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RESEARCH ARTICLE

PHARMACEUTICS

FORMULATION AND DEVELOPMENT OF COLON SPECIFIC DRUG DELIVERY USING DEXTRIN

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ABSTRACT

The objective of the present study is to develop colon targeted drug delivery system by using polysaccharide as a carrier. Matrix tablets containing various excipients and polysaccharide were prepared by wet granulation technique using different binder systems. The matrix tablets were evaluated by different IPQC tests, content uniformity, matrix index and in vitro drug release study as per IP 1996 method. Drug index profile in simulated gastric and intestinal fluid was evaluation parameter for selecting the best formulation. Drug release profile in simulated gastric, intestinal fluid from the dissolution studies was taken for selecting the best formulation. The matrix tablet containing dextrin as a carrier and ethyl cellulose as a binder found to be suitable for targeting paracetamol for local action in the colon. Same matrix tablets released fewer amounts (8-11%) of drug in simulated gastric fluid. Matrix tablets containing dextrin released 95-98 % of paracetamol in simulated colonic fluid with 4 % human fecal matter solution.

KEYWORDS

Wet granulation technique, Colon-specific drug delivery; Colon targeting, Dextrin.

INTRODUCTION

Now a days a novel oral colon-specific drug delivery system (CDDS) has been developed as one of the site-specific drug delivery systems. This delivery system, by means of combination of one or more controlled release mechanisms, hardly releases drug in the upper part of the gastrointestinal (GI) tract, but rapidly releases drug in the colon following oral administration. [1,2,3]. First as for treating localized colonic diseases, i.e. ulcerative colitis, Crohn's disease and constipation *etc.*, the optimal drug delivery system, such as CDDS, should selectively deliver drug to the colon, but not to the upper GI tract[1]. Second, the colon is referred to as the optimal absorption site for protein and polypeptide after oral administration, because of the existence of relatively low proteolytic enzyme activities and quite long transit time in the colon[2, 3]. Finally, CDDS would be advantageous when a delay in absorption is desirable from a therapeutically point of view, as for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythms, such as nocturnal asthma, angina and rheumatoid arthritis [1,4,5].

There were currently a few strategies to achieve colonic specificity, such as use of pH sensitive polymers and pressure-controlled CDDS [6]. The aim of this study was to explore the feasibility of the colonic microorganism to develop CDDS by using paracetamol as a model drug.

Polysaccharides, the polymer of monosaccharide retains their integrity because they are resistant to the digestive action of gastrointestinal enzymes. The matrices of polysaccharides are assumed to remain intact in the physiological environment of stomach and small intestine but once they reach in the colon, they are acted upon by the bacterial polysaccharides and results in the degradation of the matrices. A large number of polysaccharides such as amylose, guar gum, pectin, chitosan, inulin, cyclodextrins, chondroitin sulphate, dextrans, dextrin and locust bean gum have been investigated for their use in colon targeted drug delivery systems. The most important fact in the development of polysaccharide derivatives for colon targeted drug delivery is the selection of a suitable biodegradable polysaccharide. As these polysaccharides are usually soluble in water, they must be made water insoluble by cross linking or hydrophobic derivatisation, very important is an optimal proportional of the hydrophobic and hydrophilic parts respectively and the number of free hydroxyl groups in the polymeric molecule. [4] The objective of the present study is to develop colon targeted drug delivery system by using dextrin as a carrier for paracetamol. CDDS is also selectively delivered drug to colon but not to the upper tract.

MATERIALS AND METHODS

i.Assay of paracetamol[7]:

The paracetamol 0.5gm powder was weighed accurately and dissolved in a mixture of 10ml water and 50ml of 1M sulphuric acid. It was boiled under reflux condenser for 1hr., cooled and diluted to100 ml with water. To 20 ml of the solution add 40ml of water, 40gm of water in the form of ice, 15ml of 2M HCL and 0.1ml of ferroin solution was added and titrated with 0.1M cerric ammonium sulphate until a yellow color is

produced. Blank determination was performed and necessary correction was made. Each ml of 0.1M cerric ammonium sulphate is equivalent to 0.00756g of C8H9NO2.

ii. *Preparation of standard curve:*

The standard solution was prepared by dissolving 100 mg. of paracetamol in 100 ml of simulated gastric, intestinal and colonic fluid. The dilution was made to achieve final concentration in range of 2 mcg/ml to 20 mcg/ml. The absorbance of resultant solution was measured at 249 nm against simulated gastric, intestinal and colonic fluid as a blank using double beam UV-Vis. Spectrophotometer.

iii. Formulation development of tablet for colon drug delivery:

a. *Preparation of Granules[9]:*

Granules were prepared by using wet granulation method and by using different binder systems. Details of granulation are given in following table.

b. *Preparation of Tablets[9]:*

Initially granules were treated with lubricants like talc and magnesium stearate. Tablets were prepared by compressing the lubricated granules on rotary tablet compression machine by using 10mm SC (Shallow concave) die and punch set. Details of different trials of tablet are as given in Table 1.

Table 1.
Composition and evaluation details of Paracetamol Tablet of different trials.

Name of Ingredient	Trial Nos. (1 to 12) & Quantity (gm)											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Paracetamol	10	10	10	10	10	10	10	10	10	10	10	10
Lactose	09.75	09.75	04.75	14.75	-	-	16	05	5.25	15.25	15.25	15.75
HPMC	10	-	-	10	-	-		10	-	-	-	-
Dextrin	10	10	10	05	12	20	12	10	10	06	06	06
Alcohol	10	-	25	15	-	-	-	-	-	-	-	-
Water	-	20	-	-	-	-	-	-	-	-	-	-
MCC	-	-	-	-	10	8.50	-	4.50	4.50	8.50	8.50	8.50
Ethyl cellulose (10 % alcoholic solution)	-	-	-	-	-	-	-	-	10	-	-	9.50
Starch paste (5%)	-	-	-	-	17.50	11.00	11.50	10.25	10	-	-	
Sodium CMC (10 % Aq.Solution)	-	-	-	-	-	-	-		-	10	-	
Sucrose(70 % aq.solution)	-	-	-	-	-	-	-			-	10	
Talc	0.25	00.25	00.25	00.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Magnesium					0.25	0.25	0.25	0.30	0.15	-	-	-

stearate												
Total weight	50	50	100	50	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00
Hardness of tablet (kg/cm)	4.5	5.5	5.5	5.5	3.0	3.5	1.0	4.5	9.0	7.5	3.5	6.0
Avg. weight of tablet (mg)	498	500	512	505	440	496	501	497	510	503	501	503
Thickness of tablet (mm)	03	03	03	03	03	03	03	03	03	3.5	3.0	3.5
Friability (%)	0.26	0.20	0.32	0.27	-	0.29	0.27	0.22	0.23	0.28	0.19	0.13
Swelling index (%) in 0.1M HCl of pH 1.5	**-34**	**-27**	**-52**	**-36**	**43 & 28**	**28**	**NIL**	**NIL**	**31.44**	**23 %**	**21 %**	**19%**
Batch size - 100 tablets												

iv. Study of In-Process Quality Control Parameters of tablets[7] :

Tablets were evaluated during compression for different IPQC parameters like Weight, Hardness, Thickness, Diameter, and Friability. Thickness and the diameters of the tablets were measured using caliper scale. Hardness was evaluated manually by using Monsanto hardness tester. Friability test was performed at speed of 25 rpm with tablets dropping from height of six inches with each revolution. After the test, the tablets were dedusted and reweighed.

v. Drug content uniformity test tablet[7]

Paracetamol tablets were analyzed by Indian Pharmacopoeia method. Twenty tablets were weighed and powdered. Crushed powder of tablets equivalent to 0.15gm was taken. 50 ml of 0.1M sodium hydroxide was added to the powder and diluted with 100 ml of water .Resultant solution was exposed to shaking for 15 mins. Sufficient water was added to same to produce 200 ml of solution. The solution was mixed and filtered. 10 ml of filtrate was diluted with water up to 100 ml. 10 ml of 0.1M sodium hydroxide was added to 10 ml of resulting solution. This solution was diluted with water up to 100 ml and mixed. Finally absorbance of the resulting solution was measured at the maximum at about 257 nm. Content of paracetamol was calculated taking 715 as the value of A (1%, 1 cm) at the maximum at about at about 257 nm (Table 2).

Table 2
Results of Drug Content Uniformity Test

Sr.No.	Formulation Code	Drug Content (%)
01	D1	100.89
02	D2	98.45
03	D3	97.66

04	D4	98.04
05	D5	102.69
06	D6	98.67
07	D7	99.38
08	D8	102.56
09	D9	101.45
10	D10	97.38
11	D11	99.77
12	D12	95.58

vi.Matrix Index Study[10]

Three representative tablets from a batch were evaluated for matrix index by using standard formula in simulated gut fluid by using following method.

Methods of Preparation of Simulated gastric, intestinal and colonic fluid **–**

a) Simulated Gastric Fluid T.S –

NaCl 2.0gm and purified pepsin 3.2gm were dissolved in 7.0ml of HCl and sufficient water to make 1000ml by adjusting the PH1.2. The pepsin is derived from porcine stomach mucosa with an activity of 800-2500 units/mg of protein.

b) Simulated Intestinal Fluid T.S[11] -

6.8 gm of monobasic potassium phosphate was dissolved in 250ml of water mixed and 77ml of 0.2N Na OH and 500ml of water. 10.0gm of pancreatic mixture was added and the resulting solution was adjusted with either 0.2N Na OH or 0.2N HCl to a PH of 6.8, and then diluted with water to 1000ml.

c) Simulated colonic fluid [11] –

Human Fecal matter solution of 3% was prepared and it was added in phosphate buffer solution of PH 7.4 in1:10 proportions mixed it well and small amount of pepsin and pancreatin was added in it.

vi.Isolation of microbial flora of human fecal matter[12]:

Human fecal matter is representative of *microbial flora of colonic environment tract of human being.* GIT of human being contains various types of microbes and it was determined by isolating the microbial flora from human fecal matter. Microbial flora from GIT was isolated by following ***method:-***

PHASE 1 - Isolation of microbial flora from human fecal matter was collected.

PHASE 2 - Identification of isolated bacteria was carried out by using morphological characteristics, biochemical test, Gram reaction and by using selective medium.

PHASE 1 - Isolation of microbial flora from feces.

The fresh human feces sample was collected in sterile plastic container and used within 1 Hr. after collection. Pour plate technique was done by the following way-

The fecal sample was made in peptone water having dilution 1:100.Then Mc-Conkey agar medium (PH-7-7.2) was prepared, and it was sterilized by autoclaving at 121C temperature, 15 lbs pressure for 15 minutes. Then agar medium was allowed to cool, approx. at 40-50C. Then 0.1ml of previously diluted sample was aseptically inoculated in sterile Petri plates, the medium

was poured and mixed well and solidify the Petri plates. Then the Petri plates were incubated at 37C for 24-48 Hr. after incubation period the colonies were observed.

PHASE 2 - The isolated bacteria were identified by morpholological characteristics and routine Biochemical Test i.e. IMViC Test. The colonies from Mc-Conkey agar having different morphological characters (shape, size, opacity,) were transferred in nutrient agar slant and further Biochemical test i.e. IMViC (Indole, Methyl red (m-r), Vages-proskauer (v-p) and Citrate utilization test) tests were conducted.

vi. In-vitro drug release study [8]:

On the basis of results of matrix index formulation number D12 was tested only by *in-vitro* drug release method. Test was carried out using USP apparatus II (paddle) and the medium was Simulated gastric fluid, Simulated intestinal fluid and simulated colonic fluid (Table 3 & 4). Each dissolution medium consisted 900 ml. The speed of paddle was 50 rpm and temperature of dissolution medium was 37.5^0C. One tablet was placed in the dissolution medium and apparatus was run. At intervals of 2, 5, 8, 12, 16, 20 and 24 hours, 5 ml aliquots were withdrawn and replacement was made each time with 5 mL of fresh dissolution medium. Each 5 ml sample was filtered through Whatman filter paper no. 41. The absorbance was measured at 249 nm.

RESULTS AND DISCUSSIONS

Table 3

Standard curve data of paracetamol in simulated gut fluid.

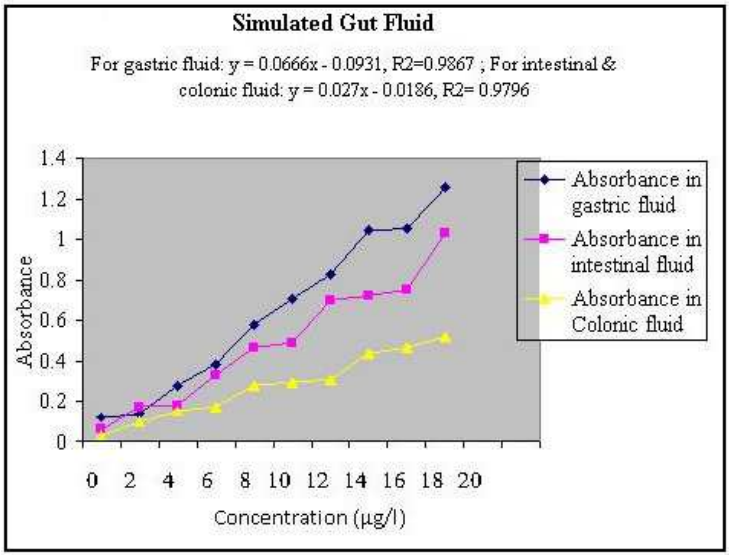
Sr.No.	Concentration (µg/l)	Absorbance in gastric fluid	Absorbance in intestinal fluid	Absorbance in colonic fluid
1	02	0.119	0.06	0.03
2	04	0.136	0.17	0.10
3	06	0.278	0.18	0.15
4	08	0.385	0.33	0.17
5	10	0.582	0.47	0.28
6	12	0.709	0.49	0.29
7	14	0.830	0.70	0.31
8	16	1.044	0.72	0.44
9	18	1.055	0.75	0.47
10	20	1.259	1.03	0.52

Table 4
In-vitro dissolution behaviour of Dextrin matrix tablet of Paracetamol.

Dissolution medium	Time (hrs)	Cumulative% Drug release
		Formulation Code D 12
Stimulated gastric fluid	02	08.96
Stimulated intestinal fluid	05	11.54
Stimulated colonic fluid with 4% human fecal matter solution	08	58.00
	12	69.06
	16	87.86
	20	96.50
	24	98.78

All three standard curves obey Beers-Lambert law and prove that concentration is directly proportional to the absorbance (Graph1).Granules were prepared successfully by using wet granulation method by using different formulation of paracetamol and pectin. These granules of different formulations were compressed on rotary compression machine. Tablets were evaluated as per I.P.Q.C. parameters as per I.P. 96 guidelines. All formulations were within the specifications given by I.P. A result of Drug content uniformity study proves that all tablets are of required purity and contains paracetamol within the specification of I.P. Resulted tablets were evaluated for Matrix index study in simulated gastric fluid to find out **stability** of tablet in simulated gastric fluid. Result of matrix index shows that none of the tablet was stable in simulated gastric fluid.

Graph 1
Standard curve data of paracetamol in simulated gut fluid.



Drug release studies showed that DF shows good release behaviour in colon and restricts release in stomach and intestine (Table 4). This study confirms that dextrin can act as good carrier in the form of matrix tablet for paracetamol to deliver it specifically in colon by using ethyl cellulose as binder. Stability study of formulation DF confirms that tablets were stable and there was no significant change in Hardness, Friability, Drug content and Dissolution profile.

CONCLUSION

This study confirms that dextrin is a good carrier for paracetamol to deliver it in colon specifically.

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