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Design And Development Of Colon Targeted Drug Delivery System

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Abstract: The goal of targeted drug delivery is to deliver the drug to the specific organ. Colon targeted drug delivery is used to deliver the substances that are degraded by the digestive enzymes in the stomach such as proteins and peptides. It is also used for the treatment of various diseases like ulcerative colitis, crohn's disease, intestinal cancer, diarrhoea, for the treatment of diseases sensitive to circadian rhythms like Asthma, Angina, for the delivery of steroids, etc. colon targeted drug delivery of drugs reduces the systemic side effects. Colon targeted drug delivery system increases the absorption of poorly absorbable drugs due to the high retention time of the colon. In present study Balsalazide colon targeted tablet prepared using HPMC K15, guar gum, chitosan, SLS and SSG by direct compression method which was confirmed by various characterization and evaluation studies. The developed formulation of Balsalazide batch F2 (150 mg of guar gum) showed good Drug Release for 24 hrs.

Index Terms - targeted drug delivery**,** ulcerative colitis, crohn's disease, HPMC K15, guar gum, chitosan, SLS and SSG.

I. INTRODUCTION

During the past decades research is going on in developing the methods to target the drug to the specific region. The goal of targeted drug delivery is to deliver the drug to the specific organ. Colon targeted drug delivery is used to deliver the substances that are degraded by the digestive enzymes in the stomach such as proteins and peptides. It is also used for the treatment of various diseases like ulcerative colitis, crohn's disease, intestinal cancer, diarrhoea, for the treatment of diseases sensitive to circadian rhythms like Asthma, Angina, for the delivery of steroids, etc. colon targeted drug delivery of drugs reduces the systemic side effects. Colon targeted drug delivery system increases the absorption of poorly absorbable drugs due to the high retention time of the colon[1].

1.1 Advantages[1]

1. Used for the effective treatment of inflammatory bowel diseases like ulcerative colitis, crohn's disease, etc.
2. Decreases the side effects in the treatment of colon diseases.
3. Prevents gastric irritation resulting due to the administration of NSAIDs.
4. Minimizes first pass metabolism.
5. Provides suitable environment for proteins and peptides that are sensitive to gastric fluid and digestive enzymes.
6. Increased patient compliance.
7. Decreased frequency of administration hence decreased cost of drugs.
8. High retention time thus increasing the bioavailability of poorly absorbable drugs.

1.2 Limitations[1]

1. Multiple manufacturing steps.
2. Incomplete release of drug.
3. Lowering of bioavailability due to binding of drugs to intestinal contents

Factors affecting colon targeted drug delivery[2-5]

1. Physiological factors
2. Pharmaceutical factors

1. Physiological factors

a. Gastric emptying

Drug delivery to the colon upon oral administration depends mainly on gastric emptying and bowel transit time. Upon reaching the colon the transit time of dosage form depends on the size of the particles. Smaller particles have more transit time compared to larger particles. Diarrhoea patients have shorter transit time whereas constipation patients have longer transit times.

b. pH of colon

The pH of GIT varies between different individuals. The food intake, diseased state, etc. influences the pH of the GIT. This change in the pH in different parts of GIT is the basis for the development of colon targeted drug delivery systems. Coating with different polymers is done to target the drug to the site.

c. Colonic microflora and enzymes

The GIT contains a variety of microorganisms that produces many enzymes need for metabolism. Growth of this microflora is controlled by the GIT contents and peristaltic movements. The enzymes released by different microorganisms E. coli, Clostridia, Lactobacilli, Eubacteria, Streptococci are responsible for the various metabolic reactions that take place in the GIT.

2. Pharmaceutical factors

a. Drug candidates:

Due to high retention time of colon, colon causes an increase in the absorption of poorly absorbed agents like peptides, etc. drugs used for treatment of inflammatory bowel diseases, etc. are suitable for colon targeted drug delivery system.

b. Drug carriers:

The selection of carrier for CDDS depends on the nature of the drug, disease for which the drug is used. the various physicochemical factors of drug that effect the carrier selection includes chemical nature, stability, partition coefficient, functional groups of drug molecule, etc.

DRUGS SUITABLE FOR CDDS[6]

Based on literature review, the following different categories of drugs are suitable for colon drug delivery.

- Drugs used to treat irritable bowel disease (IBD) require local delivery at drug to colon e.g. sulfasalazine, olsalazine, mesalazine, steroids like fludrocortisone, budesonide, prednisolone and dexamethasone.
- Drugs to treat colonic cancer require local delivery e.g. 5-fluorouracil, doxorubicin, and methotrexate.
- Protein and peptide drugs - eliminating drug degradation e.g. growth hormones, calcitonin, insulin, interleukin, interferon and erythropoietin.
- To treat infectious diseases (amoebiasis & helminthiasis) - requires site specific delivery e.g. metronidazole, mebendazole and albendazole.
- To treat rheumatoid arthritis (NSAIDS), nocturnal asthma, angina require delay in absorption due to circadian rhythms
- Drugs showing more selective absorption in colon than small intestine due to small extent of paracellular transport e.g. glibenclamide, diclofencac, theophylline, ibuprofen, metoprolol, and oxyprenolol.

NEED OF COLON TARGETED DRUG DELIVERY[7]

- Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing and fewer systemic side effects.
- Site-specific or targeted drug delivery system would allow oral administration of peptide and protein drugs, colon-specific formulation could also be used to prolong the drug delivery.
- The colon is a site where both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's disease. Such inflammatory conditions are usually treated with glucocorticoids and sulphasalazine (targeted).
- A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon.
- Formulations for colonic delivery are also suitable for delivery of drugs which are polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.

2. Formulation Development

2.1 Formulation of Balsalazide Core Tablet[8]:

Fast Disintegrating Balsalazide Core tablet (Average weight 250 mg) was prepared by Direct Compression Technique. Each powder mixture of Balsalazide Core tablet consists of Balsalazide (60 mg) Microcrystalline Cellulose PH 102 (172.5 mg), Sodium Starch Glycolate(10 mg). Sodium Lauryl Sulphate (2.5 mg), Talc (2.5 mg), and Magnesium Stearate (2.5mg), A 5 % of Sodium Starch Glycolate were added as a super Disintegrating agent to obtained fast disintegrating of Balsalazide Core tablet. The material were Weighed, Blended and Passed through Mesh (♯ 60) to ensure proper mixing. Talc & Magnesium Stearate were added to the powder blend & compressed into the tablets by using 9 mm round, flat and plain punches on a Minipress tablet machine.26-30 Compression force of Balsalazide Core tablet was 3.1 kg/cm$^{2.}$

2.2 Preparation of Balsalazide Compression Coated tablet

The formulated Core tablets were compression coated with the different coat formulation by using single polymer or mixture of different polymer i.e. using coat natural polymer such as PH responsive soluble polymer in different ratio i.e. Guar gum, Chitosan. And Time dependent hydrophilic swellable polymer HPMC K-15. The core & coat ratio is (1:1). The compression coat powder material was prepared by using different polymer Guar Gum, Chitosan, HPMC K 15 in different ratio (Table II). The Microcrystalline cellulose is added into the coat formulation as a direct compression aid. The half amount of coat was placed in the Die and then the Core tablet was carefully positioned in the center of die & then the other half portion of coat material was added. The coating material was then compression around the core tablet by using 12 mm round, flat, plain punches by using Constant compression force 6-6.5 kg/cm^2

Table No. 1: Composition of Balsalazide Core Tablet (250 mg)

Sr. No.	INGREDIENTS	QUANTITY (mg)
1.	Balsalazide	60
2.	MCC	172.5
3.	SLS	2.5
4.	Talc	2.5
5.	Magnesium Stearate	2.5
6.	SSG	10
Total		250 mg

Table No. 2: Composition of Compression Coat Powder Material for Balsalazide Core Tablet

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Chitosan	150	--	--	75	75	--
Guar Gum	--	150	--	75	--	75
HPMC K 15	--	--	150	--	75	75
MCC	92.5	92.5	92.5	92.5	92.5	92.5
Magnesium Stearate	5	5	5	5	5	5
Talc	2.5	2.5	2.5	2.5	2.5	2.5
Total	250	250	250	250	250	250

3 Evaluation of powder parameters (Pre-Formulation):-

Table No. 3: Preformulation studies of various batches

Formulation	Bulk Density ($gm/cm^{3)}$	Tapped density ($gm/cm^{3)}$	Carr's Index	Hausner ratio	Angle of Repose %
F1	0.31	0.38	18.25	1.27	29.89
F2	**0.38**	**0.45**	**15.00**	**1.18**	**29.09**
F3	0.45	0.55	18.67	1.22	29.98
F4	0.33	0.41	19.51	1.24	25.76
F5	0.45	0.55	18.18	1.22	28.88
F6	0.49	0.55	14.54	1.12	31.37

Table No. 4: Evaluation of Post Compression Parameter of Coat Material

Formulation	Thickness (mm)	Diameter (mm)	Hardness Kg/cm^2	Friability (%)	Weight Variation (mg)
F1	4.0	16.72	6.1	0.31	498.50
F2	**3.98**	**16.70**	**6.2**	**0.36**	**498.30**
F3	3.99	16.68	6.1	0.33	498.15
F4	4.1	16.65	6.5	0.27	498.65
F5	4.0	16.70	6.4	0.38	498.80
F6	4.1	16.68	6.5	0.21	498.60

Table No 5: Percent Drug Release of Balsalazide Compression Coated Tablet in Phosphate Buffer PH 1.2, 7.4 and 6.8

Batch	Times in hours										
	1	2	3	4	5	6	7	8	10	12	24
F1	2.35	5.7	6.48	8.66	12.42	17.61	24.09	31.42	39.41	52.45	93.48
F2	**3.35**	**7.7**	**8.90**	**11.49**	**15.53**	**19.64**	**24.93**	**32.05**	**41.76**	**55.88**	**99.07**
F3	1.35	4.7	4.74	6.23	8.81	11.63	16.38	22.65	32.24	44.21	89.32
F4	2.35	7.7	9.11	11.14	13.94	16.97	22.80	31.22	41.14	54.18	96.19
F5	0.85	3.2	3.78	5.19	7.5	10.43	14.75	20.26	29.85	42.90	84.69
F6	1.85	5.7	6.55	7.97	10.76	14.76	20.81	27.82	36.88	52.08	92.04

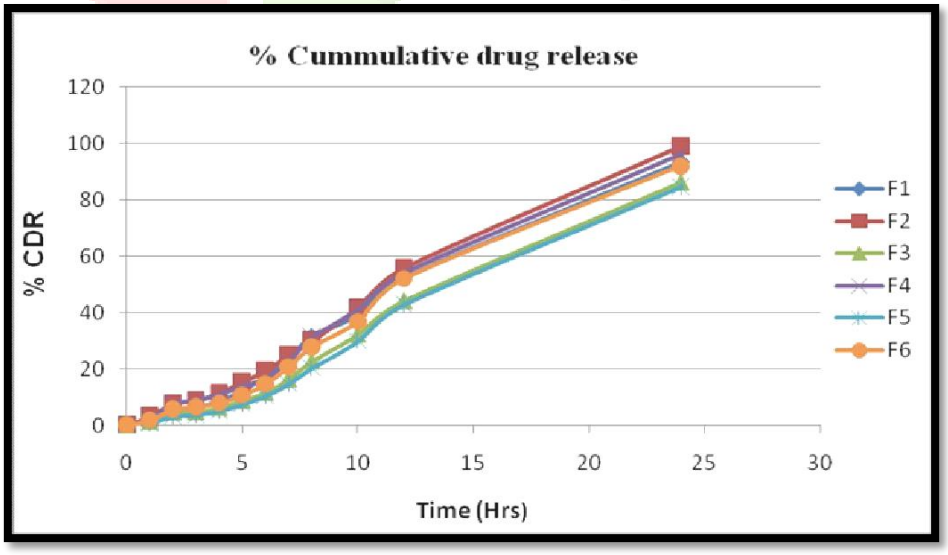

Fig. No. 1: Percent drug release of Balsalazide compression tablet

4. Conclusion

Colon Targeted tablets are those that release the drug in large Intestine. In the present study Colon Targeted tablets of Balsalazide was prepared by direct compression method using MCC, SLS, SSG, Chitosan, guar gum and HPMC K15. FT-IR study shows that Conformation of the drug. The tablets prepared were evaluated for various parameters like various density parameters, thickness, hardness, friability and in-vitro dissolution time. All the parameters were found to be within limits. The developed formulation of Balsalazide batch F2 (150 mg of guar gum) showed good Drug Release for 24 hrs.

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