FORMULATION AND IN-VITRO EVALUATION OF ORNIDAZOLE GASTRORETENTIVE TABLETS BY USING LOW DENSITY SWELLABLE POLYMERS

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ABSTRACT

Gastro retentive drug delivery systems have shown to be of better significance in controlling release rate for drugs having site specific absorption. The present study was an attempt to develop floating tablets of ornidazole which on oral administration prolongs its gastric residence time there by increasing bioavailability. Ornidazole an oral antiprotozoal having narrow absorption window in the upper and lower part of gastrointestinal tract, floating matrix tablet using gas generating agent sodium bicarbonate and hydrophilic polymer Hydroxy propyl methyl cellulose by wet granulation technique. Preformulation studies were carried out to optimize the required quantity for HPMC K4M(10%), Eudragit(8%) was used. formulations were prepared using either HPMC k50, HPMC k100, HPMC k4, Xanthan gum, Ethyl cellulose with carbopol 934P. For F1 to F8 formulation HPMC concentration was increased to control the release of drug from the dosage form and for F11 formulation Eudragit concentration was increased to obtain viscosity. Fourier transform Infrared spectroscopy confirmed the absence of any drug/polymers/excipients interactions. F11 Formulations showed in-vitro buoyancy 9 hrs. The concentration of HPMC K4 was increased to control the release of drug from the dosage form for F11 , the concentration was increased for Eudragit to increase the binding nature . The cumulative % drug release of F11 formulation was found to be Ornidazole (92.8%) at the end of 9th hr. The formulation containing HPMC k4m and Eudragit showed better results compared to other formulated batches. Further Stability studies studies can be performed to ensure the efficacy of the formulated floating tabets.

KEYWORDS: Ornidazole, HPMC, Floating lag time, swelling index, in-vitro buoyancy, Hrdro dynamically balanced systems, Gastro intestinal tract.

INTRODUCTION

The idea of gastro retention systems from the need to localize drugs at specific region of Gastro intestinal tract such as stomach in the body. Often, the extent of drug absorption is limited by the residence time of the drug at absorption site (Bardonn et al.2006). The therapeutic window of many drugs is limited by their short circulating half-life and absorption via a defined segment of the intestine. Such pharmacokinetic limitations lead in many cases to frequent dosing of these medications to achieve the required therapeutic effect. The phenomenon of absorption via a limited part of the Gastro intestinal tract has been termed the "narrow absorption window"; once the dosage form passes the absorption window, the drug will be neither bioavailable nor effective (Streubel et al.2006). A rational approach to enhance bioavailability and improve pharmacokinetic and pharmacodynamic profiles is to retain the drug reservoir above its absorption area, i.e., in the stomach and to release the drug in a controlled manner, so as to achieve a zero order kinetics (i.e., "oral infusion") for a prolonged period of time (Stithit et al.1988).

MATERIALS AND METHODS

Marerials : Ornidazole, Indian Drugs, HYD. HPMC K4, Qualikens, Vadodara. Eudragit, SD Fine Chem .Ltd. Mumbai. sodium bicarbonate, Merck, Mumbai. citric acid Finar reagents, Ahmedabad.

Method of Preparation of Ornidazole Gasro retentive tablets: Granules were prepared by using wet granulation technique. Drug and Eudragit were weighed and taken in to motor. Finally the active ingredient was mixed homogeneously according to geometric proportions. (2%) HPMC 5CPS solution acts as granulating agent.The coherent mass was thoroughly sieved through 16 mesh and then dried in hot air oven at 50ºC for 45 min. The dried granules were passed through sieve no 20 to get uniform granules.To this calculated amount of Magnesium Stearate (1%) and Talc (1%) were added as a lubricant. Citric acid and sodium bicarbonate were incorporated as a gas-generating agent.

Evaluation of floating tablets: Pre-formulation studies were performed on the drug and excipients which includes bulk density, tapped density, corr's index, Hausner's ratio and compatability studies.The formulated tablets were evaluated for its Thickness, hardness, friability, weight variation,in-vitro buoyancy, swelling index, floating lag time, in-vitro dissolution studies (Ramesh Bomma et al. 2009).

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Table.1.Composition of Floating Tablets Containing Ornidazole

Ingredients (Mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Ornidazole	500	500	500	500	500	500	500	500	500	500	500	500
Hpmc5cps	--	--	--	60	60	60	30	60	50	40	40	40
HPMCK4	--	--	--	--	--	--	--	--	--	--	40	--
HPMCK15	50	50	70	70	70	--	--	--	--	--	--	40
HPMCK100	50	--	--	--	---	---	---	--	50	50	30	--
Ethyl Cellulose	30	60	60	80	--	--	--	60	--	--	--	--
Eudragit	--	--	--	--	--	--	--	--	--	--	--	--
Xanthungum	--	--	--	--	--	--	--	--	50	70	--	80
Carbopol934	50	70	50	--	--	--	--	--	--	--	--	--
Sod..Bicarbonate	40	40	40	30	20	70	50	60	50	50	50	50
Citricacid	30	30	30	20	10	30	50	50	30	30	30	30
TOTAL (Mg)	750	750	750	750	750	750	750	750	750	750	750	750

RESULTS AND DISCUSSION

Construction of calibration curve of Ornidazole: The standard calibration curve yields a straight line, which shows that the drug follows Beer's law in the concentration range of 5- 25 µg. The solutions were scanned in U.V/Visible double beam spectro photometer against ethanol as a blank.at 302 nm a standard graph was plotted by keeping the known concentration on X – axis and obtained absorbance on Y – axis.

Drug –Polymer Compatibility Studies By FTIR: Drug polymer compatibility studies were performed by FTIR (Fourier transform infrared spectroscopy). FTIR absorption spectra of Ornidazole, HPMCK4, HPMC5cps,Eudragit, xanthan gum and the combination of drugs, polymers and excipients showed no significant interaction between Ornidazole and polymer.

Pre-formulation studies: The formulated batches were evaluated for Preformulation studies that are Angle of repose, Carr's index and Hausner's ratio, the values obtained for that studies are tabulated in Table no 2.The values were found to be in the range from 25.64˚±0.01 to 31.3˚±0.05, 9.37±0.01 to12.5±0.01, 1.07±0.01 to1.14±0.01% respectively. This indicates good flow property of the granules for compression.

Physical properties: The formulations were evaluated for physicochemical parameters like hardness, thickness, weight variation, friability, floating lag time and swelling index. The values obtained for that studies are tabulated in Table no 3. Floating properties from the evaluation results it was observed that the tablets containing Eudragit and HPMC K4M, F11 showed greater in vitro buoyancy time and when compared to other prepared formulation. Swelling index of floating tablets showed significant differences in their swelling index due to the presence of low density swellable polymers.

In-vitro drug release studies of Ornidzole: Formulations F1, F2, F3 and F4 containing HPMC alone and Combination of HPMC and Carbopol. The Formulations F1 has shown release 83.6% at the end of 9^{th} h, Formulations F2 has shown release 74.9% at the end of 9^{th} h, Formulations F3 has shown release 82.4% at the end of 9^{th} h, Formulations F4 has shown release 69.7% at the end of 9^{th} h.

Formulations F5, F6, F7, F8, F10, and F12 containing Combination of HPMC5cps and HPMC K50 were prepared. The Formulations F5 has shown release 85.2% at the end of 9^{th} h, Formulations F6 has shown release 80.6% at the end of 9^{th} h, Formulations F7 has shown release 83.2% at the end of 9^{th} h, F8 has shown release 77.1% at the end of 9th h, Formulations F9 has shown release 82.4% at the end of 9^{th} h, Formulations F12 has shown release 88.7% at the end of 9^{th} h. Formulations F10 and F11 containing Combination of HPMC and Xanthan gum, Eudragit. The Formulations F10 and F11 have shown release 92.6% and 95.3% respectively at the end of 9^{th}h. the values obtained for that studies are tabulated in Table no 4.

In-Vitro Buoyancy: In-vitro buoyancy which was greater than 9 hrs, for formulation F11. In vitro Buoyancy of the formulations F10, 11 is increased, which may be due to high concentration of HPMC. The values of In vitro Buoyancy for All formulations were given in Table no.5.

Kinetics of drug release: Based on mathematical models, it was concluded that for mulation F11,the regression(r=0.99) value was found to be 0.99 fitted into zero order release kinetics.The slope value for peppas model was found to be with in 0.45-0.89 hence it is folllows non fickens diffussion. Non fickens diffision refers to combination of both diffusion and erossion controlled.

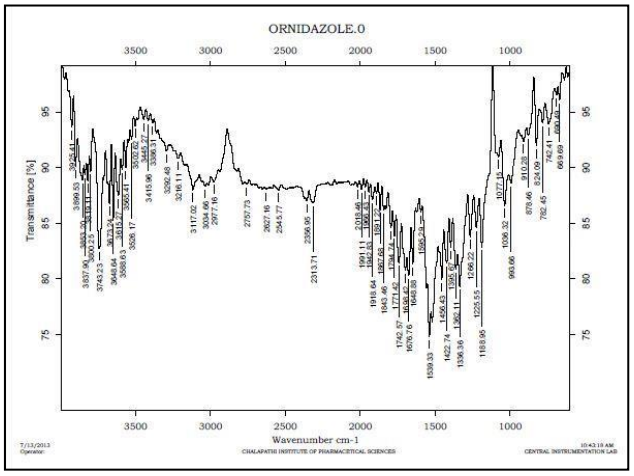


Figure.1. FTIR Spectra Data for Pure Ornidazole

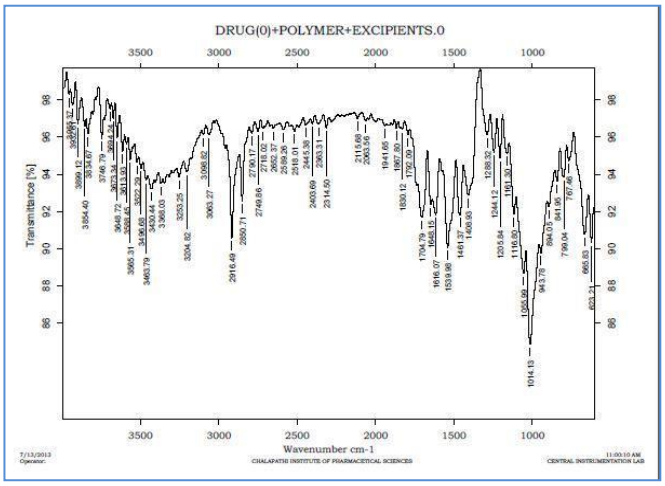


Figure.2.FTIR Spectra of Drug+ Polymers +Excipients

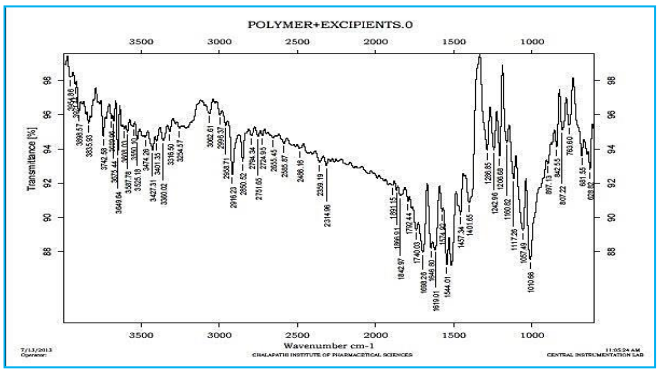


Figure.3. FTIR Spectra of Polymers+ Excipients

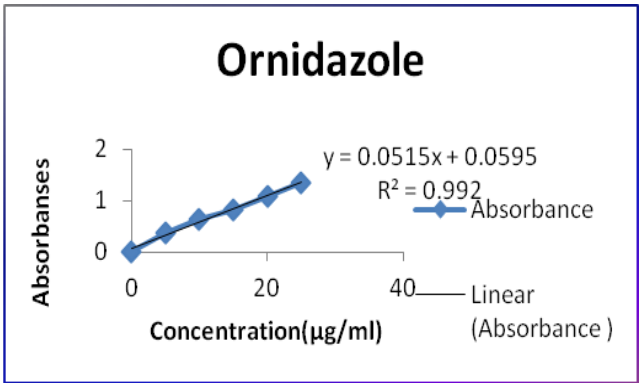


Figure.4. Standard Curve of Ornidazole.

Table.2. Results for Derived and Flow properties

Formulation code	Derived Properties		Flow Properties		
	Bulk density (mean±SD) g/ml	Tapped density (mean±SD) g\ml	Angle of repose (mean±SD)	Carr's index (mean±SD)	Hausner's ratio (mean±SD)
F1	0.29±0.01	0.33±0.04	26.5±0.01	12.1±0.01	1.137±0.01
F2	0.29±0.03	0.32±0.03	28.8±0.03	9.37±0.01	1.103±0.02
F3	0.35±0.01	0.39±0.01	27.02±0.04	10.2±0.02	1.114±0.03
F4	0.42±0.02	0.45±0.03	27.02±0.01	10.6±0.01	1.071±0.01
F5	0.35±0.01	0.39±0.01	27.1±0.05	10.2±0.01	1.114±0.02
F6	0.28±0.04	0.32±0.02	25.64±0.02	12.5±0.01	1.142±0.01
F7	0.34±0.03	0.37±0.02	27.2±0.04	12.4±0.01	1.088±0.04
F8	0.30±0.01	0.33±0.01	31.3±0.01	9.7±0.03	1.1±0.01
F9	0.37±0.02	0.42±0.04	29.2±0.03	11.9±0.02	1.135±0.02
F10	0.38±0.01	0.41±0.03	27.4±0.01	10.3±0.01	1.078±0.01
F11	0.35±0.04	0.39±0.01	27.02±0.05	10.4±0.01	1.114±0.01
F12	0.28±0.01	0.32±0.04	25.64±0.01	12.5±0.02	1.142±0.02

Table.3. Physico chemical parameters of all formulations

Formulations	Thickness (mm)	Hardness ($Kg/cm^{2)}$	Friability (%)	Weight variation (mg)	Floating lag time (Sec)	Swelling index (%)
F1	3.4	2.9	0.93	958	-	207.5
F2	3.4	3.7	0.86	964	-	192.8
F3	3.8	2.9	0.78	943	-	279.2
F4	3.2	3.4	0.92	947	-	348.6
F5	3.4	2.8	0.81	739	-	316.8
F6	3.2	2.8	0.72	742	-	184.3
F7	3.4	3.1	0.67	756	-	175.4
F8	3.5	2.6	0.91	763	-	262.5
F9	3.7	3.1	0.75	749	-	300.4
F10	3.4	2.9	0.89	743	29	324.3
F11	3.8	2.9	0.78	742	37	279.2
F12	3.2	2.8	0.72	768	26	184.3

Table.4. In-Vitro Drug Release Profile of F1 – F12

Time (hrs)	Cumulative % drug release (%)											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	19.6	18.9	15	12.9	23	21.2	23.7	17.2	15.8	19.2	18.1	15.3
2	28.2	26.4	22.2	20.2	30.3	28.7	33.8	23.7	21.6	28.6	29.8	27.1
3	38.4	33.4	29.2	27.1	38.3	35.8	41.5	29.9	33.8	39.4	37.1	38.6
4	45.6	39.9	35.4	33.3	45.4	42.2	52.1	37.2	41.8	51.7	48.3	49.8
5	56.4	46.9	42.6	40.4	52.6	49.8	58.6	44.2	49.7	63.9	59.8	57.4
6	67.2	54.6	49.6	47.1	59.9	57.2	64.9	51.4	57.8	74.3	67.4	64.8
7	76.1	61.1	55.8	53.2	68.1	64.3	71.7	58.7	64.7	82.7	81.9	74.4
8	79.2	66.6	62.8	60.2	76.5	71.4	79.2	65.3	73.7	86.3	88.3	81.1
9	83.6	74.9	86.4	69.7	85.2	80.6	83.8	77.1	82.4	92.6	95.3	88.7

Figure.5.Cumulative % Drug Releae Profile of F1-F12.

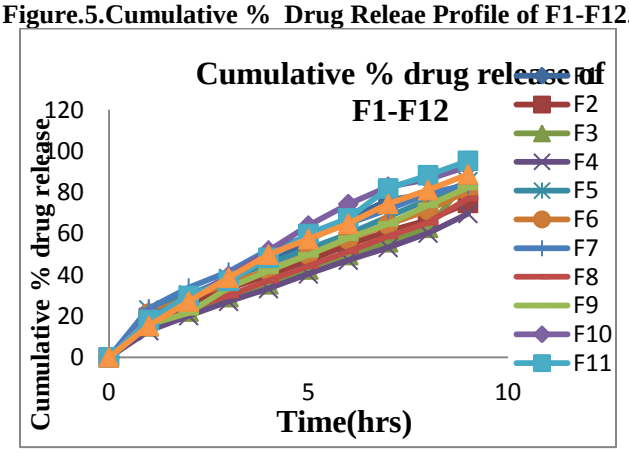


Table.5. In-Vitro buoyancy

Formulations	In vitro buoyancy(hrs)	Formulations	In vitro buoyancy(hrs)
F1	-	F7	-
F2	-	F8	-
F3	-	F9	-
F4	-	F10	08
F5	-	F11	09
F6	-	F12	<6

Figure.6.Ornidazole Drug Releae Profile of F11 Showing Zero Order Kinetics

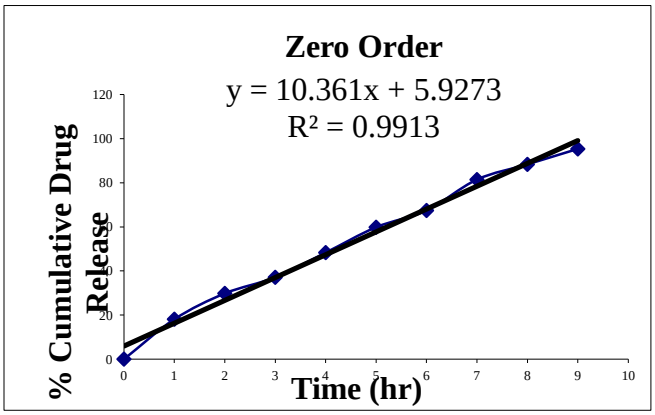
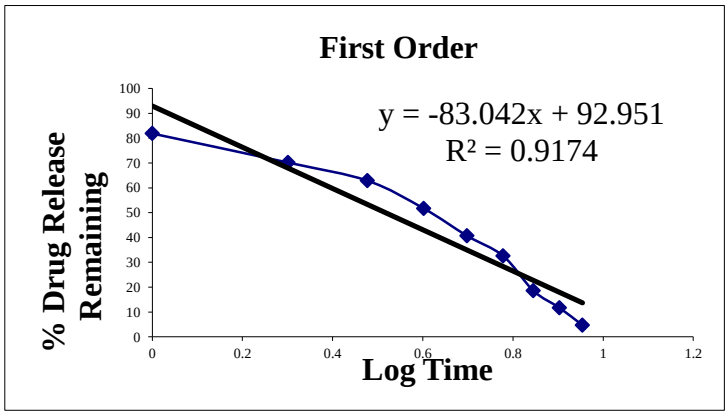


Figure.7.Ornidazole Drug Releae Profile of F11 Showing First Order Kinetics



CONCLUSSION

The present study was aimed at developing an oral floating system for Ornidazole using combination of polymers like HPMCK4 and Xanthan gum and Eudragit the floating tablets were prepared by using wet granulation technique. Granules were evaluated for Preformulation studies that are Angle of repose, Carr's index and Hausner's ratio This indicate good flow property of the granules for compression. The floating tablets of Ornidazole were evaluated for physicochemical characteristics like thickness, hardness, weight variation, friability, floating lag time and swelling index. The in-vitro buoyancy studies, in-vitro drug release studies, results were found that the optimized formulation F11 (9hrs) has better in vitro release profiles due to the presence of low density swellable polymers in the formulation and these polymers were also control the drug release rate for long period of time .

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