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Colon targeting of ornidazole and curcumin inclusion complex a novel approach in inflammatory bowel disease.

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Abstract
The present investigation was planned to formulate tablets of ornidazole and curcumin which are targeting the drug directly to colon for the treatment of inflammatory bowl disease (IBD). Inclusion complex of the drugs with β-cyclodextrin were prepared by kneading method. The 10% coating concentration of eudragit S100 shows the complete release of the drugs to colon for the treatment of IBD. Coating concentration we designed based on the full factorial design. *In-vitro* release was conducted for all the formulations in USP appratus 1, i.e. basket type for 24 h in different ph resembling different portions of gastro intestinal tract. *In vitro* dissolution studies, it was found that formulation F4 showed 99.43% of ornidazole in 24 hours and 93.14% of curcumin in 24 hours, which lies in within the acceptance criteria. That study conclude that 10% coating concentration of eudragit S100 shows the complete release of drugs to colon for treatment of inflammatory bowl disease (IBD).

Keywords: ornidazole, curcumin, β-cyclodextrin, eudragit S100, targeted drug delivery.

1. Introduction
The major disorders of the colon are IBD, colon cancer, crohns disease and schistosomiasis. Most of the conventional drug delivery systems are failed to treat such diseases as the drugs do not reach the site of action in appropriate concentration. So the site specific delivery of drugs to the colon is valuable in the treatment of colon diseases whereby high drug concentration can be achieved while minimizing the side effects that occur because of release of drugs in the upper GIT or unnecessary systemic absorption.
There are several ways in which colon-specific drug delivery has been attempted.

- The use of carriers that degrade exclusively by colonic bacteria.
- Coating with Ph dependent polymers
- Time dependent dosage forms
- Prodrugs

The present investigation is aimed by using β-cyclodextrin inclusion complex which were coated with eudragit S100, in order to achieve colon targeting.
Ornidazole,chemically,1-(2-hydroxy-3-chloropropyl)-2-methyl-5-nitroimidazole((C7H10ClN3O) as shown in figure 1 with molecular weight is 219.63 and curcumin is a 1,7-bis(4-hydxoxy 3 methoxy phenyl)-1,6-heptadiene- 3,5-dion(: $C_{12}H_{20}O_6$)as shown in figure 2 with molecular weight 368.37.

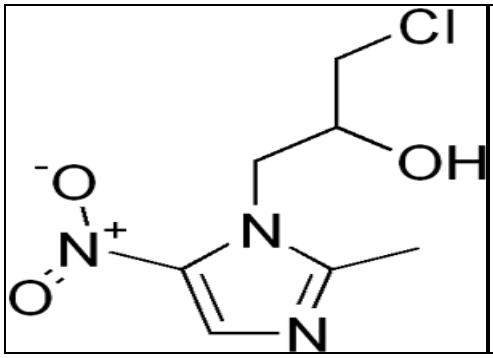

Fig 1: Ornidazole

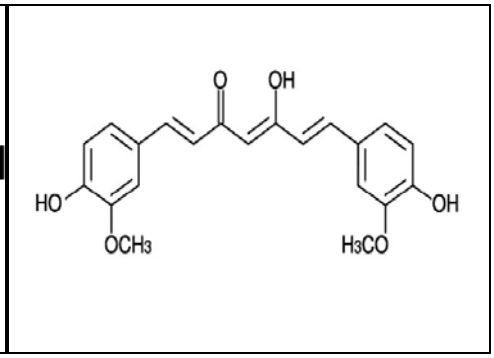

Fig 2: Curcumin

2. Materials and Methods

2.1 Materials

UV –visible double beam spectrophotometer, Shimadzu model 1800 with matched quartz cells was used for all spectral measurements. Ornidazole was obtained as a gift sample from micro lab limited, Chennai, India. Curcumin was a gift sample obtained from RYM exporters, New Delhi. Eudragit S100 from PC chem, Mumbai, India

2.2 Method

Tablet Preparation: Tablets were prepared by wet granulation method using different excipient/polymer guar gum, the mixture if talc and magnesium stearate at 2:1 ratio was used as lubricant. The composition of different formulations is shown in table 1. All the powders were weighed and grounded to finess in clean and dry mortar and pestle. The powder blend was than passed through sieve 120. The powder was kneaded with clean and dry pestle using distilled water as agranulating fluid. The wet mass was passed through mesh 16. The particules were allowed to dry for 2-3 h in an oven at 40 °C. The dried granules than passed through a mesh 20. Than the dried granules were lubricated with amixture of talc and magnesium stearate (2:1). The lubricated granules were compressed into tablets on a multi punching tablet machine using 12 mm die puch. Tablets were tested for weight variation, friability, hardness, diameter, thickness as shown in table 2 and drug content in table 3

Table 1: Formula for 1 tablet (500 mg) with formulation code

Ingredients(mg)	F1	F2	F3	F4	F5
Ornidazole : β CD complex(1:05)	270	270	270	270	270
Curcumin :β CD complex(1:05)	60	60	60	60	60
Guar gum	25	50	75	100	125
PVP	20	20	20	20	20
Lactose	10	35	60	85	110
Talc	10	10	10	10	10
Magnesium stearate	5	5	5	5	5

Table 2: Evaluation parameters of prepared tablets

Batch	Thickness (mm)	Diameter (mm)	Hardness (mm)	Weight variation(IP)	Friability (%)
F1	5.02	12	4.58	Passed	0.66.
F2	5.11	12	4.64	Passed	0.97
F3	5.26	12	4.32	Passed	0.85
F4	5.51	12	4.68	Passed	0.68
F5	6.12	12	4.38	Passed	0.60

Table 3: Drug content uniformity of ornidazole:β-CD and curcumin:β-CD

Sr. No	Ornidazole:β- CD(%)	Curcumin:β-CD(%)
1	97.1	99.3
2	99.4	98.7
3	98.8	101.4
Mean(n=3)	98.43	99.8

2.3 Tablet coating

Coating solutions were prepared using the usual concentrations of polymer used for coating. Eudragit S100 5%, 10%, 15%(m/V) was prepared using isopropyl alcohol and PEG-400 as plasticizer The tablets were coated with polymer by using full factorial design at three different concentrations as shown in table 3 and 4 .The desired volume of coating solution was spray on the tablets in coating pan. The tablets were coated and dried with the help of inlet air (temp 35-45 °C). the coating process was repeated till the desired level of coating was achieved. The percent mass increase of the tablets upon coating was taken to be indicative of the coat thickness as shown in table 6.

Table 4: Optimization of the coating concentration by using full factorial design

Ingredient	Lower(-1)	Middle(0)	Upper(+1)
Eudragit S100	5%	10%	15%

Table 5: Formulation batches of full factorial design

Batch No.	Eudragit S100
F1	5%
F2	10%
F3	15%
F4	10%
F5	15%

Table 6: Evaluation parameters for coated tablets

Sr. No.	Batch	*Hardness	*Thickness	*Diameter	*Weight variation
1	F1	6.09	5.94	14.67	Passed
2	F2	7.67	6.89	13.93	Passed
3	F3	6.93	6.31	13.67	Passed
4	F4	6.81	7.13	13.81	Passed
5	F5	7.37	6.97	14.07	passed

*Average of three determination

2.4 Dissolution studies

Dissolution studies were carried out on all the formulations to the USP apparatus 1, i.e. basket type at 100 rpm and at a temperature of 37±0.5 °C. Initial studies were carried out in 900 ml of 0.1 N hCl for 2 hours, followed by replacement of that solution with 7.4 Ph phosphate buffer for 3 hours and finally that was replaced with 6.8 ph phosphate buffer and then study was continued upto 24 hours. The samples were withdrawn at predetermined time intervals and replaced with fresh media. Then the samples were analysed using uv-spectrophotometer at the λmax 319 nm and 430 nm.

2.5 Data analysis

The raw data were analyzed using Q-absorption and Q-point method.

3. Results and Discussion

The optimized batch was prepared (as shown in table 1), and all the parameters were evaluated. The parameters were evaluated like hardness, friability, weight variation, thickness, diameter within IP limits .The drug content of ornidazole was 98.43% and curcumin was 99.43%, which were found within the specified IPlimits (85 to 115%). These prepared batches were coated with different concentrations of polymer Eudragit S100.That coated batches were evaluated by hardness, friability, weight variation, thickness, diameter of tablets (as shown in table 5).

The expected *in vitro* release pattern selected for the colon targeting was not more than 20% of drug release upto the end of small intestine (5 hrs) and more than 80% of drug release upto 18 hrs. In figure shows the dissolution profile of eudragit S100 coating with different concentration of polymer coating of ornidazole and curcumin coated tablets .in vitro dissolution batch F1 and F2 shows more than 20% drug release within 5 hours and the complete drug release in 12-15 hours. *In vitro* dissolution batch F3 shows less than 10% drug release within 5 hours and complete dur release in 18-21 hours. In case F4 shows 10% drug release within 5 hours and complete drug release in 18-24 hours. In case of batch of batch F5 shows less than 10% drug release in 5 hours and complete drug release in 60-80% in 24 hours.

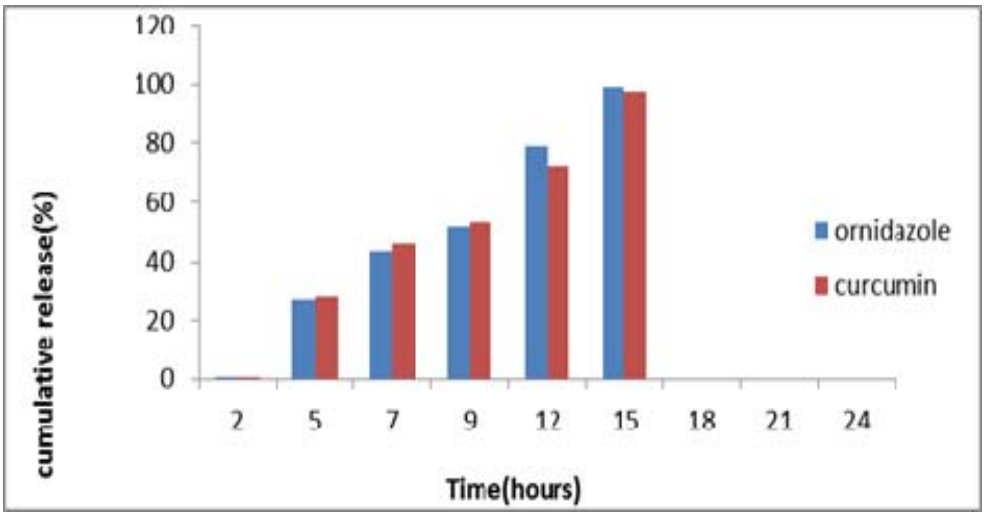

Fig 3: Percentage cumulative release profile of formulation F1

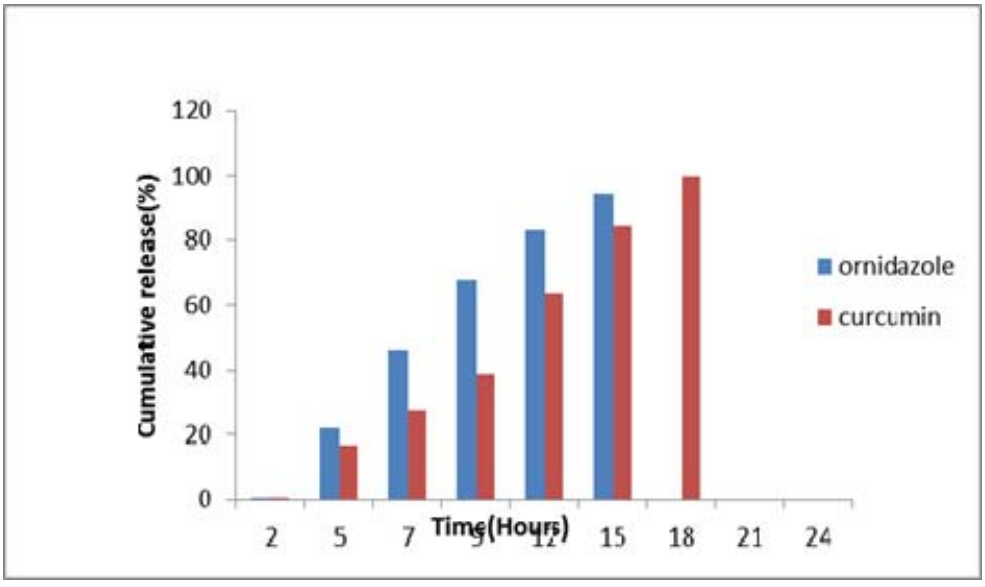

Fig 4: Percentage cumulative release profile of formulation F2

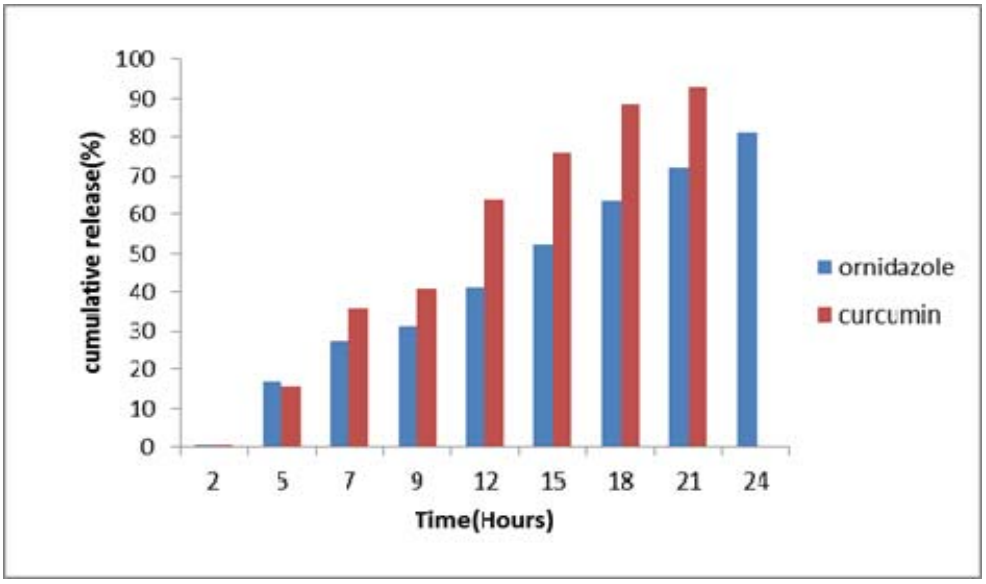

Fig 5: Percentage cumulative release profile of formulation F3

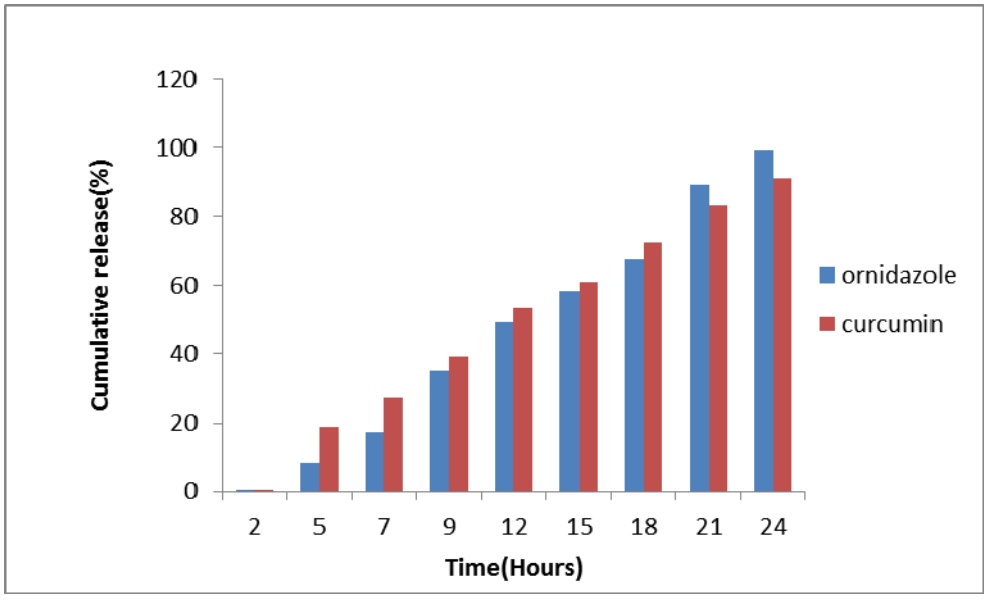

Fig 6: Percentage cumulative release profile of formulation F4

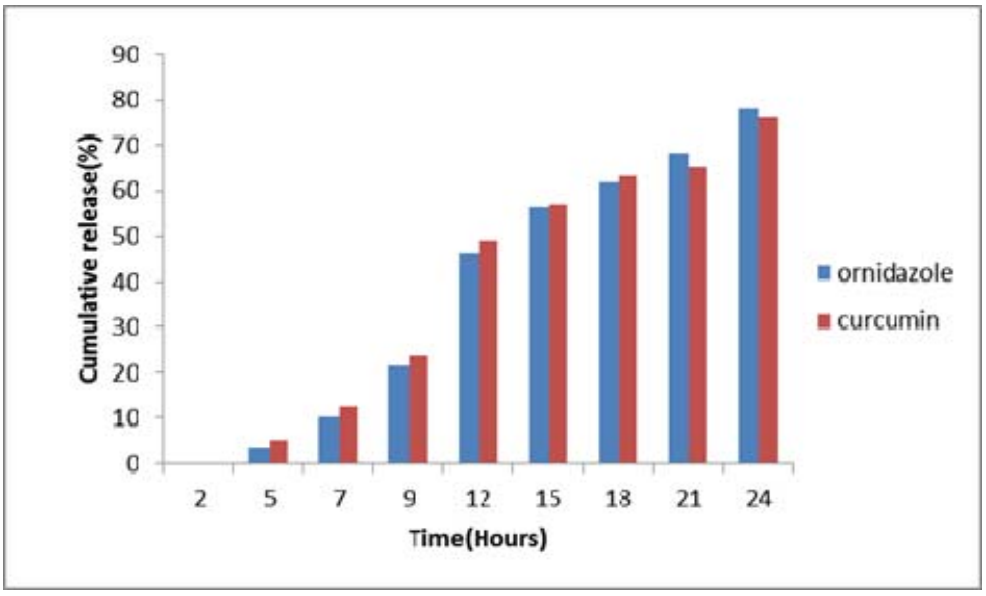

Fig 7: Percentage cumulative release profile of formulation F5

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