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Der Pharmacia Lettre, 2011, 3(1):185-192
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Formulation and *in-vitro* Evaluation of Glimepiride 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 Glimepiride 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 excipient 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: Glimepiride, Parecoxib, mucoadhesive tablet, evaluation.

INTRODUCTION

Glimepiride is a second-generation sulfonylurea that can acutely lowers the blood glucose level in humans by stimulating the release of insulin from pancreas and is typically prescribed to treat type II Diabetes Mellitus [1]. The drug is selected as model for designing sustained release because of its short biological half-life (3.4±0.7 hours) necessitates that it can be administered 2 or 3 doses with 2.5 to 10 mg per day [2-4].

Parecoxib, a non-steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic and antipyretic 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 is believed to be due to inhibition of Prostaglandin synthesis primarily through inhibition of cyclooxygenase-2 (COX-2).

Mucoadhesive Glimepiride tablets were prepared by using Sodium carboxy methyl cellulose and Hydroxy propyl methyl cellulose, carbopol-934P and Povidone. There is no availability of Glimepiride 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

Materials

Glimepiride 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.

Experimental Methods

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 ton of pressure in hydraulic press. The pellets were then scanned over range of 4000-400cm^{-1} in FTIR instrument.

Preparation of mucoadhesive Tablets: [9, 10]

Mucoadhesive tablets were prepared in 3 steps

Preparation of Core Layer's Mixture

Glimepiride, 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. 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. Then wet granules were dried in a Hot Air Oven at a temperature 50^0C for 20 minutes. To this dried granules, magnesium stearate lubricant was added. These granules were used for the preparation of backing layer of the tablet. 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 [11-13]

Compatibilities study

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

The thickness of the tablets was determined using a thickness screw gauge (Mitutoyo, New Delhi, India). Five tablets from each batch were used and average values were calculated.

Uniformity of Weight Test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Denver APX-100, Arvada, Colorado) and the test was performed according to the official method.

Hardness and Friability

For each formulation, the hardness and friability of 10 tablets were determined using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and the Roche friabilator (Campbell Electronics, Mumbai, India), respectively.

Swelling behavior of matrix tablets [14]

The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of formulation GAP-1, GAP-2, GAP-3, GAP-4 and GAP-5 were studied. One tablet from each formulation was kept in a Petri dish containing phosphate pH 7.4. At the end of 2 hours, the tablet was withdrawn, kept on tissue paper and weighed, repeated for every 2 hours till the end of 12 hours. The % weight gain by the tablet was calculated by eq.1.

$$S.I = \{(Mt-M0) / M0\} X 100 \quad \text{------ (1)}$$

Where, S.I = Swelling Index, Mt = Weight of tablet at time ‘t’ and
M0 = Weight of tablet at time 0.

Uniformity in drug content:

The formulated tablets were tested for uniformity in Glimepiride and Parecoxib contents by using UV/ Visible spectrophotometer (Elico SL 210) at 226 nm and 243 nm for Glimepiride and Parecoxib respectively.

Surface pH [15]

The surface pH of the mucoadhesive tablets was determined in order to investigate the possibility of any side effects *in vivo*. An acidic or alkaline pH may cause irritation to the mucosa. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.5 ± 0.05) for 2hr at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1min.

Moisture absorption studies of mucoadhesive tablet [15]

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 one hour. 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 [16]

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 minutes. After 15 minutes add water slowly into right beaker until the tablet detaches.

Weigh the water required for the tablet detachment. 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 [17]

Each tablet weighed (W_1) were immersed in a phosphate buffer pH 6.8 for predetermined time (1, 2, 4, 8 and 12 hours). 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 hours in an oven and kept in a desiccator for 48 hours prior to be reweighed (W_2). The matrix erosion was calculated using the formula given in the eq.3.

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

Dissolution Studies: [18]

The dissolution of the mucoadhessive tablets were performed using USP XXIII dissolution apparatus (paddle method) using 500 ml of phosphate buffer (pH 7.4) 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 minutes 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 analysed using double beam uv visible spectrophotometer (Elico SL 210) at 226 nm and 252 nm for Glimepiride and Parecoxib respectively. The cumulative amount of drug released at various time intervals was calculated. 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 aluminum packaging coated inside with polyethylene, 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 Figure 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 Glimepiride 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.

Table 1: Composition of mucoadhesive tablets core layer

Ingredients (mg)	Formulations				
	F1	F2	F3	F4	F5
Glimepiride	2	2	2	2	2
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	102	80	58	36	14
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		

The matrix erosion of formulated tablets after 2, 4, 6, 8 and 12 hours was shown in Table 5. The plots result from *in-vitro* dissolution study was shown in Figure 2. 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.

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

Formulations	% Drug content		Surface pH	% water absorption	Mucoadhession strength (g)
	Glimepiride	Parecoxib			
F1	99.95±3.26	100.29±2.54	6.91 ± 0.24	48.25 ± 0.88	17.21 ± 0.51
F2	99.99±5.48	99.95±5.29	6.99 ± 0.61	49.35 ± 0.50	16.65 ± 2.46
F3	99.85±4.52	99.11±4.47	7.06 ± 0.54	48.32 ± 2.09	19.84 ± 1.84
F4	99.25±2.56	99.65±6.54	7.05 ± 0.46	49.16 ± 1.05	18.95 ± 2.07
F5	99.98±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				
	2hour	4 hour	6 hour	8 hour	12 hour
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 (Glimepiride) 99.96±4.15 (Parecoxib)	99.97±2.98 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

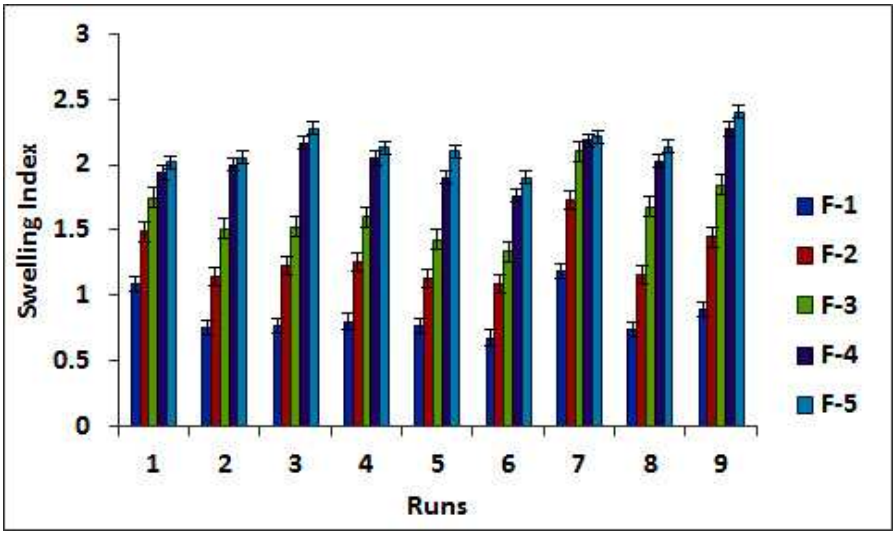

Figure 1: Swelling Index of formulated tablets

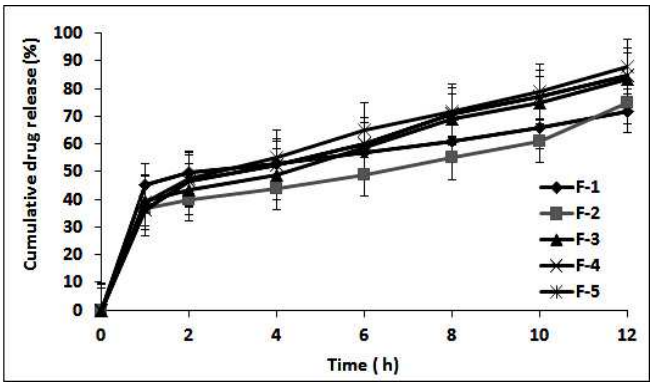

Figure 2: In-vitro drug release from formulated tablets (Glimepiride)

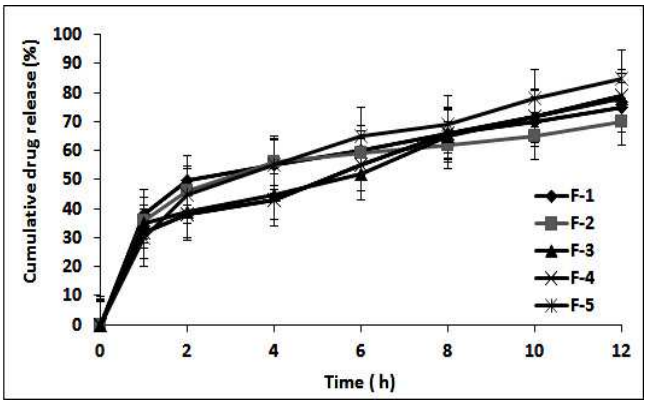

Figure 3: *In-vitro* drug release from formulated tablets (Parecoxib)

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