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Formulation and *in vitro* Evaluation Glimepiride and Parecoxib Mucoadhesive Tablets for diabetics associated with pain and inflammation

Narasimha Reddy D*[1], Srinath MS[2], Hindustan Abdul Ahad*[3], Sravanthi M[3] and Kavitha K[3]

[1]*Department of Pharmaceutics, Vivekananda College of Pharmacy, Bangalore, Karnataka India*
[2]*Department of Pharmaceutics, Sonia College of Pharmacy, Dharwad, Karnataka, India*
[3] *Department of Pharmaceutics, College of Pharmacy, Sri Krishnadevaraya University, Anantapur, Andhra Pradesh, India*

ABSTRACT

The main purpose of present study was to develop mucoadhesive tablets of Glimepiride and Parecoxib drugs were prepared to achieve controlled plasma level of the drug especially in diabetes mellitus patients with pain therapy. The mucoadhesive tablets were prepared by direct compression technique. The drug- excipient compatibility studies were performed by Fourier Transform Infrared spectroscopy (FTIR). Physicochemical characteristics and in vitro drug dissolution tests were performed. The in vitro drug release pattern and the dissolution data was treated with mathematical modeling Accelerated stability studies were also carried out to the optimized formulation (F-5). The FTIR studies revealed that drugs were compatible with the polymer used. The optimized formulations were found to have good physicochemical and in vitro release properties. The in vitro dissolution data was perfectly fitting to zero order and the release of drug from the formulation followed Higuchi's release. The accelerated stability studies revealed that the tablets retain their characteristics even after stressed storage conditions. From this study it was concluded that Glimepiride and Parecoxib combination mucoadhesive Tablets is a good combination for diabetics associated with pain and inflammation.

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. The drug is selected as model for designing sustained release because

of its short biological half-life (3.4±0.7 h) necessitates that it can be administered 2 or 3 doses with 2.5 to 10 mg per day [1].

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 [2]. It undergoes both P450 and non-P450 dependent (Glucuronidation) metabolism [3]. 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, Hydroxy Propyl Methyl Cellulose, Carbopol-934P and Poly Vinyl Pyrrolidone [4-6]. There is no availability of Glimepiride and Parecoxib mucoadhesive tablets commercially. So an attempt has been made to develop a combination sustained release mucoadhessive formulation of anti-diabetic drug with NSAID.

MATERIALS AND METHODS

Materials

Glimepiride and Parecoxib were obtained from Dr. Reddy's laboratories (Hyderabad, India). Hydroxy propyl methyl cellulose (HPMC) K4M, Carbopol-934P, Sodium Carboxy Methyl Cellulose-H, Poly vinyl Pyrrolidone-K30, Saccharin sodium, Amaranth, Ethanol and magnesium stearate were procured from SD fine chemicals, Mumbai, India and all other ingredients used were of analytical grade.

Drug-excipient compatibility studies

Fourier Transform Infrared Spectroscopic (FTIR) analysis

The FTIR spectrums of Glimepiride, Parecoxib and Formulation (F-5) blend were studied by using Fourier Transform Infrared (FTIR) spectrophotometer (Perkin Elmer, spectrum-100, Japan) using the KBr disk method (5.2510 mg sample in 300.2502 mg KBr). The scanning range was 500 to 4000 cm^{-1} and the resolution was 1 cm^{-1}. This spectral analysis was employed to check the compatibility of drugs with the polymers used.

Preparation of mucoadhesive Tablets [7-10]

Mucoadhesive tablets were prepared in 3 steps

a) Preparation of Core Layer's Mixture

Glimepiride, Parecoxib, HPMC, Carbopol-934P, Sodium Carboxy Methyl Cellulose-H, Poly vinyl Pyrrolidone-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.

b) Preparation of Backing Layer's Granules

Carbopol-934P, Poly vinyl Pyrrolidone, Magnesium stearate, Saccharin sodium were 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 Hhot Air Oven at a temperature 50^0C 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. The composition of backing layer was represented in Table 2.

Table 1: Composition of mucoadhesive tablets core layer

Ingredients (mg)	Formulation				
	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
Poly vinyl Pyrrolidone-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

Ingredients	Quantity (mg)
Magnesium stearate	15
Carbopol-934P	10
Poly Vinyl Pyrrolidone-K30	15
Amaranth	1
Peppermint oil	4
Saccharin sodium	5
Ethanol (50%)	q.s

c) 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 s. 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 s. By this way, the bilayer tablet was prepared.

Physical evaluation of tablets [11-17]

Thickness

The thickness of the tablets was determined using a screw gauge (ISC Technologies, Kochi, India). 5 tablets from each batch were used and the mean values were calculated.

Uniformity of Weight Test

20 tablets of each formulation were weighed using an electronic balance (YPX202N, China) and the test was performed as per the official procedures.

Hardness test

The hardness of the tablets was measured using Monsanto tablet hardness tester (MHT 51, China). It is expressed in kg/cm^2. Three tablets were randomly picked and analyzed for hardness. The average and standard deviation values were also calculated.

Friability test

The friability of tablets was determined using Roche Friabilator (Campbell Electronics, Mumbai, India). The friabilator was operated at 25 rpm for 4 min (totally 100 revolutions). The % friability was then calculated by the following equation.

$$F= W_{initial} - W_{final} / W_{initial} X 100$$

Where,

F= friability (%), $W_{initial}$ = initial weight and W_{final} = Final weight

Uniformity in drug content

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

Surface pH

The surface pH of the mucoadhesive tablets was determined to find out the possibility of any side effects when swallowed. An acidic or alkaline pH may cause irritation to the mucosa. The tablet was allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.5 ± 0.05) for 2h at room temperature. The pH was measured by using digital pH meter (PHS-25, China).

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 37^0C for 1 h. Then the tablets were removed and weighed and the percentage of moisture absorption was calculated by using the following equation.

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

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, later 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 equation.

Actual weight for detachment (W) = weight for detachment (g)

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 60^0C for 24 h in an oven and kept in a desiccator for 48 h prior to be reweighed (W_2). The matrix erosion was calculated using the following equation.

Matrix Erosion = $(W_1 – W_2)/ W_1 \times 100$

Swelling behavior of matrix tablets

The swelling behavior of formulation F-1, F-2, F-3, F-4 and F-5 were studied[11]. One tablet from each formulation was kept in a Petri dish containing 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. The % weight gain by the tablet was calculated by following equation.

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

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

***In vitro* Dissolution Studies [18-20]**

The dissolution of the mucoadhesive 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 ± 0.5^0C and stirred at 50 rpm. 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 226 nm and 243 nm for Glimepiride and Parecoxib respectively. The cumulative amount of drug released at various time intervals was calculated.

Accelerated Stability Studies

To assess the drug and formulation stability, stability studies were done according to ICH and WHO guidelines. Optimized formulation (F-5) was sealed in aluminum packaging coated inside with polyethylene, and then kept in stability chamber maintained at 45^0C and 75% RH for 3 months [21]. At the end of studies, samples were analyzed for the drug content, *in-vitro* dissolution, floating behavior and other physicochemical parameters

RESULTS AND DISCUSSION

Compatibility studies

The FTIR spectra of Nimesulide showed characteristic peaks at 3441.05 (3300-3500) (N-H), 2909.68 and 2805.61 (2850 – 3000) (C-H), 2805.61 (3300 - 2500 (O-H), 1521.66, 1447.00 and 1405.77 (1350 –1550) (N=O), 1217.98, 1153.91, 1127.73 and 1080.53 (1220 -1020) (C-N), 1283.52 and 12487(1000 –1300) (C-O) (Figure 1)

Whereas FTIR of Glimepiride showed characteristic peaks at 3373.70 (3300-3500) (N-H), 2934.57 and 2855.22 (2850 – 3000) (C-H), 2789.04 and 2706.85(3300 - 2500 (O-H), 1529.59, 1462.94 and 1346.73 (1350 –1550) (N=O), 1025.67 (1220 -1020) (C-N), 1157.94 and 1123.29 (1000 –1300) (C-O) (Figure 2).

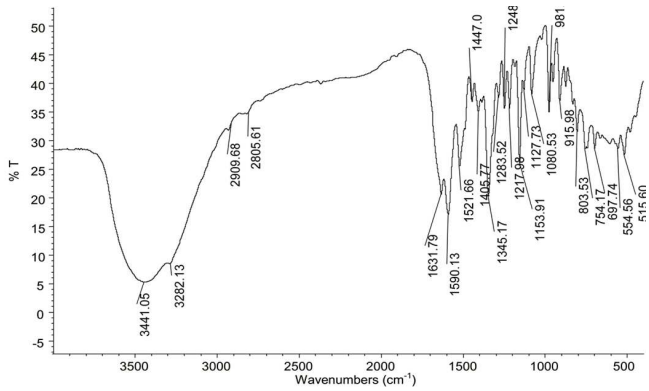

Fig.1: FTIR spectrum of Nimesulide

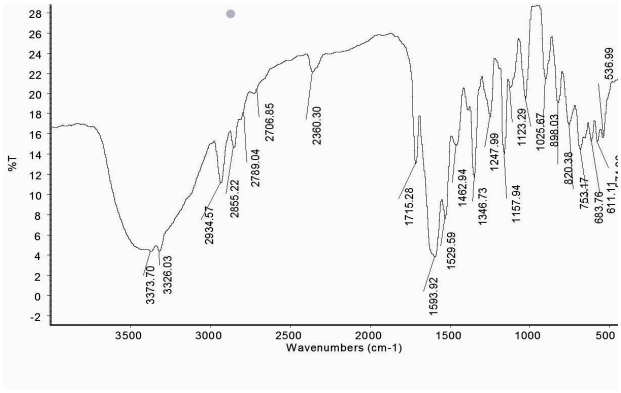

Fig.2: FTIR spectrum of Glimepiride

The formulation showed characteristic peaks at 3439.40 (3300-3500) (N-H), 2942.54 (2850 – 3000) (C-H), 2739.88 (3300 - 2500 (O-H), 1485.61, 1446.91 and 1387.02 (1350 –1550) (N=O), 1035.13 (1220 -1020) (C-N) and 1156.96 (1000 –1300) (C-O) (Figure 3).

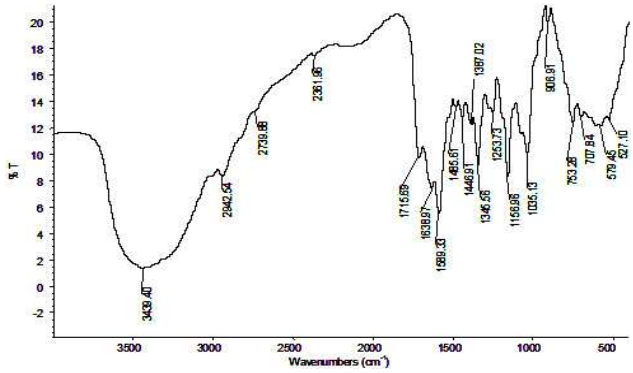

Fig.3: FTIR spectrum of formulation blend (F-5)

Evaluation of tablets

Average weights of the formulated tablets were ranged from 200±2.562 to 202±6.856 mg. The thickness of the formulated tablets were ranged from 8.0±0.139 to 8.2±0.125 mm, indicates uniformity in weight and thickness. The hardness of the formulated tablets were ranged from 6.8±0.06 to 8.9±0.08 kg/cm^2, which was more than 5 kg/cm^2 and the weight loss on friability was ranged from 0.11±0.03 to 0.85±0.05 %. The hardness and friability results revealed that the

formulated tablets have good mechanical strength, which helps in maintaining the rigidness of tablet during handling and transport. All these physical and mechanical properties of formulated tablets showed in Table 3. The swelling index increases by increasing the contact time as the polymers gradually absorbs the water due to hydrophilic nature with resultant swelling. The formulated tablets showed good Swelling behavior and showed in Figure 4.

Table 3: Evaluation of physical parameters of different mucoadhesive tablets

Formulation	Average weight (mg)	Thickness (mm)	Friability (%)	Hardness (kg/cm^2)
F1	201±8.251	8.2±0.125	0.12±0.05	8.7±0.09
F2	202±6.856	8.1±0.548	0.59±0.06	8.9±0.08
F3	201±8.987	8.0±0.139	0.11±0.03	6.8±0.06
F4	202±6.597	8.0±0.549	0.62±0.01	6.9±0.18
F5	200±2.562	8.1±0.0469	0.85±0.05	8.0±0.28
Values were mentioned in mean ±SD; Number of experiments (n) =6				

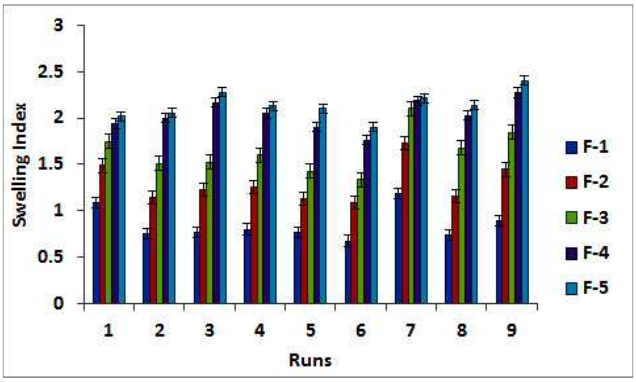

Fig.4: Swelling Index of formulated tablets

Table 4: Evaluation parameters of different mucoadhesive tablets

Formulation	Surface pH	Water absorption (%)	Mucoadhesion strength (g)	Drug content (%)	
				Glimepiride	Parecoxib
F1	6.91 ± 0.24	48.25 ± 0.88	19.21 ± 4.52	99.98±7.86	99.96±7.59
F2	6.99 ± 0.61	49.35 ± 0.50	19.67 ± 2.16	99.99±7.95	99.98±4.69
F3	7.06 ± 0.54	48.32 ± 2.09	21.84 ± 1.54	99.89±8.97	99.79±4.65
F4	7.05 ± 0.46	49.16 ± 1.05	22.95 ± 2.57	99.95±8.97	99.89±6.48
F5	6.68 ± 0.15	49.99 ± 1.22	23.68 ± 2.59	99.94±5.64	99.97±8.54
Values were mentioned in mean ±SD; Number of experiments (n) =6					

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 19.21 ± 4.52 to 23.68 ± 2.59. The mucoadhesion strength increases as the concentration of polymers increased. The percentage Glimepiride in formulated tablets was ranged from 99.89±8.97 to 99.99±7.95% and Parecoxib was ranged from 99.79±4.65 to 99.98±4.69% indicating the uniformity of drug content in formulation All these values were shown in Table 4. The matrix erosion of formulated tablets after 2, 4, 6, 8 and 12th h was shown in Table 5.

Table 5: Matrix Erosion of formulated tablets

Formulation	Percent matrix erosion after time (%)				
	2h	4 h	6 h	8 h	12 h
F1	4.56±0.39	4.79±0.15	5.85±0.45	6.46±0.25	7.51±0.05
F2	4.89±0.16	5.69±0.11	6.35±0.32	7.85±0.05	8.15±0.06
F3	5.15±0.49	5.97±0.54	6.98±0.18	7.65±0.15	8.86±0.04
F4	4.96±0.06	6.05±0.15	7.05±0.08	8.04±0.25	9.15±0.03
F5	4.78±0.55	6.88±0.51	7.95±0.05	8.68±0.35	10.18±0.47
Values were mentioned in mean ± SD; Number of experiments (n) =6					

The plots result from *in-vitro* dissolution study was shown in Figures 5 and 6. The optimized formulation (F-5) 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.

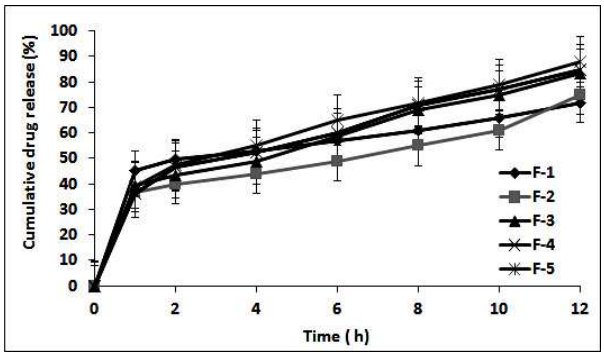

Fig.5: *In-vitro* drug release from formulated tablets (Glimepiride)

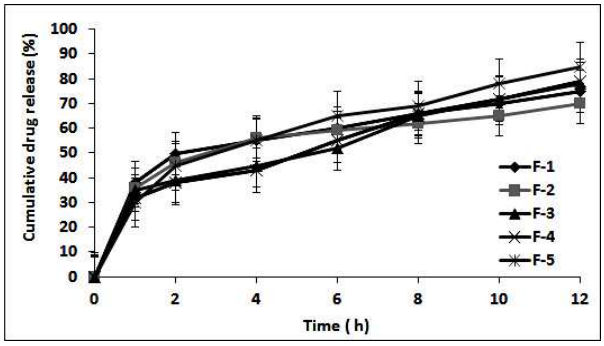

Fig.6: *In vitro* drug release from formulated tablets (Parecoxib)

Table 6: Parameters before and after stability studies of formulation F-5

Parameter	Before	After
Drug content (%)	99.94±5.64 (Glimepiride)	99.94±5.58
	99.97±8.54 (Parecoxib)	99.97±8.12
Surface pH	6.68 ± 0.15	6.68 ± 0.46
Mucoadhesive strength (g)	23.68 ± 2.59	23.67 ± 2.86
Swelling Index (%)	85.65±5.68	85.64±5.24
Values were mentioned in mean ± SD; Number of experiments (n) =3		

CONCLUSION

This study revealed that Glimepiride and Parecoxib combination mucoadhesive tablets are a good combination for treatment of diabetic patients who are with additional treatment of pain and inflammation.

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