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Preparation and evaluation of matrix tablets of indomethacin for colon specific delivery

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ABSTRACT

Matrix tablets of Indomethacin were prepared by wet granulation method. Guar gum and Pectin as a carrier, 10% starch paste, Dicalcium phosphate is used as diluents and the mixture of talc and magnesium stearate at 2:1 ratio were used. All the prepared formulations were evaluated for hardness, drug content uniformity and were subjected to in vitro drug release studies with and without rat caecal contents. The highest in vitro dissolution profile at the end of 24 h was shown by F1 followed by F7, F8. The other formulation F2, F3, F4, F5, and F6 were failed to target in colon and these formulation releases the majority of drug within 10 h of study.

Key words: Colon targeted, Pectin, Guar gum, Indomethacin, Matrix tablets, Rat caecal content.

INTRODUCTION

Colorectal cancer, is a cancer from uncontrolled cell growth in the colon or rectum (parts of the large intestine), or in the appendix as shown in Fig.1. Most colorectal cancer occurs due to lifestyle or habits (*Midgley et al., 2005*). The additional risk factors related to colon cancer, includes gender and ethnicity with a higher risk in male than female and black than white (*Soetikno et al., 2005*), old age, presence of adenomatous polyps, previous history of ovary, uterus or breast cancer, smoking and alcohol drinking habits physical inactivity and inflammatory bowel diseases. Cancers that are confined within the wall of the colon are often curable with surgery while cancer that has spread widely around the body is usually not curable and management then focuses on extending the person's life via chemotherapy and improving quality of life (*Greenwald et al., 2001*).

Colorectal cancer is the fourth most commonly diagnosed cancer in the world (*Lieberman et al., 2005*) but it is more common in developed countries. Colorectal cancer incidence rates are 5-10 times higher in the most developed regions of the world than in developing regions (*WHO., 2009*). It is estimated that worldwide, 1.23 million new cases of colorectal cancer were clinically diagnosed in 2008 that killed 608,000 people. It typically starts in the lining of the bowel and if left untreated, can grow into the muscle layers underneath, and then through the bowel wall.

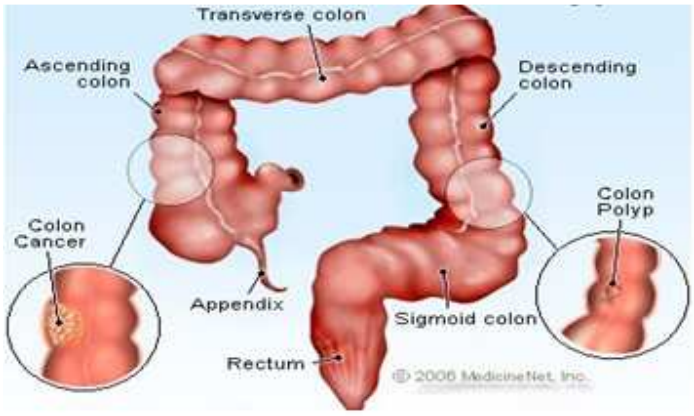

Figure 1: Colon with cancerous cell

The symptoms and signs of colorectal cancer depend on the location of tumor in the bowel and whether it has spread elsewhere in the body. Symptoms include rectal bleeding and anemia which are sometimes associated with weight loss, changes in bowel habits, fever, loss of appetite, and nausea or vomiting. Localized bowel cancer is usually diagnosed through sigmoidoscopy or colonoscopy.

Classification of Antineoplastic Agents / Anticancer
1. Alkylating Agents: Nitrosoureas, Ethyleneimines, Alkylsulfonates, Ifosfamide
2. Antimetabolites: Folate Antagonists: Methotrexate, Purine antagonists, Pyrimidine antagonists, 5- Florouracil, Cytarabibe
3. Natural Products: Vincristine and Vinblastine

Administration of exogenous hormones such as estrogen in hormone replacement therapy as well as regular use of non-steroidal anti-inflammatory drugs is reported to exert some protective effects against colon cancer (*Strate et al., 2005*). Colon drug delivery is a relatively recent approach for the treatment of diseases like ulcerative colitis, crohn's disease, colorectal cancer and amoebiasis (*Venkatesh et al., 2009*). Colonic delivery can be accomplished by oral and rectal administration. Rectal dosage forms such as suppositories and enemas are not always effective since a high variability in the distribution of these forms is observed. Suppositories are only effective in the rectum because of the confined spread and enemas solutions can only offer topical treatment to the sigmoid and descending colon. Absorption or degradation of the active ingredient in the upper part of the GIT tract is the major obstacle and must be circumvented for successful colonic delivery (*Krishnaiah et al., 2001*). Colon- specific delivery systems are also gaining importance for the systemic delivery of proteins and peptide drugs, due to negligible activity of brush-border membrane peptidase activity and less activity of pancreatic enzymes, (*Kiyoung et al., 1999*). Besides this low hostile environment, the colon transit time is long i.e. 20-30 hrs (*Khar et al., 2002*) and the colonic tissue is highly responsive to the absorption enhancers. Colon-specific drug delivery systems, which can deliver drugs to the lower gastrointestinal tract without releasing them in the upper GI-tract, can be expected to decrease the side-effects of the drugs and improve the quality of life for patients suffering from colon specific diseases (*Fujino et al., 1995*).

Approaches for Drug Targeting
There are several ways in which colon-specific drug delivery has been attempted. (*Chaurasia et al., 2004 and Krishnaiah et al., 2002*).

- The use of carriers that degrade exclusively by colonic bacteria
- Coating with pH dependent Polymers
- Time dependent dosage forms
- Prodrugs

Targeting of drugs to the colon by the oral route could be achieved by different approaches including matrix and coated systems, for which the drug release is controlled by the gastrointestinal pH, transit times or intestinal flora. The method by which the drug release will be triggered by the colonic flora appears to be more interesting with

regard to the selectivity (*Rubinstein et al., 1990*). The human colon has over 400 distinct species of bacteria as resident flora, a possible population of up to 10^{10} bacteria per gram of colonic contents. A number of synthetic azo polymers and natural or modified polysaccharides degraded by the human colonic flora have thus been investigated as colonic drug delivery carriers (*Chien et al., 1992*).

The present investigation is aimed by using the inexpensive naturally occurring polysaccharides pectin and guar gum for colon targeted drug delivery. They are having following advantages,

1. Retards drug release in the tracts of upper GIT
2. Consist of biodegradable polysaccharides as main constituents
3. They are degradable by a wider range of microbial species

Guar gum is a natural polysaccharide derived from the seeds of the *cyomopsis tetragonolobus* (Family Leguminosae). It contains about 80% galactomannan, 12% water, 5% protein, 2% acid soluble ash, and 0.7% fat (*Manjana et al., 2010*). Due to its high molecular weight it is metabolized in large intestine due to the presence of microbial enzymes. Guar gum is hydrophilic in nature and swells in cold water forming viscous colloidal dispersions or sols. The gelling property of guar gum retards release of the drug from the dosage form as well as it is susceptible to degradation in the colonic environment (*Kumar et al., 2009*).

Pectin is a polysaccharide extracted from fruit and vegetable cell walls (*Rajpurohit et al., 2010*). Depending on the plant source and preparation they contain varying degree of methyl ester substituent (*Kumar et al., 2009*). These polysaccharides remain intact in the physiological environment of the stomach and the small intestine, but are degraded by the bacterial inhabitants of the human colon. Pectin is suitable for use as colon-specific drug delivery vehicle in treatment of colon cancer and other colon diseases as it is selectively digested by microflora in colon and exhibits potential to prevent colon cancer from the implication of diet (*Wong et al., 2011*).

Active pharmaceutical ingredient i.e. Indomethacin when administration on long term basis inhibit the growth and metastasis of human tumour by non selectively inhibiting cyclo-oxygenase. It inhibits the cell proliferation. So it is selected as model drug.

MATERIALS AND METHODS

Materials

Indomethacin from La Pharma Pharmaceutical Pvt. Limited, Ludhiana (gift sample), Guar gum and Pectin Central Drug House (P) Ltd. New Delhi and all chemicals used are of analytical grade.

Preparation of matrix tablets

Matrix tablet of Indomethacin were prepared by the wet granulation technique using 10 % starch paste as shown in Table 1. Dicalcium phosphate was used as diluent, the mixture of talc and magnesium stearate at 2:1 ratio was used as lubricant. The composition of different formulation is shown in Table no.4.1.Each batch containing 75 mg of Indomethacin. The powdered ingredients were blended and granulated with 10% starch paste. The wet granules were dried at 50 ºC for 2 h. The dried granules were lubricated with a mixture of talc and magnesium stearate (2:1). The lubricated granules were compressed into tablets by tableting machine.

Table 1: Composition of matrix tablets with formulation code

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8
Indomethacin	75	75	75	75	75	75	75	75
Guar gum	100	100	100	150	150	150	200	200
Pectin	100	150	200	100	150	200	100	150
Diluents	160	110	60	110	60	10	60	10
Starch	50	50	50	50	50	50	50	50
Talc	10	10	10	10	10	10	10	10
$MgCo_3$	5	5	5	5	5	5	5	5
Total wt. (mg)	500	500	500	500	500	500	500	500

Evaluation of tablets

Physical evaluation of matrix tablets: The prepared tablets were evaluated for diameter, thickness, hardness, friability, weight variation and drug content.

Thickness and Diameter: Twenty tablets were randomly selected from each batch and there thickness and diameter was measured by using digital vernier caliper.

Friability: Twenty tablets were weighed and placed in the roshee friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dedusted and weighed again. The percentage friability was measured using the formula,

$$\% F = \{1-(Wt/W)\} \times 100$$

Where,
% F = Friability in percentage
W = Initial weight of tablet
Wt = Weight of tablets after revolution

Hardness: The crushing strength kg/cm^2 of prepared tablets was determined for 10 tablets of each batch by using monsanto tablet hardness tester. The average hardness and standard deviation was determined.

Weight Variation: 20 tablets were selected at random and average weights were determined. Then individual tablets weighed and the individual weight was compared with the average.

Uniformity of drug content: The matrix tablets of Indomethacin were tested for their drug content using 20 tablets. Quantity of the powder equivalent to 10 mg of Indomethacin was weighed and dissolved in ethanol and diluted further to estimate drug concentration using UV spectrophotometer at 320 nm.

Measurement of swelling index: Swelling index was found out using 10 ml of 0.1 N HCL (2h), in phosphate buffer pH 7.4 (3h) and pH 6.8 (24h). The tablets were removed at 2, 18 and 24 h. Excess water was removed using filter paper. The swollen tablets were reweighed and the swelling index of each tablet was calculated using the following equation.

$$\% \text{ Swelling index} = \frac{W_2 - W_1}{W_1} \times 100$$

W_1= Initial weight
W_2= Final weight

Drug-excipient compatibility study: Pure drug and prepared formulations were tested for compatibility study using IR spectrophotometer. It was found that the prepared formulations were compatible with the drug and the polymer.

Dissolution studies: In vitro drug release study was conducted at 37 ºC and 100 rpm for 2 h in 900 ml buffer of pH 1.2. The dissolution medium were replaced with 900 ml of pH 7.4 phosphate buffers and tested for drug release up to 3 h. Drug release study was continued for 24 hours in 6.8 pH phosphate buffer. Samples of 10 ml aliquot were withdrawn at predetermined time intervals and were replaced with fresh dissolution medium. Samples withdrawn were assayed spectrophotometrically at 320 nm in UV spectrophotometer.

Preparation of rat caecal contents: The caecal content is taken out from the albino rats by following procedure:
5 male Albino rats weighing 150-200 gm were maintained on normal diet and incubated with Teflon tubing and 1 ml of 2% w/v dispersion of guar gum in water and administered directly into the stomach. The tubing was removed and this treatment was continued for 7 days. Thirty minutes before the commencement of drug release studies the rat caecal content was taken out. The animal was given anesthesia and was maintained on surgical plan throughout the procedure. Hairs were removed from the abdomen by keeping the animal on dorsal side upward. Cut was made to the peritoneal skin. Large intestine was taken out and the caecal content from caecal region was removed by syringe and then survival surgery of rat was done. The caecal contents were transferred into pH 6.8 Sorenson's phosphate

buffer previously bubbled with CO_2, to have the final concentration 4% w/v. Then dissolution studies were done in the presence of rat caecal contents.

RESULTS AND DISCUSSION

Evaluation parameters of tablets: The Indomethacin matrix tablets were prepared by wet granulation method. The results of physicochemical evaluation of prepared tablets are shown in Table (2). The tablets were evaluated for weight variation, drug content, hardness, thickness, diameter and friability.

Table 2: Evaluation of prepared tablets

Batch	Thickness (mm)	Diameter (mm)	Hardness (Kg/cm^2)	Weight variation (IP)	Friability (%)	Drug Content (%)
F1	6 ± 0	12	5.9 ± 0.57	Passed	0.70	100.07 ± 0.08
F2	6 ± 0.5	12	6 ± 0.57	Passed	0.65	98.89 ± 0.42
F3	6 ± 0.5	12	5.9 ± 0.57	Passed	0.58	99.12 ± 0.09
F4	6 ± 0	12	6 ± 0.14	Passed	0.63	98.45 ± 0.16
F5	6 ± 0	12	5.7 ± 0.11	Passed	0.62	99.41 ± 0.09
F6	6 ± 0	12	5.5 ± 0.12	Passed	0.54	99.41 ± 0.09
F7	6 ± 0	12	5.9 ± 0.01	Passed	0.67	98.67 ± 0.24
F8	6 ± 0.5	12	5.8 ± 0.15	Passed	0.61	99.91 ± 0.12

Data of in vitro drug release studies

Cumulative percentage release of Indomethacin on various concentrations of guar gum and pectin as shown in Table 3.

Table 3: *In vitro* release data of Indomethacin matrix tablets

Cumulative % drug release	*Formulations (± S.D)							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
2h	8.23± 0.03	12.45± 0.26	23 ± 0.18	2.91± 0.19	27.56 ±0.23	3.45 ± 0.17	18.41± 0.31	8 ± 0.34
5h	23.66± 0.28	28.12± 0.62	36.21± 0.14	7.67± 0.11	34.41± 0.43	10.33± 0.40	29.93± 0.46	25.65± 0.49
10h	35.46± 0.17	35.49± 0.28	41.21± 0.41	25.89 ±0.38	49.31± 0.41	21.56 ± 0.33	48.59± 0.43	39.43± 0.22
12h	53.12± 0.35	49.21± 0.21	53.32± 0.07	42.34 ±0.63	56.48 ±0.38	56.59 ± 0.39	61.31± 0.53	52.69± 0.33
18h	67.45± 0.13	56.9 ± 0.10	65.42± 0.18	57.13± 0.61	61.67± 0.17	66.78 ± 0.61	76.23± 0.35	74.56± 0.58
24h	93.43± 0.18	65.48 ±0.60	70.41± 0.47	61.03± 0.54	64.34± 0.28	77.98 ± 0.47	83.45± 0.17	81.45± 0.33

** Each value is the average of three determinations*

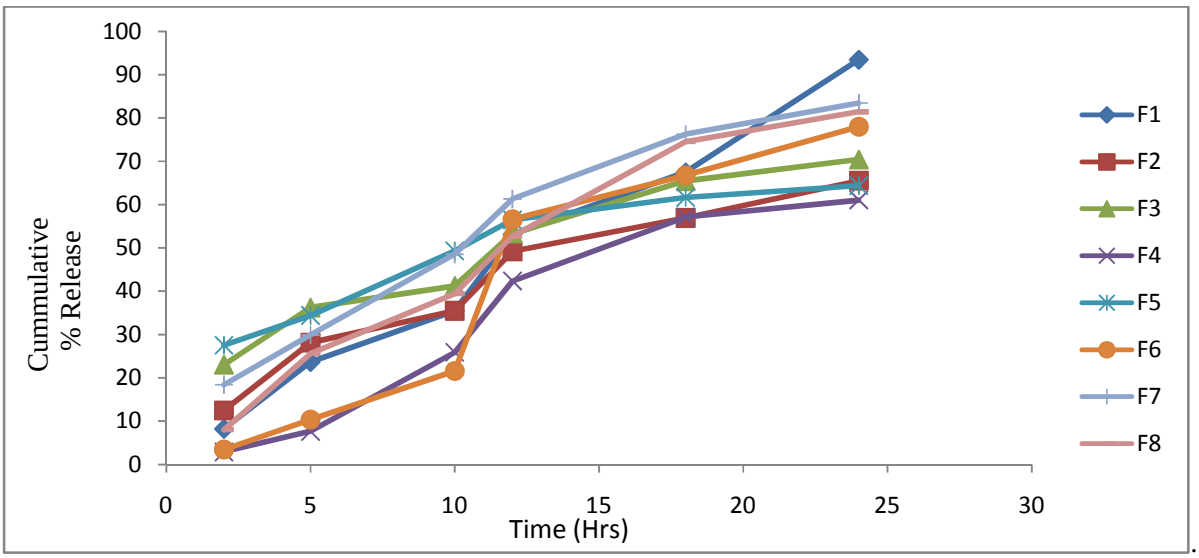

Figure 2: Cumulative percentage release profile of Indomethacin

***In vitro* drug release studies of prepared matrix tablets in presence of rat caecal content.**

In vitro drug release from matrix tablets of formulation F1 in 0.1 N HCL (2h), in pH 7.4 (3h), and in pH 6.8 (24h) with rat caecal contents.

Table 4: *In vitro* release data of indomethacin with rat caecal content

Cumulative percent drug release	Formulation(F1)
2h	3.98 ± 0.10
5h	18.59 ± 0.30
8h	39.26 ± 0.20
12h	57.05 ± 0.22
15h	65.01 ± 0.53
18h	79.28 ± 0.19
21h	88.63 ± 0.21
24h	98.48 ± 0.36

DISCUSSION

In the present work colon targeted matrix tablets were prepared by wet granulation technique using Indomethacin as a model drug and natural polymers guar gum and pectin for colon targeting. The formulations were evaluated for physical parameter like diameter, thickness, hardness, friability and drug content. Evaluations of other parameters like swelling index, in vitro drug release were also conducted.

CONCLUSION

Colorectal cancer, is a cancer from uncontrolled cell growth in the colon or rectum (parts of the large intestine), or in the appendix. It is forth most commonly diagnosed cancer in the world. The incidence rates are 5- 10 times more in developed countries. Symptoms of the disease include rectal bleeding and anemia which are sometimes associated with weight loss, changes in bowel habits, fever, loss of appetite, and nausea or vomiting. So in order to treat this disease colon targeted delivery of Indomethacin is designed using natural polysaccharides i.e. pectin and guar gum for site specific delivery. These carriers were degraded by colonic bacteria hence delivering the drug colon region.

The different ratios of guar gum and pectin were used in matrix tablets. Matrix tablets were prepared by wet granulation technique using 10% starch paste. Batches of matrix tablets were prepared as per the composition given in Table 4.1.Every batch was evaluated for flow properties, physical properties of tablets, friability testing, weight variation, and drug content and release profile. Formulation containing guar gum and pectin in 1:1 ratio gave maximum release in 0.1 N HCl, phosphate buffer pH 6.8 and pH 7.4 and in the presence of rat caecal content.

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