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CHARACTERIZATION AND EVALUATION OF COLON TARGETED ORAL MATRIX TABLETS O NAPROXEN AND ESOMEPRAZOLE

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ABSTRACT
The objective of the present study is to develop colon targeted drug delivery system of Naproxen and Esomeprazole using Ethyl cellulose, Cellulose acetate phthalate and in combination with other polymers for the treatment of inflammatory bowel diseases (IBD). The nine different tablet formulations were prepared by wet granulation technique using starch paste as a binder. Ethyl cellulose (EC), Cellulose acetate phthalate (CAP) and Pectin (PE) were included in the formulation as polymers. The granules were prepared and evaluated for the properties such as angle of repose, loose bulk density, tapped bulk density, Carr's compressibility index and Hausner's ratio. The tablets were evaluated for hardness, friability, and drug content, swelling index and in vitro drug release studies in 0.1N HCl for two hours; in phosphate buffer pH 7.4 for next three hours and finally, in a phosphate buffer pH 6.8 containing 10^9 CFU/ml of Bacteroidesfragilis. The tablets from all formulation released not more than 6% of Naproxen in 0.1N HCl and in phosphate buffer pH 7.4. Most of drug released when the drug release studies were carried out in phosphate buffer pH 6.8 containing 10^9 CFU/ml of Bacteroidesfragilis. Drug release followed the diffusion control mechanism. The optimized formulation showed no change either in physical appearance, drug content or dissolution pattern after storage at 40^oC/75% RH for three months.

KEYWORDS : *Naproxen; Esomeprazole; Cellulose acetate phthalate; Ethyl cellulose; Pectin; Inflammatory bowel diseases.*

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INTRODUCTION

Various approaches available for colon specific drug delivery include coating with pH dependent systems, design of timed release dosage forms and the use of carriers that are degraded exclusively by colonic bacteria. The pH dependent system is designed to release the drug to above a particular pH of the GIT. The poor site specificity of pH dependent system, because of large variation in the pH of the GIT, was very well established. The timed-release systems, release their load after a pre-determined time period of administration. The site specificity of these systems is considered poor because if large variation in gastric emptying time and passage across the ileo-caecal junction. The best alternative approach for colon specific drug delivery is the use of carriers that are degraded exclusively by colonic bacteria. The micro flora of colon is in the range of 10^{11} to 10^{12} CFU/ml consisting mainly of anaerobic bacteria. This vast micro flora fulfills its energy needs by fermrnting various types of substrate that have been left undigested in the small intestine, e.g. Di- and tri-saccharides, poly-saccharides etc. For this fermentation the micro flora produces a vast number of enzymes like β-glucoronidase, β-xylosidase, α-arabinisidase, β-galactosidase, nitroreductase, azoreductase, and deaminase and urea dehydroxylase. Because of the presence of the biodegradable enzymes only in the colon, the use of biodegradable polymers for colon specific drug delivery seems to be a more site-specific approach as compared to other approaches.

EC, CAP and PE are selected as matrix materials in the present work. These polymers shield the drug from the environments of stomach and small intestine and are able to deliver the drug to the colon. On reaching the colon they undergo assimilation by micro-organism or degradation by enzyme or breakdown of polymer backbone leading to a subsequent reduction in their molecular weight and thereby loss of mechanical strength.

IBD is a localized inflammation of the small and large intestine. IBD includes Ulcerative colitis and Crohn's disease. Both these are similar but distinct entities of IBD. Crohn's disease is a chronic, recurrent disease characterized by patchy transmucular inflammation involving any segment of the GIT from the mouth to the anus.

OBJECTIVE

Naproxen was used as a model drug in this study because there is a therapeutic benefit for the colonic delivery of this drug for the treatment of IBD and in addition, it possesses necessary physicochemical properties for formulating in to a controlled release product.

MATERIALSANDMETHODS

Materials

Naproxen was received as a gift sample from Emcure Pharmaceutical Limited (Pune, India). Ethyl cellulose, Cellulose acetate phthalate, magnesium Stearate, talc, other materials and solvents used were of analytical grades. *In vitro* analysis of the prepared tablets was carried out as per the requirements of matrix tablets as specified in official pharmacopoeia.

PreparationofTablets

Granules of both Naproxen and Esomeprazole were prepared by the wet granulation technique. Accurate quantity of drug and all ingredients were weighed according to formula shown in Table 1 and mixed well except Magnesium Stearate and Talc. Passed all the ingredients through mesh No. 250 separately except Magnesium Stearate and Talc. Granulated the powder blend with granulating solution (Starch paste 10%) and mixed for 15 minutes. Passed wet mass through mesh No. 12 to prepare wet granules. These wet granules then dried at 50^0C for 30 min, passed the dried granules through mesh No. 22 superimposed on mesh No. 44. Finally Magnesium Stearate and Talc were added. The quantity of granules for controlled release layer was compressed lightly using 16 Stations rotary tablet compression machine using 12.5 mm punches. Over this compressed layer, the required quantity of the fast release layer was placed and compressed to obtain hardness in the range of 4-6 kg/cm^2 to form a bilayer matrix tablets.

RESULTS

Table 1: CompositionofcolontargetedmatrixTablets (375mg)

Ingredients (mg/Tablet)	Formulations Code								
	NE1	NE2	NE3	NE4	NE5	NE6	NE7	NE8	NE9
Composition of immediate release layer									
Esomeprazole	20	20	20	20	20	20	20	20	20
Sodium starch glycolate	4	4	4	4	4	4	4	4	4
Microcrystalline cellulose	15	15	15	15	15	15	15	15	15
Starch paste (10%)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Magnesium Stearate	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1
Composition of controlled release layer									
Naproxen	375	375	375	375	375	375	375	375	375
Pectin	200	200	200	200	200	200	200	200	200
Ethyl cellulose	20	40	60	----	----	----	20	40	20
Cellulose acetate phthalate	----	----	----	20	40	60	20	20	40
Starch paste (10%)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Talc	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5
Magnesium Stearate	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Lactose	92	72	52	92	72	52	72	52	52

The quality control tests for the matrix tablets, such as hardness, friability, weight variation etc. were determined using reported procedure. The tablet crushing strength was tested by commonly used Pfizer tablet hardness tester. Friability was determined by Roche® friabilator (Electro lab Pvt. Ltd., India), which was rotated for 4 min at 25 rpm. After dedusting, the total remaining mass of the tablets was recorded and the percent friability was calculated. Weight variation was determined by weighing 20 tablets individually, the average weight was calculated and the percent variation of each tablet from the average weight of tablet was calculated. The swelling properties of tablets were determined by placing the tablet matrices in the dissolution test apparatus containing phosphate buffer pH 6.8 Containing 10^9 CFU/ml of *Bacteroidesfragilis*. In Vitro Dissolution study was Carried out by using USP Dissolution Test Apparatus I (Basket type) using 900 ml media at speed of 100 rpm with 2 hrs in 0.1N HCl, 3 hrs in phosphate buffer pH 7.4 and up to 24 hrs in phosphate buffer pH 6.8 Containing 10^9 CFU/ml of *Bacteroidesfragilis*.The samples were analyzed by UV-spectrophotometer at wavelength 301nm and 230nm for Esomeprazole and Naproxen respectively in a mixture of Acetonitrile and Water (50:50v/v).

Table no.2 Evaluatory data of Naproxen and Esomeprazole matrix tablet showing all parameter in comparative form.

S. No.	FORMULATION code	Thickness** (in mm)	Weight Variation (mg))	Hardness** (kg/cm^2)	Friability* (%)
1	NE1	4.84±0.054	1.60	5.5±0.376	0.403±0.059

2	NE2	4.87±0.083	2.22	5.4±0.274	0.382±0.072
3	NE3	4.89±0.012	1.85	5.4±0.204	0.394±0.059
4	NE4	4.96±0.134	2.88	5.4±0.376	0.425±0.023
5	NE5	4.97±0.109	1.58	5.5±0.424	0.443±0.065
6	NE6	4.99±0.083	1.74	5.6±0.376	0.401±0.030
7	NE7	4.87±0.083	2.88	5.5±0.500	0.429±0.015
8	NE8	4.85±0.057	2.77	5.4±0.252	0.424±0.023
9	NE9	4.84±0.054	2.20	5.5±0.252	0.442±0.059

*****All the values are expressed as a mean ± SD., n = 3

****** All the values are expressed as a mean ± SD., n = 6

Table no.3 Drug Content and *In-vitro* drug release studies of Naproxen and Esomeprazole matrix Tablets.

S. No.	FORMULATION code	Drug Content of Naproxen* (%)	Drug Content of Esomeprazole* (%)	Cumulative % drug release of Naproxen	Cumulative % drug release of Esomeprazole
1	NE1	98.14±2.48	99.53±0.878	98.40±0.037	97.45±0.014
2	NE2	101.67±1.58	99.47±0.767	99.28±0.076	96.78±0.007
3	NE3	97.97±1.45	99.54±0.15	96.74±0.018	97.39±0.008
4	NE4	99.20±2.94	99.59±0.698	92.42±0.012	96.83±0.018
5	NE5	100.59±3.49	99.62±0.385	86.45±0.030	98.76±0.063
6	NE6	101.60±0.54	99.74±0.252	74.93±0.063	98.63±0.015
7	NE7	100.99±1.458	99.66±0.947	78.39±0.100	97.47±0.110
8	NE8	98.78±0.864	99.63±0.635	88.75±0.061	97.82±0.011
9	NE9	99.55±0.791	99.78±0.221	72.59±0.070	98.45±0.013

*****All the values are expressed as a mean ± SD., n = 3

Kinetics of *In-vitro* Drug Release:

To study the release kinetics of *In-vitro* drug release, data was applied to kinetic models such as zero order, first order, Higuchi and Korsmeyer-Peppas.

Zero order: $C = K_o t$

K_0 - zero-order rate constant expressed in units of concentration/time, t - time in hrs.

First order: $Log\ C = Log\ C_o - Kt / 2.303$

Where C_0 - is the initial concentration of drug, K - first order constant, t - time in hrs.

Higuchi: $Qt = Kt^{1/2}$

Where Q_t - amount of the release drug in time t, K- kinetic constant, t- time in hrs.

Korsmeyer Peppas: $Mt / M_\infty = Kt^n$

Where M_t - represents amount of the released drug at time t,

M_∞- is the overall amount of the drug (whole dose) released after 24 hrs

K- is the diffusional characteristic of drug/ polymer system constant.

n- Is a diffusional exponent that characterizes the mechanism of release of drug.

For matrix tablets, an "n" value near to 0.5 indicates diffusion control and an "n" value near to 1 indicates relaxation or erosion control. The intermediate value suggests that diffusion and erosion contributes to overall release mechanism.

STABILITY STUDIES

From the results it was found that formulation F2 is the best formulation amongst the 9 formulations. Thus formulation F2 was selected for stability studies.

Table no.4 Comparison of various parameters of formulation NE2 at initial and different stability periods

Parameters		Stability Period			
		Initial	***First month***	***Second month***	***Third month***
Hardness (kg/cm^2)		5.4±0.274	5.5±0.225	5.7±0.200	5.7±0.225
Drug content (%)	Naproxen	101.67±1.58	100.89±1.02	100.01±0.891	99.76±1.26
	Esomeprazole	99.47±0.767	99.21±1.242	99.01±0.856	98.96±1.135
Cumulative % Drug release	Naproxen	99.28±0.076	99.13±0.046	99.03±0.031	98.97±0.065
	Esomeprazole	96.78±0.007	96.51±0.056	96.38±0.086	96.18±0.046

DISCUSSION

Physical characterization of the Tablets

All the formulations were prepared according to the formula given in Table 1. The prepared matrix tablets were evaluated for various physical properties as indicated in Table no (2, 3). All the batches were produced under similar conditions to avoid processing variables. All the formulations were evaluated for various physical Parameters such as weight variation, thickness, hardness, friability and drug content. The thickness of formulations was found to be in the ranged from 4.84±0.054 to 4.99±0.083 mm.The percentage deviation from average tablet weight for all the formulations ranged from 1.58 to 2.88 %. The Hardness of tablets was found that the values are ranged from 5.4±0.204 to 5.6±0.376 kg/cm^2. The results of Percentage Friability are ranged from 0.394±0.059 to 0.443±0.065 %. Drug content was found to be uniform among different formulation of tablets and ranged from 97.97±1.45 to 101.67±1.58 % for Naproxen and 99.47±0.767 to 99.78±0.221 % for Esomeprazole. The *In-vitro* drug release studies revealed that formulations F1, F2 and F3 contains Ethyl Cellulose showed a release of 98.40±0.037, 99.28±0.076 and 96.74±0.018 % respectively at the end of 24 hours. Formulation F4, F5 and F6 contains Cellulose acetate phthalate showed a release of 92.42±0.012, 86.45±0.030 and 74.93±0.063 % of drug cumulative drug release respectively at the end of 24 hours. The drug release from formulation F7, F8 and F9 containing Ethyl Cellulose and Cellulose acetate phthalate in different ratios were found to be 78.39±0.100, 88.75±0.061 and 72.59±0.070 % respectively at the end of 24 hours for Naproxen.

Formulation F1, F2,F3 F4, F5,F6 F7, F8 and F9 showed drug release of 97.45±0.014, 96.78±0.007, 97.39±0.008, 96.83±0.018, 98.76±0.063, 98.63±0.015, 97.47±0.110, 97.82±0.011and 98.45±0.013 % respectively at the end of 2 hours for Esomeprazole. The difference in cumulative drug release and pattern of drug release from the different formulations might be due to the difference in concentration of polymers and also might be due to the different ratios of polymers used in formulations.

STABILITY STUDIES

From the results it was found that formulation F2 is the best formulation amongst the 9 formulations. Thus formulation F2 was selected for stability studies.

No statistically significant differences were observed in the percentage drug released; Hardness and % drug content in optimized formulation at the end of three months of stability studies. (Table no.4).So it can be concluded that the formulation was stable for short term storage conditions.

CONCLUSION

Results of the present research work demonstrate that the combination of both hydrophilic and hydrophobic polymers successfully employed for formulating the Controlled release matrix tablets of Naproxen and Esomeprazole. It is observed that 10% of each the polymer in combination was able to produce desire formulation which release more than 90% drug in 24 hours. The mechanism of drug release was observed the combined effect of diffusion for controlled drug release. So, combination of both

hydrophilic and hydrophobic polymer was suitable to produce the matrix tablet rather than the using a single type of polymer.

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