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Colon targeting oral matrix tablets of mesalamine: Design, development and *invitro* evaluation

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ABSTRACT

The principle in this present research is to formulate Mesalamine containing colon targeted tablets by using different polymers and evaluate the effect of different polymers in drug release pattern. The matrix tablets of Mesalamine are formulated by polysaccharides based polymers like Cellulose acetate phthalate (CAP), Ethyl cellulose (EC), Guar gum (GG) and Xanthan gum (XG) which protects the drug to release in Stomach and Small Intestine. The invitro drug dissolution investigation of F2 (GG and XG) Matrix tablet was controlled by swelling into a viscous gel in colonic pH, which have been accomplished as the best tablet. The optimized tablet F2 was found to be stable in stability study (short term) with reproducible evaluation data, which also shows the highest swelling index, increased viscosity in colonic pH. The drug release pattern from the F2 formulation follows swelling and erosion behavior. From the data it show that F2 tablets suitable for providing colon targeted drug delivery.

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INTRODUCTION

The general objective for ideal treatment is to coordinate the requirements of the patient by enhances the effectiveness and safety of in-take drugs. Different medication approaches have constantly played a difficult and significant role in guaranteeing and anticipating the delivery of promising and effective medications to the objective site of delivery in the human body. Oral medication is the favored route of delivery. Although oral delivery has become a broadly acknowledged site of administration of therapeutic drugs, the gastrointestinal (GIT) tract presents a few imposing obstructions to drug delivery. Present scenario, impressive attention has grown in colon targeting drug delivery system [1, 2].

Colon precise delivery of drug has increased expanded significance, not only for the delivery the drug to colon but it also targets the therapeutic peptide and proteins in colon tissues. To accomplish effective colon focutilized drug delivery, a drug should be shield from degradation, release followed by absorption in the upper segment of the GIT followed by controlled discharge of drug in proximal portion of colon. Medication changes through covalent linkages with carrier, prodrug approach and preparation based methodologies can be utilized for colonic delivery [3, 4].

The chance to decrease unfavorable impacts in the treatment of colonic inflammation and colonic motility diseases carried out by topical utilization of medications active at the mucosal level. Oral delivery of medications to the colon is significant in the treatment of ailments like carcinomas, ulcerative colitis, chron's disease and infections. The one of a kind metabolic movement of colon, which makes it as an elective organ for drug delivery sys-

tem. Mesalamine is an anti-inflammatory agent fundamentally utilized in treatment of Inflammatory Bowel Disease (IBD's) [5, 6].

Mesalamine is the 5-amino derivative of salicylic acid and therefore is related structurally to salicylates. Though it is not considered as a true salicylates, as there is limited in-vitro evidence of metabolism of Mesalamine to salicylates (ionized salicylic acid). Mesalamine is the most active and exceptionally safe anti-inflammatory action as compared to any other NSAID in its class. Therefore Mesalamine was selected to carry out to develop colon targeting tablet for treatment of IBD's. This type of system will be able to deliver approximately 100 % of drug to the site where causative organism of disease is present. Colon targeted drug delivery system (colon targeted tablet) inhibits drug release GIT and releases most of the drug into colonic lumen. Availability of drug at targeted site will be near to 100 %. Since, in colon targeting drug delivery system most of drug that is present in system (colon targeted tablet) is targeted to colonic lumen where inflamed tissues are present. Thus almost drug is available to these inflamed tissues [7, 8].

To improve the target specificity of pH dependent systems (large variation in pH of GIT) and variable results with time dependent systems (variation in small transit time and emptying time in GIT) led to development of alternative technique for colon specific drug delivery based on a variety of like pectin and its salts, inulin HP, chondrotin sulphate, amylose and guar gum etc [9, 10].

The present project is based on to develop a colon targeted specific formulation which delivers the drug that is Mesalamine in the colon by using the approaches of degradable disaccharides and pH sensitive polymers. Mesalamine is utilized as effectively treat Crohn's disease and Ulcerative colitis. Mesalamine is unstable in stomach, rapidly absorbed in the small intestine and which leads to significant adverse events and consequently a very less concentration of drug reaches the target site of action, as Mesalamine is required in a sufficient concentration in the local tissues of the colon to elicit its anti-inflammatory effects. Therefore, the development of solid dosage forms that release the drug in the colon, independent of the physiological environment is required. This present formulation aims to deliver the drug as per the requirements explained earlier. The formulation employs a disaccharide, a sugar that is responsible for the drug release, via the activity of the microorganisms present in colon. Depending upon the depletion of the pH sensitive polymer coatings and degradation of that disaccharide this system is capable to achieve a colon targeted delivery. Thus Mesalamine would be protected from the upper GI conditions and allowed for a rapid release in the designated colonic region [11–16].

At present colon targeted tablet of Mesalamine are available in the market employing only one type of formulation approach. Therefore it was proposed to develop such a formulation which employs more than one formulation approach, here the application of degradable disaccharides coupled with pH responsive polymers and that are degraded by the activity of the colonic microorganisms is done. This directly releases drug into colon for cure of ulcerative colitis and Crohn's disease. The developed colon targeted tablet formulation would be promising in reducing dose and dosing frequency of drug with more effective therapy than presently available products in market. Thus it leads to a dose reduction, enhanced safety and efficacy and a targeted delivery [17].

The purpose of this research is to formulate Mesalamine containing colon targeted tablets by using different polymers and evaluate the effect of different polymers in drug release pattern.

Materials

Mesalamine was acquired as a gift sample form Zydus Cadila, Gujarat, Guar Gum, Xanthan Gum, Cellulose Acetate Phthalate, Ethyl Cellulose; Lactose was purchased from Loba Chemicals, Mumbai. Equipments like UV-Visible spectrophotometer (Shimadzu, Japan), 16 Stations rotary tablet compression machine (Cadmach, Ahmedabad, India), FTIR Spectrophotometer (Bruker, germany), Dissolution test apparatus (Lab India) are utilized for formulation and evaluation of tables.

METHODOLOGY

Preformulation Studies

Drug - Polymers Compatibility Studies

A drug polymer study holds great importance in designing a formulation. In formulation of dosage form it is necessary to evaluate the possible interaction between the drug and polymers, to choose the polymer and excipients to formulate the stable product.

Fourier Transform Infra-Red Spectroscopy (FTIR) Study

Mesalamine mixed with polymers in the ratio (1:1). The prepared samples were scanned with FTIR (Perkin Elmer-Pharmaspec-1) over a wave number range 4000-400 cm^{-1} [18, 19].

Differential Scanning Calorimetry Study (DSC)

Mesalamine mixed with various polymers in the ratio of 1:1. The mixture of drug with polymers to maximize the like hood of obscuring an interaction. Over a temperature range, this will encompass any thermal changes due to the mixture of drug with polymers. Thermograms of pure drug are utilized as a reference. Differences in thermograms of drug with polymer are considered as interaction [20–22].

PREPARATION OF GRANULES AND COMPRESSION OF TABLET

The colon focused matrix tablets containing GG, XG, EC and CAP were formulated by wet granulation method. Lactose was utilized as diluents. Talc and Magnesium stearate (1:1) was utilized as a glidant and Lubricant. The composition of matrix formulation was detailed in Table 1. Pass all the ingredients through mesh No. 20 separately except magnesium stearate and Talc. Granulate the powder mix with granulating solution and mixed for 15 minutes. Wet mass was passed through mesh No. 12 to prepare wet granules. Wet granules are then dried at 50^0C for 30 min. The semidried granules are passed through sieve no 22 superimposed on mesh No. 44. Finally required quantity of magnesium stearate and talc were blended. . Accurately weighed 300 mg of granules were fed manually in to 16 stations Cadmach tablet compression machine and compressed with 14 mm flat faced punches The prepared granules were evaluated as follows Table 1 . [20–31].

Evaluation of micromeritic properties of granules

Angle of Repose

The angle of repose, was found out by the funnel method. The precisely weighed (10 gms) granules were taken funnel. The height of the funnel was balanced so that the tip of the funnel simply contacted the peak of the pile of granules. The granules were allowed to pour freely onto a clean surface. The angle of repose was calculated using the following equation

$q = \tan^{-1} h/r$

Where, h is the height of granules pile and r is the radius of the granules pile [28].

Bulk Density and Tapped Bulk Density

A precisely weighed (10 gms) granule was taken into a measuring cylinder. The volume occupied by the granules was measured which give bulk volume. The measuring cylinder was tapped until no further change in volume was noted which give the tapped volume. Both Bulk Density (BD) and Tapped Bulk Density (TBD) of granules were determined using the following formulae [29].

BD = Weight of the granules/Volume of the granules

TBD = Weight of the granules/Tapped volume of the granules

Carr's Compressibility Index and Hausner's ratio

The compressibility index and Hausners ratio of the granules was resolved utilizing following compressibility index formula [30, 31].

Carr's Compressibility Index (%) = [(TBD-LBD)/ TBD] x100

Hausner's ratio = tapped density /bulk density.

Physico-Chemical Properties of Tablets

Appearance

The tablets were inspected for any changes in physical appearance like colour, texture (chipping, capping and lamination).

Size and Thickness

The size and thickness of tablet can shift with no adjustment in weight because of distinction in Density of granulation, the weight applied to the tablets and speed of the tablet pressure machine. The thickness of the tablets was resolved utilizing a Vernier caliper. Three tablets from each sort of batch were utilized and normal qualities were determined [32]
.

Hardness

There is a sure prerequisite of hardness in tablets to withstand the mechanical stuns during dealing with, assembling, bundling and delivery. Hardness analyzer (Monsanto analyzer) was utilized to gauge hardness of tablets. The tablet was held along its elliptical hub in the middle of the two jaws of the analyzer. Now, perusing ought to be taken as a zero kg/cm2. At that point steady power was applied by turning the handle until the tablet broke. The incentive now was noted in kg/cm2.

Friability

Friability is the proportion of tablet quality. This test subjects various tablets to the joined impact of shock abrasion by using a plastic chamber which spins at a speed of 25 rpm for four minutes, dropping the tablets to a space of 6 inches in each upheaval. Preweighed tablets was put in Roche friabilator which was then operated for 100 revolutions. The tablets were then dedusted and rechecked. Percent friability (% F) was determined as follows,

% Friability = (Initial weight - Final weight / Initial weight) x 100.

Table 1: Composition of Colon Targeted Matrix Tablets of Mesalamine

Sl. No.	Ingredients (mg/tablet)	Formulations Code							
		F1	F2	F3	F4	F5	F6	F7	F8
1	**Mesalamine**	100	100	100	100	100	100	100	100
2	**Guar gum**	100	100	100	100	100	100	100	100
3	**Xanthan gum**	—	120	—	—	60	60	—	40
4	**Ethyl cellulose**	—	—	120	—	60	—	60	40
5	**Cellulose acetate phthalate**	—	—	—	120	—	60	60	40
6	**Starch paste (5%)**	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.
7	**Magnesium stearate**	2%	2%	2%	2%	2%	2%	2%	2%
8	**Talc**	2%	2%	2%	2%	2%	2%	2%	2%
9	**Lactose**	20	20	20	20	20	20	20	20

Weight Variation

The weight variety test is finished by taking 20 tablets haphazardly and they were weighed separately. The composite weight isolated by 20, gives a normal load of tablet. Not more than two of the individual weight veers off from the normal load by % deviation permitted and none should go astray by more than twice its rate.

Content Uniformity

The measure of the active substance can be determined by taking 10 tablets, they are weighed and powdered. Amount of powder identical to 10 mg of Mesalamine was weighed precisely into a 100 ml volumetric flask and dissolved with the aid of water. The solution was diluted to volume with water, blended and sifted. 1 ml of filtrate was diluted up to 10 ml water, blended and absorbance was measured at 298.5 nm utilizing UV Spectrophotometer.

Swelling Index of Tablets

The swelling properties of tablets were determined by setting the tablet grids in the disintegration tester containing 0.1N HCl at $37^oC \pm 0.5^oC$. The tablets were withdrawn back intermittently from the dissolution medium and softly smeared with a tissue paper to expelled overabundance test fluid and reweighed. The swelling index was calculated as follows:

$$Swelling\ Index = \frac{Weight\ of\ Swollen\ Tablet - Initial\ Weight\ of\ Tablet}{Initial\ Weight\ of\ Tablets}$$

In-vitro Dissolution of Tablets

The drug release studies examines were directed in 0.1N HCl, Phosphate buffer pH 7.4 and Phosphate buffer pH 6.8 containing rat caecal substance so as to emulate the conditions like the gastro intestinal tract of human body. The media have been utilized in the past to assess colon specific drug delivery, e.g., mimicked colonic liquid, human stool suspension.

Drug release studies in 0 1 N HCL

Drug release a study contemplates was done by utilizing USP dissolution type I test apparatus. The tablets were tried for drug release for 2 hours in 0.1N HCl (900ml) as the average gastric emptying time is about 2 hours. 1ml of tests were pulled back at the interval of 1 hour and diluted up to 10 ml with 0.1N HCl. The absorbance and concentration of mesalamine was estimated at 302 nm by using double beam UV spectrophotometer.

Drug release studies in pH 7 4 phosphate buffer

After drug release studies carried out in 0.1 N HCl, the dissolution medium was supplanted by pH 7.4 phosphate buffer (900ml) and analysed for drug release for 3 hours as the average small intestinal transit time is about 3 hours. 5 ml of test samples were withdrawn at the interval of 1 hour and diluted up to 5 ml with pH 7.4 phosphate buffer. The absorbance and concentration of mesalamine was estimated at 302 nm by using double beam UV spectrophotometer.

Preparation of rat caecal contents

To survey the susceptibility of guar gum being followed upon by the colonic microbes, drug release analysis was carried out in the presence of rat caecal contents due to its similitude with human intesti-

nal microflora. So as to incite enzymes explicitly following up on guar gum in the caecal, male albino rats weighing 150-200 gms and and kept up on typical eating regimen were hatched with Teflon tubing and 1 ml of 2% w/v dispersion of guar gum in water was administered into the stomach. The tubing was expelled and this treatment was proceeded for 7 days. 30 minutes before the beginning of medication discharge examines, four rodents were killed by spinal footing. The abdomen were opened, the caecam were disconnected, ligated at two ends, cut free and promptly moved in to pH 6.8 PBS. The caecal packs were opened; their substance were separately gauged, pooled and afterward suspended in PBS to give a last caecal weakening of 4% w/v.

Drug release studies in the presence rat caecal contents

The drug release studies were done utilizing a USP Dissolution Rate Test Apparatus with slight adjustments. The tests were done utilizing 100 ml of pH 6.8 PBS in a 150 ml beaker immersed in the water maintained in the jar, which in turn in the water kept up in the container. The tablets were set in the basket and submerge in the dissolution medium containing rat caecal matter. At the interval of 1 hour, 1ml sample was withdrawn without a pre-channel and supplanted with 1ml of new PBS and the analysis as proceeded as long as 7 hours The volume as made up to 10ml with pH 6.8 PBS. 1 ml of this solution withdrawn in to 10 ml volumetric flask and volume made sufficient with pH 6.8 PBS. At that point the supernatant was sifted and the filtrate was examined for Mesalamine released at 330.5 nm utilizing double beam UV spectrophotometer.

Kinetics of In-vitro Drug Release

To examine the release kinetics of In-vitro drug release, data was applied to kinetic models such as zero order, first order, Higuchi and Korsmeyer- Peppas to decide the mechanism of drug release from dosage form.

Stability Studies

Stability studies were done at 40°C / 75% RH for the best formulation for 3 months. The tablets were put away at 40°C/75% RH in shut high thickness polyethylene bottles for 3 months. The samples were withdrawn at 1, 2 and 3 months and examined for its hardness, drug content and In-vitro drug release.

RESULTS AND DISCUSSION

Drug - Polymers Compatibility Studies:

Fourier Transform Infra-Red Spectroscopy (FTIR)

The Interpretation of IR frequencies are appeared in Figure 1. The significant peaks are indistinguishable to functional group of Mesalamine. From the figure 1, It can be seen that, the major functional group peaks observed in spectras of Mesalamine with GG, XG, EC, CAP and Mesalamine with all the polymers stays unaltered as compared with spectra of Mesalamine. So from the IR spectra data it may be seen that there is no interaction between Mesalamine and Polymers utilized in the formulations (Figure 1).

Differential Scanning Calorimetry (DSC)

The consequence of DSC considers are given in above Figure 1. Unaltered Mesalamine demonstrated sharp endotherm at 274.22°C comparing to its liquefying point. There was no considerable change in the liquefying endotherms of Mesalamine with GG, XG, EC and CAP when contrasted with the thermogram of Mesalamine. Along these lines, it could be inferred that there is no interaction among Mesalamine and Polymers utilized in tablet (Figure 1).

Evaluation of micromeritic properties of granules

Formulations

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

The outcomes for angle of repose are indicated in Table 2. Angle of repose varies from 22.14±0.42 to 23.48 ± 0.12 The flow properties of granules in all formulations display good flow. The outcomes are appeared in Table 2. The estimations of BD and TBD were seen as in the range from 0.531±0.004 to 0.575±0.006 gm/ml and 0.60±0.002 to 0.64±0.002 gm/ml respectively. In this way, it shows that all batch having great flow properties and packability. The outcomes for Carr's Compressibility Index are recorded in Table 2 . The Carr's Compressibility Index were in the gone from 12.52 ± 0.182 to 13.32 ± 0.202%. This indicates good flow properties of granules. The outcome was summed up in Table 2. The Hausner's ratio was found in the range from 1.132 ± 0.022 to 1.162 ± 0.010. So it shows great flow properties.

Evaluation of Tablets

The tablets were experimental visually and didn't show any imperfections, for example capping, chipping and lamination after punching. The thickness of tablets in batches ranged from 4.12± 0.01 to 4.13 ± 0.010 mm. The values are recorded in Table 3. The percentage deviation from average

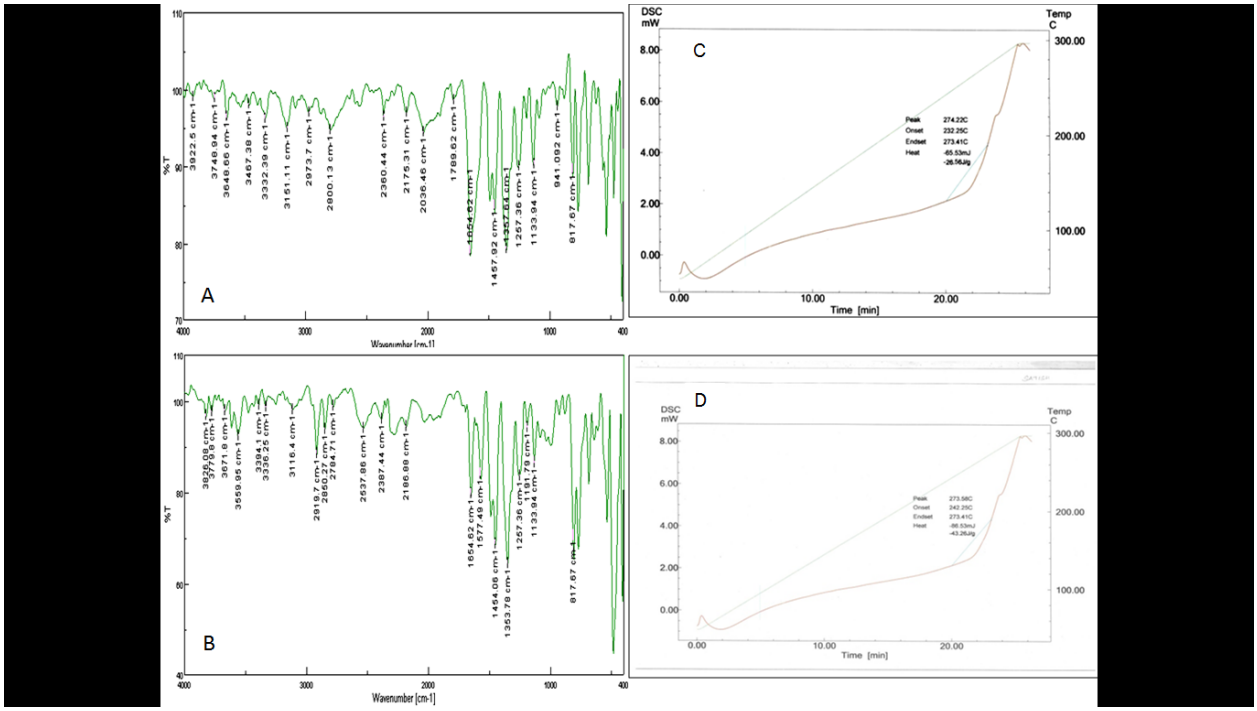

Figure 1: (A) IR Spectra of Mesalamine ; (B) IR Spectra of Formulation Mixture; (C) DSC Thermogram of Mesalamine ; (D) DSCThermogram of Formulation Mixture

Table 2: Micromeritic Properties of Prepared Granules

Formulations Code	Angle of Repose (θ) (^{o})	BD(gm/ml)	TBD (gm/ml)	Carr's Index (%)	Hausner's ratio
F1	22.14±0.42	0.531±0.004	0.60±0.002	12.60±0.162	1.152±0.002
F2	23.35±0.60	0.532±0.002	0.60±0.002	13.30±1.234	1.162±0.010
F3	24.36±0.11	0.533±0.002	0.62±0.004	13.32±0.202	1.151±0.002
F4	23.48±0.12	0.554±0.004	0.64±0.002	12.52±0.182	1.152±0.006
F5	24.40±0.93	0.552±0.006	0.62±0.002	13.02±1.510	1.132±0.022
F6	23.72±0.14	0.552±0.004	0.62±0.002	12.10±1.872	1.152±0.050
F7	24.44±0.25	0.574±0.006	0.64±0.002	13.14±0.432	1.142±0.020
F8	23.75±0.28	0.575±0.006	0.62±0.004	13.22±1.532	1.140±0.020

tablet weight for all the tablets varied from 0.98 to 1.52 %. The outcomes are with desired range and appeared in Table 3 as per IP. The results of Hardness of tablets was found that the values are ranged from 6.16±0.258 to 7.25±0.273 kg/cm^2, were acceptable and demonstrated great mechanical quality of tablets. The Percentage Friability are ranged from 0.27±0.030 to 0.42±0.023%. In this way, the rate loss of Friability of the considerable number of tablets was seen as under 1 %. Drug content was seen as uniform among various batches of tablets and varied from 96.32 ± 1.631 to 103.20 ± 1.520%. These outcomes showed that the all formulations having percentage drug content within the possible limits according to USP.

Figure 2: Comparison of swelling Index of formulations F1 - F8

Swelling Index Study

The most extreme swelling has been seen in formulation F2 prepared with Guar gum with Xanthan gum seen as to be 3.608 when compared with dif-

Table 3: Physico-Chemical Properties of Tablets

Formulatio	Thickness**(mr	Weight Variation(%)	Hardness** (kg/cm^2)	Friability* (%)	Drug Content* (%)
F1	4.12±0.01	1.42	6.33±0.258	0.29±0.096	97.49±1.134
F2	4.12±0.01	1.52	6.25±0.273	0.27±0.030	103.20±1.520
F3	4.12±0.01	1.13	6.75±0.273	0.33±0.074	99.41±0.760
F4	4.13±0.01	1.32	6.83±0.258	0.34±0.025	96.32±1.631
F5	4.12±0.01	1.32	7.25±0.273	0.42±0.023	96.39±1.069
F6	4.13±0.01	1.24	6.16±0.258	0.34±0.008	97.39±0.712
F7	4.12±0.01	1.32	6.75±0.265	0.38±0.052	103.06±0.609
F8	4.12±0.01	0.98	6.33±0.258	0.35±0.008	100.98±0.977

Drug Content* (%). *All the values are expressed as a mean SD., n = 3

ferent plans as appeared in Figure 2. The formulation F2 contains both Guar gum and Xanthan gum, the water take-up limit of this is more when compared to F1, which contains guar gum alone and it was seen that the proportionality in swelling capacity with drug release pattern. The formulations F3 and F4 containing EC and CAP along with GG seen to be lesser swelling Index 2.522 and 2.960 respectively. Formulations F5 to F8 containing XG, EC, and CAP in a combination along with GG also seems to be lesser swelling Index than the other remaining matrix tablet indicating lesser uptake of buffer. The comparative swelling Index data of all the formulations were appeared in Figure 2. From this Figure, it tends to be seen that the swelling Index of various formulations diminished in the accompanying order; F2 > F1 > F4 > F3 > F7 > F5 > F8 > F6

In-Vitro Dissolution Profile of Tablets

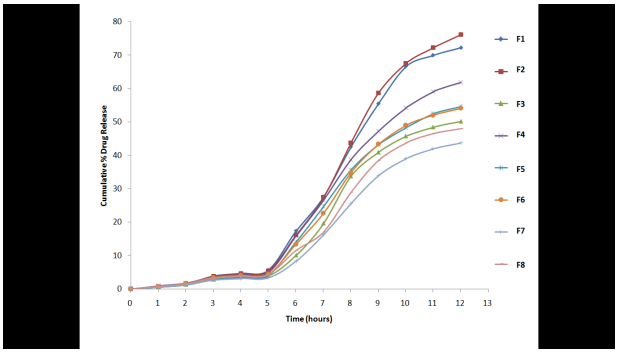

Figure 3: Cumulative % Drug release profile of formulation F1 - F8

The motivation behind colon targeted drug delivery system is not only to shield the medication from being released in the physiological condition of the Stomach and Intestine but also to release the drug in the colon after enzymatic degradation of polysaccharides from the matrix tablets. Henceforth the capacity of the gums utilized in the formulations (F1 to F8) to hold the uprightness of tablets in upper GIT were evaluated by conducting drug release studies in 0.1N HCl for 2 hours and pH 7.4 phosphate buffer for 3 hours (Figure 3). Following 5 hours of testing not over 6% of Mesalamine was released from any formulations (F1 to F8). This shows that GG, XG, EC, CAP are equipped for shielding the medication from being released totally in the physiological condition of stomach and small intestine. On introduction to dissolution fluids, a gum experiences hydration and forms the viscous gel layer that hinders further leaking in drug dissolution fluid towards the matrix tablet. The drug release from formulation F1 having GG alone was seen as 72.203% at 12 hrs. This is because lesser buffer uptake capacity of guar gum alone. But the Tablet F2 containing GG and XG showed the drug release of 76.10% toward the finish of 12 hours. This maximum drug release may might be because of the most elevated Swelling Index of tablet. Results of drug released from formulation F3 and F4 containing EC and CAP in mix with GG were found to be 50.19% and 61.88% separately towards finish of 12 hrs. The drug released from formulation F5-F7 containing different combinations of XG, EC and CAP along with GG were found to be 54.64%, 54.06% and 43.72% respectively at the end of 12 hrs. F8 formulation containing all the polymers shows the drug release of 48.05%. Drug release from all the tablet formulations followed diffusion control mechanism with R^2 value nearer to one.Kinetics of In-vitro Drug Release

Kinetics of In-vitro Drug Release

The drug diffusion through most type of polymeric system is regularly best depicted by Fickian diffusion (diffusion exponent, n=0.5), however different procedure notwithstanding to diffusion are important. There is additionally an unwinding of the polymer chain, which impacts the drug release mechanism. This procedure is depicted as non- fickian or anomalous diffusion (n=0.5-1.0). Release

from initially dry, hydrophilic glassy polymer that swell when added to water and become rubbery, show anomalous diffusion because of the adjustment of macromolecular chain. The thermodynamics state of the polymer and penetrant concentration are responsible for the different type of the diffusion. A third class of diffusion is case-II diffusion (n=1), which is an extraordinary instance of non-Fickian diffusion. To get active parameter of dissolution profile, information were fitted to various active models.

CONCLUSION

An effective colon targeted drug delivery system was frame worked with the activating system that reacts to the physiological conditions specific to colon. From the dissolution study and other data of F2 Matrix tablet containing Guar gum and Xanthan gum was concluded as the best formulation by comparing to other tablets, which showing the most desired drug release and shows a maximum potential in providing colon targeted drug delivery tablet.

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Conflict of Interest

Authors declared no conflict of interest.

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