tissues were separated and washed thoroughly with phosphate buffer solution (pH 6.8). The membrane was then tied to the bottom of the lower vial-using rubber band. The vial was kept in glass bottle which was filled with phosphate buffer solution at 37 ± 1 ºC in such way that buffer just reaches the surface of mucosal membrane and kept it moist. The tablet to be tested was stuck on the lower side of the hanging Glass vial by using adhesive tape and the weight (2 gm) on the right pan was removed(Venkatesan et al., 2006).

This lowered the left side of the pan along with tablet over the mucosa. It was kept undisturbed for three minutes and the weights were added on right side of pan till the tablet just separated from the membrane surface. The excess weight on the right pan i.e. total weight minus 2 gm was taken as measure of bioadhesive strength. Bioadhesive force was calculated by using following equation(Mansuri et al., 2016).

Bioadhesive force = Bioadhesive strength x 9.81/100

Residence Time

The ex-vivo residence time was determined using a locally modified USP disintegration apparatus. The disintegration medium was composed of 900 ml (pH 6.8) of phosphate buffer maintained at 37 ± 1 ºC. The bovine intestinal mucosa was tied to the surface of a wooden scale, vertically attached to the disintegration apparatus. The tablet was hydrated using phosphate buffer (pH 6.8) and the hydrated surface was brought in contact with the mucosal membrane by keeping the backing membrane outside. The wooden scale allowed moving up and down, so that the tablet was completely immersed in buffer solution at the lowest point and was out at the highest point. The time taken for complete displacement of the tablet from the mucosal surface was noted and repeated thrice (Sabale et al., 2016).

In vitro Dissolution studies

The United State Pharmacopeia (USP) type II dissolution apparatus was used to study the release of drug from tablets. The dissolution medium consisted of 900 ml of phosphate buffer (pH 6.8). The release was performed at 37 ± 0.5 ºC, at a rotation speed of 50rpm Samples (5 ml, at each time for 12 h) were filtered with fresh medium. The amount of drug release was analyzed spectrophotometrically at 231 nm against phosphate buffer as blank.

In vitro drug release kinetic modeling of drug dissolution profile

In order to examine the release mechanism of drug from the tablets, the In-vitro drug release data of

best muccoadhesive tablet formulation were subjected to following release models Zero order, First order, Higuchi and Peppas models

RESULTS AND DISCUSSION:

Construction of Calibration curve

The standard graph of Sitagliptin Phosphate has shown good linearity with R2 values with 0.9996 in Buffer pH 6.8 which confirms that it obeys Beers Lamberts law over this concentration range Fig 1.

Evaluation Pre-Compression Parameters

The results of the granules evaluation suggested that all the granules exhibited the good flow properties (Table 2). The formulation blends were directly compressed using 8 mm flat faced punch on 8 stages rotary tablet compress machine and in- vitro drug release studies were performed.

Evaluation Post-Compression Parameters

All the prepared mucoadhesive tablets of Sitagliptin Phosphate were evaluated for thickness, hardness, friability, weight variation and drug content and data is shown Table 3. The hardness of prepared mucoadhesive tablets was range of 5.2 - 7.4 kg /cm2 and hardness was increased as the concentration of Methocel was increased in the formulation. The thickness of the tablets was in the range of 4.1 - 4.45 mm, which shows uniform thickness of the tablets. The friability was in the range of 0.65% to 0.99%. Less than 1% indicates good mechanical strength to withstand the rigors of handling and transportations. Weight of the prepared tablets were found to be in the range of 195 to 201 mg. The drug content was in the range of 89.5% to 95.43%, suggesting uniform mixing of drug.

Swelling Studies

The swelling index of all formulation was found in the range 14.42 % to 82.42% for 6 h. Swelling studies indicates that swelling index of F5 was found to be higher followed by F4>F3>F2>F1. Swelling of tablets increases with increase in Methocel K4M polymer concentration Fig.2.

Surface pH and Mucoadhesive Strength and Ex-vivo Residence Time

The values of surface pH were in the range between 6.5 - 6.9 which indicates that all the formulation provides an acceptable pH in the range of intestinal pH 6 -7.4. The mucoadhesion of all the tablets of varying ratio of polymers were tested and weight required to pull off the formulation from the mucous tissue was recorded as mucoadhesion strength in grams. The mucoadhesion of tablets was found to be maximum in case of formulation F4 and F6 i.e. 21.26 and 23.33 gm respectively. The mucoadhesion was mainly due to the mucoadhesive nature of the polymer used. The residence time of tablets ranged between 4.1 - 7.6 h and noted this much time required tablets to detach from the intestinal mucosa (Fig.3).

Invitro Drug Release Studies

The drug release pattern was studied for all formulations. (F1 to F5) for 12 h following standard procedure and the results are provided in Fig 4. The in-vitro cumulative drug release of formulation F-1 in 8 h, F-2 in 10 h and F-3 in 12 h. The F-4 was resealed 89.11 % and F5 81.53% at the end of 12 h. This may be attributed to increased hydration followed by increased swelling of polymer with increase in concentration of polymer. The overall data on the in-vitro dissolution studies closely indicated that among the six formulations, the formulation F3 was found to be the best with high percentage of drug release (100 %), with extended period of time for about 12 h. This confirming the prolong action of the mucoadhesive tablets. The concentration of Methocel significantly influence the drug release the higher concentration (20 and 100 mg) decrease the release rate of Sitagliptin Phosphate.

Table 1: Composition of mucoadhesive tablets of Sitagliptin Phosphate

Ingredients (mg)	F1	F2	F3	F4	F5
Drug	50	50	50	50	50
Methocel K4M	20	40	60	80	100
Gelzan	25	25	25	25	25
Avicel PH 101	85	65	45	25	05
Magnesium stearate	10	10	10	10	10
Talc	10	10	10	10	10

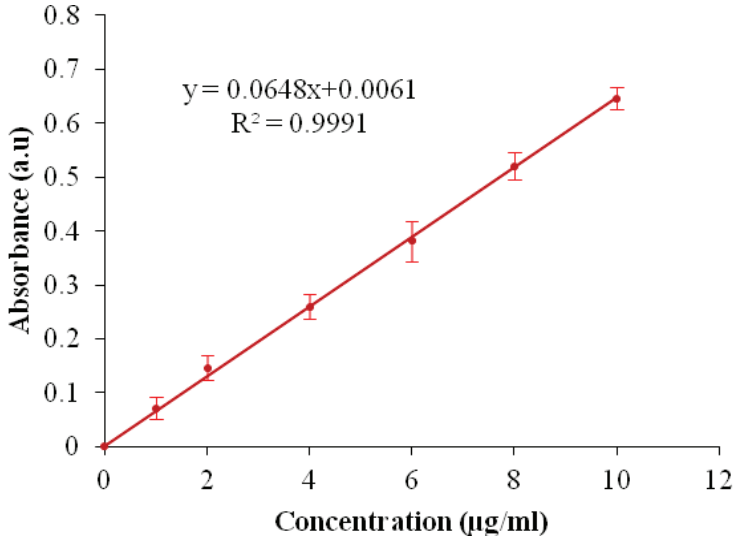

Fig 1: Standard graph of Sitagliptin phosphate

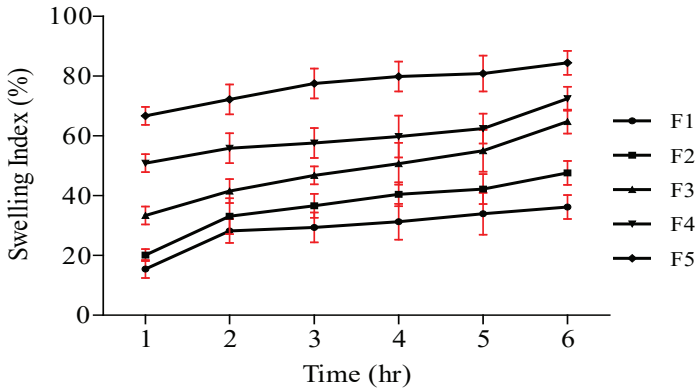

Fig 2: Swelling index of Mucoadhesive tablets

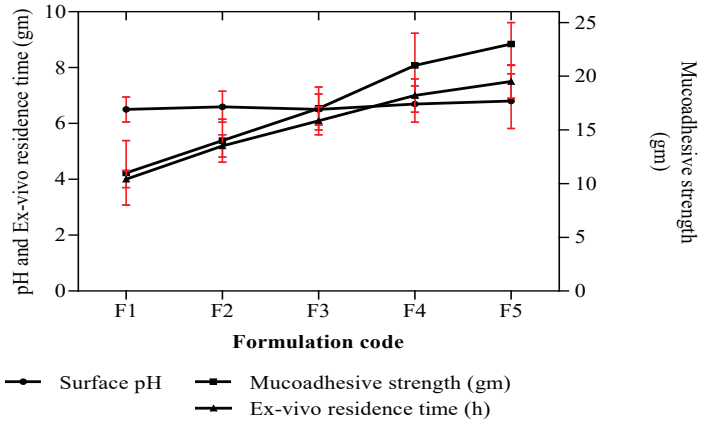

Fig 3: Surface pH, mucoadhesive strength and ex-vivo residence time of mucoadhesive tablets

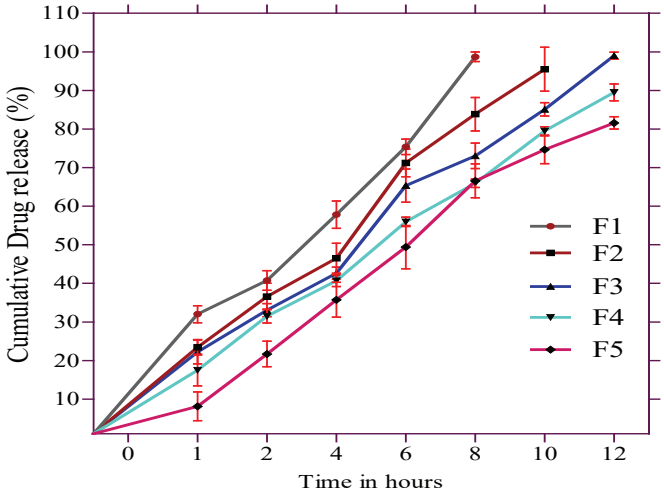

Fig 4. In - vitro dissolution profile of formulation F1 – F5

Table 2: Pre-compression Evaluation of parameters of powder blend

Formulation code	Bulk density (gm/cc)	Tapped density (gm/cc)	Hausner's ratio	Compressibility index	Angle of repose (º)
F1	0.34 ± 0.00	0.39± 0.00	1.18 ± 0.05	17.26 ± 0.84	28.68 ± 0.84
F2	0.32 ± 0.00	0.34 ± 0.00	1.09 ± 0.05	9.68 ± 0.87	24.89 ± 1.47
F3	0.29 ± 0.00	0.32 ± 0.00	1.12 ± 00	11.82 ± 0.78	24.82± 1.45
F4	0.27 ± 0.00	0.29± 0.00	1.15 ± 00	9.2 ± 0.59	25.31 ± 0.64
F5	0.24 ± 0.00	0.26 ± 0.00	1.06± 00	9.36 ± 0.65	26.26 ± 2.2

Table 3: Evaluation post compression parameters of Sitagliptin phosphate mucoadhesive tablets

Formulation code	Weight variation (mg)	Hardness (kg/ cm2)	Thickness (mm)	Friability	Drug content (%)
F1	195±2.24	5.2±0.24	4.1±0.15	0.99±0.00	89.50 ± 3.47
F2	197±2.11	5.6±0.32	4.4±0.14	0.94±0.00	91.30 ± 2.34
F3	198±1.25	6.1 ±0.21	4.4±0.11	0.76±0.00	95.43 ± 3.34
F4	200±2.13	6.7±0.16	4.3±0.15	0.76±0.00	93.19 ± 2.69
F5	201±1.24	7.4±0.05	4.2±0.15	0.65±0.00	90.50 ± 1.35

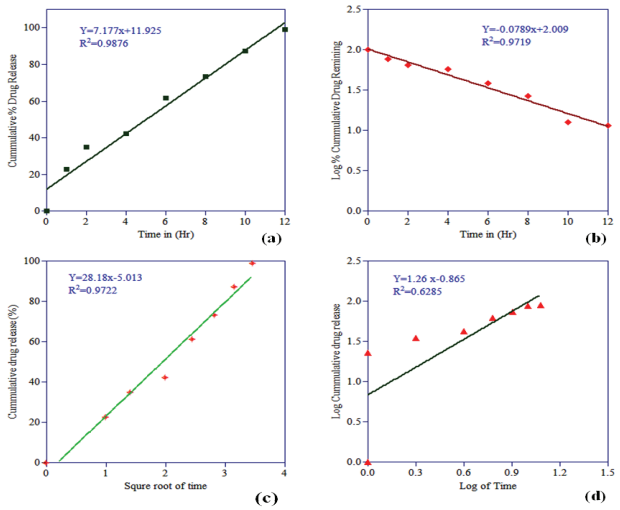

Fig 5. In - vitro release kinetics of F3 (a) Zero order kinetic model (b) First order kinetic model (c)

Drug release kinetics

Release data for F-3 formulation was fitted into various kinetic equations to determine the order and mechanism of drug release. The correlation coefficient showed that the release profile followed the Zero order model (R2=0.9876) indicates that the drug release independent to the concentration and suitable for sustained release of the drug. In case of Korsemeyer peppas model, the release exponent, n was found to be 0.7218 (0.43<n<0.85) which indicated the anomalous release behaviour and also shows that release process was diffusion controlled, as shown in fig.5.

CONCLUSION:

The present research was carried out to develop mucoadhesive tablets of Sitagliptin Phosphate using polymers Methocel K4M. The preparation process was simple, reliable, and inexpensive. All the prepared tablet formulations were found to be good without capping and chipping. The prepared mucoadhesive Sitagliptin Phosphate tablets were in acceptable range of weight variation, hardness, thickness, friability and drug content as per pharmacopeial specification. The surface pH of prepared tablets was in the range of salivary pH, suggested that prepared tablets could be used without risk of mucosal irritation. The mucoadhesive tablets showed good swelling up to 6 h in distilled water maintaining the integrity of formulation which is required for bioadhesion. The in-vitro release of Sitagliptin Phosphate was extended for 8 -12 h. Formulations F3 batch shows good in- vitro drug release 100%. All the tablets showed good residence time 4 - 7.9 h indicated good adhesive capacity of polymer and all the tablets showed good mucoadhesive strength of 11.12 – 23 g with high force of adhesion. All the evaluation parameters were found to be within limits of pharmacopoeia. Sitagliptin tablets release the required dose in predetermined time and prolong the release up to 12 hrs. Hence such tablets can be used for the treatment of Diabetes.

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