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Formulation development and evaluation of a novel bi-dependent clarithromycin gastroretentive drug delivery system using Box-Behnken design

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ABSTRACT

Helicobacter pylori is the main representative of gastritis, gastrointestinal ulcers, and gastric carcinoma. Therefore its suppression is a precondition for treatment of gastric and duodenal complications. The objective of present work was to develop a novel bi-dependent gastroretentive tablet (BDGRT) formulation containing clarithromycin and to evaluate pharmacokinetics in beagle dogs. Bi-dependent gastroretentive tablets were effectively developed using both sublimation material and effervescent agent. BDGRT formulation was optimized using 3-level-3-factor, Box-Behnken experimental design. The selected independent variables were amount of HPMC K4M (X_1), $NaHCO_3$ (X_2), and camphor (X_3). The dependent variables were Floating lag time (Y_{FLT}), % friability (Y_{FR}), tablet crushing strength (Y_{TCS}) and % Cumulative drug release at 5th h (Y_{Q5}) & at 10th h (Y_{Q10}). Floating properties of tablets was affected by sublimation of camphor. The predicted responses by the optimization model were 13.05 Sec, 0.990%, 3.52 kg/cm^2, 51.29%, and 86.32% for Y_{FLT}, Y_{FR}, Y_{TCS}, Y_{Q5} and Y_{Q10} respectively with X_1, X_2 and X_3 of 119.76 mg, 10.66% and 11.69% respectively. The optimized BDGRT also evaluated for surface morphology, compatibility and stability studies. The delayed t_{max}, increased Mean residence time of BDGRT believed it can be a competent tool for effective delivery of clarithromycin for the eradication of *H. pylori*.

1. Introduction

Helicobacter pylori is the main causative representative of gastritis, gastrointestinal ulcers, and gastric carcinoma. Therefore its suppression is a precondition for treatment of gastric and duodenal complications. In the living body, *H. pylori* sited at both within and beneath mucus layer and it also remain in epithelial cells of stomach. A promising substitute to promote *H. pylori* suppression would be the administration of gastroretentive drug delivery system that can retain elevated levels of antibiotics for prolonged period of time. Clarithromycin is a macrolide antibiotic, frequently prescribed for the suppression of *H. pylori* associated gastric ulcers. As the drug is efficient when blood vacillations are diminished, prolong release drug delivery system containing clarithromycin is advantageous. Moreover, the shorter biological $t_{1/2}$ (3–5 h) of clarithromycin encourages improvement of prolong release drug delivery system.

In the past couple of decades variety of strategies of gastroretentive drug delivery systems have been reported such as effervescent [1–3], non-effervescent [4,5], low density [6–8], high density [9,7], raft formed [10,11], expandable [12,13], in situ gelling [14,15], mucoadhesive [16–18], gastroretentive drug delivery systems in the form of capsules [19–21], bi-layer tablets [22,23], microspheres [24,25], granules [26], pellets [27–29] and beads [30,31].

Although the floating system has been generally designed using gas generators (e.g. carbonates), gastroretentive tablets (GRT) containing low-density material such as polypropylene and calcium silicate were also reported [45,46]. These GRT are valuable in that they could float immediately on gastric fluid surface due to low-density, thus they would not be in risk of premature emptying in a stomach. However safety and clearance of low density materials might be suspicious. In the current investigation, our researchers developed a novel gastroretentive tablet which attained floatation by two different strategies, highly porous low-density and gas-producing systems. These bi-dependent gastro retentive

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Table 1
Variables and constrains in Box–Behnken experimental design.

Independent variable	Level			Constrains
	−1	0	1	
X_1: amount of HPMC K4M (mg)	50	100	150	In range
X_2: amount of $NaHCO_3$ (%)	8	10	12	In range
X_3: amount of camphor (%)	8	11	14	In range
Dependent variables				
Y_1: floating lag time (sec)				Target as 0
Y_2: friability (%)				Target as 1
Y_3: tablet crushing strength (kg/cm^2)				Target as 5
Y_4: cumulative drug release at 5th h (%)				Target as 50
Y_5: cumulative drug release at 10th h (%)				Target as 90

tablets (BDGRT) have floatation without any lag time or less for low density. Camphor and sodium bicarbonate were incorporated as sublimating agent for highly porous low density system and gas-producing agent for effervescent system, respectively. Above the sublimation temperature, camphor can be sublimated into the tablet matrix, producing pores in the matrix which facilitates BDGRT buoyant on the medium with zero lag time by diminishing density of the system. The density of gastroretentive tablets could be easily controlled by the amount of sublimation materials. Additionally, gas-producing agent contributes a vital function in sustaining floatation of BDGRT [32].

A Box-Behnken design is a type of response surface design that does not contain an embedded factorial or fractional factorial design. They are very useful in the same setting as the central composite designs. Their primary advantage is in addressing the issue of where the experimental boundaries should be, and in particular to avoid treatment combinations that are extreme. So, we chosen Box-Behnken design for designing the experiments.

The objective of the current investigation was to develop a novel bi-dependent gastroretentive tablet (BDGRT) formulation containing clarithromycin. BDGRT was optimized using 3-level, 3-factor, 15 run Box-Behnken experimental design. The selected independent variables were amount of HPMC K4M (X_1), $NaHCO_3$ (X_2), and camphor (X_3). The dependent variables were Floating lag time (Y_{FLT}), % Cumulative drug release at 5th h (Y_{Q5}) and at 10th h (Y_{Q10}), % friability (Y_{FR}) and tablet crushing strength (Y_{TCS}). Statistically optimized formulation was evaluated for pharmacokinetics in beagle dogs.

2. Materials and methods

2.1. Materials

Clarithromycin was generously provided by Savan Pharmaceuticals Pvt., Ltd. Hyderabad, India. Hydroxy propyl methylcellulose K4M was procured from Dr. Reddy's Laboratories, Hyderabad, India. Magnesium stearate, talc, camphor and Sodium bicarbonate were purchased from SD Fine chemicals Pvt., Ltd., Mumbai, India.

2.2. Methods

2.2.1. Box-Behnken experimental design

A 3-level, 3-factor, 15 run experimental Box-Behnken design was adopted to optimize levels of variables in the novel BDGRT formulations [33–36]. The selected independent variables were amount of HPMC K4M (X_1), $NaHCO_3$ (X_2), and camphor (X_3). The dependent variables were Floating lag time (Y_{FLT}), % Cumulative drug release at 5th h (Y_{Q5}) and at 10th h (Y_{Q10}), % friability (Y_{FR}) and tablet crushing strength (Y_{TCS}). In this work, the generation of experimental runs, ANOVA study and optimization were carried out by Design-expert® software 8.0.1. (Stat-Ease Inc., Minneapolis). The non-linear quadratic model by this design is given as $Yi = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{11}X_{21} + b_{22}X_{22} + b_{33}X_{23}$. The optimum formulation was chosen depending on the condition of managing the 0 Sec, 1%, 5 kg/cm^2, 50%, and 90% for Y_{FLT}, Y_{FR}, Y_{TCS}, Y_{Q5} and Y_{Q10}, respectively. All selected dependent and independent variable with coded and actual values and constrains applied for the optimization were represented in Table 1. Total fifteen runs with three replicates on center point according to Box-Behnken design were represented in

Table 2
Observed responses in Box-Behnken design for BDGRT.

Formula code	Independent variables			Dependent variables				
	X1	X2	X3	Y_{FLT} (sec)	Y_{FR} (%)	Y_{TCS} (kg/cm^2)	Y_{Q5} (%)	Y_{Q10} (%)
F1′	−1	−1	0	250 ± 5	0.7 ± 0.18	3.03 ± 0.25	60.50 ± 3.79	90.25 ± 5.42
F2	1	−1	0	200 ± 12	0.6 ± 0.15	4.03 ± 0.75	44.31 ± 7.80	82.10 ± 4.71
F3	−1	1	0	88 ± 3	0.8 ± 0.14	3.50 ± 0.30	69.30 ± 5.89	98.32 ± 8.19
F4	1	1	0	50 ± 4	0.9 ± 0.17	3.23 ± 0.21	45.05 ± 4.33	84.90 ± 1.23
F5	−1	0	−1	320 ± 10	0.5 ± 0.17	4.87 ± 0.80	59.90 ± 4.77	93.85 ± 5.23
F6	1	0	−1	254 ± 7	0.6 ± 0.05	5.03 ± 0.25	40.10 ± 2.12	82.93 ± 7.65
F7	−1	0	1	0 ± 0	1.4 ± 0.13	2.20 ± 0.20	64.36 ± 9.13	94.15 ± 4.48
F8	1	0	1	0 ± 0	1.6 ± 0.28	2.50 ± 0.40	43.94 ± 6.03	86.78 ± 4.61
F9	0	−1	−1	412 ± 13	0.6 ± 0.05	4.70 ± 0.20	45.50 ± 8.32	72.03 ± 7.55
F10	0	1	−1	210 ± 22	0.5 ± 0.08	5.20 ± 0.30	52.10 ± 7.15	90.20 ± 3.36
F11	0	−1	1	0 ± 0	1.8 ± 0.09	2.40 ± 0.20	44.44 ± 6.25	93.19 ± 4.49
F12	0	1	1	0 ± 0	1.8 ± 0.14	2.20 ± 0.10	53.31 ± 6.04	84.82 ± 3.48
F13	0	0	0	65 ± 13	0.9 ± 0.13	3.30 ± 0.20	55.01 ± 7.50	86.99 ± 8.85
F14	0	0	0	54 ± 6	0.8 ± 0.11	3.50 ± 0.30	56.36 ± 9.80	84.29 ± 4.46
F15	0	0	0	50 ± 5	0.8 ± 0.07	3.57 ± 0.35	51.58 ± 4.60	87.13 ± 5.24

Coded values	Actual values		
	X_1 (mg)	X_2 (%)	X_3 (%)
−1	50	8	8
0	100	10	11
1	150	12	14

X_1 – Amount of HPMC K4M; X_2- % of $NaHCO_3$; X_3- % of Camphor; Y_{FLT}-Floating lag time; Y_{Q5}- % Cumulative drug release at 5th h; Y_{Q10}- % Cumulative drug release at 10th h, Y_{FR}- % friability, Y_{TCS}- tablet crushing strength, All formulas containing 1% of each talc and magnesium stearate. Total tablet weight was adjusted to 550 mg with MCC.