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Formulation and Evaluation of Colon Targeted Drug Delivery

Amresh Kumar[1]*, Md. Zulphikar Ali[2], Himani Tiwari[3] and Kaushal Kishor Chandrul[4]

1, Student of B. Pharm. 4th Year; 2, Assistant Professor; 3, HOD; 4, Principal

Department of Pharmacy, Mewar University, Gangrar Chittorgarh, (R.J.) - India

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Abstract

The primary aim of this study is to create a targeted drug delivery system for Mesalamine, specifically aimed at the colon. Nine different formulations of Mesalamine tablets were developed using a combination of microbial degradation polymers such as Inulin, Locust bean gum, and Xanthan gum, along with MCC, PVPK30, magnesium stearate, and talc through the direct compression method. Various parameters including hardness, weight variation, drug content uniformity, friability, and in vitro drug release were evaluated for all the prepared tablets. FTIR studies indicated the absence of interactions between the drug and polymers. Among the formulations, F9 demonstrated the highest in vitro drug release of 96.25% over 12 hours, thus establishing it as the optimized formulation.

Key words: Mesalamine, Microbial degradation polymers, Colon targeted drug delivery systems

Introduction

Colon targeted drug delivery system

Colon-targeted drug delivery systems have gained significance due to the advantages they offer over conventional oral drug delivery methods. Historically, oral ingestion has been the preferred route for drug delivery due to its convenience and high patient acceptance. The oral route allows for sustained and controlled release systems, offering greater flexibility in dosage form design compared to parenteral routes. However, targeting specific regions of the gastrointestinal tract, such as the colon, has become a focus for modified release technologies.

Directing drug delivery to the colon has several benefits. It enables targeted treatment at the site of the disease, leading to lower dosing requirements and reduced systemic side effects. Moreover, the colon can serve as a gateway for systemic drug absorption, enhancing the efficacy of therapeutic interventions. In the case of conditions like ulcerative colitis, which affects the colon and rectum, targeted drug delivery becomes even more crucial.

The drug under investigation in this research, Mesalamine, is a monohydroxybenzoic acid derivative known for its anti-inflammatory properties. To develop a colon-targeted drug delivery system, various materials were employed, including Mesalamine itself, as well as guar gum, xanthan gum, karaya gum, PVP K30, microcrystalline cellulose, magnesium stearate, and talc. These materials play essential roles in formulating the drug delivery system to achieve the desired release profile and target the colon effectively.

***Corresponding Author**

Preparation of Standard Calibration Curve For Mesalamine:

Accurately weigh 100mg of Mesalamine and will be transferred into a 100ml of volumetric flask. Suitable Buffer(pH 1.2) will be added to dissolve the drug and the primary stock solution was made by adding 100ml of suitable solvent which is 1000µg/ml. From this primary stock 10ml will be transferred into another volumetric flask and made upto 100ml with simulated gastric fluids pH 1.2. From this secondary stock different concentrations of 5, 10,15, 20, 25, 30 µg/ml will be prepared respectively. The absorbance will be measured at 261nm using U.V spectrophotometer. Similarly, Mesalamine standard graphs will be plotted in simulated intestinal fluids (pH 6.8) and for pH 7.4 respectively, by following the above procedures and calibration curves will be plotted respectively.

FT-IRspectroscopy

The infrared spectra of mesalamine, physical mixture of drug (mesalamine) and excipients and placebo willbe recorded between 400 to 4000 cm-1 on FTIR to detect the drug-excipients interactions. The IR spectra forthe test samples will be obtained using KBr disk method using an FTIR spectrometer . The resultant spectrawillbecomparedforanypossiblechanges in thepeaks of thespectra.

DifferentialScanningCalorimetry(DSC)

The possibility of any interaction between drug, polymers, and its mixture of part I and II was assessed byDSC (SHIMADZAU).The thermogram of the samples were obtained at a scanning rate of 10°C/min.conducted over a range of 0- 300°C under an inert atmosphere flushed with nitrogen at a rate of 20 ml/min.Preparation of Mesalamine Tablets : Each tablet(average weight 700 mg) for consists of Mesalamine,MicrobialdegradationpolymerslikeInulin,Locustbeangum&Xanthangum,PVPK30,MCC,Magnesuimsterate and Talc. The materials will be weighed, mixed and passed through mesh no:60 to ensure completemixing and the powdered blend will be evaluated for pre-compression parameters like angle of repose, Bulkdensity, Tapped density, Hausner's ratio respectively and the thoroughly mixed materials will be directlycompressedintotablets using12mm roundflat andplainpunches usingmultiple stationtablet machine.

Tablet quality control tests such as weight variation, hardness, friability, thickness and dissolution in differentmediawill beperformedon the matrix tabets.

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Tablet quality control tests such as weight variation, hardness, friability, thickness and dissolution in differentmediawill beperformedon the matrix tablets.

Evaluationofthelubricatedblend:

Angle of repose :A glass funnel was selected to with a stem of 15-30 mm and fixed to the funnel stand; agraph paper was placed on table. Granules were allowed to flow to form a heap. The circumference of theheap was marked and measured the height of the pile using two rulers. The height was measured and noted itas (h).The area (πr2) was determined, radius(r) was calculated and substituted in the formula (θ =tan-1 h/r). toobtainthe angle ofrepose. Repeated theexperiment twicemoreandcalculate averageangle of repose.

Tanθ = h/r

Thereforeθ= Tan-1h/r

Bulkdensity: Weighaccurately 25goflubricated blend,whichwas previouslypassedthrough 20#sieveandtransferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read theunsettledapparentvolume (V0).Calculate theapparent bulkdensity ingm/ml bythefollowing equation.

Bulkdensity=Weightof powder/Bulk volume

Tapped density: Weigh accurately 25 g of drug, which was previously passed through 20# sieve andtransferredin

100mlgraduatedcylinder.Thenmechanicallytapthe cylindercontainingthesample byraisingthe cylinder and allowing it to drop under its own weight using mechanically tapped density tester thatprovides a fixed drop of 14±2 mm at a nominal rate of 300 drops per minute. Tap the cylinder for 500 timesinitially and measure the tapped volume (V1) to the nearest graduated units, repeat the tapping an additional750 times and measure the tap volume (V2) to the nearest graduated units. If the difference between the twovolumes is less than 2% then final the volume (V2). Calculate the tapped bulk density in gm/ml by thefollowingequation.

Tappeddensity = Weightofpowder/ Tappedvolume.

Carr's Index : Compressibility index of the powder blend was determined by Carr's compressibility index. Itis a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula forCarr'sindex is as belowequation:

Carr'sindex(%)= [(TD-BD)×100]/TD

Hausner'sRatio: Hausner'sRatio isa numberthatiscorrelatedtotheFlowabilityofapowder .TheformulaforHausner'sRatio is asbelow equation.

Hausner'sRatio= TD/BD

Table1:FormulationChart ofMesalamine Tablets usingMicrobialDegradation Polymers

Ingredientsmg/tablet	F1	F2	F3	F4	F5	F6	F7	F8	F9
Mesalamine	400	400	400	400	400	400	400	400	400
Inulin	100	125	150	-	-	-	-	-	-
Locustbeangum	-	-	-	100	125	150	-	-	-
Xanthangum	-	-	-	-	-	-	100	125	150
PVPK 30	16	16	16	16	16	16	16	16	16
MCC	154	129	104	154	129	104	154	129	104
Magnesium stearate	16	16	16	16	16	16	16	16	16
Talc	14	14	14	14	14	14	14	14	14
Total	700	700	700	700	700	700	700	700	700

Evaluationoftablets:

Fivetabletsfromallbatcheswererandomlyselectedan dorganolepticpropertiessuchascolour,odourandsha pewereevaluatedand the data was presented.

Thickness:

The thickness for all the 5 tablets for all batches was measured using vernier calipers. The diameter was alsodeterminedby using verniercalipers. Thicknessand diameterdatawas presented.

Hardnesstest:

Hardness of for five tablets for all the batches was tested using monsanto hardness tester.. The tester consistsofa barrelcontainingacompressiblespringheldbetweent woplungers.Thelowerplungerisplacedincontact with the tablet and a zero reading is taken. The upper planger is then forced against a spring by turninga thread Bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barreltoindicate theforce, which is a measureof hardness.

Friabilitytest:

The Roche Friabilator was used for this test,the device subjects as number of tablets to the combined effectsof abrasion and shock by utilising a plastic chamber that revolves at 25 RPM for 4 minutes by dropping thetabletsfromthedistance of6inches witheachrevolution. Normallyapreweighed tentabletsareplacedinthefriabilatorwhich is operated for100 revolutions. Thetabletsarethen dedusted andreweighed.

Amaximum loss of weight not greaterthan 1%present is acceptablefor mosttablets.

%Friability = (Initial weight –Final weight) ×100Initialweight

Weightvariationtest

Weighed 20 tablets selected at random and calculate the average weight. Then percentage deviation from theaverage was calculated. According to IP standards, not more than two of the individual weight deviate fromthe average weight by more than the percentage shown in the table below, and none deviates by more thantwicethat percentage.

Drugcontentuniformity: The test for uniformity of single dose preparations is based on the assay of the individual contents of theactive substance of a number of single dose units to determine whether the individual contents are set withinlimitswith referenceto theaveragecontent ofthe sample.

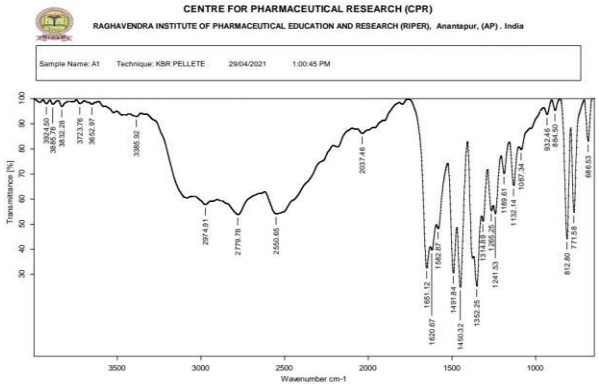
***Invitro* drug releasestudies :**

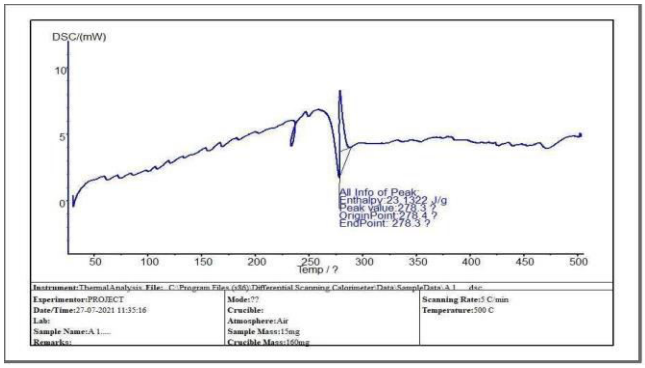
Drugreleasestudiesofmatrixtablets:

The matrix tablets containing 400 mg of mesalamine will be tested in SGF (pH 1.2), and SIF (pH 6.8)solutionsfortheirdissolutionrates.Dissolutionstudieswillbeperformedusing USPdissolutiontestapparatus (Apparatus 1 50 rpm, 37±0.5 °C). At various time intervals, a sampleof 5 ml will be withdrawn andreplaced with equal volume of fresh medium. The samples will be analyzed spectrophotometrically at 261 nm.The release of diloxanidefuroate from matrix tablets will be carried out using USP basket-type dissolutionapparatusatarotationspeedof100rpm,andatemperatureof37±0.5°C.Fortablets,simulationof gastrointestinal transit conditions will be achieved by using different dissolution media. Thus, drug releasestudies will be conducted in simulated gastric fluid without pepsin (SGF, pH 1.2) for the first 2 h as theaveragegastricemptying timeis about2 h. Then, the dissolution mediumwill bereplaced withenzyme-free simulatedintestinalfluid(SIF,pH 6.8)andtestedfor drug releasetomimic coloniconditions. Drug release will be measured from Mesalamine matrix tablets and will be added to 900 mL ofdissolutionmedium.Sampleswillbewithdrawnatvarioustimeintervalsandwereanalyzedspectrophotometricallyat261 nm

Fourier Transform Infrared (FT-IR) Spectroscopy:

Mesalamine:



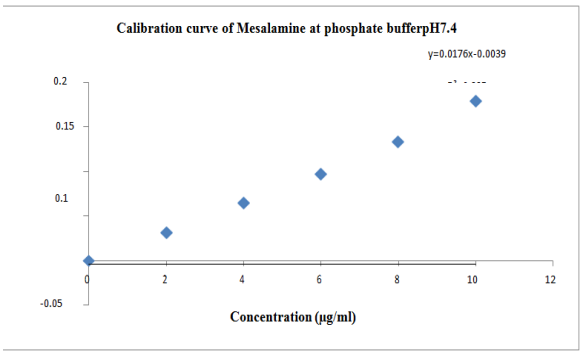


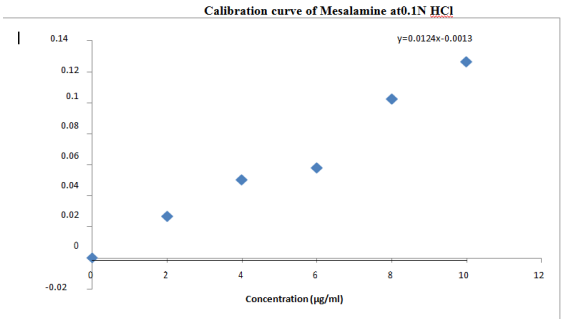
TheDscthermogramofpuredrugwasfoundtobe278.3°

Constructionofcalibrationcurvesformesalaminein0.1NHCl,Phosphate BufferPH7.4 andPhosphateBufferPH 6.8

Table 2 : Calibration Curve for the mesalamine in 0.1 N HCl, Phosphate Buffer PH 7.4 and Phosphate BufferPH6.8

S. No.	Concentration(µg/ml)	Absorbance in0.1N Hcl(±S.D)	Absorbanceinp H7.4buffer(±S.D)	AbsorbanceinpH6.8 buffer(±S.D)
1	0	0	0	0
2	2	0.0267	0.0316	0.0084
3	4	0.0503	0.0644	0.0159
4	6	0.0579	0.0965	0.0238
5	8	0.1022	0.133	0.0315
6	10	0.1263	0.179	0.0388





From the above observations Kinetic analysis (r^2) of release data based on best curvefitting method for selected optimized formulation the Drug release showed First orderreleaseindicating thatthe Drugreleasedependsontheconcentrationofte Drug.

Conclusion

From the FTIR study & Physical observation it could be concluded that these was knowsignificant drug excepient interactions so formulations were subjected to evaluation of allphysicochemical parameters. Developed Mesalamine colon targeted tablets have the requiredparameter of hardness, friability, weight variation, drug content, the optimized formulationsF9 shows better controlled drug release of 96.25% in 12 Hours. From the above invitrodissolution studies F9 with Microbial degradation polymer using Xanthan gum showed bettercontrolled drug release, this developed dosage form will be benefical for treating Ulcerativecolitisin colon region

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