Section A-Research paper
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OPTIMIZATION AND EVALUATION OF COLON-SPECIFIC MATRIX TABLET OFPIROXICAM FOR INFLAMATORY BOWEL DISEASE.

[1] Mohammed Abduljalil*, [2] Abubakar Salam Bawazir, [3] Barrawaz Aateka Yahya, [4] SannaSaffiruddin Shaikh

Y.B. Chavan College of Pharmacy, Dr. Rafiq Zakaria Campus, Aurangabad, Maharashtra, India.

Corresponding Author: Mohammed Abduljalil

Mail ID: mohamjalil22@gmail.com

ABSTRACT

Present study is intended to formulate and evaluate the piroxicam (PXM) colon-specific enteric-coated matrix tablets using time-dependent polymers hydroxypropyl methylcellulose K4M and PH-sensitive Eudragit S100 that delays the release of drug (PXM) in the upper gastrointestinal system and also helps in the continuous release of PXM in colon area in inflammatory bowel disease (IBD). Enteric-coated tablets containing a combination of the above polymers can prevent PXM from entering the upper gastrointestinal system (i.e. stomach and small intestine).A promising system for delivering PXM to the colon was found in the in-vitro drug release studies with formulation F10. The zero-order model was best fitted for the release pattern of the above formulations. The mechanism involved in drug release was a non-fickian (super case-II) transport system. There was no interaction found in the FTIR spectral studies between the PXM and the excipients, concluding the development of HPMC K4M-Eudrgit S100 enteric-coated tablet as a viable strategy for treating inflammatory bowel disease by targeting the PXM in colon.

Keywords; Piroxicam, Enteric-coated matrix, Inflammatory Bowel Disease, Colon, HPMC K4M, Eudrgit S100.

INTRODUCTION

A system used for delivering drugs specifically to the colon preserves the potency of drugs absorbed primarily from the colon region by avoiding their degradation in the upper gastrointestinal tract (GIT)[12].

Treatment of localized colonic disorders like inflammatory bowel disease, ulcerative colitis, Crohn's disease, etc. which can be handled more effectively by local drug delivery, colon-targeted delivery systems are convenient[3].

For the delivery of drugs that are only effective in the colon, several different systems have been established. Some examples are the following: enzymatically regulated delivery system, covalent drug-carrier linkage, pH-sensitive polymer coating, and time-dependent release mechanism[4].

Although enteric-coated delivery systems are most commonly used for delivering drugs into the colon, one drawback is that the pH variation between the small intestine and colon is well known, while time-dependent release systems are unable to detect changes in transit time of the upper gastrointestinal tract. This means that even small changes in the time of gastric emptying causes the small intestine to release drug, where it will eventually arrive. The use of an enzymatically controlled mechanism to deliver drugs to the colon is clearly the most convenient method currently used[567]Both of these factors have led to new research advances using non-toxic polysaccharides, for which colon-specific degradation is specific. Therefore, the time-dependent system and the pH-sensitive system are the most commonly applied colon-specific drug delivery systems[8910].

Enteric polymers are employed because they can deliver the drug at a specific pH between 6 and 7 pH some polymers, such as both types of Eudragit S&L and methacrylic acid/methyl methacrylate copolymers, dissolve, which is equivalent to distal ileum drug release.[11].

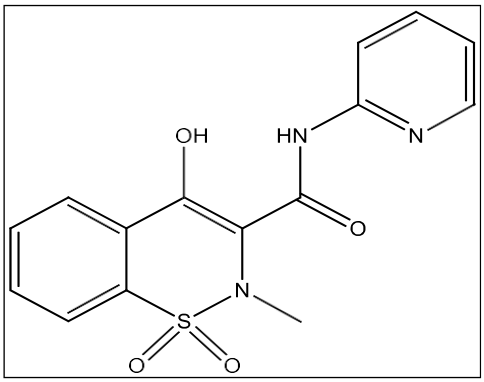
There are a variety of treatments that can be administered directly to the colon, including anti-inflammatory, antibiotic, antibacterial, antiamoebic, and protein drugs[12].

NSAIDs, which are nonsteroidal anti-inflammatory drugs, are frequently used as a remedy inflammatory condition and are showing promise in the prevention of colitis and the treatment of colon cancer[131415].

Anti-inflammatory Piroxicam works by interfering with the synthesis of prostaglandins, which is derived from oxicam. NSAIDs are known to work therapeutically by inhibiting the cyclooxygenase enzyme piroxicam is used to treat rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, dysmenorrhea, and acute gout with antipyretic, analgesic, and anti-inflammatory properties[16].According to recent research, colon cancer chemotherapy may be improved by using piroxicam[1718].

Taking into consideration all of the above, our goal with this study was to create piroxicam enteric-coated time release matrix tablets using the pH-dependent polymer Eudragit S100 and HPMC as time-dependent polymer.

Figure 1: Chemical structure of Piroxicam



MATERIALS AND METHODS

Materials

Piroxicam sample was taken as a gift from KP labs, Hyderabad, India. Sodium alginate and Eudragit S100, HPMC K4M, were procured as a gift sample from KP lab Hyderabad, India. Everything else in the study was of analytic grade, including the chemicals and reagents.

Methods

Preparation of PXM Matrix Tablets

PXM Tablets (average weight 150 mg) were prepared by direct compression (Jacoby, et al., (1996), Each tablet contains Lactose, polymer (HPMC K4M, Sodium alginate), Talc, and Magnesium Stearate. A mesh No. 60 was used to make sure the good mix was complete and uniform. A tablet punching machine used a 7mm round, flat, and plain punch to compress the carefully mixed materials. (Table 1 and 2). Tablets have been tested for various qualities including: friability, weight variation, thickness hardness and hardness as well as dissolution in various media

Table1: Composition of PXM-HPMCK4M matrix tablets

Ingredients (mg)	F_1	F_2	F_3	F_4
PXM	20	20	20	20
HPMC K4M	15	30	60	90
Lactose	109	94	64	34
Mg stearate	3	3	3	3

Talc	3	3	3	3
Total weight (tablet)	150	150	150	150

Table 2: Composition of PXM-Sodium alginate matrix tablets

Ingredients (mg)	F_5	F_6	F_7	F_8
PXM	20	20	20	20
Sodium alginate	15	30	60	90
Lactose	109	94	64	34
Mg stearate	3	3	3	3
Talc	3	3	3	3
Total weight (tablet)	150	150	150	150

The enteric coating of core tablets with coating material Eudragit S-100 containing 0.5% plasticizer in the polymeric solution prepared in acetone.The coat weight was increased by 10%-20% (165mg and 180 mg) of matrix tablets. (Table 3)

Table 3: Composition of PXM enteric coated core tablets

ingredients (mg)	F_9	F_{10}
PXM	20	20
HPMC K100M	60	60
% Coat Weight	10	20
Lactose	64	64
Mg stearate	3	3
Talc	3	3
Total weight (tablet)	165	180

Characterization of the powder mixture

The physicochemical properties of blends are what determine tablet quality. Formulations and processes involved in mixing can all have an impact on the final blend's characteristics. To make sure the blend was of high quality, the following equations were put to the test (Table 4).

1-Angle of reposetan(θ) = h/r

2-Bulk density

$\rho_b = M / Vo$

3-Tapped density

$\rho_{tap} = M / V_f$

4-Powder compressibility

Carr's Index = $[(\rho_{tap} - \rho_b) / \rho_{tap}] / \times 100$

Where :(h) is the height of the cone , (r) radius of the cone base, (M) weight of sample, (V0) volume of powder and (V_f) tapped volume of powder.

Evaluation of tablets

Physicochemical characterization of tablets

A variety of quality control tests were performed on the developed formulations' core and matrix coated PXM tablets, including tests for hardness, weight variation, friability, thickness, and drug content (PXM).

Weight variation test

Using a digital balance and 20 tablets, the researchers calculated the average weight of each tablet. The percentage weight deviations of each tablet were calculated using the formula below.

$$\% D = (I_W - A_W) / A_W \times 100$$

Where: (%D) The percent weight deviation, (I_W) Individual weight and (Aw) Average weight. (Table 5).

Tablet hardness

Using a Monsanto hardness tester, we measured the average and standard deviation of the hardness of six different formulations of matrix tablets (both core and enteric-coated).(Table 5).

Tablet thickness

There were twenty tablets measured with a Digital Micrometer (Digital Caliper, Aerospace, India), and the mean (average) thickness for each formulation (core and enteric-coated tablet) was computed. (Table 6).

Friability

The Roche friabilator was used to evaluate each formulation's degree of friability (Electro lab, Mumbai, India). Tablets (20) were put in a friabilator and rotated at 25 rpm for 4 minutes. Friability was calculated by weighing again and then computing the percent loss of weight for each tablet. (Table 5).

$$\% \text{ Friability} = [(W_1 - W_2) / W_1] \times 100$$

Where, W_1 = Initial weight of 20 tablets; W_2 = Weight of the 20 tablets after testing

Determination of drug content

PXM enteric-coated, and core tablets were analysed for drug content. Ten tablets had been pulverized into a fine powder. 50 mg of PXM powder weighed accurately, transferred to a methanol-containing volumetric flask of 100 mL and sonicated for five hours to ensure the PXM complete solubility. Methanol was used to bring the volume up to 100ml. UV-Visible spectrophotometer was used to measure absorption at 333nm as the maximum wavelength after the solution was appropriately diluted. An estimated drug concentration was derived from the calibration curve (Figure 2).

***In-vitro* drug release studies**

0.1N HCl was used to test the PXM core tablets for2hrs followed by in phosphate buffer pH 5.5 for 3 hrs. than in phosphate buffer pH 7.4 for up to one day (24 hrs.).The dissolution studies employed the USP dissolution test apparatus (Apparatus 2, 50 rpm, 370.5°C).5ml aliquots were taken at various intervals (keeping the sink going) and analyzed spectrophotometrically at 333 nm as the maximum wavelength. (Table 7,8, and 9).

Evaluation of release rate kinetics

The drug release kinetics were explained using various test models (Table 10). We used the data to investigate how drug release rates are calculated using models such as zero-order, first-order, Korsmeyer-Peppa, and Higuchi:

1- Zero-order release rate kinetics

$F= K_o t$

2- First-order release rate kinetics

$Log (100 - F) = kt$

3- Korsmeyer and Peppas release model

$M_t/M_\infty=Kt^n$

4- Higuchi release model

$F = K_H t^{1/2}$

Where "F" is the value of the drug release at the time, "M_t/M_∞" is a fraction of drug release at time, "n" is the release exponent and "K_0, K, K_H" represent Zero-order release constant, First-order release constant, Higuchi release constant and Korsmeyer and Peppas release constant. In order to calculate the values of K0, K, and KH, we fitted the release data to the appropriate equations.

IR spectroscopy

Between 600 and 4000 cm-1, PXM infrared spectra on FTIR were captured to identify drug-excipient interactions in physical mixtures of the drug (PXM) and excipient and placebo. On an FTIR spectrometer, we measured the sample's IR spectra using the KBr disc method (Perkin Elmer BX-I System). The resulting spectra were compared to see if there were any differences in the peak heights (Figure 5).

RESULTS AND DISCUSSION

Powder characterization

Table 4 shows the results of testing different powder formulations for micrometric properties such as bulk and tapped densities, angle of repose, and compressibility index.

Table 4: Micromeritic characterization of the powder mixture

Formulation code	Angle of Repose (°)	Bulk density (gm/cc)	Tapped Bulk density. (gm/cc)	Carr's Index (%)
F_1	30.22±1.34	0.324±0.032	0.392±0.068	20.169±0.59
F_2	29.33±1.22	0.312±0.056	0.402±0.078	17.417±0.24
F_3	31.25±1.45	0.313±0.041	0.396±0.065	18.180±0.68
F_4	30.46±1.36	0.343±0.025	0.388±0.048	19.844±0.67
F_5	28.32±1.23	0.335±0.085	0.425±0.095	20.753±0.67
F_6	29.75±1.15	0.342±0.059	0.402±0.018	19.317±0.52
F_7	30.25±1.25	0.355±0.023	0.449±0.037	21.184±0.42
F_8	31.22±1.64	0.346±0.075	0.446±0.064	20.100±0.82
F_9	30.56±1.36	0.353±0.025	0.398±0.038	18.634±0.77
F_{10}	29.66±1.46	0.343±0.035	0.418±0.048	19.744±0.57

Between 0.312 to 0.365 is the bulk density, while between 0.386 to 0.469 is the tapped density. This varies from 27.121.13 to 32.121.84 for the angle of repose and from 15.769 to 22.17 for compressibility index (%). The powder mixture has fair to passable flow properties, as indicated by the angle of repose (< 35) and compressibility index (< 23).(Table 4).

Evaluation of Tablets

PXM Tablet Characteristics

Direct compression with lactose as a vehicle was used to compress PXM powder directly into a matrix core tablet[19]. According to the results, the PXM core tablets had a uniform drug content, with a mean percent drug content of 99.21.76 percent. (Table 5). PXM's core tablets have a hardness range of 4.4±0.58 to 6.0±0.76kg/cm2. The PXM tablets also passed the friability test, with a weight loss of between 0.26% and 0.78%. The thickness of the core matrix tablets was calculated to be 5.74±0.023 mm. It was found that the enteric-coated tablet thickness ranged from 6.38±0.74 to 7.57±0.039 mm and from 0.64±0.74 to 1.83±0.039 mm for coated tablets, respectively (Table 6) For tablets that contain more than 300 mg, the pharmacopeial limit was ±2.5% in weight variation tests. According to the Indian-Pharmacopoeia (1996), the pharmacopoeia deviation limit was within all tested tablet formulations' average percentage deviation (both core and matrix coated). Thus, the formulated tablets of PXM in the study were found to have the required characteristic.

Table 5: QC tests of PXM core and compression coated tablets.

	Hardness (Kg/cm^2)	Weight variation (mg)	Friability (%)	Drug Content (%)
F_1	5.1±0.71	151.2±1.66	0.38	94.9±0.31
F_2	5.0±0.45	149.4±1.22	0.36	97.8±1.54
F_3	5.3±0.32	148.6±2.34	0.27	101.2±0.5
F_4	5.2±0.35	147.1±2.58	0.34	99.7±0.28
F_5	5.3±0.54	150.3±1.46	0.26	102.0±0.76
F_6	4.5±0.60	151.3±2.35	0.54	95.8±0.71
F_7	4.2±0.78	149.6±1.73	0.64	98.2±0.28
F_8	6.0±0.76	151.2±2.03	0.59	96.4±0.61
F_9	5.0±0.25	150.1±2.58	0.44	98.6±0.28
F_{10}	5.0±0.25	151.1±1.68	0.34	99.6±0.28

Table 6: Thickness of core and enteric-coated tablets

Formulation Code	Total Thickness of Tablets	Coat Thickness (mm)

	(mm)	
Core	5.54±0.033	-
F9-F10	6.48±0.64to 7.67±0.029	0.63±0.54 to 1.73±0.039

***In-vitro* dissolution data**

A USP paddle method was used to determine the in-vitro dissolution profile of all the prepared formulations under various pH conditions and for varying periods to assess the formulations' suitability for colon specificity. In Table 7-9 and Figure 4-6, sodium alginate formulations' cumulative percentage release was calculated and tabulated, and they were found to be poor compared to HPMC formulations. However, F4 formulation, which releases drug release in a sustained manner up to 98% after 15 hours, dissolved and released PXM faster than the core tablets (F4 formulation contains 60% HPMC K4M). As a result of these findings, it can be said that HPMC K4M is superior to sodium alginate in this study. When compared to other batches, the F4 formulation prepared with 60% HPMC K4M released more drugs, so it was chosen for enteric coating.

Insoluble in an acidic medium, anionic acrylic polymer such as Eudragit S100 have carboxyl groups, and only dissolve in the neutral to the weakly alkaline medium of the small intestine[20].

On exposure to alkaline dissolution fluids, the coat gets broken down then drug release has occurred in a controlled manner on exposes of core tablets. Hydration of HPMC K4M causes swelling and the tablet's surface is covered with a viscous gel layer which slows down the release from the core tablets by diffusion. From the dissolution of enteric-coated tablets, it was indicated that the Eudrgit has a clear effect on prolonging drug release, and further it was gradually increased by increasing the coating thickness. From the comparison of F4, F9, and F10 formulations (Table 9 and Figure 4), F10 is the better formulation that has shown only 8% drug release in upper GIT (5 hrs. lag period equal to upper GIT transit time) and gradually increased up to 97% drug release in 21 hrs. (most of the drug released in the colon).

Table 7: *In vitro* dissolution studies of PXM-HPMC K4M matrix tablets

Figure2: In vitro dissolution studies of PXM-HPMC K4M matrix tablets

Time(hr.)	F_1	F_2	F_3	F_4
0	0	0	0	0

1	73.96±1.23	68.48±2.01	48.32±1.59	31.07±1.89
2	84.5±1.23	74.06±2.31	57.78±2.35	41.93±1.56
4	99.25±1.35	84.42±1.03	71.56±2.45	47.02±1.56
5	-	99.87±1.04	83.77±1.67	54.55±1.45
7	-	-	95.59±1.59	62.79±1.23
9	-	-	-	77.05±1.35
11	-	-	-	91.82±1.34
15	-	-	-	98.04±1.56

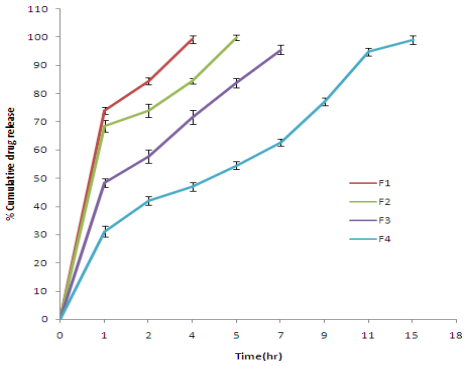


Table 8: In vitro dissolution studies of PXM-Sodium alginate matrix tablets

Figure 3: *In vitro* dissolution studies of PXM-Sodium alginate matrix tablets

Time(hr)	F_5	F_6	F_7	F_8
0	0	0	0	0

1	70.84±1.05	45.34±.99	39.93±1.25	68.48±.01
2	83.8±1.05	64.99±.25	49.58±1.25	82.5±.98
4	99.37±1.09	71.39±1.56	59.39±1.56	92.91±1.62
5	-	78.6±1.65	74.7±1.45	108.4±1.82
7	-	92.26±1.25	89.04±1.25	-
9	-	-	-	-
11	-	-	-	-
15	-	-	-	-

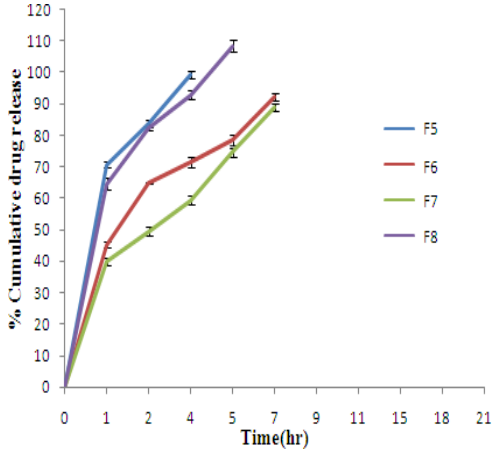
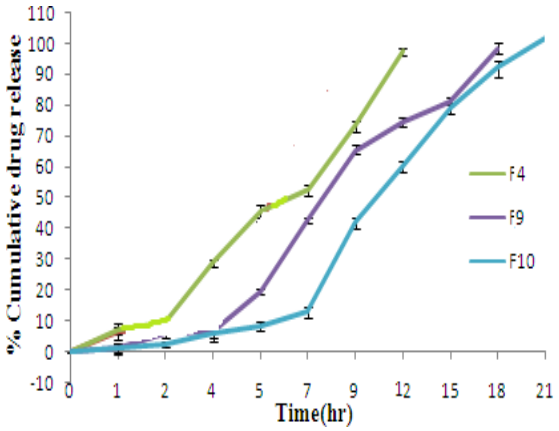


Table 9: Effect of Eudrgit on drug release from PXM enteric coated tablets

Figure 4 Effect of Eudrgit on drug release from PXM enteric coated tablets

Time (hr)	F_4	F_9	F_{10}
0	0	0	0
1	31.07±1.89	1.02±1.56	0.99±1.59
2	41.93±1.56	5.98±1.64	2.59±.95
4	47.02±1.56	6.38±1.68	5.98±2.67

5	54.55±1.45	19.63±1.02	8.46±1.45
7	62.79±1.23	42.63±1.05	12.78±1.56
9	77.05±1.35	65.37±1.45	41.90±1.76
11	91.82±1.34	74.56±1.25	59.98±1.87
15	98.04±1.56	81.35±1.02	78.87±1.78
18		98.37±1.58	91.90±2.67
21		-	97.37±1.59



Kinetic results

Models such as the Korsmeyer Peppas, Higuchi, zero-order, and first-order kinetics are used to establish the mechanism and kinetics of PXM drug release as shown in Table. As their r2 values range from 0.905 to 0.984, most tablet formulations follow the zero-order release method. A non-fickian diffusion (super case-II) fits best because its r2 values range from 0.884 to 0.961 and its n value is higher than one. (Peppas., 1985). This shows that polymer swelling, relaxation, and erosion control drug release, which is dependent on zero-order kinetics of release.

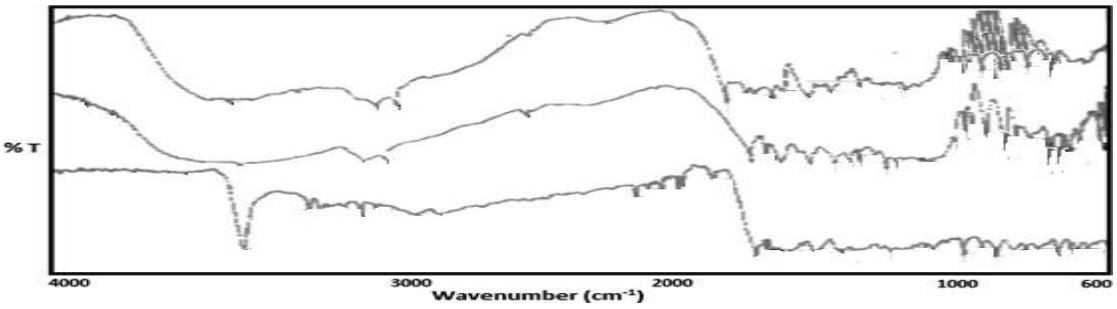
Table 10 :Drug release kinetics

Formulation Code	Zero order	First order	Higuchi	Korsmeyer Peppas
F_4	0.905	0.885	0.974	0.951
F_9	0.923	0.721	0.943	0.884
F_{10}	0.984	0.859	0.717	0.961

FTIR Studies

In the infrared spectrum, the characteristic absorption bands of pure piroxicam were found to be: tertiary amine at 3337.9cm-1, aromatic C-H stretching at 3102, 3067cm-1,aliphatic CH3 stretching at 2931,2879cm-1, C-H stretching of pyridine at 3067, 3031cm-1, amidic keto group at 1629 cm-1, sulphoxide stretching at 1065, and 2-substituted pyridine bending mode at772-731cm-1.Figure 12 shows no drug-polymer interaction in FTIR spectra for the powder mixture of the optimized formulation because the drug's absorption peak could still be found in the mixture.

Figure 5: FTIR Spectra of a) physical mixture of F10 formula, b) placebo c) PXM pure drug



CONCLUSION

Enteric-coated tablets containing a combination of HPMC K4M, a time-dependent polymer, and Eudragit S100, a pH-sensitive polymer, can prevent the upper gastrointestinal system from releasing PXM (i.e., stomach and small intestine). Formulation F10 was found to be the most effective and promising system for delivering PXM to the colon in patients with inflammatory bowel disease (IBD).

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CONFLICT OF INTEREST

The author declares that it does not have conflict of interest.

Corresponding Author: Mohammed Abduljalil*

Address: Y.B. Chavan College of Pharmacy, Dr.RafiqZakaria Campus, Aurangabad, Maharashtra, India.

Phone number: +91 9160262759

E-mail: mohamjallil22@gmail.com

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