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Development and *In Vitro* Evaluation of Timolol Maleate Mucoadhesive Tablets For Niddm

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Abstract: *The objective of the present work was to develop an oral Mucoadhesive Timolol Maleate tablet for the sustained-release. Timolol Maleate is an oral antihypertensive agent which belongs to BCS class II drug with half life of 4 hours. The tablets were prepared by the Wet Granulation method, using biodegradable mucoadhesive polymer HPMC at different concentrations. All the batches were evaluated for thickness, weight variation, hardness, drug content uniformity, in vitro drug release, and mucoadhesion strength. Mean dissolution time is used to characterize the drug release rate from a dosage form, and indicates the drug release-retarding efficiency of the polymer. The Timolol Maleate release effectively controlled for 12 h with HPMC, 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. The study reveals that HPMC have highest mucoadhesive strength.*

Keywords: *Sitagliptin, Xanthan gum, pectin, mucoadhesive tablets.*

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I. INTRODUCTION:

Controlled release formulation describes sustained action along with its predictability of release of drug ingredients from the drug delivery system.Out of drug delivery systems the mucoadhesive drug delivery is more reliable than traditional drug delivery systems.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.Trans-mucosal drug delivery bypass first pass effect in gastrointestinal tract and avoid Gastro intestinal side effects.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.

Mucoadhesion is also defined as the interaction between mucin and synthetic/natural Polymer. The principle of mucoadhesive preparation offers a simple practical approach and it's practically useful to prolong the retension time of dosage form in the stomach, thereby improving oral bioavailability of drug. 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.

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.

II. MATERIALS AND METHODS:

MATERIALS

Timolol maleate (BP/USP) was the active pharmaceutical ingredient obtained as a gift sample from Ven Petro-Chem & Pharma (India) Pvt. Ltd., Mumbai .HPMC, Magnesium stearate and talc was purchased from SD fine chemicals.

Preparation of tablets:
Wet granulation method was used to prepare Timolol Maleate 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. Timolol Maleate 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 mucoadhesive tablets of Sitagliptin

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug(mg)	50	50	50	50	50	50	50	50	50
HPMC (%)	15	22	20	15	15	7.9	20	10	10
Magnesium stearate(mg)	10	10	10	10	10	10	10	10	10
Talc(mg)	90	76	90	104	76	92.6	70	90	110

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.
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.
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.

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

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

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.

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

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.

III. 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 Timolol Maleate 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

Table3: 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

Table4: 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%

Table5: 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:

IV. Conclusion:

Mucoadhesive tablets of Timolol Maleate were successfully formulated by using different concentrations of polymer. All the evaluation parameters were found to be within limits of pharmacopoeia. Timolol Maleate tablets release the required dose in predetermined time and prolong the release up to 12hrs.Hence such tablets can be used for the treatment of Diabetes.

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