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STUDIES ON FORMULATION AND EVALUATION OF GLIPIZIDE AND PARECOXIB COMBINATION MUCOADHESIVE TABLETS

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ABSTRACT

The main purpose of present investigation is to extend the release of drug from the dosage form at a particular site and controlling the release of drug from the dosage form and achieving controlled plasma level of the drug as well as improving bioavailability. The study was performed by selecting Glipizide and Parecoxib drugs. The mucoadhesive tablets were prepared to achieve controlled plasma level of the drug which is especially in diabetes mellitus patients with pain therapy. The tablets were prepared by direct compression technique. Both the drugs were found compatible with the excipients used. All the formulations were found to have good pre compression and post compression parameters. The optimized formulation was subjected to accelerated stability studies.

KEYWORDS: Glipizide, Parecoxib, mucoadhesive tablet, evaluation.

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INTRODUCTION

Glipizide is an oral hypoglycemic agent, which is a commonly prescribed drug for the treatment of patients with type II diabetes mellitus[1]. Glipizide is a weak acid (pKa = 5.9) which is practically insoluble in water and acidic solutions but as per the Biopharmaceutical Classification System (BCS) it is highly permeable (class 2). The oral absorption is uniform, rapid and complete with a bioavailability of nearly 100% and an elimination half-life of 2–4 h[2-4]. Glipizide is reported to have a short biological half-life (3.4 ± 0.7 h) requiring it to be administered as 2.5 to 10 mg twice or thrice daily. Hence we have selected Glipizide for the development of once daily controlled release matrix tablets. The pharmacokinetics and dosage schedule supports once daily controlled release formulations for Glipizide for better control of blood glucose levels to prevent hypoglycemia, enhance clinical efficacy and patient compliance.

Parecoxib, a non-steroidal anti-inflammatory drug, which exhibits anti-inflammatory and analgesic properties, was chosen as a model drug due to its high first pass metabolism[5]. It undergoes both P450 and non-P450 dependent (glucuronidation) metabolism[6-8]. The mechanism of action Parecoxib is believed to inhibit the Prostaglandin synthesis by acting on cyclooxygenase-2 enzyme (COX-2).

Mucoadhesive Glipizide tablets were prepared by using Sodium carboxy methyl cellulose and Hydroxy propyl methyl cellulose, carbopol-934P and Povidone. There is no availability of Glipizide and Parecoxib mucoadhessive tablets commercially. So an attempt has been made to develop a combination sustained release mucoadhessive formulation of anti-diabetic drug with NSAID.

MATERIAL AND METHODS

Glipizide and Parecoxib were obtained from Dr. Reddy's laboratories, Hyderabad, India with a purity of >99%. HPMC K4M, Carbopol-934P, Povidone, magnesium stearate were procured from SD fine chemicals, Mumbai, India. Deionized water was used in all experiments and all other ingredients used were of analytical grade.

Pre Formulation Studies for Drug Excipients Compatibility

The pure drug and formulation (F5) were separately mixed with IR grade potassium bromide in a ratio (1:100) and pellets were prepared by applying 10 metric Tons of pressure in hydraulic press. The pellets were

then scanned over range of 4000-400cm^{-1} in FTIR instrument.

Preparation of Mucoadhesive Tablets

Mucoadhesive tablets were prepared in 3 steps.

Preparation of Core Layer's Mixture

Glipizide, Parecoxib, Hydroxy propyl Methyl Cellulose, Carbopol-934P, Sodium Carboxy Methyl Cellulose-H, Povidone-K30 and Magnesium stearate were mixed well by using glass mortar and pestle[9]. This mixture was used for the preparation of core layer of the tablet. The composition of core layer was represented in **Table 1**.

Preparation of Backing Layer's Granules

Carbopol-934P, Povidone, Magnesium stearate, Saccharin sodium was mixed well using glass mortar and pestle. In a separate glass beaker, solution of Amaranth was prepared using ethanol as a solvent. By gradually adding the color solution to a dry mixture; a wet mass/lump was prepared. Peppermint oil was added to this lump and mixed properly. Then this lump was passed through the sieve # 40, dried in a Hot Air Oven at a temperature 50^{0}C for 20 min. To this dried granules, magnesium stearate lubricant was added. These granules were used for the preparation of backing layer of the tablet[10]. The composition of backing layer was represented in **Table 2**.

Compression

For this purpose an I.R. hydraulic press and Die Punch Set having diameter of 10mm was used. Firstly, the mixture of drug and polymers (weighed quantity-150mg) was compressed using a pressure of 50kg/cm^2 for 5 seconds. Then upper punch was removed and then granules of backing layer (weighed quantity –75mg) were added over the first layer and compressed at a pressure of 200kg/cm^2 for 15 seconds. By this way, the bilayer tablet was prepared.

Evaluation of Tablets

Compatibilities Studies

The compatibility of drugs and excipients used under experimental condition were studied. The study was performed by taking 2 mg sample in 200 mg KBr (Perkin Elmer, spectrum-100, Japan). The scanning range was 400 to 4000 cm^{-1} and the resolution was 1cm^{-1}. This spectral analysis was employed to check the compatibility of drugs with the excipients used.

Physical Evaluation of Tablets

Thickness

Five tablets from each batch were selected, the thickness was determined using a screw gauge (Mitutoyo, New Delhi, India) and average values were calculated[11].

Uniformity of Weight Test

Twenty tablets of each batch were individually weighed using an electronic balance (Denver APX-100, Arvada, Colorado) and the test was performed as per official method[12].

Hardness and Friability

The hardness and friability of 10 tablets from each formulations were determined by using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and the Roche friabilator[13] (Campbell Electronics, Mumbai, India), respectively.

Swelling Behavior of Matrix Tablets

The swelling behavior of formulated tablets viz., F-1, F-2, F-3, F-4 and F-5 were studied. One tablet from each batch was kept in a Petri dish with phosphate (pH 7.4). At the end of 2 h, the tablet was withdrawn, kept on tissue paper and weighed, repeated for every 2 h till the end of 12 h[14]. The percent weight gain by the formulated tablets was calculated by eq.1.

S.I = {(Mt-M0) / M0} X 100 ------ (1)

Where, S.I = Swelling Index, Mt = Weight of tablet at time 't' and

M0 = Weight of tablet at time 0.

Uniformity of Drug Content

The formulated tablets were tested for uniformity in Glipizide and Parecoxib contents by using UV/ Visible spectrophotometer (Elico SL 210) at 223 nm and 243 nm for Glipizide and Parecoxib respectively.

Surface pH

The surface pH of the mucoadhesive tablets was determined to find out any possibility of side effects when consumed. Acidic/alkaline pH may cause irritation to the gastric mucosa. Digital pH meter (Eutech Instruments, Singapore) was used. The formulated tablet was allowed to swell by keeping the tablet in 1 ml of distilled water (pH 6.5 ± 0.05) for 2h at room temperature. The pH was measured by keeping in contact with the surface of the tablet and allowing it to equilibrate for 1min[15].

Moisture Absorption Studies of Mucoadhesive Tablet

A 5% w/v solution of Agar prepared in hot water and transferred into petri dishes and allowed to solidify. Five pre weighed tablets from each formulation were placed in vacuum oven overnight to remove moisture and laminated on one side with a water impermeable backing membrane. The tablets were placed on the surface of the agar and incubated at 37°C for 1 h[15]. Then the tablets were removed and weighed and the percentage of moisture absorption was calculated by using eq. 2.

% Moisture absorption = {(final weight – initial weight)/initial weight} x100 ---- (2)

Mucoadhesive Force Measurement

Mucoadhesive force measurement of tablets was done by modifying balance method. The right pan was replaced with a glass beaker container and on the left side beaker

with a copper wire. Teflon block of 1.5 cm diameter and 3 cm height was adhered strongly with the glass beaker. The two sides were then adjusted, so that the left hand side was exactly 5 g heavier than the right. Stick the stomach on the Teflon block with help of the cynoacrylate glue and fill the beaker with acidic buffer till the tissue remains in a moist condition. Stick the tablet to beaker and put on the tissue for 15 min. After 15 min add water slowly into right beaker until the tablet detaches. Weigh the water required for the tablet detachment[16]. Calculate Actual weight for detachment and force of adhesion in dynes by following eq.2.

Actual weight for detachment (W) = weight for detachment (g) ……..(2)

Matrix Erosion

Each tablet weighed (W_1) were immersed in a phosphate buffer pH 6.8 for predetermined time (1, 2, 4, 8 and 12 h). After immersion, tablets were wiped off by the excess of surface water by the use of filter paper. The swollen tablets were dried at 60ºC for 24 h in an oven and kept in a desiccator for 48 h prior to be reweighed (W_2)[17]. The matrix erosion was calculated using the formula given in the eq.3.

$$\text{Matrix Erosion} = \frac{(W_1 - W_2)}{W_1} \times 100 \quad \text{……. (3)}$$

***In Vitro* Dissolution Studies**

The dissolution of the mucoadhessive tablets were performed using USP XXIII dissolution apparatus (paddle method) using 500 ml of phosphate buffer of pH 7.4 was used as the dissolution medium, which was maintained at 37±0.5^{0}C and stirred at 50 r.p.m. Tablet was glued with Cyanoacrylate adhesive (Evobond) from backing layer side to the glass slide and it was placed at the bottom of jar of dissolution apparatus to avoid movement of tablet. Aliquots of 5ml of samples were withdrawn with a bulb pipette at different time intervals of 30, 60, 120, 180, 240, 300 and 360 min and replaced with equal volume of phosphate buffer (pH 7.4) at each withdrawal, filtered it through Whatmann Filter Paper No.1. The samples were then analyzed using double beam uv visible spectrophotometer (Elico SL 210, India) at 223 nm and 252 nm for Glipizide and Parecoxib respectively. The cumulative amount of drug released at various time intervals was calculated[18]. This test was done in triplicates.

Accelerated Stability Studies

To assess the drug and formulation stability, stability studies were done according to ICH and WHO guidelines. Optimized formulation (F5) was sealed in inside polyethylene coated aluminum container and then kept in stability chamber maintained at 45°C and 75% RH for 3 months. At the end of studies, samples were analyzed for the drug content, *in-vitro* dissolution, floating behavior and other physicochemical parameters[19].

RESULTS AND DISCUSSION

The thickness of formulated tablets was ranged from 8.0±0.02 to 8.2±0.03 mm, the tablets of all the formulations were passed the uniformity in weight test-IP, the hardness of formulated tablets was range from 5.8±0.25 to 7.0±0.21kg/cm^2 which was more than 5 kg/cm^2 and the loss on friability was less than 1% indicates the formulated tablets were found to have good mechanical strength. All these values were shown in **Table 3**.

The swelling index of the formulated tablets was evaluated and the results were provided in **Fig.1**. The swelling index increases by increasing the contact time as the polymers gradually absorbs the water due to hydrophilic nature with resultant swelling. The percentage Glipizide in formulated tablets was ranged from 99.25±2.56 to 99.99±5.48% and Parecoxib was ranged from 99.11±4.47 to 100.29±2.54% indicating the uniformity of drug content in formulations. The surface pH was ranged from 6.68 ± 0.15 to 7.06 ± 0.54. The percentage water absorption was ranged from 48.25 ± 0.88 to 49.99 ± 1.22%. The formulated tablets showed good mucoadhesive strength which was ranged from 16.65 ± 2.46 to 19.84 ± 1.84 g. All these values were shown in **Table 4**.

The matrix erosion of formulated tablets after 2, 4, 6, 8 and 12 h was shown in **Table 5**. The plots result from *in-vitro* dissolution study was shown in **Fig.2** and **3**. The optimized formulation (F5) was tested for drug content, Surface pH, mucoadhesion strength and Swelling Index before and after accelerated stability studies. The study proved that the formulations retain their characteristic parameters before and after accelerated stability studies. The values were shown in **Table 6**.

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Table 1: Composition of mucoadhesive tablets core layer

Ingredients (mg)	Formulations				
	F1	F2	F3	F4	F5
Glipizide	10	10	10	10	10
Parecoxib	20	20	20	20	20
Hydroxy Propyl Methyl Cellulose	5	10	15	20	25
Carbopol-934P	10	20	30	40	50
Sodium Carboxy Methyl Cellulose-H	5	10	15	20	25
Povidone-K30	2	4	6	8	10
Spray dried Lactose	94	72	50	28	06
Magnesium stearate	4	4	4	4	4
Total Weight = 150 mg					

Table 2: Composition of mucoadhesive tablet backing layer

S. No	Ingredients	Quantity (mg)
1.	Magnesium stearate	15
2.	Carbopol-934P	10
3.	Povidone-K30	15
4.	Amaranth	0.06
5.	Peppermint oil	5
6.	Saccharin sodium	5
Total Weight = 50 mg		

Table 3: Evaluation of physical parameters of different mucoadhesive tablets

Formulation	Average Weight (mg)	Thickness (mm)	Friability (%)	Hardness (kg/cm^2)
F1	202±1.54	8.2±0.03	0.15±0.08	5.9±0.06
F2	204±2.45	8.1±0.06	0.11±0.02	6.9±0.05
F3	201±1.26	8.0±0.05	0.61±0.03	5.8±0.25
F4	205±2.51	8.0±0.02	0.22±0.02	6.6±0.15
F5	205±5.15	8.1±0.05	0.45±0.02	7.0±0.21
Number of trials (n) =5				

Table 4: Evaluation parameters of different mucoadhesive tablets

Formulation	% Drug content		Surface pH	% water absorption	Mucoadhession strength (g)
	Glipizide	Parecoxib			
F1	9.95±3.26	100.29±2.54	6.91 ± 0.24	48.25 ± 0.88	17.21 ± 0.51
F2	9.99±5.48	99.95±5.29	6.99 ± 0.61	49.35 ± 0.50	16.65 ± 2.46
F3	9.85±4.52	99.11±4.47	7.06 ± 0.54	48.32 ± 2.09	19.84 ± 1.84
F4	9.25±2.56	99.65±6.54	7.05 ± 0.46	49.16 ± 1.05	18.95 ± 2.07
F5	9.98±2.29	99.96±4.15	6.68 ± 0.15	49.99 ± 1.22	19.66 ± 1.90

Table 5: Matrix Erosion of formulated tablets

Formulation	% matrix erosion after time				
	2h	4 h	6 h	8 h	12 h
F1	4.51±0.38	4.88±0.04	5.29±0.09	6.65±0.06	8.51±0.05
F2	4.89±0.16	5.64±0.11	6.65±0.05	6.98±0.05	9.15±0.06
F3	5.15±0.56	5.89±0.54	6.94±0.18	7.85±0.15	9.86±0.04
F4	4.96±0.06	6.11±0.15	7.05±0.08	9.04±0.25	10.15±0.03
F5	4.78±0.55	6.88±0.51	7.84±0.05	8.48±0.45	10.69±0.02

Table 6: Parameters before and after stability studies of formulation F5

Parameter	Before	After
Drug content (%)	99.98±2.26 (Glipizide)	99.97±2.98
	99.96±4.15 (Parecoxib)	99.87±6.56
Surface pH	6.68 ± 0.15	6.68 ± 0.51
Mucoadhesion strength (g)	19.66 ± 1.90	19.65 ± 1.85
Swelling Index (%)	88.9±3.25	87.8±2.56

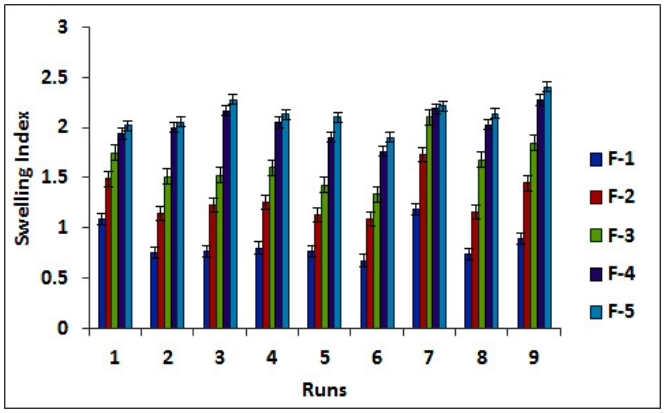

Fig.1. Swelling Index of formulated tablets

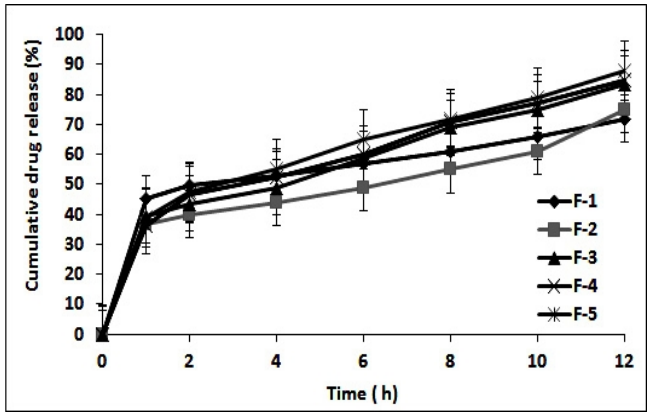

Fig.2. *In-vitro* drug release from formulated tablets (Glipizide)

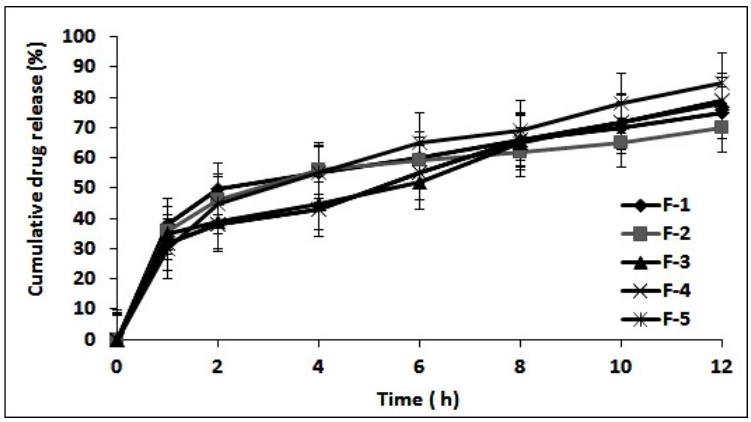

Fig.3. *In-vitro* drug release from formulated tablets (Parecoxib)

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