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Original Article

Preparation and Clinical Evaluation of Naproxen Enteric Coating Tablets using Shellac-HPMC as Coating Polymer

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ABSTRACT

Objective: Naproxen is a non steroid anti-inflammatory drug with analgesic and antipyretic properties. The present study is undertaken with an aim to prepare naproxen as an enteric coated tablet to avoid its gastric irritation effect and evaluated its clinical efficacy.

Method: Five formulas of naproxen core tablets were prepared by wet granulation techniques using lactose or starch as diluents, Avecil 102 or Crosspovidone as disintergrants, and P VA either in aqueous or alcoholic solution as binder were used. The flow characteristics of the granules were assessed by determining their angle of repose and Carr's index. The physicochemical properties of the all prepared tablets as weight variation, hardness, friability, disintegration test, and drug release study were done to select the best formula. The coating mixtures either shellac alone (5 %, 10% and 15%) or shellac -HPMC combination was used to coat the selected formula and evaluate its effect on drug release. In clinical study the selected prepared naproxen tablets with or without enteric coating were given to two groups patients suffering from renal pain, each group of ten patients.

Results: The F4 (contain lactose as diluents, binder, and aqueous solution of PVA and Crosspovidone as disintergrants) gave the fast drug release of 98% after 20 min with accepted weight variation hardness, friability, and disintegration time of 25 seconds. In addition to that, the prepared granules gave good flow properties.

Moreover, it has been found that 10% shellac- 5% HPMC mixture gave best release for enteric coated naproxen tablet and comports with requirements of drug release targeted for small intestine. The clinical study indicated the effectiveness of the both prepared formulas as pain killer without gastric irritation for enteric coating one.

Key words: Naproxen, shellac, HPMC, enteric coated polymer, clinical study.

1. INTRODUCTION

Tablets are solid dosage forms usually prepared with the aid of suitable pharmaceutical excipients [(1).] Coating is a process by which an essentially dry, outer layer of coating material is applied to the surface of a dosage form in order to confer specific benefits that broadly ranges from facilitating

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product identification to modifying drug release from the dosage form. After making a good tablet, one must often coat it [2]. Film coatings are applied for several reasons for:

- Taste masking and moisture, light protecting coatings.
- Improve product appearance.
- Improve mechanical resistance of the coated product (e.g. reduced friability [3]. Types of coatings:

1.Protective coatings: Modified drug release (e.g. gastric resistant or extended release coatings [4].

2 .Functional coatings : Film coatings, which are applied to achieve a certain desired release profile of the incorporated drug, are generally called functional or modified-release coatings,which is two type Enteric coatings and Extended release coatings.

Enteric coatings are prepared from gastric resistant polymers. The coatings prepared from such polymers remain intact in acidic environment, but dissolve readily at the elevated pH of the small intestine. This property is related to the chemical structure of the applied polymer. The most effective enteric polymers contain many carboxylic acid groups with a pKa of 3-5 [5].

Extended release coatings

The patient compliance is strongly decreasing in such cases, when multiple daily a administrations are necessary to maintain constant blood levels of the drug. Therefore, extended release polymers were developed, which are able to provide a sustained action by a controlled release over time [6].

Film coating formulations

Usually the film contains polymer, plasticizer, colorants/ opacifiers and solvent/ vehicle.

Shellac is the purified product of a natural resinous oligomer (MW ≈1000 D) secreted by the parasitic insect Kerria lacca on various host trees in India and Thailand. Shellac consists of polyesters of mainly aleuritic acid, shellolic acid, and a small amount of free aliphatic acids Due to its acidic character, shellac is used primarily as enteric coating. Other applications are sustained release [7], colon targeting [8], and microencapsulation. Shellacis non-toxic and physiologically harmless [9] .

Naproxen is 2-(6-methoxynaphthalen-2- yl) propanoic acid. It is a non-steroidal anti-inflammatory drug (NSAID) with analgesic properties. The mechanism of action of naproxen, like that of other NSAIDs may be related to prostaglandin synthesize inhibition . It works by inhibiting both the COX-1 and COX-2 enzymes [10] .It use for the treatment the signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis [11].

2. MATERIALS AND METHOD

Materials: Naproxen powder (Samara Drug Industry, Iraq), Ammonium hydrogen carbonate (Colorcon Asia Pvt.Ltd), Crospovidone (BDH,England), Glycerol (Himedia Lab.Pvt.ltd, India), Hydroxy propyl methylcellulose (HPMC) (Colorcon Asia Pvt.Ltd), Lactose BDH, England), Microcrystalline cellulose (Avicel 102) (Schar Lab.S.L.Spain), Poly vinyl pyrrolidine (PVP) (Gailand chemical company, U.K.), Shellac (Schar Lab.S.L.Spai Merck, Germany).

Formulation of naproxen enteric coated tablets.

Formulation the core tablet

Different formulas as demonstrated in table (1)were prepared by wet granulation method .The naproxen powder was added to diluents and disintegrants and mixed well, then the binder (poly vinyl pyrrolidine in liquid form) was added in concentration of 1mg dissolve in 10 ml water or alcohol to powder mixture to form wet mass according to ball test, then coarse screening of wet mass using suitable sieve of 0.8 mesh. Drying of moist granules, then screening of dry granules through suitable sieve of 0.6 meshes. The granules were mixed with 1%w/w of talc and 0.5%w/w of stearic acid as lubricant for two minutes and finally compressed using a single punch tablet machine at a constant load (7KN) to form flat tablet of diameter 9mm and weight 325mg.

Table 1: Formulation of Naproxen Core Tablet

Constituents(mg)	Formula number				
	F1	F2	F3	F4	F5
Naproxen	250	250	250	250	250
Lactose	37	37		60	57
Starch	32	32	32	-	-
PVP in aqueous solution	0.5		0.5	0.5	0.5
PVP in ethanolic solution		0.5			
Avicel			37		
Crospovidone	-	-	-	9	6
Talc	4	4	4	4	4
Stearic acid	1.5	1.5	1.5	1.5	1.5
Total weight	325	325	325	325	325

Tablet coating

The selected formula was coated by dipping method. Each tablet was held by forceps and dipped in the coating mixture in and out 15 times; the coat was dried by stream of warm air between each dip [1].

The coating mixtures either shellac alone (5 %, 10% and 15%) or shellac -HPMC combination was used to coat the selected formula and evaluate its effect on drug release.

Preparation of coating liquid

Two coating liquids were used to coat the best selected formula with shellac and shellac with HPMC combination.

1. Shellac coating liquid (organic solution)

Alcoholic shellac solution (table 2) was prepared by dissolving shellac in isopropranol to produce a concentration of 5 %, 10%, and 15(w/w). Glycerol was used as plasticizing agent, which has good plasticization property with shellac [12] .Glycerol is used in percent 10% based on polymer mass .

Table 2: Formulation of Alcoholic Shellac Coating Solution[13]

Composition	Weight(gm)	Weight(gm)	Weight(gm)
	Coat 1	Coat 2	Coat 3
Shellac	5	10	15
Glycerol	0.5	1	1.5

Isopropyl alcohol	94.5	89	83.5

2. Preparation of shellac- HPMC coating solutions

The polymeric solution (HPMC) powder was mixed with the shellac/plasticizer solution under stirring for one hour and isopropyl alcohol was then added to achieve the desired wheight that was used for coating. The solution was then stirred for an extra additional 30 min to ensure good mixing. The final formula of shellac -HPMC coated solution is shown in the table 3

Table 3: Formulation Mixture of Shellac –HPMC Coating Solution [14-15]

Material	Amount
Shellac	10gm
HPMC	5 gm
Isopropranol	84gm
Glycerol	1gm

Characterization and evaluation of prepared core tablet.

1. Weight variatin test

It was done for the 20 precoated and post coated tablets which were randomly selected from the prepared formula. The weight of the prepared tablet was 325mg and which means, that the acceptable percentages 5% [16].

2.Hardness test

The hardness of precoated tablets of the prepared formulas was determined individually using Monsanto hardness tester [17].

3. Friability test

This test was done by subjecting 20 tablets utilizing a plastic chamber that revolves at 25 rpm. A pre weighed tablets sample were placed in the friabilator which was then operated for 100 revolutions, the reweighed. Compressed tablets that lose a maximum of not more than 1% of their weight are generally considered acceptable [16].

$$\%\text{Friability} = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100$$

4. Disintegration test

The in-vitro disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus using the specified medium as the immersion fluid maintained at 37 ± 2°. Six tablets of enteric coated tablets were weighed individually and placed in acid phase (0.1N HCL) for 2 hours in USP basket rack assembly after which they were removed and inspected for cracking or disintegration. The same tablets were then placed in phosphate buffer pH 6.8 and subjected to the same procedure and observed for disintegration [18]

5. Drug release

Drug release was studied for the tablet formulations pre and post coating tablets by USP apparatus II (paddle) and 900 ml was filled with the at 37±0.5°C and the rotation was 50 rpm. The first two hours of dissolution was in 0.1N HCl (only for coated tablet), followed in phosphate buffer pH 6.8 for one hour. Samples were taken and filtered for analysis at different time intervals and replaced with the same volume of fresh media, after that the absorbance of collected samples was determined spectrophotometrically [19].

Clinical Study

The selected formula (F4) of naproxen tablet either as plane or enteric coating tablets was given to two groups of ten patients suffering from pain at dose of one tablet twice daily for one week.

The data measuring during treatment were clinical response of pain relief and gastrointestinal side effects.

3. RESULT AND DISCUSSION

Precompression parameters

Many technologies which used in the development of enteric coated tablets and in the preset investigation core tablets of naproxen were prepared by wet granulation metho d followed by enteric coating. The prepared naproxen powder blend were evaluated for angle of repose, Hausner's ratio and compressibility index (Table 4).The flow characteristics of the granules were assessed by determining their angle of repose and Carr's index .The angle of repose of all formulation was less than 30 º (25 to 28) which indicate the good flowability of the prepared granules.

Table 4: Precompression parameters of naproxen powder blend

Formula No.	Carr's index (%)	Angle of repose	Hausner ratio	Type of flow
F1	16	28	1.4	Good
F2	14	26	1.3	Good
F3	15	27	1.2	Good
F4	13	26	1.25	Good
F5	12	25	1.1	Good

Post compression parameters of naproxen core tablet

The naproxen core tablets were prepared by wet granulation method and were evaluated for their hardness, weight variation, content uniformity, friability, thickness and disintegration time .The data obtained for post compressional parameters are shown in Table 5.

Table 5: post compressional parameters for naproxen tablets

Formula code	Weight average	Thickness (mm)	Friability %	Hardness(Kg)	Drug content	Disintegration time
F1	322.6	4.1	0.41	5.0	95	9min
F2	323.3	4.5	0.42	4.1	96	9min
F3	324.2	4.6	0.40	5.9	96.5	11min
F4	324.4	4.2	0.46	5.5	98.2	25 sec
F5	326.1	4.4	0.45	5.3	97.5	40 sec

In vitro drug release of naproxenof core tablets

The in vitro drug release of naproxen core tablets is shown in Figure (1) .The formulation (F4) showed most satisfactory results, gave the fast drug release

98% after 20 min . The best formula was chosen to be coated with different concentration of shellac solution in combination with HPMC mixture .

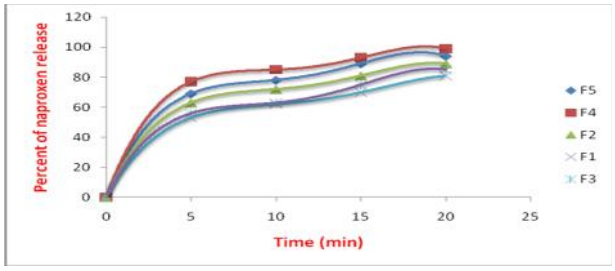

Fig 1: Release of naproxen from formulas (F1 , F2 , F3,F4 and F5) in phosphate buffer (pH6.8) at 37°C. Best formula coated with shellac - HPMC mixture

Shellac is mostly used for enteric coating [15]. Due to its pKa values of 5.6– 6.6 it is assumed to remain undissolved in the stomach [20] . it requires high pH for dissolution, usually pH 7.2 or even more. Because of it is high dissolution pH and low solubility in the intestinal fluid, shellac is not suitable for conventional enteric coating [13, 21] .It needs to be modified to enhance its dissolution at lower pH. Additional materials to improve its intestinal solubility have been applied. These materials act as pore formers or swelling agents. Addition of hydroxypropyl methylcellulose will result in increased solubility of shellac films in simulated intestinal fluid [22].

Water-soluble polymers may be added to shellac to aid in controlling its release characteristics and to provide channels or pores in the film. HPMC polymer was used for this application. The release patterns can be modified by addition of different amounts of the shellac/plasticizer and soluble polymer. Figure (3) shows the effect of incorporation of a constant amount of HPMC and different amount of shellac/plasticizer [22].

Different concentration shellac alcoholic solution in combination with 10% w/w HPMC gave very thick solution that restricted the uniform so we used 5% w/w of HPMC. The best release profile of naproxen tablet after coating was formula F4b (10% Shellac -5% HPMC) as show in figure (2) since there was no release in pH 1.2 for 2 hours, and 98% of naproxen was released from coated tablet in pH 6.8 after (30min) .In addition the tablet showed good appearance with no signs of cracking or splitting or peeling .

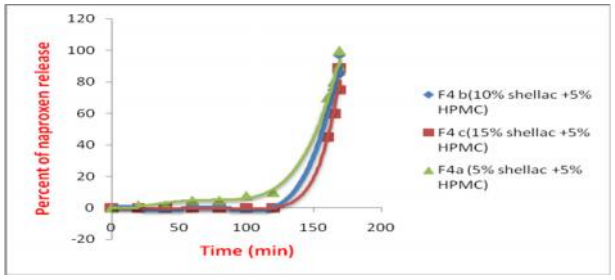

Fig 2: Cumulative release of naproxen for formulas (F4a, F4b and F4c) from enteric coated tablet in 0.1N HCl (pH 1.2) for 2 hours and phosphate buffer (pH 6.8) for 1 hour at 37°C.

The results of clinical study had provided strong pain relief for all 20 patients with potent reduction in gastrointestinal irritation for patients that received enteric coating formula as demonstrated in table 6.

Table 6: Clinical Responses of the prepared coated and non coated naproxen tablets

Group one receiving non enteric coating naproxen tablet						
Patient No.	Age	Sex	Dose	Duration	Response	GI upset
1	20	Male	Twice daily	One week	Good	Mild Present
2	25	Female	Twice daily	One week	Good	Mild Present
3	22	Female	Twice daily	One week	Good	Present
4	30	Male	Twice daily	One week	Good	Mild Present
5	28	Male	Twice daily	One week	Mild	Absence
6	20	Female	Twice daily	One week	Good	Absence
7	30	Male	Twice daily	One week	Good	Present
8	24	Female	Twice daily	One week	Good	Present
9	21	Female	Twice daily	One week	Mild	Mild Present
Group one receiving enteric coating naproxen tablet						
10	30	Male	Twice daily	One week	Good	Disappearance
11	29	Male	Twice daily	One week	Good	Disappearance
12	28	Female	Twice daily	One week	Good	Disappearance
13	25	Male	Twice daily	One week	Good	Disappearance
14	28	Female	Twice daily	One week	Mild	Disappearance
15	22	Male	Twice daily	One week	Good	Disappearance
16	26	Female	Twice daily	One week	Good	Disappearance
17	23	Male	Twice daily	One week	Good	Disappearance
18	21	Male	Twice daily	One week	Good	Disappearance
19	29	Male	Twice daily	One week	Good	Disappearance
18	22	Female	Twice daily	One week	Mild	Disappearance
19	26	Female	Twice daily	One week	Good	Disappearance
20	25	Female	Twice daily	One week	Good	Disappearance

4. CONCLUSION

1-Among the diluents utilized, it was found that using lactose was the best in preparing naproxen tablets than Avicel.

2-Using ethanolic PVP as binding solutions in the formulation increase the release of naproxen compared to the formula prepared by aqueous granulating solution of PVP, because water act as binder .

3- The best disintegrant used was crospovidone . It gave the shortest disintegration time.

4. Mixture of 10 % (w/v) shellac and 5% HPMC polymer solution which used in coating of selected formula showed the best release.

5-The release mechanism of naproxen tablet followed first order kinetics and it was found that no change in the mechanism of naproxen release after coating the selected formula.

6- Clinical study of the prepared naproxen had provided good response with strong reduction in GI upsets for enteric coated one.

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