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DEVELOPMENT AND *IN VITRO* EVALUATION OF SITAGLIPTIN PHOSPHATE GASTRO RETENTIVE TABLETS

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ABSTRACT

The purpose of the present investigation is to formulate a novel gastro retentive system, floating tablets of Sitagliptin Phosphate, an anti diabetic agent by direct compression technique using lactose as diluent. The drug-excipients interaction was ruled out through FTIR studies. Nine formulations of Sitagliptin Phosphate tablets were prepared using HPMC K100 and HPMC K4M as release retarding agents in different concentrations of 10, 15 and 20% w/w. The prepared batches were evaluated for organoleptic properties, hardness, friability, weight variation and in vitro drug release. All the formulations showed low weight variation with rapid dispersion time and rapid in vitro dissolution. One amongst nine promising formulations, the formulation prepared by using 15% of HPMC K100 emerged as overall the best formulation. This optimized formulation showed good release profile with complete drug release within 24 hours. It was concluded that floating tablets of Sitagliptin Phosphate can be successfully formulated by using release retarding polymers.

KEYWORDS: Sitagliptin, Xanthan gum, pectin, mucoadhesive tablets.

INTRODUCTION

Oral drug delivery is by far, the most preferable route of drug delivery due to ease of administration, patient compliance and flexibility of formulations. Patients being treated with conventional oral formulations containing drugs with shorter half-lives require frequent dose administrations, which effect the patient compliance. This can be overcome by sustaining the

drug release. The real issue in the development of orally controlled release forms is not just to prolong the delivery of drug but prolong the presence of dosage form in the stomach or upper gastrointestinal tract (GIT) until all the drug is released for the desired period of time. So gastro retentive systems were developed. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GIT is to control the gastric residence time (GRT). Dosage forms with a prolonged GRT, i.e. gastroretentive dosage forms (GRDFs), will provide us with new and important therapeutic options. The most novel systems are Floating Drug Delivery Systems (as first described by Davis in 1968) have bulk density lower than that of the gastric fluid (1.004 g/cm3) and thus remain buoyant in the stomach for the prolonged period causing improved bioavailability, less wastage of drug, improved solubility of poorly soluble drugs and localized action.

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.

MATERIALS AND METHODS

MATERIALS

Sitagliptin was purchased from Caplin pvt ltd, Chennai. HPMC, Magnesium stearate and talc was purchased from SD fine chemicals.

Preparation of tablets

Wet granulation method was used to prepare Sitagliptin Mucoadhesive tablets using HPMC as polymer. Mucoadhesive matrix tablet each containing 50mg were prepared by Non-aqueous granulation method using Isopropyl alcohol. All the ingredients except drug and lubricants were weighed and mixed in motor and pestle.Sitagliptin was added to this mixture and mixed for two min for uniform mixing. Granulation was done with Poly vinyl pyrrolidone .Obtained wet granules were dried in hot air oven and passed through 30-40mesh sieve.The dried granules were lubricated using magnesium stearate (1% w/w) and talc (1%

w/w) and compressed using 8-station rotary compression machine with 8 mm flat punch. The total weight of the resultant tablets was 204mg and had 5-8 kg/cm^2 hardness. Formulations composition of the prepared mucoadhesive buccal tablets of Itraconazole is given in **Table 1**.

Table 1: Composition of gastro retentive tablets of Sitagliptin.

S.NO	Ingredients	Purpose	F1	F2	F3	F4	F5	F6	F7	F8 (1:1)	F9 (1:2)
1.	**Sitagliptin phosphate**	Model drug	50	50	**50**	50	50	50	50	50	50
2.	**Lactose monohydrate**	Diluents	86	66	**76**	61	51	41	31	76	86
3	**Poly ethylene glycol**	Plasticizer	8	8	**8**	8	8	8	8	8	8
4.	**HPMC (K4M)**	Release controlling polymer	-	-	**-**	30	40	50	60	10	10
5.	**HPMC(K100)**	Release controlling polymer	20	40	**30**	-	-	-	-	10	20
6.	**Sodium bicarbonate**	Gas generating agent	20	20	**20**	20	20	20	20	20	20
7.	**Carbomer**	Binder	-	-	**-**	16	16	16	16	-	-
8.	**Aerosil**	Glidant	6	6	**6**	10	10	10	10	6	6
9.	**Magnesium stearate**	lubricant	6	6	**6**	5	5	5	5	6	6
10.	**Talc**	Glidant	4	4	**4**	-	-	-	-	4	4
11.	**Tablet weight**	-	200	200	**200**	200	200	200	200	200	200

Tablet total weight is 200mg.

Preformulation studies

Angle of repose

The flow property of granules was determined by measuring Angle of repose.

$$\text{Tan}(\theta) = h / r$$

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

Bulk density

Bulk density was measured by taking the ratio of Mass of powder to its bulk volume.

$$\text{Bulk density} = M / V0$$

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

Tapped density

True density was determined by taking ratio of mass of powder to its true volume.

$$\text{Tapped density} = M / Vr$$

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.

$$\text{Compressibility index} = \frac{\text{1 - Bulk density}}{\text{Tapped density}} \times 100$$

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Post compression Parameters

Hardness: The hardness of the tablets was determined using a Monsanto hardness tester. It is expressed in Kg/cm^2.

Friability: This test was conducted by placing the tablets in a Roche friabilator. It is conducted to know the ability of tablet to withstand abrasion.

$$\% \text{ friability} = (W_1\text{-}W_2) / W_1 \times 100$$

W1 = Weight of tablets before test, W2 = Weight of the tablets after the test.

Weight variation test: It was Comparison of the weight of the individual tablets (xi) of sample of tablets with an upper and lower percentage limit of the observed sample average (x-mean).

Average weight of tablet (mg)	% Difference allowed
130 or less	10%
130-324	7.5%
>324	5%

Thickness: The thickness of the tablets was determined by screwgage.it is expressed in mm.

Content uniformity: It was determined to assure that each tablet contain equal quantity of drug in a batch.

Swelling studies: The swelling property of bio adhesive polymer plays an important role in bio adhesion. 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.

$$\text{Swelling index} = W_{t.} - W_o / W_o \times 100$$

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 21 hours. After 2 hours the pH was determined.

Invitro Dissolution studies

Invitro dissolution studies were carried out in USP Dissolution test apparatus employing paddle stirrer at 50 rpm and using pH 6.8 Phosphate buffer as dissolution medium. The release studies were performed at 37+0.5C. Samples of 5 ml withdrawn at predetermined intervals and replaced with fresh medium. The samples were filtered through Watt man filter paper and analyzed for Itraconazole after appropriate dilution by measuring the absorbance.

RESULTS AND DISCUSSION

Construction of Calibration curve

The standard graph of Sitagliptin Phosphate has shown good linearity with R^2 values with 0.996 in Buffer PH 6.8 which confirms that it obeys Beers Lamberts law over this concentration range.

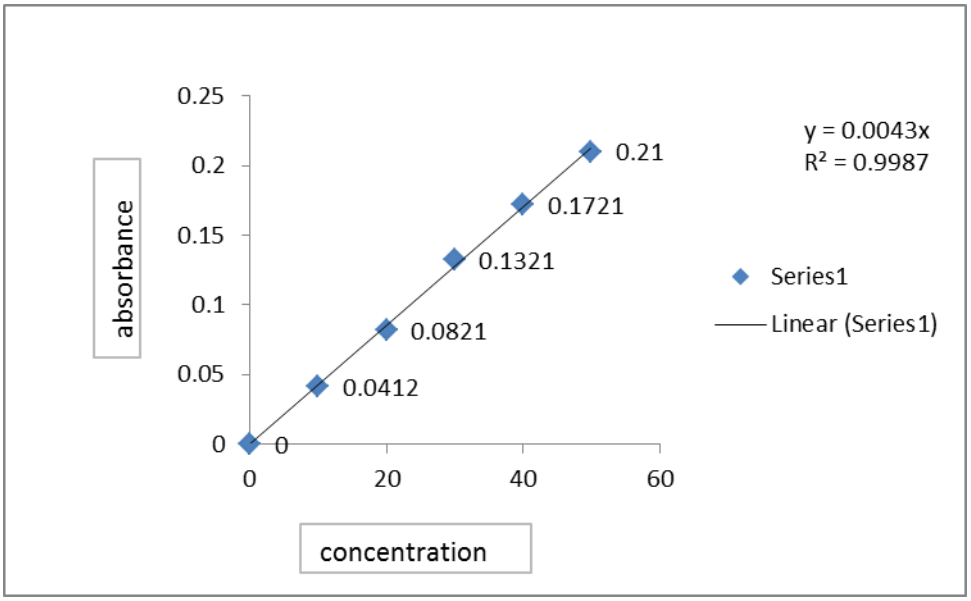


Fig 1: Standard graph of sitagliptin in buffer.

Table 2: Precompression parameters.

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
F6	0.26± 0.00	0.27 ± 0.00	1.06 ± 0.05	9.40 ± 1.40	27.27 ± 2.5
F7	0.28±0.00	0.28±0.00	1.16±0.05	9.45±0.65	28.26±1.45
F8	0.30±0.00	0.29±0.00	1.18±0.05	9.50±0.65	29.54±0.25
F9	0.31±0.00	0.31±0.00	1.2±0.05	10.18±1.4	22.54±0.56

Table 3: Post compression parameters.

Formulation no	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	% Friability	%Drug content
F1	Passed	7.2±0.24	4.1±0.15	0.99±0.00	89.5±0.47
F2	Passed	7.3±0.32	4.4±0.1	0.94±0.00	91.30±0.34
F3	Passed	7.6±0.21	4.45±0.1	0.76±0.00	91.43±0.34
F4	Passed	7.8±0.16	4.3±0.15	0.76±0.00	93.19.84±0.69
F5	Passed	6.9±0.05	4.2±1.5	0.65±0.00	90.5±0.5
F6	Passed	7.4±0.20	4.2±0.2	0.77±0.00	90.19±0.94
F7	Passed	7.0±0.12	4.12±0.15	0.98±0.15	75±0.95
F8	Passed	7.12±0.25	4.25±0.18	0.95±0.00	78±0.47
F9	Passed	7.12±035	4.5±0.21	0.94±0.25	80±0.58

Table 4: Swelling index values of Muco-adhesive tablets.

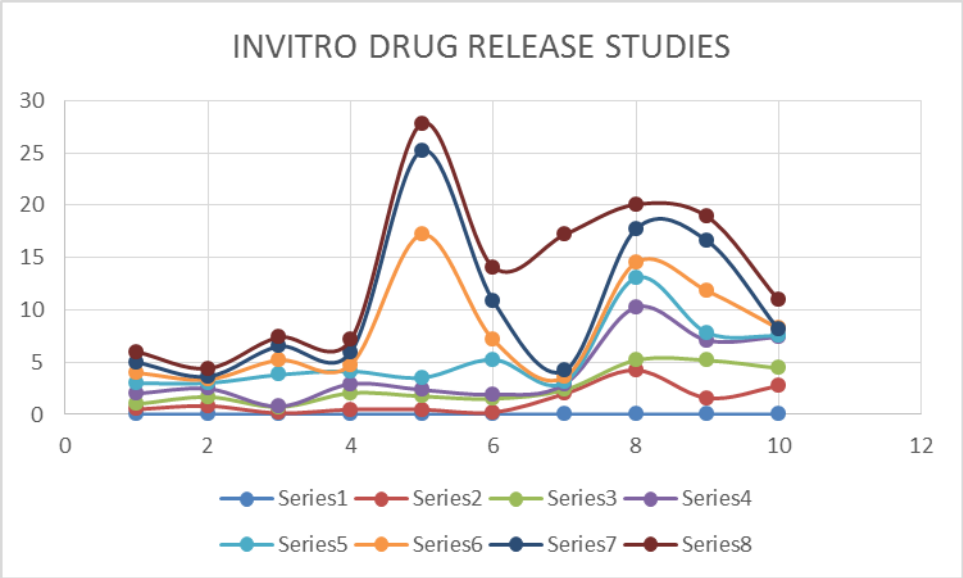
Formulation no	1	2	3	4	5	6
F1	15.42%	28.23%	27.34%	24.31%	33.94%	36.20%
F2	20.13%	33.16%	36.59%	30.49%	42.19%	45.65%
F3	33.34%	41.58%	43.83%	36.69%	55.00%	59.77%
F4	52.91%	50.91%	46.66%	42.76%	62.42%	72.47%
F5	66.73%	72.21%	77.50%	79.85%	80.84%	84.42%
F6	59.11%	61.12%	65.01%	55.17%	62.13%	74.97%
F7	61.11%	63.12%	64.01%	53.17%	64.13%	73.97%
F8	58.11%	59.12%	63.01%	53.17%	60.13%	70.97%
F9	59.11%	61.12%	62.01%	57.17%	64.13%	72.97%

Table 5: Surface pH study.

Formulation code	Surface pH
F1	6.5 ± 0.04
F2	6.5 ± 0.01
F3	6.5± 0.05
F4	6.8 ± 0.05
F5	6.9 ± 0.05
F6	6.5± 0.05

F7	6.5 ± 0.05
F8	6.5 ± 0.05
F9	6.5 ± 0.05

INVITRO DRUG RELEASE STUDIES



CONCLUSION

Floating drug delivery based novel drug delivery system has been developed to provide a once daily controlled release tablets for per oral delivery of Sitagliptin Phosphate. The formulation F3 showed better release retardation of drug indicating better potential of delivery system.

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