



INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND DEVELOPMENT (IJPRD)

Platform for Pharmaceutical Researches & Innovative Ideas
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FORMULATION AND EVALUATION OF MUCOADHESIVE TABLETS OF NSAID COMBINATION WITH PROTON PUMP INHIBITOR

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ABSTRACT

The term arthritis means “joint inflammation” but is generally used to describe inflammatory and degenerative conditions of the joints. It can affect anyone at any age. There are several kinds of arthritis the most of which is the osteoarthritis (OA), rheumatoid arthritis (RA) and gout. To treat these conditions prolonged action dosage forms are very much needed. The aim of the present study was designed to develop novel sustained-release (SR) Mucoadhesive tablet formulations of naproxen sodium a non-steroidal anti-inflammatory drug. Pantoprazole Sodium is added to the naproxen to overcome the side effect such as ulcer and bleeding. Sustained release tablets Naproxen formulated by using polymers such as sodium alginate, gelatin and carbopol 934P. A combination of hydrophilic polymers was used in the ratio of 1:1:1 to 1:1:5 along with usual tablet additives like lactose and MCC. . The compressed Mucoadhesive tablets were evaluated for various parameters like hardness, friability, weight variation, drug content uniformity which shows the drug content was uniform in all the formulations of the tablets prepared. IR studies indicated that the drug is compatible with the polymers and stability studies also performed were no appreciable difference was observed. The in-vitro release of Naproxen and Pantoprazole were studied by using the buffer solution of pH 1.2. The in-vitro release of drug showed that tablets (batch F9) of combined S: G: C is 1:1:5 containing tablets (96%) at the end of 10th hour and was found to release the drug.

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Key Words

Mucoadhesive tablets: Sustained
release: Naproxen: Pantoprazole:

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of the drug to the proper site in the body to achieve promptly, and then maintain, the desired drug concentration as well as to recover the side effects. Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improved bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment.

Mucoadhesive Tablets, in general, have the potential to be used for sustained release drug delivery, but coupling of mucoadhesive properties to Tablet has additional advantages, e.g. efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer. Mucoadhesive Tablets can be tailored to adhere to any mucosal tissue including those found in stomach, thus offering the possibilities of localized as well as systemic controlled release of drugs. The application of mucoadhesive Tablets to the mucosal tissues of gastric epithelium is used for administration of drugs for localized action. Mucoadhesive Tablets are widely used because they release the drug for prolonged period, reduce frequency of drug administration and improve the patient compliance.

Characteristics of an Ideal Mucoadhesive Polymer:

1. The polymer and its degradation products should be nontoxic and should be nonabsorbable from the GI tract.
2. It should be nonirritant to the mucus membrane.
3. It should preferably form a strong non-covalent bond with the mucin-epithelial cell surfaces.
4. It should adhere quickly to most tissue and should possess some site specificity.

5. It should allow easy incorporation of the drug and should offer no hindrance to its release.
6. The polymers must not decompose on storage or during the shelf life of the dosage form.
7. The cost of polymer should not be high so that the prepared dosage form remains competitive.

OBJECTIVE

The objective of the present study was to develop Mucoadhesive tablet of NSAIDs & PPI such as Naproxen Sodium and Pantoprazole Sodium by simple and cost effective direct compression technique. Develop a Mucoadhesive tablet formulation for the treatment of Arthritis & as well as protection from Ulcer.

Experimental Work or Actual Materials and Methods:

1. Preformulation Study: Performed pre formulation studies such as the Colour, odor, taste and appearance, melting point determination, bulk density, tapped density, % compressibility index & Hauser ratio.
2. Preparation of mucoadhesive tablet: Different Naproxen Sodium & Pantoprazole Sodium formulations were prepared by direct compression technique. A combination of hydrophilic polymers was taken in a ratio of 1:1:5.
3. Evaluation of Tablet: Evaluate the parameters of finished tablet hardness, friability, weight variation, swelling index and mucoadhesive force.
 - Tablet dimensions: - The dimensions determined for formulated tablets were tabulated in Table No 1. Tablets mean thickness were uniform in F1 to F13 formulations and were found to be in the range of 5.2 ± 0.2 mm to 5.2 ± 1.2 mm.
 - Hardness test: - The hardness of tablets of each batch ranged between 5.3 ± 0.16 to 7.5 ± 0.18 kg/cm³ (Table

No1). This ensures good handling characteristics for all batches.

- Friability Test: -The values of friability test were tabulated in Table No 1. The Percentage friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.
- Weight Variation Test: - The percentage weight variations for all formulations were tabulated in Table No 2. All the formulated (F1 to F13) tablets passed weight variation test as the % weight variation was within the standard pharmacopoeial limits of 15% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.
- Mucoadhesive Strength: The apparatus consist of a modified double beam physical balance in which the right pan has been replaced by a glass slide with

copper wire and additional weight, to make the right side weight equal with left side pan. A taflone block of 3.8 cm diameter and 2 cm height was fabricated with an upward portion of 2 cm height and 1.5 cm diameter on one side. This was kept in beaker filled with buffer media 0.1N HCl pH 1.2, which was then placed below right side of the balance. Goat or rat stomach mucosa was used as a model membrane and buffer media 0.1N HCl pH 1.2 was used as moistening fluid.

4. Performed dissolution studies for all the formulations and plotted the graph then results where match with the kinetics equations for confirming the release by diffusion principle.

Formulation of Mucoadhesive Tablets

INGREDIENTS	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11	F-12	F-13
Naproxen Sodium	250	250	250	250	250	250	250	250	250	250	250	250	250
Pantoprazole Sodium	20	20	20	20	20	20	20	20	20	20	20	20	20
Carbapo934	20	20	20	20	20	40	60	80	100	20	20	20	20
Sodium Alginate	20	40	60	80	100	20	20	20	20	20	20	20	20
Gelatin	20	20	20	20	20	20	20	20	20	40	60	80	100
Magnesium Sterate	10	10	10	10	10	10	10	10	10	10	10	10	10
Sodium Bi Carbonate	35	35	35	35	35	35	35	35	35	35	35	35	35
Microcrystalline Cellulose	15	15	15	15	15	15	15	15	15	15	15	15	15
Lactose	110	90	70	50	30	90	70	50	30	90	70	50	30

Formulation of Mucoadhesive Tablets

RESULTS AND DISCUSSION

There are the different other parameters are also checked that for the ideal formulation. F9 is an ideal

formulation. The formulation F9 Weight Variation is (0.509±0.007), thickness (5.2±0.12), Hardness (6.1±0.07) & Friability (0.26).

BATCH NO.	WEIGHT VARIATION	THICKNESS (mm)	HARDNESS (kg/cm ³)	FRIABILITY (%)
F1	0.509±0.008	5.2±0.12	5.4±0.15	0.13
F2	0.507±0.003	5.2±0.04	5.7±0.17	0.35
F3	0.506±0.009	5.2±0.02	6.3±0.20	0.23
F4	0.509±0.015	5.2±0.02	7.2±0.18	0.28
F5	0.508±0.006	5.2±0.02	7.5±0.18	0.25
F6	0.500±0.004	5.2±0.02	5.3±0.16	0.30
F7	0.506±0.009	5.2±0.12	5.4±0.14	0.31
F8	0.509±0.011	5.2±0.12	5.8±0.21	0.24
F9	0.509±0.007	5.2±0.12	6.1±0.07	0.26
F10	0.505±0.014	5.2±0.12	6.3±0.09	0.31
F11	0.511±0.012	5.2±0.12	7.0±0.17	0.20
F12	0.510±0.013	5.2±0.12	7.3±0.15	0.25
F13	0.515±0.004	5.2±0.12	7.4±11	0.40

Table no1: Physical properties of tablets

Mucoadhesive force depends on the viscosity and concentration of the polymer. Formulation F1 was having lowest Mucoadhesive force because the Gelatine, Carbapol 934P, Sodium Alginate having (1:1:1)

lower concentration. While formulation (F 9) containing Carbopol 934P (1:1:5) shows higher mucoadhesion force due to higher viscosity (Figure no.). In order to increase the Mucoadhesive strength of low viscosity polymer

containing Gelatine and Sodium Alginate was combined with carbopol 934 (1:1:5) having good Mucoadhesive property. From the above results it was found that polymers having high molecular weight and high

viscosity exhibited higher adhesion. Sodium Alginate (1:1:5) and Carbopol 934P (1:1:5) were found to be having good Mucoadhesive strength as per increasing their concentration.

Formulation No.	Mucoadhesive Strength(gm)	Mucoadhesion Force(dyne)
F 1	23.45±1.32	2.3243
F 2	22.89±1.17	2.2664
F 3	22.93±2.37	2.2570
F 4	21.89±4.92	2.2455
F5	26.78±4.46	2.6271
F 6	28.27±1.06	3.0618
F 7	30.69±1.73	3.1087
F 8	31.43±1.08	3.1718
F 9	31.37±2.89	3.1564
F 10	23.48±1.87	2.3296
F 11	22.93±2.64	2.2772
F 12	22.46±2.55	2.2228
F13	22.89±2.29	2.2869

Table no 2: Mucoadhesive Force Measurement

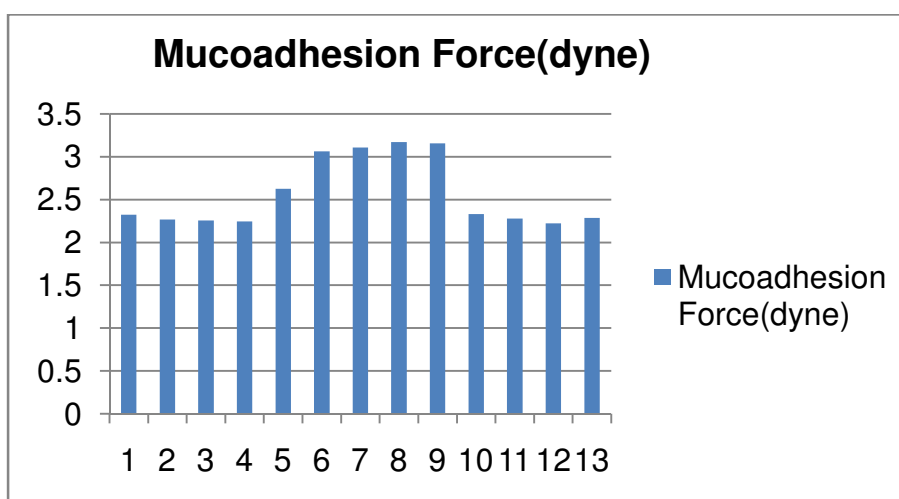


Figure no 1: Mucoadhesive Force

Swelling index of Different Formulation:

Swelling of tablet excipients particles involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule, breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in terms of % weight gain by the tablet.

$$\text{Swelling Index (S.I.)} = (W_t - W_o) / W_o$$

Where, S.I. = Swelling index

W_t = Weight of tablet at time t

W = Weight of tablet before placing in the beaker

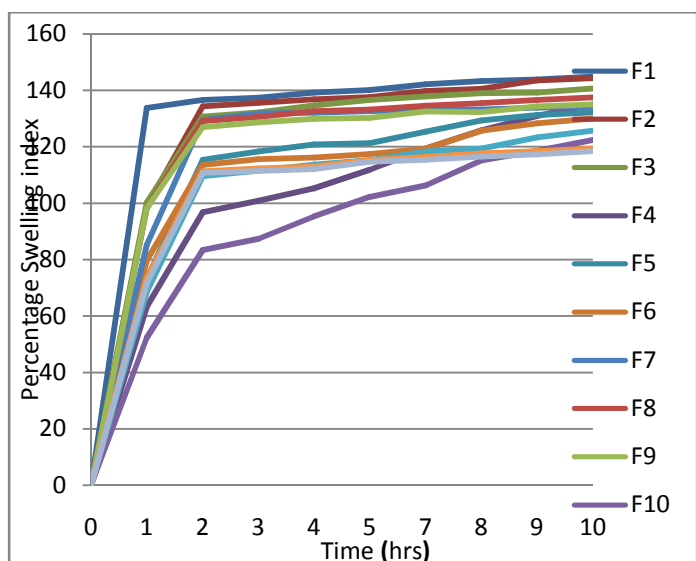


Figure no 2: Swelling Index of different Formulation

Dissolution Studies

The in-vitro release of Naproxen Sodium and Pantoprazole Sodium from formulated tablets was carried out for 10 hours in 1.2 acid buffers. The studies were performed in USP dissolution apparatus II at 37 ± 0.5° C and 100 rpm speed. Samples were taken at 1, 3, 5, 7 & 10hours and diluted to suitable concentration and analyzed for Naproxen Sodium and Pantoprazole

Sodium content at 263.0 nm & 305.0 nm respectively by using UV-visible spectrophotometer. The values are shown in plots for the same are shown in Figure 3 to 4.

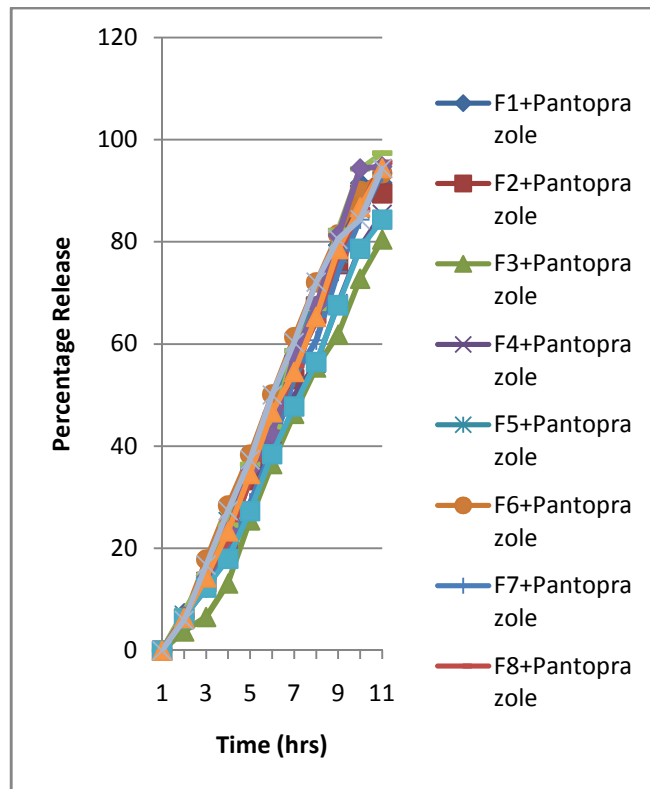


Figure no 3: Dissolution Profile Naproxen Sodium

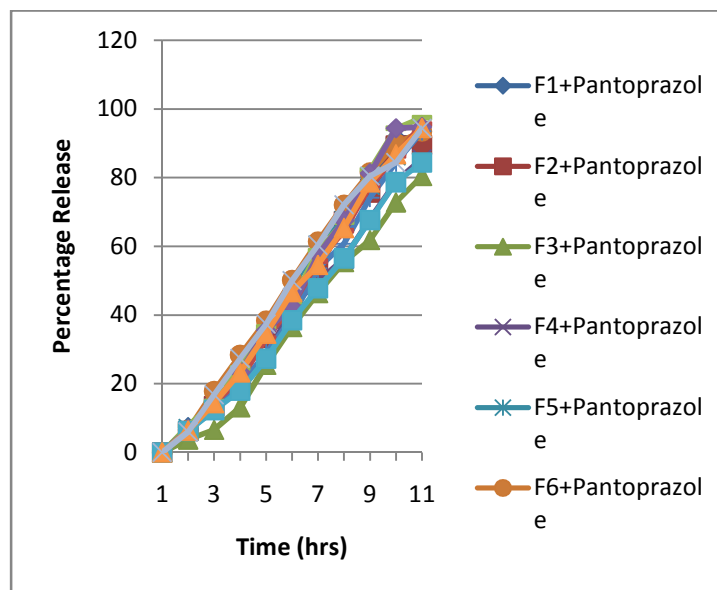


Figure no 3: Dissolution Profile Pantoprazole Sodium

Among all formulations prepared and evaluated F6 (95.3%, 93.4%) for Naproxen and Pantoprazole, F8 (93.05%, 95.54%) and F9 (97.42%, 97.38) appeared to have desired release pattern than others. But the formulation F9 nearly matches release pattern with that of Innovator release at each hour release. Formulations F1 (91.30%, 91.50%), F3 (81.34%, 80.42%) and F4 (84.32%, 85.37%) showed sudden drug release which might be due to low level of the polymer in the tablets.

Stability Studies:

The optimized formulation F9 was kept for stability at room temperature for 1 month. Then comparative dissolution study of Optimized formulation F9 of 1 month is taken. The results of dissolutions with Innovator are shown in tables 3 & 4 and plots for the same are shown in Figures 5 & 6

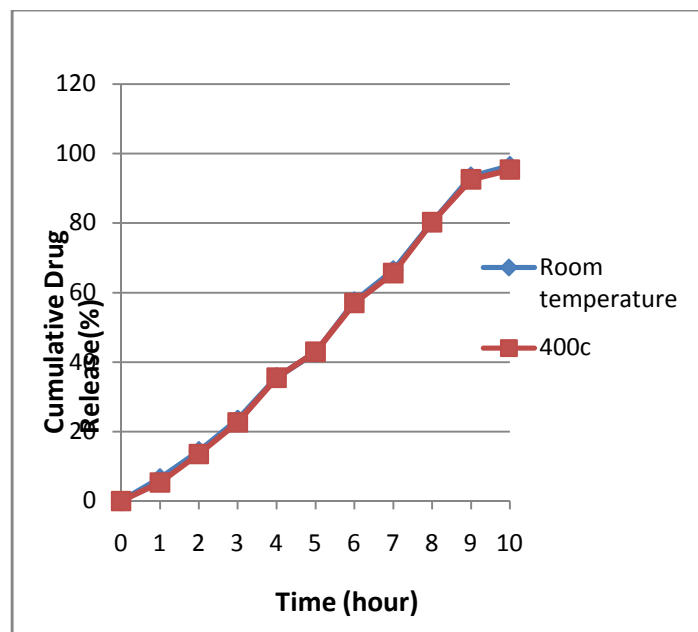


Figure no.5 :Percent cumulative drug release Vs time of stability batch of F9 for Naproxen

Time in Hour	Storage conditions	
	Room temperature	40 ⁰ c
1	6.54	5.34
2	14.34	13.54
3	23.38	22.63
4	35.57	35.48
5	42.78	42.94
6	57.47	56.95
7	66.38	65.57
8	80.22	80.23
9	93.36	92.54
10	96.42	95.34

Table no 3: Stability Studies Formulation Naproxen Batch F9 at Room Temperature and At 40 °C

Time in Hour	Storage conditions	
	Room temperature	40 ⁰ c
1	6.34	5.24
2	13.24	13.04
3	23.23	22.53
4	34.45	35.48
5	41.37	42.94
6	55.48	54.59
7	66.38	65.37
8	80.26	80.01
9	93.56	92.33
10	96.52	95.24

Table no 4: Stability Studies Formulation Pantoprazole Batch F9 at Room Temperature and At 40 °C

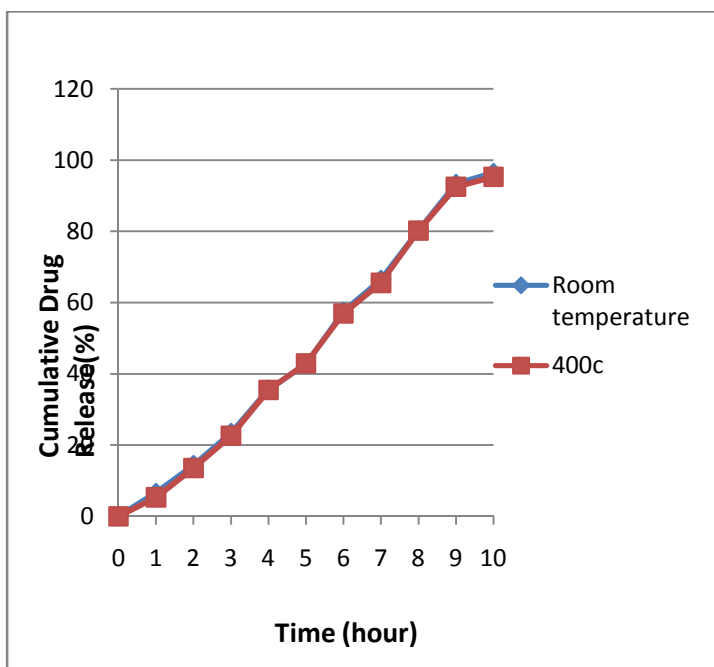


Figure no.6: Percent cumulative drug release Vs time of stability batch of F9 for Pantoprazole

Hence in present investigation, an attempt was made to deliver drugs via oral mucoadhesive drug delivery system to the vicinity of absorption site by prolonging the gastric residence time of the dosage form. For the formulation of oral mucoadhesive tablet various polymer used like Gelatin, Sodium Alginate and Carbopol 934P, used as hydrophilic matrix forming and mucoadhesive polymer in varying concentration along with Magnesium stearate, sodium bi carbonate and Lactose as filler. Tablets were subjected to various evaluation parameters such as drug content, hardness, weight variation, friability, mucoadhesive strength, swelling index, and in vitro drug release study. It was revealed that the tablets of all batches had acceptable physical parameters. Tablets of batch F8 and F9 had good Mucoadhesion along with good swelling behaviors and in vitro drug release. It was observed that the tablets of all batches followed equation of zero order rate, Higuchi matrix and Peppas drug release profiles. Tablet of batch F8 and F9 did not show any physical or chemical interaction between drug and

polymer. Which was concluded from the FTIR study showed similar peaks for pure drug and tablet formulation. A result of the study of individual polymers shows that the, Gelatin, Sodium Alginate and Carbopl 974P, alone was also able to sustained the release in 10 hour. Release of drug, from combination of Gelatin, Sodium Alginate with Carbopl 934P, (1:1:5 ratio) gave the good results compared to employing other combination of polymers. Tablets of Batch F9 and F8 were selected as an optimum batch and evaluated for further parameters like accelerated stability study and characterization using IR spectroscopy.

The stability study revealed that there was no significant change in dissolution profile and mucoadhesive strength for a period of one month.

ACKNOWLEDGEMENTS

Authors are thankful to Prof. (Dr.) B. Jayakar Principal, Prof. (Dr.) B. S. Venkateswarlu, Head, Department of Pharmaceutics and Mr. V. Muruganatham, Assistant Professor, Department of Pharmaceutics, Vinayaka Missions College of pharmacy, Salem, Tamilnadu, India providing all the facilities for this research Project.

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