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Formulation, development and optimization of metronidazole compression coated tablets

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ABSTRACT

The aim of present work was to develop colon-specific drug delivery systems based on polysaccharide chitosan, were evaluated using in-vitro method. Metronidazole is choice of drug for intestinal amoebiasis. These drugs are to be delivered to the colon for their effective action against E. histolytica wherein the trophozoites reside in the lumen of the caecum and large intestine and adhere to the colonic mucus and epithelial layers. But the pharmacokinetic profile of metronidazole indicates that the drug is completely and promptly absorbed after oral administration reaching a concentration in plasma of about 10 μg/ml approximately 1 hr after a single 500 mg dose. The administration of this drug in conventional tablet dosage form provides minimal amount of metronidazole for local action in the colon, still resulting in the relief of amoebiasis, but with unwanted systemic effects.[4,5]The factors Amount of chitosan (X_1), amount of carbopol 934P (X_2) showed significant effect on the release of metronidazole from the colon specific tablet formulation. Optimizing was performed using a 3^2 full factorial design to yield tablet that released a >80% in 12 hour.batch(0,0) as per the contour plot s shows the optimize batch. Present study summarized that chitosan and carbopol can be used successfully to deliver the drug in to colon.

Key Words: Metronidazole, carbopol, optimization.

INTRODUCTION

Natural polysaccharides are now extensively used for the development of solid dosage forms for delivery of drug to the colon. The rationale for the development of a polysaccharide based

delivery system for colon is the presence of large amounts of polysaccharides in the human colon as the colon is inhabited by a large number and variety of bacteria which secrete many enzymes e.g. β-D-glucosidase, β -D-galactosidase, amylase, pectinase, xylanase, β -D-xylosidase, dextranase, etc. Various major approaches utilizing polysaccharides for colon-specific delivery are fermentable coating of the drug core, embedding of the drug in biodegradable matrix, formulation of drug-saccharide conjugate (prodrugs). A large number of polysaccharides have already been studied for their potential as colon-specific drug carrier systems, such as chitosan, pectin, chondroitin sulphate, cyclodextrin, dextrans, guar gum, inulin, amylose and locust bean gum[1].

The present investigation was aimed to formulate a dosage that
1. retard drug release in the tracts of the upper GIT (stomach and small intestine),
2. consists of biodegradable polysaccharide as the main constituent,
3. the dosage form is degradable by a wider range of microbial species,
4. shows rapid drug release in the presence of degradable polysaccharides in the tablet.[2,3]

The aim of present work was to develop colon-specific drug delivery systems based on polysaccharide chitosan, were evaluated using in-vitro method.

Metronidazole is choice of drug for intestinal amoebiasis. These drugs are to be delivered to the colon for their effective action against E. histolytica wherein the trophozoites reside in the lumen of the caecum and large intestine and adhere to the colonic mucus and epithelial layers. But the pharmacokinetic profile of metronidazole indicates that the drug is completely and promptly absorbed after oral administration reaching a concentration in plasma of about 10 µg/ml approximately 1 hr after a single 500 mg dose. The administration of this drug in conventional tablet dosage form provides minimal amount of metronidazole for local action in the colon, still resulting in the relief of amoebiasis, but with unwanted systemic effects.[4,5]

Present study was carried out with following objectives
(1) Preparation and in-vitro evaluation of compression-coated tablets based on natural polysaccharide, chitosan and carbpol 934P as a carrier for metronidazole as model drug which retard the drug release in the physiological environment of stomach and small intestine and delivered the drug in the colon.
(2) The susceptibility of chitosan to undergo degradation in colon was assessed by conducting in-vitro drug release studies in the presence of rat caecal contents in pH-6.8 phosphate buffer.

MATERIALS AND METHODS

Table: 1 Composition of fast-disintegrating core tablets of metronidazole

Ingredients	Quantity (mg)
Metronidazole	200
DCP	22.5
Sodium starch glycolate	10
PVP-K30 (as binder)	10
Talc	5
Magnesium stearate	2.5

Preparation of metronidazole core tablets:
The core tablets (average weight 250 mg) of metronidazole for compression coating with Chitosan and Carbopol 934 P, were prepared by wet granulation technique using PVP-K30 as binder. The composition of core tablets is given in Table 5.1 DCP was used as a diluent and SSG (10 mg) was added to obtain a fast disintegrating tablet. Metronidazole, DCP and SSG were passed through the 100 # sieve and thoroughly mixed then granulated using PVP-K30 solution as the binder. The granules so obtained were dried at 40 °C for 2 hr in the oven. Dried granules were passed through 20 # sieve and the fines were separated using 40 # sieve to obtain 20-40 # granules. These granules were lubricated with mixture of talc and magnesium stearate (2:1). The lubricated granules were compressed into tablets using Minipress Tablet Compression Machine. (Rimek minipress-11 MT, Karnavati Engineearing Ltd. , Ahmedabad, India). Weight variation, hardness, friability, and disintegration test were performed for the core tablets.[6]

Preparation of metronidazole compression coated tablets:
The core tablets of metronidazole were compression coated with different coat formulation. The compression coat formulations were prepared using varying ratio of chitosan and carbopol 934 P (Table 2). Metronidazole core tablets were compression coated with a different coating mixture. Initially, 40% of coat weight was placed in a 12.4 mm die cavity of a Multipunch tablet compression machine followed by carefully centering the core tablet and addition of reminder of coat weight. The coating material was compressed around the core tablet with high compression force.

Table: 2 Composition of chitosan and carbopol 934 P coat

Ingredients	Quantity (mg) present in the coat formulation						
	P1	P2	P 3	P4	P5	P6	P7
chitosan	-	200	20	30	40	50	60
carbopol 934 P	200	-	180	170	160	150	140
PVP-K30 (as binder)	10	10	10	10	10	10	10
talc	4	4	4	4	4	4	4
magnesium stearate	2	2	2	2	2	2	2

Evaluation of tablets[7]:
Thickness:
The thickness of the tablets was determined by using vernier caliperse. Five tablets from each formulation were used and average values were calculated.

Weight variation test :
To study weight variation 20 tablets of each formulation were weighed using a Sartorious electronic balance and the test was performed according to the official method.

Hardness and friability:
For each formulation, the hardness and friability of 6 tablets were determined using the validated dial type hardness tester and the Roche friabilator (Camp-bell Electronics, Mumbai, India), respectively.

Determination of metronidazole content in tablets:
The Metronidazole tablets were tested for their drug content. Ten tablets were finely powdered; quantities of the powder equivalent to 50 mg of metronidazole were accurately weighed and transferred to a 100-ml of volumetric flask. The flask was filled with 0.1 M HCl solution and mixed thoroughly. The solution was made up to volume and filtered. Dilute 10 ml of the resulting solution to 250 ml with 0.1 M HCl and measure the absorbance of the resulting solution at the maximum at 279 nm using a Systronic-2201 UV/Vis double beam spectrophotometer. The linearity equation obtained from calibration curve as described previously was use for estimation of metronidazole in the tablets formulations.

In-vitro drug release studies[6]:
The compression coated tablets of metronidazole to remain intact in the physiological environment of stomach and small intestine was assessed by conducting in vitro drug release studies. Drug release studies were carried out using a USP XXIII dissolution rate test apparatus (Apparatus 1, 100 rpm, 37±1°C) for 2 hr in 0.1 M HCl (900 ml) as the average gastric emptying time is about 2 hr. Then the dissolution medium was replaced with pH-7.4 phosphate buffer (900 ml) and tested for drug release for 3 hr as the average small intestinal transit time is about 3 hr. After 5 hr, the dissolution medium was replaced with pH 6.8 Phosphate buffer (900 ml) and tested for drug release up to 24 hr. At the end of the time period 10 ml of the samples were taken and analyzed for metronidazole content as described previously. A 10 ml volume of fresh and filtered dissolution medium was added to make the volume after each sample withdrawal.

Drug release study in the presence of 4%w/v rat cecal content:
To access the susceptibility of the chitosan to undergo degradation in the presence of colonic bacteria was assessed by continuing the drug release studies in the presence of rat cecal content medium because of the similarity of the microflora of the rat cecam to that of the human colon.[8,9] The drug release studies were carried out in USP XXIII dissolution rate test apparatus (apparatus 1, 100 rpm, 37°C) with slight modification. A beaker (capacity 150 ml) containing 100 ml of dissolution medium was immersed in the water contained in the 1000 ml vessel, which in turn, was the water bath of the apparatus. The swollen formulations after completing the dissolution study in 0.1 M HCl (2 hr) and pH-7.4 phosphate buffer (3 hr) were placed in the baskets of the apparatus and immersed in the dissolution medium containing rat caecal content medium. The drug release studies were carried out up to 24 hr and 1 ml samples were withdrawn at specified time intervals without a pre- filter and replaced with 1 ml of fresh phosphate buffer. 1 ml of methanol was added in sample and was analyzed for metronidazole content as per above described method. Methanol was added to the dissolution samples to ensure the complete dissolution of the slightly soluble metronidazole particles that may be eroded out from the tablets.

Full factorial design:
A 3^2 randomized full factorial design was used in this study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations. The Amount of Chitosan (X_1) and Amount of Carbopol 934P (X_2) in Coating layer were selected as independent variables. A statistical model incorporating interactive and polynomial terms was utilized to
evaluate the response.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where, Y is the dependent variables, b_0 is the arithmetic mean response of the nine runs, and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity

RESULTS AND DISCUSSION

Characterization of tablets:

Table: 3 Characteristics of metronidazole tablets (n=3) containing Chitosan and Carbopol 934 P in various proportion

Tablets	Thickness (mm)	Hardness (kg/cm^2)	Friability (%) (n=1)	Weight variation (mg)	Drug content (%)
M1	3.9 ± 0.1	2.2 ± 0.4	6.75	461 ± 3	98.79 ± 0.36
M2	3.9 ± 0.1	1.6 ± 0.2	13.53	458 ± 2	97.34 ± 0.12
M3	3.9 ± 0.1	5.3 ± 0.6	0.60	463 ± 4	98.96 ± 0.23
M4	3.9 ± 0.1	5.2 ± 0.4	0.56	455 ± 3	98.67 ± 0.31
M5	3.9 ± 0.1	5.3 ± 0.5	0.49	467 ± 4	98.95 ± 0.51
M6	3.9 ± 0.1	4.9± 0.2	1.2	463 ± 3	99.02± 0.14
M7	3.9 ± 0.1	5.4± 0.9	0.34	464 ± 2	99.04 ± 0.56
M8	3.9 ± 0.1	3.0 ± 0.4	0.5	462 ± 2	98.95 ± 0.51
M9	3.9 ± 0.1	3.1± 0.4	0.5	461 ± 3	96.12± 0.56

Optimization of compression coated tablets formulation using 3^2 full factorial designs

It is desirable to develop an acceptable pharmaceutical formulation in shortest possible time using minimum number of man hours and raw materials. Traditionally pharmaceutical formulations after developed by changing one variable at a time approach. The method is time consuming in nature and requires a lot of imaginative efforts. Moreover, it may be difficult to evolve an ideal formulation using this classical technique since the joint effects of independent variables are not considered. It is therefore very essential to understand the complexity of pharmaceutical formulations by using established statistical tools such as factorial design.[10]

Simple linear: ($Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3$)

or

Interactive: ($Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3$ ----)

or

Quadratic: ($Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3$ --- $+ b_{11}X_1^2$ ---)

In addition to the art of formulation, the technique of factorial design is an effective method of indicating the relative significance of a number of variables and their interactions. The number of experiments required for these studies is dependent on the number of independent variables selected. The response/s (Yi) is/are measured for each trial and then either

Model is fitted by carrying out multiple regression analysis and F-statistics to identify statistically significant terms.

The full Equation, an Equation containing only statistically significant terms, is then used for drawing counter plots to visualize the impact of changing variables at a glance. The optimum point may be identified from the plot and replicate trials may be run to verify the prediction of optimum response. For simplicity, it was decided to perform a three variable study at three experimental levels to achieve the set objectives efficiently.

A 3^2 randomized full factorial design was utilized in the present study. In this design two factors were evaluated, each at three levels, and experimental trials were carried out at all nine possible combinations. The factors were selected based on study described in above chapter 4. The Amount of chitosan (X1) and Amount of Carbopol 934P (X2) was selected as independent variables. The formulations of the factorial batches (M1 to M9) are shown in Table 4

Optimization of formulation variables:

Table 4 Composition of factorial batches

Batch	Variable level in coded form	
	X_1	X_2
M1	-1	-1
M2	0	-1
M3	1	-1
M4	-1	0
M5	0	0
M6	1	0
M7	-1	1
M8	0	1
M9	1	1

Independent variable	Real values		
	low(-1)	medium(0)	high(+1)
Chitosan (X_1)	45	50	55
Carbopol 934 P (X_2)	145	150	155

All the batches contain 200 mg of metronidazole.

In vitro drug release study of Factorial design batches:

The in vitro release profile of formulations for 24 hour was tested. The in vitro drug release profile of factorial batches are shown Table 5.

Time (hr)	Table 5 In vitro release profile of factorial Batch Cummulative percentage drug release (%)								
	M1	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**
1	0.09	0.14	0.16	0.11	0.15	0.14	0.13	0.12	0.41
2	0.37	0.61	0.64	0.24	0.62	0.37	0.58	0.77	0.94
3	0.91	1.16	1.22	0.97	1.39	1.03	1.07	1.74	4.72
4	1.99	2.28	3.02	1.84	3.64	2.66	2.81	3.81	13.81
5	4.52	6.82	7.17	5.79	7.76	6.14	6.57	8.17	36.12
6	6.47	8.61	9.24	7.69	9.91	8.23	8.17	19.27	49.32
7	17.16	21.22	24.62	20.19	26.17	19.17	21.16	27.94	64.71
8	30.29	35.12	37.04	32.39	39.84	31.73	34.12	44.13	76.81
9	43.73	45.03	49.76	45.71	52.12	43.52	46.52	54.47	92.14
10	52.42	58.02	61.44	61.16	64.64	64.01	58.17	66.41	99.87
11	63.17	66.81	72.99	69.87	74.47	75.27	69.24	78.32	-
12	76.14	80.13	84.51	80.24	86.51	83.11	82.19	89.34	-
24	86.09	91.38	96.21	91.18	97.34	93.13	94.67	98.01	-

The statistical analysis of the factorial design batches was performed by multiple linear regression analysis carried out in Microsoft Excel 2003. The t_{10}, t_{80} values for the 9 batches (M1 to M9) showed a wide variation; the results are shown in Table 5.5. The data clearly indicate that the values of t10, t_{50}, are strongly dependent on the independent variables. The fitted Equations relating theresponse t10, t80 to the transformed factor are shown in following Equations.

$T_{10} = 3.09\text{-}0.0.21X_1\text{-}0.29X_2\text{+}0.03X_1^2\text{-}0.095X_2^2\text{+}0.195X_1X_2$
(R square = 0.9437)

$t80 = 10.89\text{-}1.67X_1\text{-}1.55X_2\text{+}0.50X_1^2\text{+}0.65X_2^2\text{+}0.62X_1X_2$
(R square = 0.7386)

The values of the correlation coefficient indicate a good fit. The polynomial Equation can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries, (i.e. positive or negative).

Figures 5.5 and 5.6shows the Counter plot of Amount of chitosan(X1) and amount of carbopol 934P (X2) versus t10 and t80, respectively. The plot was drawn using Sigma Plot Software 8.0 demonstration version (Jandel Scientific Software, San Rafael, CA). The data demonstrate that both X_1 and X_2 affect the in vitro drug release (t10 and t80). The shaded area in the Figures 5.6demonstrated the optimize area of the individual dependent variable (t10 and t80). Figure 5.6shows the overlapping the Figure 5.5. And 5.6 which gives optimize area for both dependent variable (t10 and t80).[11,13]

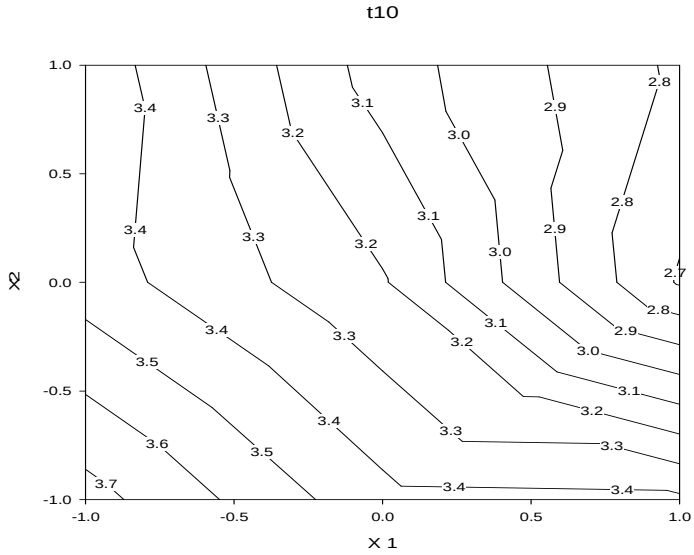

Figure: 1 Counter plot of the X1 (Amount of chitosan) X 2 (amount of carbopol934P) Verses t_{10}

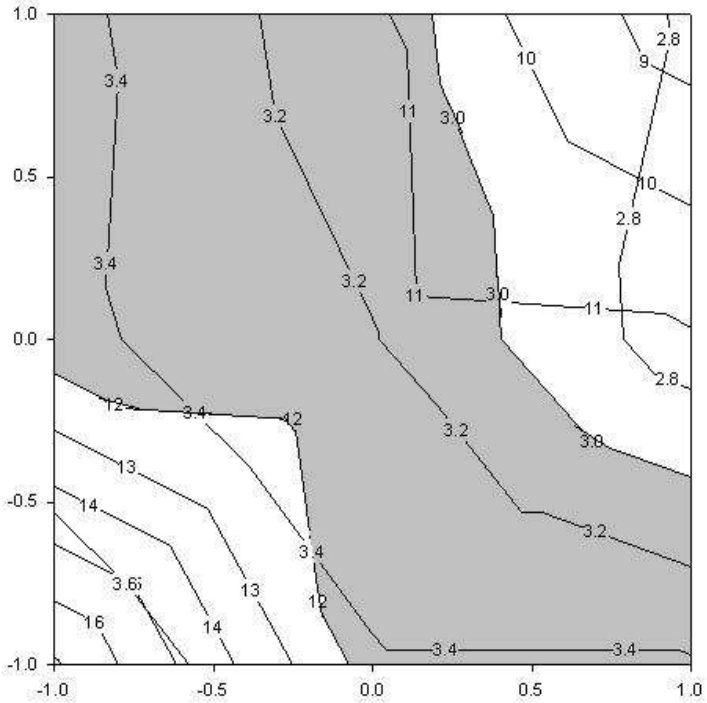

Figure: 2 Overlap Counter plot of t_{10} and t_{80}

It may also conclude that the X1(Amount of chitosan) X 2 (amount of carbopol 934P) appear to favor the preparation of metronidazole colon specific tablets. It can conclude that the drug release profile may be changed by appropriate selection of the X_1 and X2 levels. The shaded area in counter plot (Figure 5.6) shows if we selected X_1 and X2 in this range we get the desired release profile of metronidazole colon specific tablet.

CONCLUSION

The factors Amount of chitosan (X_1), amount of carbopol 934P (X_2) showed significant effect on the release of metronidazole from the colon specific tablet formulation. Optimizing was performed using a 3^2 full factorial design to yield tablet that released a >80% in 12 hour.batch(0,0) as per the contour plot s the optimize batch.

The present investigation was carried out to develop colon specific drug delivery systems using chitosan and carbopol 934P as a carrier for metronidazole as model drug compression-coated tablets of metronidazole were prepared using chitosan and carbopol 934P and to assess the susceptibility of the chitosan and carbopol 934P, the drug release studies were carried out with and without rat cecal content. Chitosan and carbopol 934P in the form of compression-coat over metronidazole core tablets remains intact in the physiological environment of stomach and small intestine in the ratio of chitosan 50 and cabopol 150mg. The pure chitosan coat was found insufficient to protect metronidazole core till 5 hr dissolution studies. The compression coated metronidazole tablets coated with chitosan:carbopol 934 P in 50:150 ratio provided best degradation in simulated colonic fluids.

The factors Amount of chitosan (X_1), amount of carbopol 934P (X_2) showed significant effect on the release of metronidazole from the colon specific tablet formulation. Optimizing was performed using a 3^2 full factorial design to yield tablet that released a >80% in 12 hour.batch(0,0) as per the contour plot s shows the optimize batch. Present study summarized that chitosan and carbopol can be used successfully to deliver the drug in to colon.

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