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A NOVEL FORMULATION OF CELECOXIB IN THE TREATMENT OF FAMILIAL ADENOMATOUS POLYPOSIS

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ABSTRACT

In the present study, an attempt was made to prepare celecoxib modified release tablets using a controlled release polymer HPMCK4M and an enteric polymer Eudragit L100-55 in the treatment of Familial Adenomatous Polyposis (FAP) a condition where numerous polyps mainly in the large intestine are present, which may be cancerous. According to European Medicines agencies celecoxib can be used to treat FAP, so tablets were prepared using varying concentrations of polymers by direct compression method. The selected polymers were found to be compatible as proven by FTIR study. Pre compression and post compression parameters data was found to be satisfactory and *in vitro* dissolution data proved that formulation F3 exhibited prolonged drug release for 6 hrs in intestinal pH where the drug was expected to release to treat intestinal polyps. Enteric polymer use prevented the drug release in stomach region pH as shown by the *in vitro* dissolution data.

INTRODUCTION

In the area of oral delivery, a growing attention has been given over the past few decades on the design and manufacturing of advanced formulations intended for release of bioactive compounds to selected regions of the gastrointestinal tract. By controlling the site of drug liberation throughout the gut, it would be possible to limit the tolerability issues associated with treatments that mainly affect specific GI districts, enhance the bioavailability of drugs that regional differences in their stability and/or permeability profiles or, alternatively, improve the therapeutic outcome in the management of widespread local pathologies (e.g. phlogosis, ulcers, microbial infections, motility disorders). Due to inherent anatomical characteristics and physiological role, the colon has long been considered unsuitable for absorption of substrates other than water or small inorganic ions and, consequently not viable as a release site for systemically acting drugs. However, it has been representing as elective GI region for targeted delivery of locally acting molecules. Currently the benefits sulting from selective release of steroidal and non steroidal anti inflammatory drugs into the large bowel are well recognized and widely exploited in clinics for the long term therapy of IBD, including crohn's disease, ulcerative colitis.[1]

Familial Adenomatous Polyposis (FAP), also known as familial polyposis coli, is a hereditary disease characterized by the progressive appearance of numerous polyps mainly in the large intestine. Polyps develop as early as in childhood. The average number of polyps in FAP patients is around 1,000, but this may vary between 100 and 2,500. Polyps are initially benign but can easily become cancerous. FAP may lead to cancer of the large intestine, and as such is a life-threatening condition. Available therapeutic methods consisted of endoscopic surveillance with removal of polyps when required. Prophylactic surgery to remove a part of the large intestine is performed if the polyps are numerous or the polyps are becoming cancerous. The patients also receive genetic counselling as the disease is inherited.[2] Celecoxib is an anti-inflammatory medicine. Its mode of action has been attributed to the inhibition of prostaglandin synthesis, via inhibition of an enzyme (protein molecules that act as catalysts in the cells biochemical reactions) called cyclooxygenase-2 (COX-2). Prostaglandins are a class of hormone-like (chemical messenger) lipids (fats) present in tissues and bodily fluids.

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They are involved in processes such as pain, inflammation and kidney function. In FAP, Celecoxib is thought to induce cell death, and thus prevent or delay the growth of polyps. Hence in this study an attempt was made to prepare oral controlled release celecoxib tablets using pH dependent solubility polymers like eudragit and a rate controlling polymer like HPMC in different ratios.

MATERIALS AND METHODS

Materials

Celecoxib was obtained as a gift sample from Hetero labs and all other ingredients like eudragit, HPMCK4M, aerosil, microcrystalline cellulose were purchased from sigma aldrich and they are of Pharamceutical grade and safe to use.

Experimental

Preparation of tablets

Required quantities of pure celcoxib, polymers, diluent, and lubricant, anti-adherant were passed through sieve no 100 and weighed accurately as per formula F1 to F4 given in **table no 1**. The above ingredients were mixed in mortar for 30 min. The mixed powder was compressed into tablets using 8 mm punches of compression machine.

Evaluation tests

Bulk density (D_b)

The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder (m) was carefully poured into the graduated cylinder and volume (V_0) was measured. The bulk density was calculated by using formula

$$D_b = m/V_0.$$

The increase in bulk density of a powder is related to its cohesiveness.

Tapped density (D_t)

Required grams of powder (m) was introduced into a clean, dry 100 ml measuring cylinder. The cylinder was then tapped 100 times from a constant weight in a tap density tester and tapped volume (V_i) was read. The tapped density was calculated using the following formula,

$$D_t = m/V_i$$

Carr's Index (CI)

The simplest way for measurement of free flow of powder is compressibility. Compressibility indices are a measure of the tendency for arch formation and the ease with which the arches will fall and as such, it is a useful measure of flow. Carr's index is calculated as follows

$$C.I = [(D_t - D_b)/D_t] \text{ X } 100$$

Hausner's Ratio (HR)

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula

$$HR = D_t/D_b$$

Angle of repose (θ)

It is defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane. Open ended cylinder method was used. When powder was poured into an open ended cylinder after placing onto a horizontal surface, it forms a cone. The angle is a measure of the cohesiveness of the powder, as it represents the point at which the inter particle attraction exceeds the gravitational pull on a particle. A free - flowing powder will form a cone with shallow sides and hence a low angle of repose, while a cohesive powder will form a cone with steeper sides. Angles less than 30 are usually indicative of good flow, while powders with angles greater than 40 are likely to be problematic.

$$\theta = \tan^{-1} (h / r)$$

Where,

h : height of the pile.

r : radius of the base of the pile.

Application

During tabletting, improper flow of granules from the hopper leads to under – fill or over filling of die cavity. As a result, tablets will have weight variation and content uniformity.

Post-compression parameters

Weight variation test

20 tablets were selected randomly and average weight was determined. Then individual tablets were weighed and was compared with average weight. The comparison variation within the I.P limits, it passes the weight variation test.

Tablet hardness

Tablet crushing strength or hardness, the force required to break a tablet in a diametric compression, was measured using Pfizer tablet hardness tester.

Thicknes

The thickness of individual tablets was measured using Vernier calliper, which permits accurate measurements and provides information of the variation between tablets

Tablet friability

The friability of the tablets was measured in a Roche friabilator. Tablets sample of a known weight (W_0) were dedusted in a drum for a fixed time (100 revolutions) and weighed (W_1) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %.[3]

Table 1. Formulation ingredients

S.No	Ingredients	F1	F2	F3	F4
1.	Celecoxib	100mg	100mg	100mg	100mg
2.	Eudragit	12.5mg	25mg	31.25mg	37.5mg
3.	HPMC K_4M	12.5mg	25mg	31.25mg	37.5mg
4.	Aerosil (1%)	2.5mg	2.5mg	2.5mg	2.5mg
5.	Micro crystalline cellulose	122.5mg	97.5mg	85mg	72.5mg

Table 2. Pre-Compression Parameters of prepared formulations F1-F4

Parameter	F1	F2	F3	F4
Bulk density (g/ml)	0.35	0.3	0.34	0.55
Bulkiness (ml/g)	2.86	3.33	2.94	1.82
Bulk volume (ml)	4.4	7.4	6.4	3.5
Angle of repose (^{0})	21.30	17.74	24.08	27.89
Carr's Index (%)	27.3	38	15	32.9
Hausner's ratio	1.375	1.608	1.176	1.491
Flow ability (sec)	100	30	60	140

Table 3. Post Compression Parameters

Parameter	F1	F2	F3	F4
Thickness (mm)	4	4	4	4
Diameter (mm)	8	8	8	8
Uniformity of weight (mg)	238.3±11.69	243.3±17.51	243.3±5.16	250±20
Hardness (kg/cm^2)	13.4±1.4	12.8±1.4	11.7±3.43	13.1±0.8
Friability (%)	0.01	0.02	0.02	0.01

Determination was made in triplicate.

$$\% \text{ Friability} = \frac{\text{Initial weight of tablets} - \text{Final weight of tablets}}{\text{Initial weight of tablets}}$$

Assay

1 tablet was taken in mortar and powdered, then it is taken into 100 ml volumetric flask and 40 ml of ethanol was added and shaken for 30 min, the volume was made up to the mark with pH – 6.8 phospahte buffer. The above solution was suitably diluted and assayed for celecoxib content by measuring absorbance at 255 nm using UV- Spectrophotometer (UV - 3092).

In vitro Drug Release Studies

Dissolution rate test conditions

- Apparatus --USP-II, Paddle Method
- Dissolution Medium – pH 1.2 buffer for 2 hours and pH 6.8 phosphate buffer for next 6hrs
- RPM -- 75
- Sampling intervals (hrs) --0.5, 1,2,3,4,5,6,7,8
- Temperature-- 37°c + 0.5°c

Procedure

900ml o f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c + 0.5°c. The dissolution is carried in 0.1NHcl medium for 2hrs followed by pH 6.8 Phosphate buffer was taken and process was continued for 8 hrs at 75 rpm. At definite time intervals of 5 ml of the fluid was withdrawn, filtered and again 5ml fluid was replaced. Suitable dilutions were done with the sample fluid and analyzed by spectrophotometrically at 255 nm using UV-spectrophotometer.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

RESULTS AND DISCUSSION

The compatibility between the drug and the selected polymers were evaluated using FT – IR peak matching method. The IR spectra of pure drug and final formulation were shown in the **fig 1 and 2** respectively. The standard peaks 1159 cm^{-1} is due to S=O stretching, 3338 cm^{-1} by NH_2 stretching and 1563 cm^{-1} by N-H stretching.[4] There was no appearance or disappearance of peaks in formulation, which confirmed the absence of chemical interaction between drug and polymers.

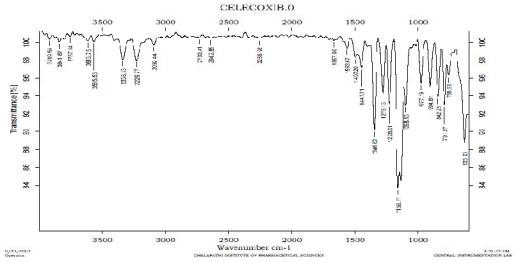


Figure 1.FTIR spectrum of pure drug celocoxib

Table 4. Comparative Dissolution data of prepared formulations F1 – F4

Time(hr)	% drug released			
	F1	F2	F3	F4
0.083	1.85	0.27	0.05	0.12
0.166	2.45	0.69	0.05	0.14
0.333	2.65	1.11	0.05	0.18
0.5	4.89	1.22	0.09	0.35
1	8.58	1.59	0.16	0.67
2	9.18	1.61	0.53	0.78
3	63.75	35.55	15.3	9.59
4	86.25	51.59	19.49	22.05
5	95.85	78.15	27.6	29.7
6	-	80.69	37.35	36.9
7	-	80.85	70.65	49.35
8	-	81.75	96.45	63.9

Table 5. Kinetic data of prepared formulations F1-F4

Formulation	Zero order plot		First order plot		Higuchi plot		Korsmeyer peppas plot	
	K_0	r	K_1	r	K_H	r	n	r
F_1	18.88	0.9626	0.491	0.9351	32.66	0.8997	0.997	0.9352
F_2	11.8	0.9635	0.228	0.7669	26.64	0.9329	1.373	0.9281
F_3	8.578	0.9713	0.200	0.9626	18.32	0.8538	1.846	0.9283
F_4	6.585	0.9272	0.089	0.9412	14.32	0.8953	1.501	0.9419

The numerical values of pre compression parameters like Hausner's ratio, carr's index and angle of repose were within the official limits and suggested excellent flow properties for all formulations as mentioned in the **table no 2.**

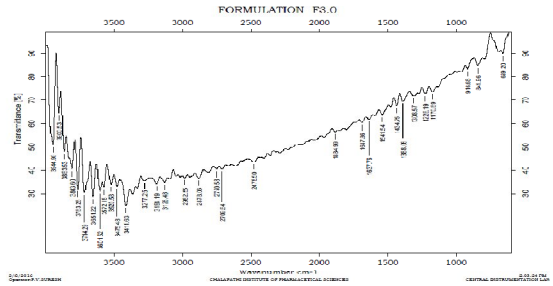


Figure 2. FTIR spectrum of formulation F3

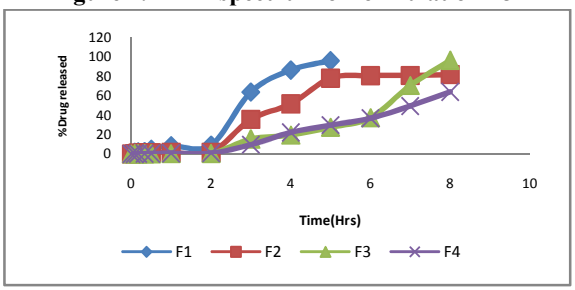


Figure 3. Zero order rate plot of formulations F1-F4

The punches used to compress the F1 – F4 tablets were 8 mm, round, concave shaped. The shape and size of the prepared tablets were found to be within the limit. The average weight was found to be within the prescribed limit. The hardness of the tablets was found to be 7kg/cm^2. Thickness of the tablets was found to be in the range of 4 mm. The friability of the tablets was found to be less than 1%. All the post compression evaluation parameters values were within the official limits and experimental results were given in the Table 3.

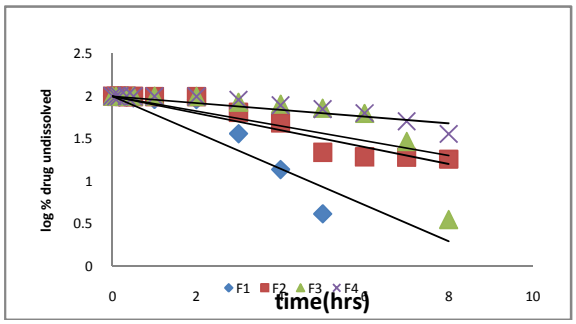


Figure 4. First order rate plot of formulations F1-F4

The prepared formulations were subjected to dissolution study and the obtained data were fitted into different kinetic modeling to identify the drug release model and mechanism. The comparative dissolution data and kinetic data were given in the **table 4 and 5** respectively. Graphs were plotted for each kinetic model and they were shown in the **figure 3, 4, 5 and 6.** The dissolution data revelaed that use of HPMCK4M and eudragit used at a concentration of 12.5% each in F3 released the drug for 8hrs upto 96% whereas other formulations does not show characteristic release patterns. Use of pH dependent polymer like eudragit does not release the drug in stomach region but released the drug for prolonged period in intestinal region for about 6 hrs. by fitting the data into kinetic models it showed that drug release follows zero order kinetics with diffusion mechanism with super case II transport as indicated by n value.

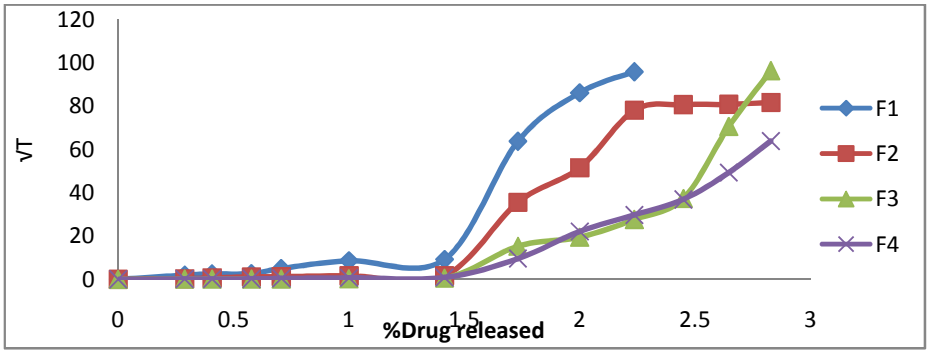
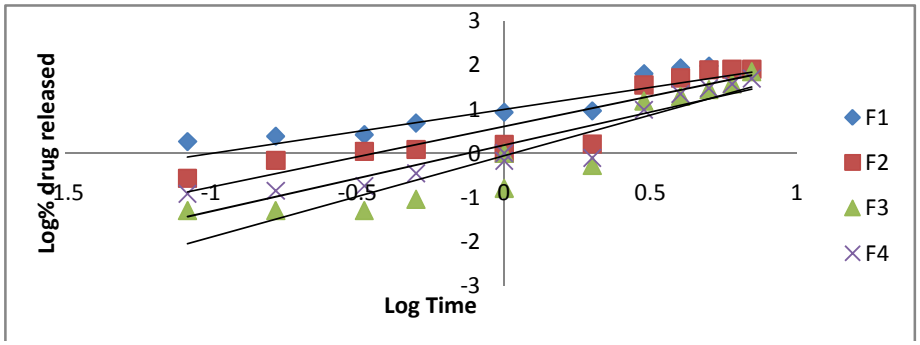


Figure 5. Higuchi plot of formulations F1-F4



CONCLUSION

In conclusion, the use of HPMCK4M with Eudragit permits the retardant drug release behaviour in gastric conditions and higher drug release at intestinal pH conditions, which are of great interest for the delivery of drugs required to be released at the site of action. Presence of eudragit in the tablets causes the release of drug in colon when administered orally.

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