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Gas powered controlled drug delivery system of Secnidazole for spatial and temporal control

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ABSTRACT

One of the most vulnerable gastro intestinal tract infections affecting the human population worldwide are H pylori infections. It causes complicated gastric problems such as gastritis, gastro duodenal ulcers, gastric cancer and primary B-cell gastric lymphoma. In the present study, Secnidazole was used for preparing floating dosage forms that are designed to retain in the stomach for a long time and have developed as a drug delivery system for better eradication of Helicobacter Pylori in peptic ulcer diseases. Hydroxy Propyl Methyl Cellulose (HPMC) and carbopol in different concentrations were used as floating agents; sodium alginate was used as a gel forming agent and sodium bicarbonate and citric acid as effervescent agents for spatial and temporal control of Secnidazole. Eight formulations (F1-F8) were prepared and evaluated for various physical parameters, Hardness, friability, content uniformity, floating ability and release profiles as well as kinetics of release were assessed. Selected formulations were able to float with the lag time of 1-10 minutes and showed buoyancy for at least 8 hrs. Meanwhile, sustained profiles of drug release were also obtained.

Keywords: *H pylori*, Secnidazole, spatial and temporal, buoyancy, effervescent.

INTRODUCTION

In the last decade, the number of patients suffering from peptic ulcer and gastric cancer due to *H. pylori* infection has increased tremendously. *H. pylori* are spiral, gram-negative, microaerophilic rod-shaped bacteria with multiple flagella.[1, 2] *H. pylorus which remain on the luminal surface of the gastric mucosa under mucous gel layer, are highly motile, and produces* enzyme urease to alter the surrounding pH to protect itself from gastric acid[2]. Acute infection with *H pylori* during childhood can be accompanied by diarrhea and slowing of weight gain. In adults, however, acute infection usually passes unnoticed except for transient and mild dyspepsia, nausea and vomiting[3]. According to the statistics, it causes peptic ulcer disease approximately one in six (17%) persons and each year 1% to 2% of these will experience a major or life threatening complication, such as bleeding or gastric outlet obstruction[4]. *H pylori* is such a threat that the World Health Organization's (WHO) International Agency for Research into Cancer (IARC) in 1994 has classified as a “Class-I-Carcinogen”[5].

When the presence of *Helicobacter pylori* is associated with peptic ulcer disease, eradication of this bacterium leads to the cure of the disease, despite the fact that an optimal antibiotic schedule for its eradication has not yet been found. The complexity and adverse effects of treatment and bacterial resistance to the medications provide different eradication rates, with several treatment regimens used to date. As a general rule concerning bacteria that are sensitive to antibiotics, a longer period of treatment and different types of medication promote a higher eradication rate for the chosen regimen. However, this longer treatment regimen may also bring more side effects and result in lower compliance[6].

Currently, therapy with 2 antibiotics plus a proton pump inhibitor, one of them clarithromycin and the other a nitroimidazole compound, have resulted in high eradication rates in several countries.[7]

Therapy for *H. pylori* infection consists of 10 days to 2 weeks of one or two effective antibiotics, such as amoxicillin, tetracycline (not to be used for children <12 yrs.), metronidazole, or clarithromycin, plus either ranitidine bismuth citrate, bismuth subsalicylate, or a proton pump inhibitor.

Secnidazole is a nitroimidazole derivative and does not differ from metronidazole. However, it has a prolonged plasma half-life, and for this reason, Secnidazole is the first choice treatment for many diseases[8].

We used Secnidazole instead of metronidazole because of it's longer half-life, permitting an alternate day-dosing schedule, thereby ensuring better patient compliance. The convenience and ease of administration associated with single dose therapy, combined with good tolerability profile, makes Secnidazole a suitable option over the other single dose treatments and an attractive alternative to multiple dose regimens with other drugs in this class.[8]

GRDDS are designed to localize the action of drug on gastric region and prolong the gastric residence time of the drugs. Now a day's research is going on these dosage forms for effective treatment of *H pylori*. Drug delivery to the site of infection *i.e.* gastric mucosa may help to solve the problems associated with the other therapies.

MATERIALS AND METHODS

Chemicals/Materials:
The drug Secnidazole was provided by Cipla pharmaceutical Pvt. Ltd. , and Excipients such as HPMC K4M (ozone chemicals Pvt. Ltd.), Carbapol (Himedia Pvt. Ltd) , sodium Alginate (Research-lab fine chem. industries, Mumbai), sodium bicarbonate (Research-lab fine chem. industries, Mumbai) citric acid, Ethyl cellulose, Microcrystalline cellulose(Research-lab fine chem. industries, Mumbai).

Analytical method for estimation of Secnidazole:
Detection of Absorption Maxima:
In order to ascertain the wavelength of maximum absorption (λ max) of the drug, different solutions of the drugs (4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml, 12 µg/ml) in double distilled water was scanned using spectrophotometer within the wavelength region of 200–400 nm against double distilled water as blank. The absorption curve showed characteristics absorption at 320 nm for secnidazole.

Calibration curve for estimation of secnidazole in distilled water:
In this method, the drug was dissolved in little amount of distilled water to get a clear solution, volume was adjusted with distilled water. Then the maximum absorbance was measured at 320 nm. Beer's law obeyed in concentration range of 2-12 mcg/ml.

Calibration curve for estimation of secnidazole in 0.1N HCl:
In this method, the drug was dissolved in little amount of 0.1N HCl to get a clear solution, volume was adjusted with 0.1N HCl. Then the maximum absorbance was measured at 320 nm. Beer's law obeyed in concentration range of 2-12 mcg/ml.

Table no1: composition of floating tablets of Secnidazole

Sr.no	Ingredients	Quantity per tablet (mg)							
		F1	F2	F3	F4	F5	F6	F7	F8
1	Secnidazole	250	250	250	250	250	250	250	250
2	HPMC K4M	50	80	100	140	50	50	60	70
3	Carbopol	100	70	50	10	-	-	-	-
4	Sodium alginate	-	-	-	-	30	40	50	60
5	Ethyl cellulose	10	20	20	20	-	-	-	-
6	Microcrystalline cellulose	30	30	30	30	-	-	-	-
7	Di-calcium phosphate	-	-	-	-	30	20	30	40
8	Sodium starch glycolate	-	-	-	-	20	20	30	30
9	Sodium bicarbonate	50	50	50	50	50	50	70	60
10	Citric acid	25	20	20	20	15	10	10	10
11	Magnesium stearate	5	10	10	10	5	5	5	5
12	Talc	10	10	10	10	10	10	10	10
Total weight (mg)		530	540	540	540	460	455	515	535

Formulation of floating tablets:
The floating tablets of Secnidazole were prepared by both wet granulation and direct compression method. Formulations F1-F4 was prepared by direct compression method whereas formulations F5-F8 were prepared by wet granulation. All the ingredients of the formulation were weighed separately and passed through sieve #40 and then mixed thoroughly. Formulations F5-F8 were wet granulated using absolute ethanol as a wet granulating agent. Granules were dried and punched using 12mm punches. Ingredients of formulations F1-F4 were mixed and compressed directly using 12mm punch.

EVALUATION OF FLOATING TABLETS OF SECNIDAZOLE:
Precompressional evaluation: [9, 10, 11.]
The flow properties of blends (before compression) were characterized in terms of Angle of repose, Bulk density and tapped density, Carr's index and Hausner's ratio.

Post compressional evaluation:
Physical evaluation of floating tablets: [12]
Two tablets from each formulation were randomly selected and Organoleptic properties such as color, odor, taste and shape were evaluated. Thickness and diameter of ten tablets were measured using vernier calipers. The prepared floating tablets were evaluated for weight variation using 20 tablets, hardness (Monsanto tester), and friability using 10 tablets (Roche type friabilator).

Buoyancy lag time and total floating time: [13]
On immersion of tablets of different formulations in 0.1N HCl solution at 37±0.5°C, the tablets floated, and remained buoyant without disintegration, the results of the buoyancy lag time (BLT) and total floating time (TFT) were shown in Table below.

Drug content estimation: [12]
The drug content in each formulation was determined by triturating 10 tablets and powder equivalent to 50 mg was added in 0.1N HCl followed by stirring. The solution was filtered through a 0.45 µ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 320 nm using 0.1NHCl as blank.

Swelling index: [14]
Weight gain or water uptake/ swelling index can be studied by considering the swelling behavior of Floating dosage form. The study is done by immersing the dosage form in simulated gastric fluid at 37^{o}C and determining the dimensional changes like tablet diameter and/ or thickness at regular 1-h time intervals until 24 h, the tablets were removed from beaker, and the excess surface liquid was removed carefully using the paper. The swollen tablets were then reweighed and WU is measured in the terms of percent weight gain, as given by equation

$$WU = (Wt - Wo) \times 100 / Wo$$

In which Wt and Wo are the weights of the dosage form at time t and initially, respectively[15]

In-vitro dissolution studies:
The release rates of Secnidazole from floating tablets were determined using United State Pharmacopeia (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl at 37° ± 0.5°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through 0.45 µ membrane filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions were measured at 320 nm using a UV/Visible spectrophotometer. The Cumulative percentage drug release was plotted against time to determine the release profile.

In-vitro drug release kinetic studies: [15]
Kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release from the tablets, drug release data was analyzed according to Zero order and Higuchi square root. The criterion for selecting the most appropriate model was chosen on the basis of goodness of fit test. The data were processed for regression analysis using PCP Disso V3 software.

Infra Red Spectral analysis:[16] IR Spectral analysis was used to study the interactions between the drug, polymer and the excipients. The drug and excipients must be compatible with one another to produce a product stable, efficacious and safe.

RESULTS AND DISCUSSION

Analytical method for estimation of Secnidazole:
UV Spectrum of Secnidazole in 0.1 N HCl:

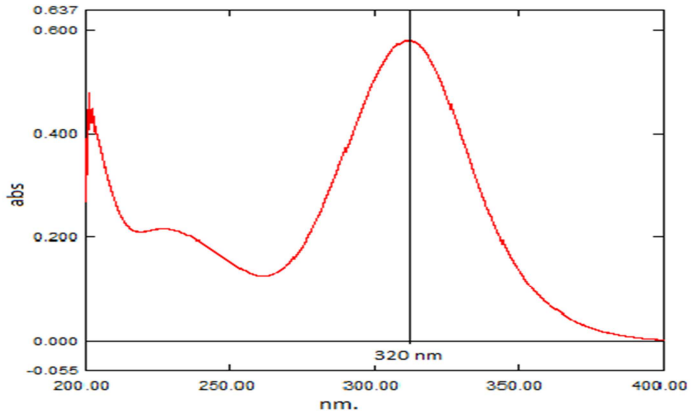

Fig.1. UV Spectrum of Secnidazole in 0.1 N HCl

Standard calibration data of secnidazole in distilled water and 0.1 N HCl:

Table 2: Standard calibration data of secnidazole in distilled water and 0.1 N HCl

Concentration (mcg/ml)	Absorbance in distilled water	Absorbance in 0.1 N HCl
0	0	0
2	0.125	0.077
4	0.228	0.151
6	0.337	0.208
8	0.462	0.283
10	0.561	0.345
12	0.686	0.411

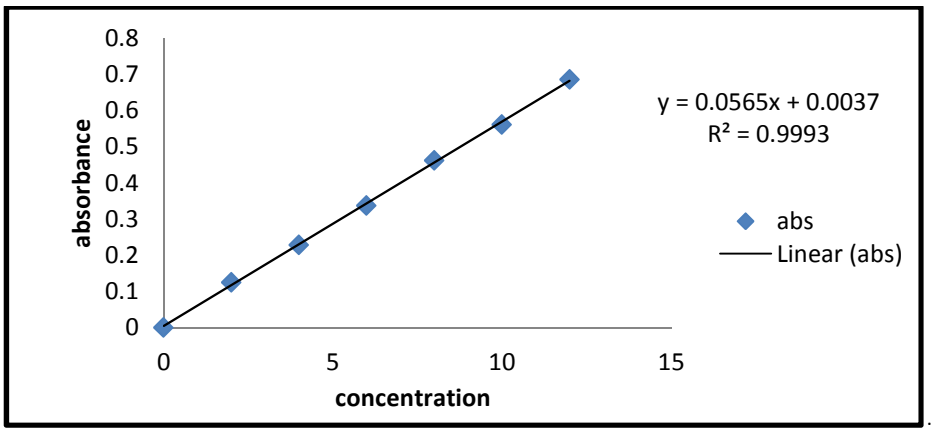

Fig.2: Standard calibration curve of secnidazole in distilled water

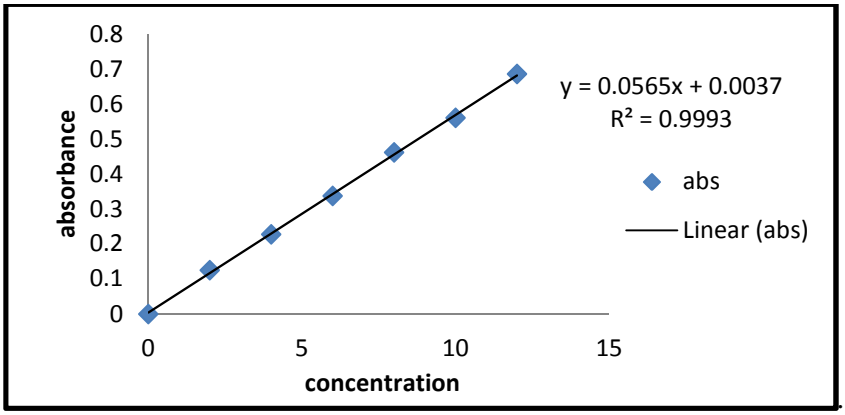

Fig.3: Standard calibration curve of secnidazole in 0.1N HCl

Precompressional parameters:

The formulations showed good flow property and Carr's index (Table no.2). Angle of repose ranged from 25^0 to 32.43^0 Carr's index ranged from 17.87±0.07 to 21.06±0.11 and the Hausner's ratio ranged from 1.21±0.11 to 1.27±0.10.

Table no.3: results of pre-compressional flow properties

Batch	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index I_C	Hausner's ratio H_R	Angle of repose (ɵ)
F1	0.3658±0.06	0.3945±0.03	19.48±0.11	1.24±0.08	25.54±0.02
F2	0.3325±0.05	0.4114±0.08	19.18±0.11	1.23±0.12	29.21±0.08
F3	0.3253±0.07	0.4545±0.07	17.87±0.07	1.21±0.11	23.32±0.04
F4	0.3343±0.04	0.4235±0.04	21.06±0.11	1.27±0.10	32.43±0.03
F5	0.3488±0.02	0.4166±0.04	19.18±0.09	1.22±0.03	32.12±0.06
F6	0.3409±0.04	0.4545±0.03	18.73±0.10	1.23±0.02	29.23±0.09
F7	0.3658±0.07	0.4166±0.06	19.20±0.06	1.24±0.07	34.34±0.04
F8	0.3332±0.01	0.4166±0.02	20±0.09	1.25±0.05	27.45±0.05

Table no.4: results of post compression properties of tablets

Batch	Average wt (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)
F1	530	4.30±0.02	12.03±0.02	7.7±0.03	0.80±0.06
F2	539	4.40±0.06	12.03±0.04	7.0±0.02	0.76±0.06
F3	538	4.38±0.09	12.06±0.05	7.6±0.07	0.91±0.09
F4	535	4.35±0.01	12.02±0.03	8.2±0.06	0.72±0.08
F5	458	3.19±0.08	12.01±0.06	7.8±0.02	0.71±0.04
F6	450	3.04±0.09	12.04±0.05	7.2±0.07	0.66±0.03
F7	513	4.17±0.12	12.03±0.08	8.1±0.06	0.75±0.04
F8	550	4.50±0.03	12.05±0.07	8.3±0.05	0.76±0.05

Table no.5: results of physicochemical properties of the tablets

Batch	Drug content (%)	Swelling index
F1	101.58±0.20	74.5±0.12
F2	99.63±0.12	98.20±0.63
F3	98.68±0.20	96.40±0.23
F4	99.38±0.12	85.4±0.19
F5	103.37±0.14	64.5±0.26
F6	104.73±0.13	68.2±0.80
F7	98.68±0.20	72.5±0.12
F8	96.38±0.21	78.42±0.45

Postcompressional parameters of floating tablets:

The shape of tablets of all formulations remained smooth, convex faced circular with no visible cracks. The thickness of tablets was measured by vernier caliper and was ranged between 3.04±0.09mm to 4.50±0.03mm. The hardness of the tablets was measured by Monsanto tester (Thermo Lab, Mumbai, India) and was in between7.0±0.02 to 8.3±0.05kg/cm2. The friability was measured by friabilator (Roche friabilator) and was found to be 0.66±0.03to 0.91±0.09, which is an indication of satisfactory mechanical resistance of the tablets. The drug content estimations showed values in the range of 96.38% to 104.73% which reflects good uniformity in drug content among different

formulations. All the tablets passed weight variation test as the % weight variation was within Pharmacopoeial limits. The results are shown in Table no.4 & 5.

In-vitro bouyancy studies:

The tablets were prepared by both direct compression and wet granulation followed by compression. Sodium bicarbonate was added as gas generating agent. On contact with dissolution medium (0.1N HCl), carbon dioxide gas was generated. It was observed that the gas generated is trapped and protected within gel, formed by hydration of polymers (HPMC, sodium alginate etc), thus decreasing the density of the tablet below 1 and tablet becomes buoyant. All the batches of tablets were found to exhibit varying floating lag time due to presence of varying ratio of sodium bicarbonate and citric acid. The tablets with HPMC with proportionate ratios of carbopol showed good floating time. Increase in HPMC level in formulations prolonged the floating lag time upto certain extent with proportionate increase in sodium alginate content. With reference to buoyancy studies results it can be concluded that the batches containing HPMC and carbopol showed good floating lag time (FLT) and Total floating time (TFT). (Table no.6).

Table no.6: results of in-vitro buoyancy study

Batch	Floating lag time (FLT)	Floating duration (hrs) (TFT)
F1	2min34sec	11
F2	3min24sec	12
F3	3min15sec	12
F4	4min12sec	12
F5	10min54sec	11
F6	12min48sec	8
F7	20min5sec	12
F8	21min36sec	11

Table no.7: results of in-vitro dissolution study

Time (hrs)	% Drug Release							
	F1	F2	F3	F4	F5	F6	F7	F8
1	18.8%	24.16%	21.03%	18.15%	25.16%	43.01%	21.22%	25.6%
2	28.29%	33.37%	28.23%	28.98%	34.99%	48.38%	28.29%	37.37%
3	37.75%	43.63%	36.87%	36.31%	43.13%	54.52%	34.49%	48.64%
4	52.02%	51.65%	43.7%	45.56%	51.71%	65.29%	41.63%	57.72%
5	59.41%	59.97%	51.02%	52.65%	59.03%	72.43%	48.77%	64.98%
6	72.18%	66.42%	56.47%	59.41%	64.5%	79.26%	55.59%	79.89%
7	79.26%	71.49%	62.42%	66.5%	75.75%	84.20%	62.60%	81.39%
8	85.71%	75.81%	65.17%	78.19%	88.27%		71.99%	90.16%
9	100%	80.16%	67.61%	80.13%	95.66%		88.88%	95.23%
10		86.43%	75.31%	85.23%	98.12%		89.97%	100%
11		90.76%	85.3%	92.43%	100%		95.12%	
12		93.34%	86.81%	97.89%			100%	

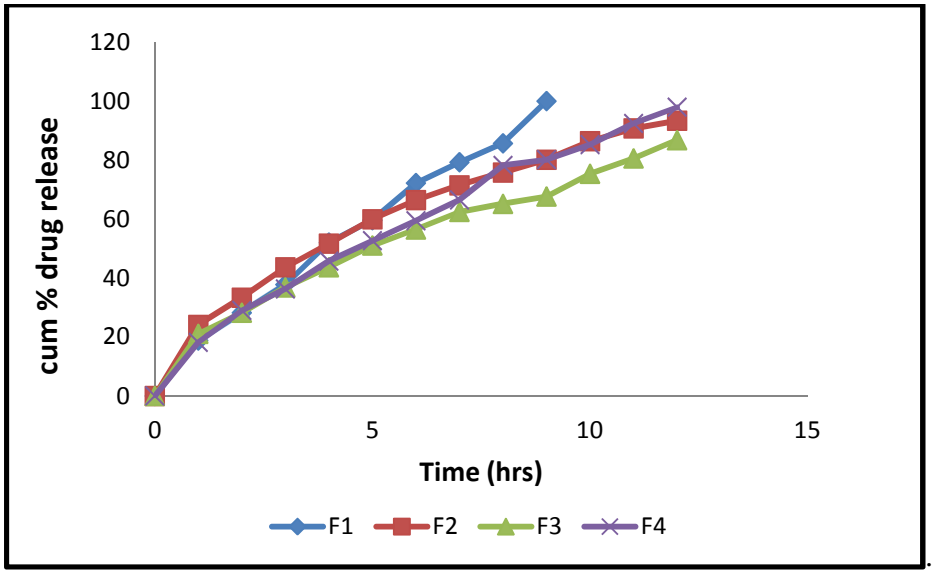

Fig.4. in-vitro release data of formulation F1-F4

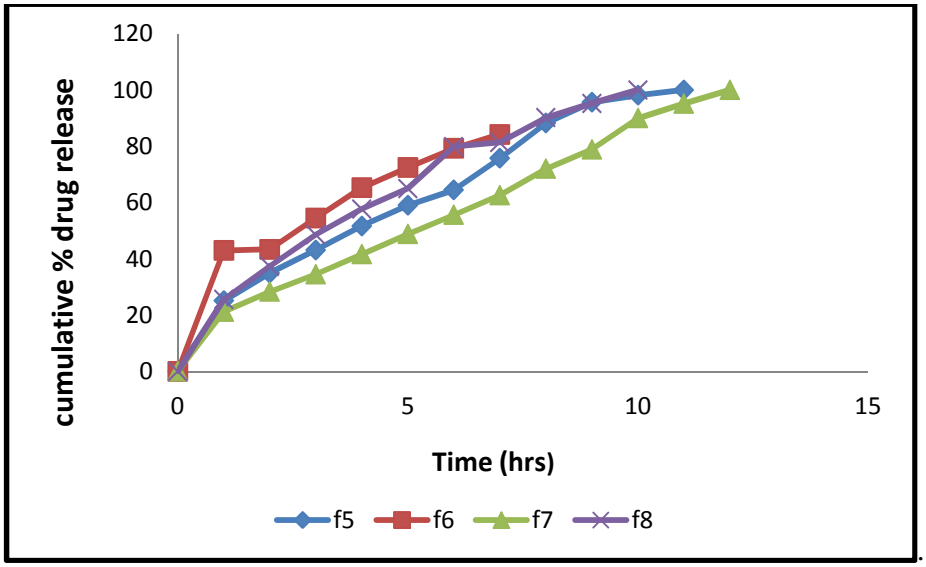

Fig.5. In-vitro release data of formulation F5-F8

In vitro dissolution studies:

In vitro dissolution studies of all the formulations of floating tablets of secnidazole were carried out in 0.1N HCl. The study was performed for 12 hours and cumulative drug release was calculated for every one hour time interval. In vitro dissolution studies of all the formulations are shown in Fig no. HPMC, carbopol and Na-alginate were used to formulate the floating tablets. It was observed that the type of polymer influences the drug release pattern. All the formulation containing varying amount of sodium bicarbonate. A significantly higher amount of drug release was observed from the batches based on HPMC and carbopol ratios.

Table no.8 in-vitro kinetic data

Formulation	Zero order (R)	First order (R)	Higuchi's (R)	Peppa's	
				R	N
F1	0.9903	0.971	0.952	0.992	0.0258
F2	0.9381	0.972	0.997	0.997	0.0433
F3	0.9563	0.965	0.990	0.995	0.0426
F4	0.9775	0.874	0.978	0.997	0.6972
F5	0.966	0.848	0.975	0.985	0.0379
F6	0.871	0.975	0.979	0.908	0.0418
F7	0.987	0.860	0.956	0.975	0.0380
F8	0.952	0.940	0.989	0.996	0.0349

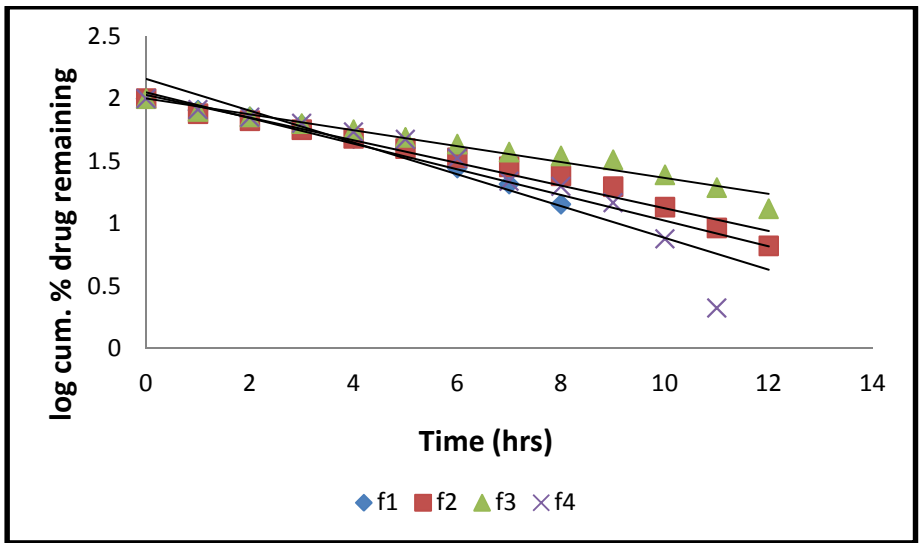

Fig.6. First order plot of formulations F1-F4

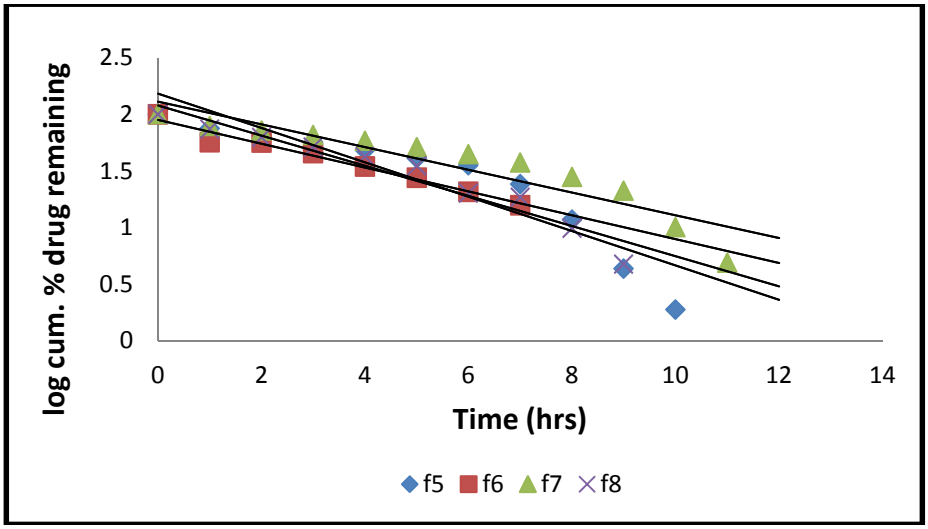

Fig.7. First order plot of formulations F5-F8

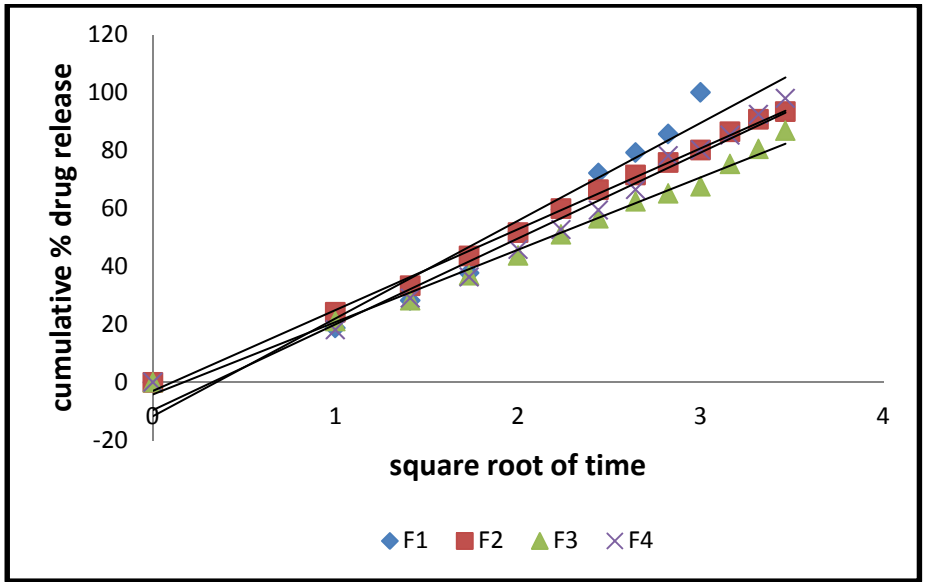

Fig.8. Higuchi's plot of formulations F1-F4

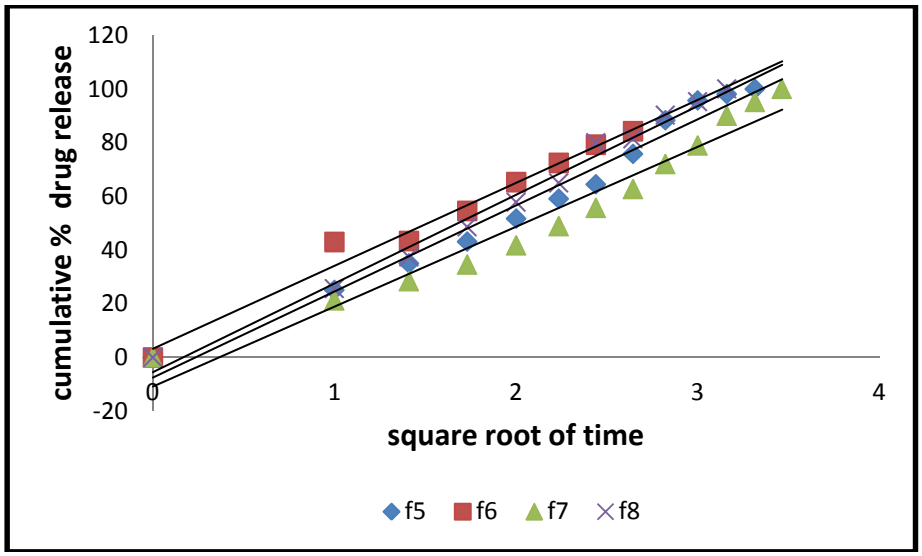

Fig.9. Higuchi's plot of formulations F5-F8

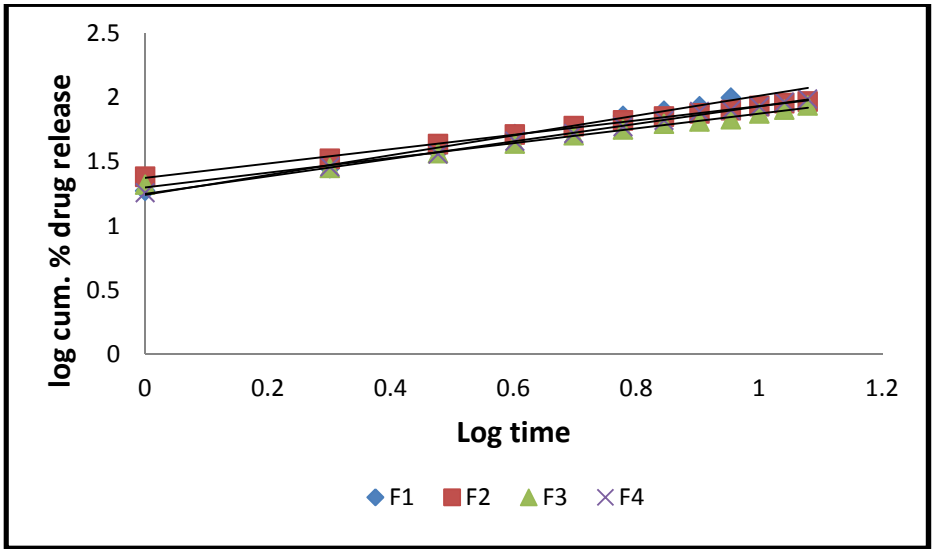

Fig.10: Peppa's plot of formulations F1-F4

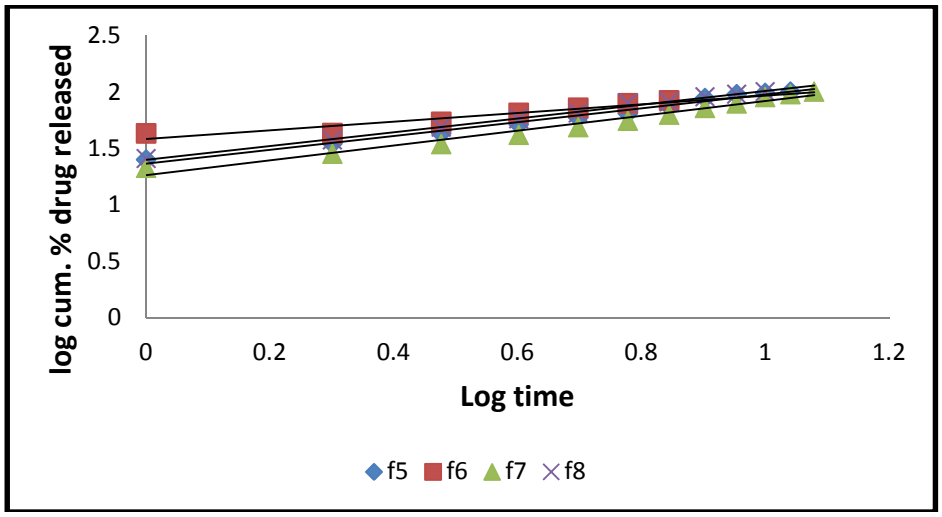

Fig.11: Peppa's plot of formulations F5-F8

Analysis of release mechanism:

The drug release data of Secnidazole were fitted to models representing Zero order and Higuchi's kinetics to know the release mechanisms. The data were processed for regression analysis using PCP Disso V3 software. The results are shown in Table no. 7 and graphs in Fig no.3 to 8. Diffusion is related to the transport of drug from the dosage form in the *in vitro* fluid depending on the concentration. In the present study, in vitro release profiles could be best expressed by Higuchi's equation as formulation showed good linearity (R2: 0.9906) indicates that the diffusion is dominant mechanism of drug release with these formulations.

Infra Red Spectral analysis:

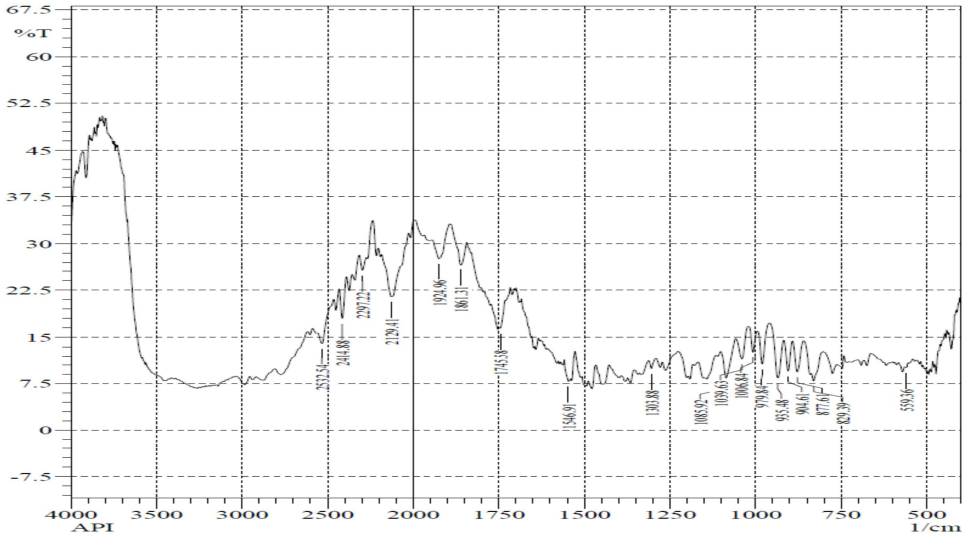

Fig.12. IR Spectrum of Secnidazole

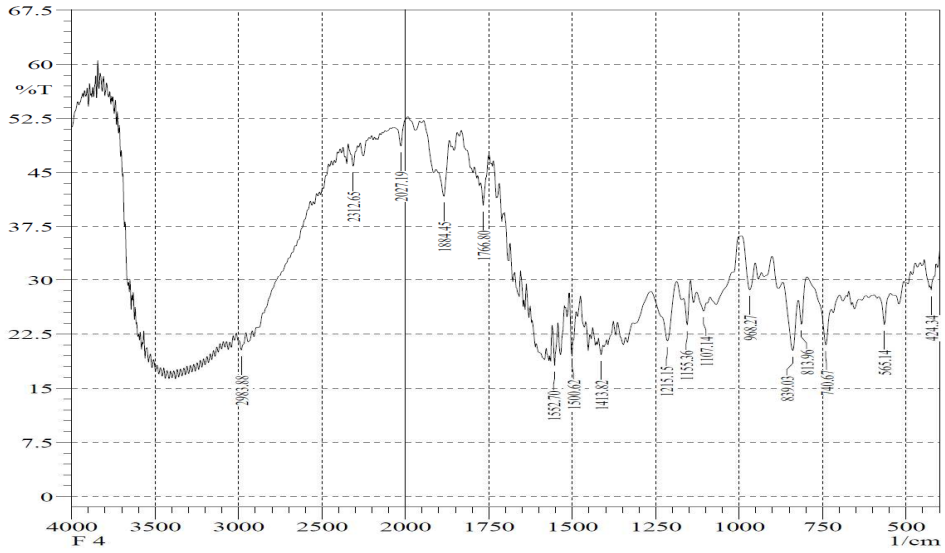

Fig.13. IR Spectrum of formulation F4

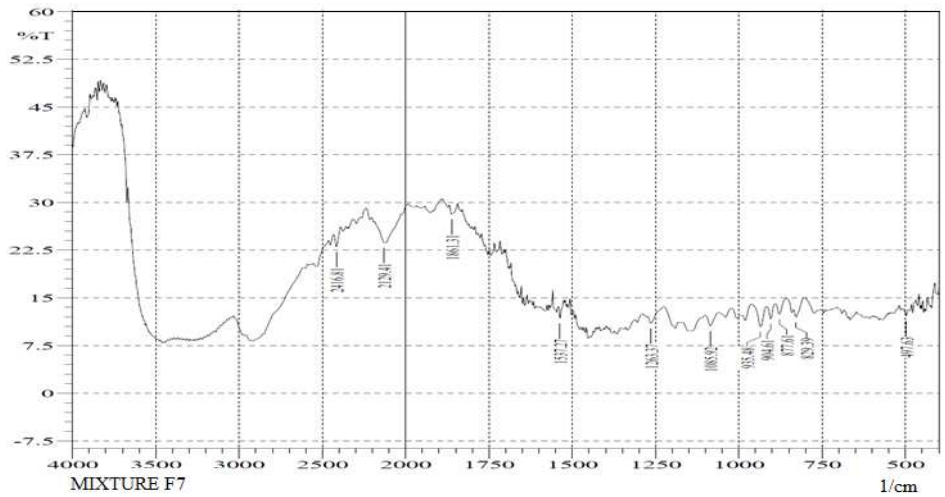

Fig.14. IR Spectrum of formulation F7

Interpretation of IR Spectra:

Group	Stretching
C═N	1665-1480
NO_2	1370-1300
O-H	1350-1260
C-O	1120-1030
C-H	840-790
C═C	1580-1520

The results revealed that there is no significant interaction between the drug and the other excipients used.

CONCLUSION

According to the present invention, the floating drug delivery system of secnidazole includes swelling agent hydroxyl propyl methyl cellulose, carbopol, sodium starch glycolate and a gel forming polymer sodium alginate. Together these agents form a hydrated gel matrix. The tablets also contain a gas generating agent such that a gas is generated in a controlled manner and is entrapped in hydrated gel matrix. The gas generating agent sodium bicarbonate interacts with the acid source citric acid by contact with gastric fluid to generate carbon dioxide.

The floating tablets are evaluated for different precompressional and post compressional parameters. The results revealed that all the formulations shows good precompressional properties showing better flowability, harness is maintained in the range of 7.0to 8.3kg/cm^2 which provides good mechanical strength to the tablets. Other parameters like weight variation, friability, thickness, drug content are in the range of prescribed IP limits.

The in-vitro drug release study suggests that the drug is released by mixed order kinetics. To ascertain the drug release mechanism the in vitro release data were also subjected to higuchi's diffusion and peppa's plots. Results of these kinetic plots and n values, suggests that the drug was released by Non-Fickian control (Anomalous diffusion) with swelling. The results of buoyancy study revealed that the tablets remained buoyant over a period of 10 hrs in the release medium and the amount of sodium bicarbonate found to be significant for not only to remaining buoyant without causing disintegration of the tablet but also to release of drug in acidic medium.

In the present study gastric floating delivery of secnidazole was successfully developed in the form of tablets to improve its local action and also gastric residence time that increases its bioavailability also.

REFERENCES

[1] Marshall BJ. *Lancet* **1983**;1:1273-5.
[2] Marshall BJ, Warren JR. *Lancet* **1984**;1:1311-5.
[3] Javier Torres, Guillermo Perez-Perez, Karen J. Goodman, *Archives of Medical research*, 31, **2000**,431– 469.
[4] Waqar A Qureshi, David Y, Graham, *Upper GI disorders*, 5, 18-29.
[5] The *H pylori* and stomach ulcer report, Empowering You with Knowledge and Solutions for good health. Edition no 12(CPA), Nov 2009.
[6] Savarino V, Zentilin P, Bisso G et al. - *Aliment Pharmacol Ther* **1999**; 13: 43-47.
[7] Chiba N, Rao BV, Rademaker JW et al. - *Am J Gastorenterol* **1992**; 87: 1716-1727.
[8] Gillis JC & Wiseman LR - Secnidazole. *Drugs* **1996**; 51: 621-638.
[9] Newman AW. Micromeritics: Brittain HG; Physical Characterization of Pharmaceutical Solids. Marcel Dekker Inc, Newyork; Basel, **1995**; 70; 293-294.
[10] Newman AW. Micromeritics: Brittain HG; Physical Characterization of Pharmaceutical Solids. Marcel Dekker Inc, Newyork; Basel, **1995**; 70; 271-275.
[11] Wells J; Pharmaceutical Preformulation: AultonME; Pharmaceutics: The Science of dosage form design. 3rd edi, Edinburg, London, Melbourne, Newyork, **1998**; 247.
[12] Banker GS, Anderson NR; Tablets: Lachman L, Lieberman HA, Kanig JL; The Theory and Practice of Industrial Pharmacy. 3rd edi,Varghese Publication House, Bombay, **1987**; 296-303.
[13] Aulton ME. Pharmaceutics: The Science of Dosage Form Design. 2nd Ed. London: Churchill Livingstone. **2002**.
[14] Gergogiannis YS, Rekkas DM, Dallos PP, Chailis NH. *Drug Dev Ind Pharm* **1993**; 19: 1061-1081.
[15] Costa P, Lobo JMS. *Eur J Pharm Sci*, **2001**; 13; 123-133.
[16] S.K. Sreekanth, S. Palanichamy, T. Raja Sekharan, A. Thanga Thirupathi.: *International Journal of Pharma and Bio Sciences.* 1 (2);**2010**. pp. 1-8.

[17] Amol S. Bansode, et.al, *International Journal of Universal Pharmacy and Bio Sciences* 2(4): July-August **2013**, pg.no.19-26