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Formulation and in Vitro Evaluation of Ornidazole Gastro Retentive Microballoons

KEYWORDS: Ornidazole, HPMC, Eudragit, Ethyl cellulose, In vitro buoyancy, Non-fickian diffusion.

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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. In present study, an attempt made to prepare floating micro balloons by modified Quasi-emulsion diffusion technique using synthetic polymers. Polymers such as HPMC K15, Eudragit RS100 and EC are used as retarding polymers. It was also found that the micro balloons formulation retarded the drug release for 12hr. Prepared Microballoons of ornidazole were evaluated for percentage yield, drug content (or) drug entrapment efficiency, scanning electron microscopy (SEM), micromeritic properties, in vitro buoyancy, in-vitro release studies and short term stability studies. The drug release from F10 formulation having EC and Eudragit RS100 was governed by Non-fickian diffusion and zero order release. Among all formulations F10 showed drug release of 99.6% at 12hr. Hence it is optimized formulation. Stability studies have revealed that there are no significant changes during the period.*

Introduction:

Microballoons are gastro-retentive drug delivery systems based on non-effervescent approach. Microballoons are in strict sense, spherical empty particles without core and idesally having a size less than 200 micrometer. These are primarily controlled release drug delivery systems, which gets retained in the stomach for longer periods of time, thus helping in absorption of drug for the intended duration of time. Gastric retentive drug delivery devices can be useful for the spatial and temporal delivery of many drugs because of buoyancy[1].

One reason may be the degradation of antimicrobial agents by gastric acid, therefore, the administration of high doses of antimicrobial agents on a daily basis is necessary for *H. pylori* eradication, but they are usually accompanied by adverse effects and poor patient compliance. Another reason for incomplete eradication is the probably that residence time of antimicrobial agents in the stomach is so short[2] Recently Ornidazole is proved to be one of the potential drugs against *H.pylori* infection, responsible for peptic ulcers and various cytotoxic complications. This leads to the formulation of acceptable sustained-release dosage forms Ornidazole in the stomach to promote a fast and effective eradication of *H.pylori* to cure peptic ulcer.[3] Basic physiology of gastrointestinal tract The anatomy and physiology of GIT must be understood, although developing floating drug delivery systems. The different factors are affecting GI motility like nature, pH and volume of gastric mucus and gastric secretion [4,5].

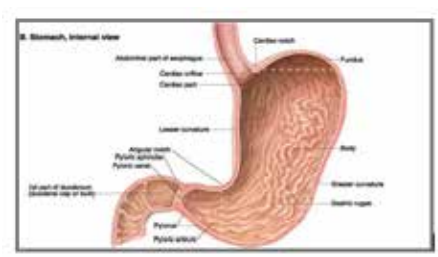

Fig 1. Diagrammatic representation of internal view of stomach

Hollow Microspheres / Micro balloons:

Hollow microspheres are measured as one of the mainly promising buoyant systems, as they have the unique advantages of multiple unit systems as well as superior floating properties, because of central hollow space inside the microsphere. The general techniques concerned in their preparation include solvent diffusion and evaporation and simple solvent evaporation. Polymers such as Eudragit S, polycarbonate and cellulose acetate were used in the preparation of hollow microspheres, and the drug release can be adjusted by optimizing the polymer quantity and the polymer-plasticizer ratio[6].

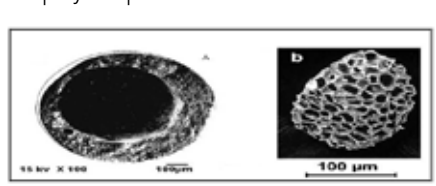

Fig 2. Hollow Microsphers

Volume : 6 | Issue : 5 | May 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

Material:
(ACTIVE)Ornidazole, HPMC K15 M, Eudragit RS100, Ethyl cellulose, Sodium bicarbonate, Tween 80, Ethanol, HCl, Dichloromethane, ornidazole was received as a gift sample for inventes pharma Pvt.Ltd. Hyderabad. All the material used in this research work are of analytical grades.

Method:
Preformulation studies:
a) Physical appearance b) Solubility c) Melting point d) UV analysis of Ornidazole e) Bulk density and Tapped density f) Particle size g) Angle of repose h) Compressibility index (or) Carr's index (i) Hausner's ratio.

Experimental Work:
Preperation of calibration curve: 0.1 N HCl

Transfer exactly weighed 8.5 ml of concentrated hydrochloric acid solution was diluted with distilled water upto 1000 ml to give 0.1 N HCl

0.2 M potassium chloride solution

Transfer accurately weighed 14.911 g of potassium chloride was dissolved in 1000 ml of distilled water, to prepare

Hydrochloric acid buffer (pH 1.2)

50.0 ml of 0.2 M potassium chloride was placed in a 200 ml volumetric flask, to this 85.0 ml of 0.2 M hydrochloric acid was added and then made up to the volume with water.

Preparation of aliquots:
Accurately weighed Ornidazole (100mg) was dissolved in 100ml of 0.1N HCl pH 1.2 buffer and further diluted to get a stock solution of 100 µg/ml (stock-I). Solutions were prepared with 0.1N HCl pH 1.2buffer to get concentration of 10-50 µg/ml. And absorbance measured at 277 nm wave length against blank. A standard graph was plotted by keeping the known concentration on x-axis and absorbance on y-axis.

Drug –polymer compatibility studies by FTIR:
FTIR Studies were carried out for pure Ornidazole drug with combinations of those micro balloons formulations which showed best drug release pattern were recorded in a Fourier transform infrared (FTIR) spectrophotometer (Shimadzu) with KBr pellets. The physicochemical compatibility of the drug and the excipients were established through compatibility studies by FTIR. (Fourier transform infrared spectroscopy).

Formulation of hollow microspheres:
Floating microspheres with a central hollow cavity were prepared by using a modified Quasi-emulsion diffusion technique. Weighed quantities of Ornidazole, ethyl cellulose, eudragit RS100 and hydroxy propylmethyl cellulose (HPMC K15M) were dissolved in a mixture of ethanol and dichloromethane (1:1 solvent ratio) at room temperature in a magnetic stirrer at 50 rpm for 50 min. This solvent was poured drop wise into 100 ml distilled water containing 2 ml of Tween 80 maintained at a temperature of 50 ± 2 °C. The resultant solution was stirred with a pitched-blade-type impeller type agitator at 1100 rpm for 3 h to allow the volatile solvent to evaporate. This resulted in the formation of microspheres. Different ratios of polymers were used to prepare the microspheres. Fourteen formulations were prepared by changing the amount of ingredients as shown in table and diagrammatic representation of preparation of hollow

Formulation Code	Active	HPMC K15M	Ethyl cellulose	Eudragit RS-100	Sodium bicarbonate	Solvent ratio Ethanol: DCM	Tween 80
F1	0.5	0.25	0.125	-	1	1:1	2
F2	0.5	0.375	0.25	-	1	1:1	2
F3	0.5	0.5	0.5	-	1	1:1	2
F4	0.5	1	0.5	-	1	1:1	2
F5	0.5	1.5	1	-	1	1:1	2
F6	0.5	2	1	-	1	1:1	2
F7	0.5	1	-	-	1	1:1	2
F8	0.5	-	0.125	0.25	1	1:1	2
F9	0.5	-	0.25	0.375	1	1:1	2
F10	0.5	-	0.5	0.5	1	1:1	2
F11	0.5	-	0.5	1	1	1:1	2
F12	0.5	-	1	1.5	1	1:1	2
F13	0.5	-	1	2	1	1:1	2
F14	0.5	-	-	1	1	1:1	2

Table 1: Formulation code
Note: All the quantities mentioned in grams. Solvents in ml. HPMC: Hydroxy propyl methyl cellulose, DCM: Dichloromethane

Physicochemical Evaluation**:**

Percentage yield[7]

The prepared micro balloons were collected and weighed. The actual weight of obtained micro balloons divided by the total amount of all non-volatile material that was used for the preparation of the micro balloons multiplied by 100 gives the% yield of micro balloons

$$\% \text{ yield} = \frac{\text{Actual weight of product}}{\text{Total weight of excipients and drug}} \times 100$$

In Vitro Drug Release Studies[8]

The release rate of drug from formulations was determined using USP dissolution testing apparatus II (basket type). The dissolution test was done by using 900 ml of 0.1 N HCl, at 37± 0.5 ^{O}C and 50 to 100 rpm. Aliquots (5mL) were withdrawn at regular intervals for 12 hrs, sample was replaced by its equivalent volume of fresh dissolution medium to maintain the sink condition. The samples were analyzed spectrophotometrically at wavelength corresponding to absorption maxima of the drugs.

Sample preparation
Transfer micro balloons into each dissolution bowels and

Volume : 6 | Issue : 5 | May 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

run the dissolution apparatus as per dissolution parameters. Withdraw 5 ml of sample solution through sampler containing free flow filter, at the sampling time. Replace aliquots withdrawn for analysis with equal volumes of dissolution medium which is maintained at 37 ± 0.5°C.

One formulation containing 500mg of Ornidazole was used in each test. Samples of dissolution fluid (5ml) were withdrawn at different time intervals and were assayed at 277nm for Ornidazole using a Shimadzu UV double beam spectrophotometer. The sample (5ml) taken at each sampling time was replaced with fresh dissolution medium (5ml) to maintain sink conditions.

Data analysis

The results of *in vitro* release profiles obtained for all formulations were fitted into three kinetic models of data treatment as follows:

1. Cumulative percentage drug released versus time (zero-order kinetic model).
2. Cumulative percentage drug released versus square root of time (Higuchi's model).
3. Log cumulative percentage drug released versus log time (Korsmeyer-Peppas equation).

Stability Studies[9]

The stability studies were carried out on optimized formulation i.e.F10 as per ICH guidelinesCHcccxxx. The optimized formulation was sealed in alluminium foil and stored in different temperatures 25°c -60%RH and 40°c -75%RH respectively for three months. After an interval of 90 days, samples were withdrawn and retested for drug content. The amount of drug was detected UV spectrophotometrically at 277nm against blank. The results indicate that these formulations remained stable for three months.

Result

S.NO	Concentration **(µg/ml)**	**Absorbance**
1	0	0
2	10	0.055
3	20	0.111
4	30	0.162
5	40	0.211
6	50	0.271

Table.2 Data for Calibration curve in 0.1N HCl pH 1.2 buffer

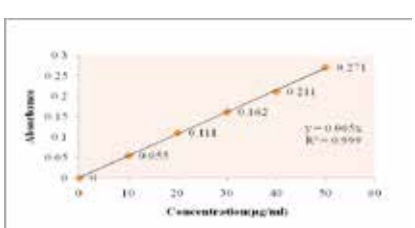

Fig .3 Calibration Curve of Ornidazole in p^H 1.2 HCl buffer

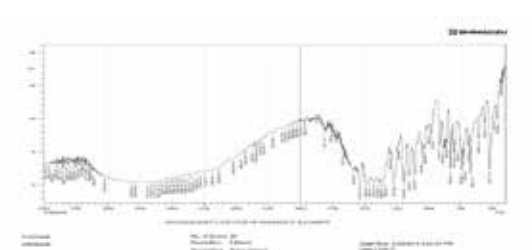

Fig 4 FT-IR spectra of Ornidazole

S.NO	F.CODE	Percentage yield
1	F1	60.0
2	F2	63.2
3	F3	70.0
4	F4	68.3
5	F5	85.3
6	F6	64.3
7	F7	72.0
8	F8	62.2
9	F9	68.5
10	F10	76.3
11	F11	73.0
12	F12	90.3
13	F13	69.5
14	F14	72.5

Table 5 : Percentage yield of micro balloons

S.NO	F CODE	Particle size (µm)
1	F1	262±5
2	F2	281±3
3	F3	324±5
4	F4	353±4
5	F5	446±3
6	F6	515±6
7	F7	313±3
8	F8	275±2
9	F9	306±6
10	F10	343±3
11	F11	376±4
12	F12	425±2
13	F13	534±6
14	F14	334±7

Table 6: Particle size of micro balloons

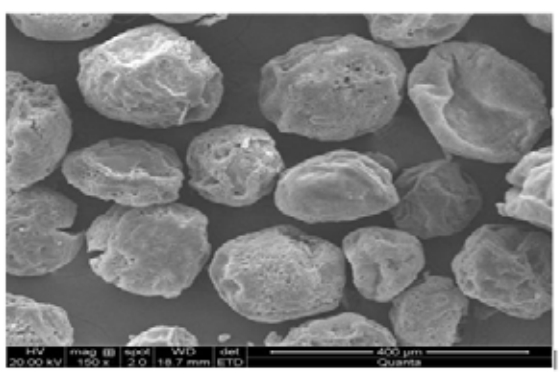

Fig 5 Scanning electron microscopic photographs of microspheres at different magnifications

S.No	Time(hr)	Cumulative percentage of drug release			
		F8	F9	F10	F11
1	0	0	0	0	0
2	1	21.6	18.8	17.7	14.1
3	2	33.4	28.6	26.4	20.2
4	3	45.6	39.1	34.3	26.1
5	4	56.8	48.5	43.9	36.3
6	5	69.2	59.1	52.4	43.2
7	6	78.1	70.6	60.2	50.2
8	7	90.3	81.1	68.3	59.5
9	8	99.8	91.2	77.1	68.1
10	9	--	99.6	84.8	76.3

Volume : 6 | Issue : 5 | May 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

11	10	--	--	91.1	84.7
12	11	--	--	96.3	91.1
13	12	--	--	99.6	96.3

Table 7: *In vitro* drug release data for formulations (F8 – F11)

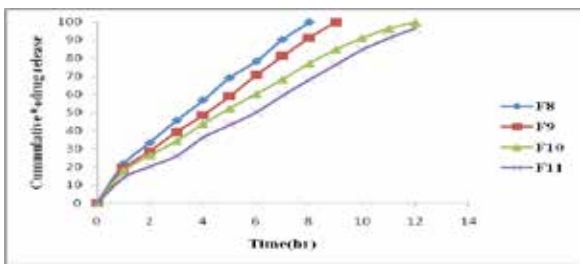

Fig 6 *In vitro* **drug release studies for formulations (F8-F11)**

S.No	Time	Sq.rt time	Cumulative percentage of drug release			
			F8	F9	F10	F11
1	0	0	0	0	0	0
2	1	1	21.6	18.8	17.7	14.1
3	2	1.414	33.4	28.6	26.4	20.2
4	3	1.732	45.6	39.1	34.3	26.1
5	4	2	56.8	48.5	43.9	36.3
6	5	2.236	69.2	59.1	52.4	43.2
7	6	2.449	78.1	70.6	60.2	50.2
8	7	2.645	90.3	81.1	68.3	59.5
9	8	2.828	99.8	91.2	77.1	68.1
10	9	3	--	99.6	84.8	76.3
11	10	3.162	--	--	91.1	84.7
12	11	3.316	--	--	96.3	91.1
13	12	3.464	--	--	99.6	96.3

Table 8: Higuchi data for formulations (F8 – F11)

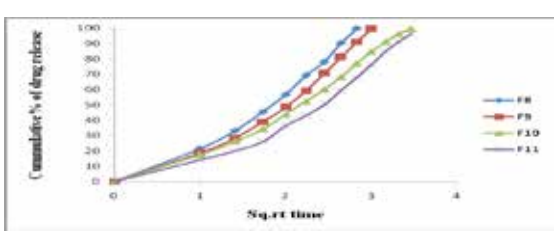

Fig 7 Higuchi plot for formulations (F8-F11)

S.no	Log Time	Log cumulative percentage of drug release			
		F8	F9	F10	F11
1	0	1.334	1.274	1.247	1.149
2	0.301	1.523	1.456	1.421	1.305
3	0.477	1.658	1.592	1.535	1.416
4	0.602	1.754	1.685	1.642	1.559
5	0.698	1.84	1.771	1.719	1.635
6	0.778	1.892	1.848	1.779	1.7
7	0.845	1.955	1.909	1.834	1.774
8	0.903	1.999	1.959	1.887	1.833
9	0.954	--	1.998	1.928	1.882
10	1	--	--	1.959	1.927
11	1.041	--	--	1.983	1.959
12	1.079	--	--	1.998	1.983

Table 9: Peppa's data for formulations (F8 – F11)

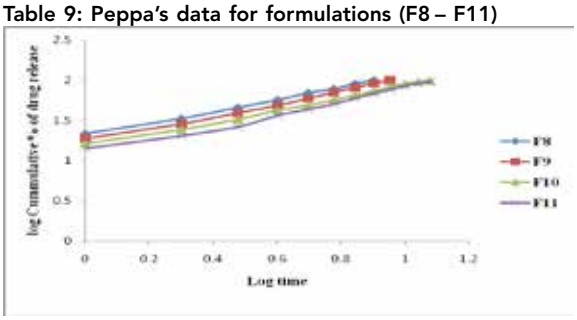

Fig 8 Peppa's plot for formulations (F8-F11)

S.N0	F CODE	Coefficient Of Correlation (R^2)			n value
		IVDR	HIGUCHI	PEPPA'S	
1	F1	0.982	0.971	0.977	0.722
2	F2	0.989	0.962	0.994	0.717
3	F3	0.983	0.97	0.985	0.631
4	F4	0.986	0.969	0.99	0.661
5	F5	0.968	0.971	0.988	0.594
6	F6	0.958	0.976	0.986	0.561
7	F7	0.987	0.985	0.996	0.641
8	F8	0.989	0.961	0.996	0.746
9	F9	0.994	0.947	0.993	0.777
10	F10	0.991	0.956	0.994	0.764
11	F11	0.996	0.935	0.986	0.822
12	F12	0.996	0.922	0.979	0.846
13	F13	0.993	0.903	0.964	0.85
14	F14	0.99	0.968	0.995	0.731

Table 10: Diffusion characteristics of Ornidazole formulations

S.No	Temperature And RH	No. of Days	Physical Appearance	Drug Content optimized formulation F10
1	AT 25^{0}C - 60%RH	30	No change	84.3
		60	No change	83.9
		90	No change	83.1
2	AT 40^{0}C - 75%RH	30	No change	83.8
		60	No change	83.1
		90	No change	82.7

Table 11: Characteristics of F10 formulation after storage

Conclusion:

Formulation of hallo microsphere were developed and evaluated by using Quassi emulsion method which was suitable for poor water soluble drugs, because the drug was soluble in the internal organic phase The particle size

Volume : 6 | Issue : 5 | May 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

of microspheres ranged between 262-534µm. Among all the formulations the F10 considered as the best as they released the drug 99.6% at 12th hr, which is greater than the other formulations, thus it may have fair clinical efficacy. Hence, the formulation **F10** has met the objectives of the present study. Results of the stability studies showed that there were no significant changes in the drug content and physical appearance

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