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# Formulation and evaluation of colon targeted drug delivery system

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## Abstract

The main objective of the present study was to develop colon targeted drug delivery systems for Nitrofurantoin using guar gum as a carrier. Matrix tablets containing various proportions of guar gum were prepared by wet granulation technique using starch paste as a binder. The in-vitro drug release study was undertaken at 37±0.5°C in 0.1N Hcl for 2 hr; followed by pH 7.4 phosphate buffer (3hr) finally in simulated colonic fluid pH 6.8 phosphate buffer containing 4% w/v rat ceacal content for 10 hr. It was found that 10.04% drug is released in first 5hr from F4 (GG-20%), where as the other matrix tablets released 20-30% of Nitrofurantoin in physiological environment of stomach and small intestine. When studies were continued in colonic fluids, matrix tablets released almost 100% drug. The results of the study show that matrix tablets containing 20% of guar gum are most likely to provide targeting of Nitrofurantoin in the colon.

Key-Words: Colon targeted drug delivery, Nitrofurantoin, *In-Vitro* dissolution, Guar gum, Rat caecal content

## Introduction

The oral route of drug administration is the most convenient and important method of administering drugs for systemic effect. Nearly 50% of the drug delivery systems available in the market are oral D.D.S. and these systems have more advantages due to patient acceptance and ease of administration [1, 2] . During the last decade there has been interest in developing site-specific formulations for targeting drug to the colon. Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn's disease, ulcerative colitis, irritable bowel syndrome and constipation but also for the systemic delivery of proteins, therapeutic peptides, antiasthmatic drugs, antihypertensive drugs and antidiabetic agents [3, 4] . There are various methods or techniques through which colon drug targeting can be achieved, for example, formation of prodrug, coating with pH-sensitive polymers, coating with biodegradable polymers, designing formulations using polysaccharides, timed released systems, pressure-controlled drug delivery systems, osmotic pressure controlled systems [5, 6] . Coating of the drugs with pH-sensitive polymers provides simple approach for colon-specific drug delivery.

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## Material and Methods

### Materials

Nitrofurantoin was a gift sample from Taj Pharmaceuticals Ltd., Mumbai. Guar gum, lactose, starch, talc, magnesium stearate, other chemicals and the solvents used were of analytical grade

### Preparation of Nitrofurantoin matrix tablets

Matrix tablets of Nitrofurantoin were prepared by wet granulation method. Lactose was used as diluent and a mixture of talc–magnesium stearate (1:1) was used as lubricant. Guar gum was included in the formulations in various proportions. The compositions of different formulations used in the study containing 50 mg of Nitrofurantoin in each case are shown in Table 1. In all the formulations, guar gum was sieved (<250 µm) separately and mixed with Nitrofurantoin (<150 µm) and MCC (<250 µm). The powders were blended and granulated with 12% starch paste. The wet mass was passed through a mesh (1680 µm) and the granules were dried at 60 $^0$C for 2 hr. The dried granules were passed through a mesh (1190 µm) and these granules were lubricated with a mixture of talc–magnesium stearate (1:1). The lubricated granules were compressed at a compression force of 4000–4500 kg using 9 mm round, flat and plain punches on a single station tabletting machine (M / s Cadmach Machinery, India).

**Table 1: Composition of Nitrofurantoin matrix tablets containing 5% (F1), 10% (10%), 15% (F3) and 20% (F4) of guar gum**

| Ingredients | Quantity (mg) present per each matrix tablet | | | |
|---|---|---|---|---|
| | F1 | F2 | F3 | F4 |
| Nitrofurantoin | 50 | 50 | 50 | 50 |
| Guar gum | 15 | 30 | 45 | 60 |
| Lactose | 187 | 172 | 157 | 142 |
| Starch | 36 | 36 | 36 | 36 |
| Talc | 3 | 3 | 3 | 3 |
| Magnesium Stearate | 3 | 3 | 3 | 3 |
| Total | 300 | 300 | 300 | 300 |

**Evaluation of tablets**

**Physicochemical Parameters**

**Thickness of Tablets**

The thickness of five tablets was measured using Vernier calipers. The extent to which the thickness of each tablet deviated from ± 5% of the standard value was determined. [11-15]

**Hardness of Tablets**

Hardness of the Tablet was determined by Monsanto Hardness Tester. Five tablets from each batch were selected and evaluated, and the average value with standard deviation was recorded. [11-15]

**Friability of Tablets**

Friability of Tablets was performed in a Roche Friabilator. Ten tablets were weighed together and then placed in the chamber. The friabilator was operated for 100 revolutions and the tablets were subjected to the combined effects of abrasion and shock because the plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets are then dusted and re-weighed. [11-15]

**Weight Variation**

Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with the average weight. The percentage deviation was calculated and checked for weight variation. Using this procedure weight variation range of all batches of formulations were determined and recorded. [11-15]

***In-Vitro* dissolution Studies**

The in-vitro dissolution studies were carried out using USP dissolution apparatus type II in different medium.

**Preparation of reagents & solutions**

**Preparation of 0.1 N HCl**

0.1N HCl was prepared by diluting 8.5 ml of concentrated hydrochloric acid to 1000 ml with distilled water. [16]

**Preparation of pH-6.8 phosphate buffer**

28.80 g of disodium hydrogen phosphate & 11.45g of potassium hydrogen phosphate were dissolved in water & volume was made up to 1000 ml. [16]

**Preparation of pH-7.4 phosphate buffer**

2.38 g of disodium hydrogen phosphate, 0.19 g of potassium dihydrogen phosphate & 8.0 g of sodium chloride were dissolved in water & volume was made up to 1000 ml. Adjust the pH if required. [16]

**Preparation of pH 6.8 phosphate buffer with 4% w/v rat caecal contents**

Male Wistar rats weighing 105-150 gm and maintained on a normal diet were used for the study. Thirty minutes before the commencement of drug release studies, four rats were killed by spinal traction. The abdomen were opened, the caecal were traced, ligated at both ends, dissected and immediately transferred into pH-6.8 phosphate buffer, previously bubbled with carbon dioxide gas. The caecal bags were opened; their contents were individually weighed, pooled and then suspended in pH-6.8 phosphate buffer to give 4 %w/v dilution. As the caecum is naturally anaerobic, all these operations were carried out under $CO_2$ gas. [17, 18]

In-vitro dissolution study was performed by using USP Type II Apparatus (Basket type) [Electrolab (ETC-11L) Tablet Dissolution Tester] at 100 rpm for 2 h in 0.1 N HCl (900 ml). Then the dissolution medium was replaced with pH 7.4 phosphate buffer (900 ml) and tested for 3 h as the average transit time of small intestine is 3 h. After 5 h, the dissolution medium was replaced with pH 6.8 phosphate buffer and tested for next 10 h. At the end of the time period 10 ml of the sample were taken and analyzed for Nitrofurantoin content as described previously. A 10 ml fresh and filtered dissolution medium (buffers) was added to make the volume after each sample withdrawal. [11-15]

## Result and Discussion

Thickness of all the formulations was acceptable; it ranged from 2.42 mm to 2.52 mm. The hardness of all the tablet formulations ranged from 4.5 to 6.4 kg/cm$^2$. The average friability of all the formulations lies around 0.49%. Average weight of the tablet was 250 mg, and all the formulations were found to be complying with the standards given in IP. All the colon targeted matrix tablet formulations of Nitrofurantoin were evaluated for in vitro dissolution studies in the presence of 4 % w/v rat caecal content as per the procedure described in methodology section. The highest in-vitro dissolution profile at the end of 15 hr was shown by F4 containing 20 % of guar gum (94.12%) followed by F3 containing 15 % of guar gum (80.01%), F2 containing 10 % of guar gum (70.22%).

F1 containing 5% of guar gum (60.34%) failed to target the Nitrofurantoin in the colon & these formulation releases the majority of drug within 5 hr of study, it may be due to the less proportion of guar gum to retard the drug release. From the in-vitro dissolution studies it can be discussed that the colon targeted matrix tablet containing 20% guar gum was the best formulation to target the Nitrofurantoin to the colon. From the in-vitro dissolution studies in the presence of rat caecal content it was found to be that the drug release increased in the presence of 4 % w/v rat caecal content and the colon targeted matrix tablet containing 20% guar gum released 94.12% of Nitrofurantoin. It may be due to the presence of colonic bacteria which act on the guar gum & digest it. Therefore released maximum quantity of Nitrofurantoin in colon & retard the drug release in the environment of stomach & small intestine.

## Conclusion

All the physical characteristics of the formulations like thickness, hardness, weight variation, friability and in vitro dissolution study were found to be well within the limits and official standards. The susceptibility of the matrix tablets to the enzymatic action of colonic bacteria was assessed by performing the drug release studies in medium containing rat caecal material (4%). From the in-vitro dissolution studies it was found to be that formulation F1 with 5% guar gum failed to retard the drug release, it might be due to the release of majority of drug within 5 hr in the region of stomach & small intestine. Formulation F4 with 20% guar gum emerged to be the best one, because it exhibits the best overall general appearance, hardness of 6.4±0.01 Kg/cm2, friability and a maximum percentage drug release of 94.12% with rat caecal content at the end of 15 hr in in-vitro dissolution studies. In the present study, the matrix formulation containing 20% guar gum is most likely to target drug to colon without being released significantly in stomach and small intestine.

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**Table 2: Evaluation of tablets**

| Formulation | Hardness ($Kg/cm^2$ ±SD) | Thickness (mm) | Friability (%) | % Drug Release |
|---|---|---|---|---|
| F1 | 4.5±0.15 | 2.42±0.1 | 0.41±0.216 | 60.34 |
| F2 | 5.3±0.17 | 2.65±0.15 | 0.60±0.141 | 70.22 |
| F3 | 5.5±0.19 | 2.47±0.13 | 0.52±0.10 | 80.01 |
| F4 | 6.4±0.01 | 2.52±0.17 | 0.42±0.01 | 94.12 |

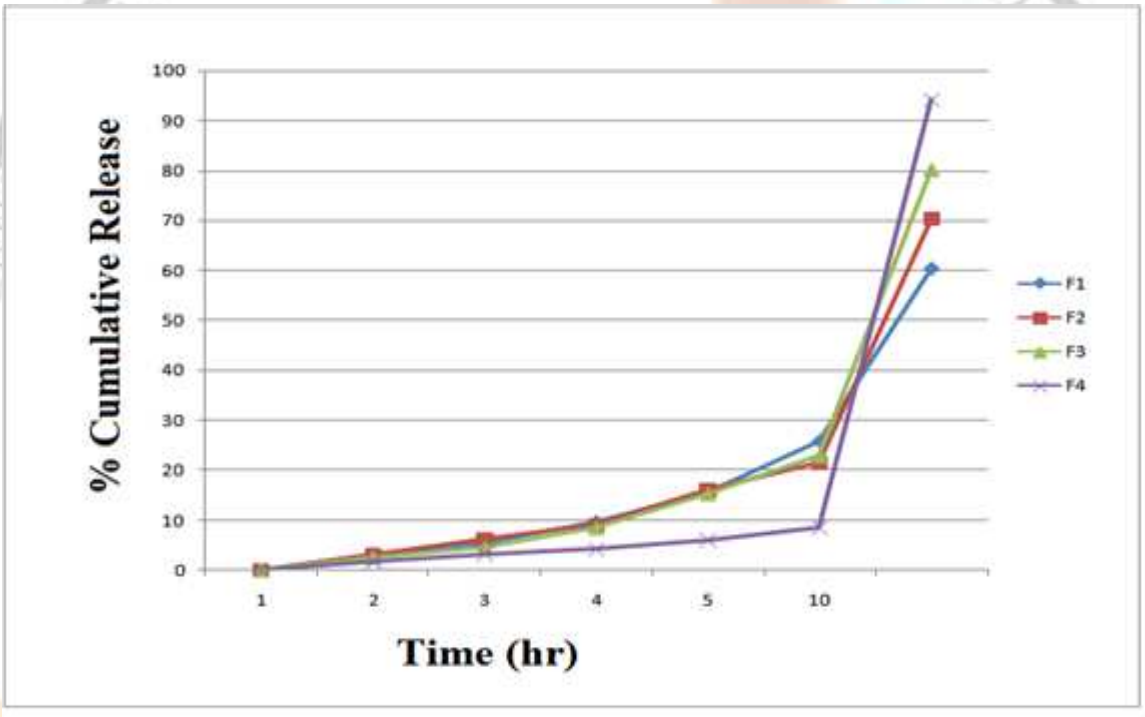


**Fig. 1: % Cumulative Release of drug from colon targeted matrix tablet in the presence of 4 % w/v rat caecal content**