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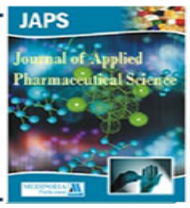

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Formulation and Evaluation of Gastroretentive Floating Tablets of Domperidone Maleate

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ABSTRACT

The low bioavailability (15%) and good solubility of Domperidone Maleate in acidic pH following oral administration favours development of a gastro retentive formulation. Gastroretentive floating matrix tablets of Domperidone Maleate were successfully prepared with hydrophilic polymers like HPMC K4M, HPMC K15M and HPMC K100M. From the Preformulation studies for drug excipients compatibility it was observed that there was no compatability problem with the excipients used in study. The drug release from most of the formulations follows fickian diffusion. From in-vivo X-ray studies, it was clearly observed that the floating tablets showed a gastric residence of nearly 4.5 hrs in fed state.

Keywords: Domperidone Maleate, floating tablets, gastric residence time, gastroretentive drug delivery system.

INTRODUCTION

Gastric emptying is a complex process that is highly variable and alters in vivo performance of drug delivery systems. Domperidone Maleate is a synthetic benzimidazole compound that acts as a dopamine D2 receptor antagonist, which is used as a prokinetic agent for the treatment of upper gastrointestinal motility disorders. The goal of the present work is to develop hydrodynamically balanced system or floating drug delivery system for Domperidone Maleate, which increases the gastric residence time, minimizes the problems associated with oral sustained release dosageforms. The bioavailability of Domperidone Maleate is about 15% only. It has good solubility in acidic pH (Prabakaran, 2006), but solubility reduces when it enters into alkaline pH. Hence the low bioavailability and good solubility in acidic pH following oral administration favours development of a gastro retentive formulations for Domperidone Maleate.

MATERIALS AND METHODS

Materials

Domperidone Maleate was a generous gift from Dr. Reddy's Labs India ltd. Hyderabad, India. Hydroxypropyl Methylcellulose K4M (HPMC K4M), Hydroxypropyl Methylcellulose K15M (HPMC K15M) and Hydroxypropyl Methylcellulose K100M (HPMC K100M) were obtained from Colorcon Asia Pvt. Limited. Other excipients were procured from S.D. Fine Chemicals, Mumbai, India.

Methods

Formulation of floating matrix tablets of Domperidone Maleate

Preparation of floating matrix tablets of Domperidone Maleate with various polymers

Accurately weighed quantities of polymer and MCC were taken in a mortar and mixed thoroughly, to this mixture required quantity of Domperidone was added and mixed slightly with pestle. Accurately weighed quantity of Sodium bicarbonate was taken separately in a mortar and powdered with pestle. The powder is passed through sieve #40 and mixed with the drug blend which is also passed through sieve #40. The whole mixture was collected in a plastic bag and mixed for 3 minutes. To this Magnesium stearate was added and mixed for 5 minutes, later Talc was added and mixed for 2 minutes. This mixture was compressed into tablets using a 16-station punching machine (Riddhi, Ahmadabad, India) with 8 mm round flat faced punches at a hardness of 5kg/cm^2.

The drug and polymer ratio was varied to get floating tablets of varying polymer concentrations as shown in Tables from 1 to 3.

Table. 1: Composition of tablets formulated with HPMCK4M.

Ingredients	Weight (mg)			
	FH 1	FH 2	FH 3	FH 4
Domperidone	30	30	30	30
HPMC K4M	15	30	45	60
M.C.C	116.1	101.1	86.1	71.1
$NaHC0_3$	16.2	16.2	16.2	16.2
Mg.Stearate	0.9	0.9	0.9	0.9
Talc	1.8	1.8	1.8	1.8
Total Weight	180	180	180	180

Table. 2: Composition of tablets formulated with HPMCK15M.

Ingredients	Weight (mg)		
	FH 5	FH 6	FH 7
Domperidone	30	30	30
HPMC K15 M	30	45	60
M.C.C	101.1	86.1	71.1
$NaHC0_3$	16.2	16.2	16.2
Mg. Stearate	0.9	0.9	0.9
Talc	1.8	1.8	1.8
Total Weight	180	180	180

Table. 3: Composition of tablets formulated with HPMCK100M.

Ingredients	Weight (mgs)		
	FH 8	FH 9	FH 10
Domperidone	30	30	30
HPMC K100M	30	45	60
M.C.C	101.1	86.1	71.1
$NaHC0_3$	16.2	16.2	16.2
Mg.Stearate	0.9	0.9	0.9
Talc	1.8	1.8	1.8
Total Weight	180	180	180

Characterization of tablets

Compressed tablets of Domperidone Maleate were characterized for weight variation and uniformity in thickness using analytical balance (DENVER APX 60, Denver Instrument GmbH, Germany), and digital micrometer (Mitutoyo, Japan), respectively. Crushing strength was measured with Pfizer hardness tester, friability with Roche type friabilator. The drug content in each formulation was determined by triturating 20 tablets in a mortar and powder equivalent to average weight was added in 100 ml of 0.1 N HCL, followed by shaking for overnight. The solution was filtered through 0.45µm membrane filter, diluted suitably and analyzed by using UV/VIS double beam spectrophotometer (Elico SL 159 pvt ltd, Hyderabad) at 284 nm against 0.1 N HCl as blank.

Tablet density

The density (D) of Floating tablets was calculated from tablet height, diameter, and weight using the following equation

$$D\ (g/cm3) = \frac{w}{(m/2)^2 \times \pi \times h}$$

Here, m is the diameter of tablets, π is the circular constant, h is the height of a tablet and w is the weight of a tablet. All measurements were performed in six replicates.

Floating properties of tablets

The tablets were placed in a 100 ml glass beaker containing 0.1 N HCl.

1. Floating Lag Time: The time required for the tablet to rise to the surface of the medium and float was determined as floating lag time
2. Floating Duration Time: The time for which the tablet remained floating on the surface of medium was determined as floating duration time.

Dissolution profile modelling

There are several linear and non-linear kinetic models to describe release mechanisms and to compare test and reference dissolution profiles are as follows:

Zero order kinetics

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation:

$$W_0 - W_t = K_0 t$$

Where W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the amount of drug in the pharmaceutical dosage form at time t and k is proportionality constant.

Dividing this equation by W_0 and simplifying:

$$f_t = k_0 t$$

Where $f_t = 1 - (W_t / W_0)$ and f_t represents the fraction of drug dissolved in time t and k_0 the apparent dissolution rate constant or zero order release constant (Brahma, 2000).

First order kinetics

This type of model to analyze drug dissolution study was first proposed by Gibaldi and Feldman and later by Wagner. The relation expressing this model:

$$\text{Log } Q_t = \text{Log } Q_0 + K_1 t/2.303$$

Where Q_t is the amount of drug released in time t, Q_0 is initial amount of drug in the solution and K_1 is the first order release rate constant (Park, 1998; Baumgartner, 2000).

Korsmeyer Peppas model

Korsmeyer developed a simple semi empirical model, relating exponentially the drug release to the elapsed time (t).

$$Q_t/Q_\alpha = K_k t^n$$

Where K_k is a constant incorporating structural and geometric characteristic of the drug dosage form and n is the release exponent, indicative of the drug release mechanism as shown in Table 4.

Table. 4: Various drug transport mechanisms.

Release exponent (n)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
0.5<n<1.0	Anomalous transport	t^{n-1}
1.0	Case-II transport	Zero-order release
Higher than 1.0	Super Case-II transport	t^{n-1}

The Release exponent can be obtained from the slope and the Constant (K_k) obtained from the intercept of the graphical relation between logarithmic versions of left side of the equation versus log t.

Higuchi Model

$$Q_t = K_H t^{1/2}$$

Where Q_t = the amount of drug released at time t and
K_H = the Higuchi release rate;

This is the most widely used model to describe drug release from pharmaceutical matrices. A linear relationship between the square root of time versus the concentration indicates that the drug release follows strict Fickian diffusion (Lingam, 2008; Lingam, 2009; Ramesh, 2009; Suresh, 2010).

***In vivo* (x-ray) studies**

For this study the tablets with 180 mg in weight were prepared. To make the tablets X-ray opaque the incorporation of $BaSO_4$ was necessary. Barium Sulphate has a high density (4.4777 g/cm^3) and poor floating properties. Part of the drug was replaced with $BaSO_4$ for in vivo studies.

In-*Vivo* X-Ray study protocol

The *in-vivo* study was carried out by administering to humans Domperidone Maleate floating tablets and monitoring them through a radiological method. Four healthy male subjects (mean age 27year: mean weight 60±10 kg) participated after giving informed consent. The study was approved by the Human Ethical Committee, UCPSc, Kakatiya Univeristy, Warangal and was conducted by administering to each subject one floating tablet on two separate sessions.

a) Fasted state: The subjects fasted overnight then swallowed the floating tablets with 150 ml water. Afterwards the subjects were not allowed to eat, 150 ml of water was given after every 1 hr.

b) Fed state: After a meal, the subjects swallowed the floating tablet immediately after ingestion of a standardized lunch composed of a bread and milk (150g solid, 200 ml liquid). Afterwards the subjects were not allowed to eat but were given 150 ml water after every 1 hr

During the experiments the subjects remained in a sitting or upright posture. In each subject the position of the floating tablet was monitored by X-ray photographs (Konica Minolta, Siemens, Karlsruhe, Germany) of the gastric region at determined time intervals. All X-ray films were taken in anterior positions.

RESULTS AND DISCUSSION

Drug-excipients compatability studies

Domperidone Maleate was mixed with different proportions of all excipients to be used in formulation in different ratios and kept at 40ºc for four weeks**.** The physical properties (colour change) were monitored regularly. The change in colour in and assay value of drug any mixture was basis for discarding from study. There was no significant change in the drug content which was shown in Table 5.

Table. 5: Different combinations of API and excipients for drug-excipient compatibility study.

Exposed conditions 40ºc/75% RH for 30 days						
Ingredients	**D:E**	**Initial observation**	**Week 1**	**Week 2**	**Week 3**	**Week 4**
Drug alone	----	White powder	NC	NC	NC	NC
Drug +HPM CK4M	1:1	White powder	NC	NC	NC	NC
Drug+HPM CK15M	1:1	White powder	NC	NC	NC	NC
Drug+HPM CK100M	1:1	White powder	NC	NC	NC	NC
Drug +magnesium stearate	1:0.5	White powder	NC	NC	NC	NC
All physical mixture with drug	---	White powder	NC	NC	NC	NC
Physical mixture with out drug	---	White powder	NC	NC	NC	NC

NC - No color change
D: E- Drug:Excipient

The physical properties like compressibility index, angle of repose and hausner ratio.
were calculated and the values ranged as follows

Cars index: 11.2-15.9
Hausner ratio : 1.13-1.19
Angle of repose : <30° for all formulations

The results of the physical tests of many of the blends were in the limits and comply with the standards.
The standard graph of Domperidone in 0.1N HCl showed a good linearity with R^2 of 0.999, in the concentration range of 0-40 µg/ml Figure 1.

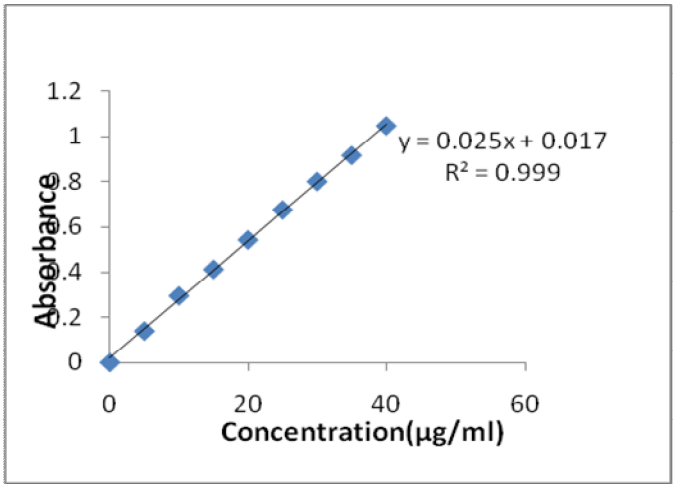


Fig. 1: Standard graph of Domperidone Maleate in 0.1 n Hcl.

Evaluation of the prepared tablets for physical parameters

All the tablets of different formulations were subjected to various evaluation tests such as thickness, hardness, weight variation and drug content in prepared tablets (Table 6). The results of the tests were tabulated. The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good.

Table 6: Physical parameters of the prepared formulations

Formula-tion	Hardness (kg/cm2)	Thickness (mm)	Weight Variation (mg)	Fria-bility (%)	Drug Content (%)
FH 1	5.50±0.24	3.384±0.05	180.60±2.12	0.1	99.23
FH 2	5.65±0.18	3.276±0.06	178.33±1.45	0.27.	100.12
FH 3	5.45±0.37	3.186±0.03	182.80±1.63	0.19	99.82
FH4	5.80±0.26	3.186±0.04	178.09±2.43	0.22	99.54
FH 5	5.55±0.54	3.234±0.06	179.05±4.51	0.18	99.43
FH 6	5.40 ±0.35	3.45 ±0.06	179.37±3.89	0.21	100.85
FH 7	5.50±0.48	3.38±0.05	180.09±4.12	0.16	98.97
FH 8	5.45±0.25	3.45±0.25	178.65±4.20	0.16	99.28
FH9	5.50±0.54	3.50±0.04	182.15±4.61	0.12	99.73
FH10	5.50±0.71	3.50±0.07	180.50±4.39	0.1	98.12

Floating properties of prepared formulations

All the formulations were tested for floating properties like floating lag time and total floating time. The results of the tests were tabulated. All the formulations floated within 71 sec (Table 7) and total floating time was greater than 12 hrs except for formulations F1-F3 (Figure 2).

Table. 7: Floating properties of prepared formulations.

S.No	Formulation code	Floating lag time	Total floating time
1	FH 1	68 sec	4 hrs
2	FH 2	57 sec	6 hrs
3	FH 3	60 sec	8 hrs
4	FH 4	70 sec	> 12 hrs
5	FH 5	58 sec	> 12 hrs
6	FH 6	49 sec	> 12 hrs
7	FH 7	61 sec	> 12 hrs
8	FH 8	69 sec	> 12 hrs
9	FH 9	71 sec	> 12 hrs
10	FH 10	67 sec	> 12 hrs

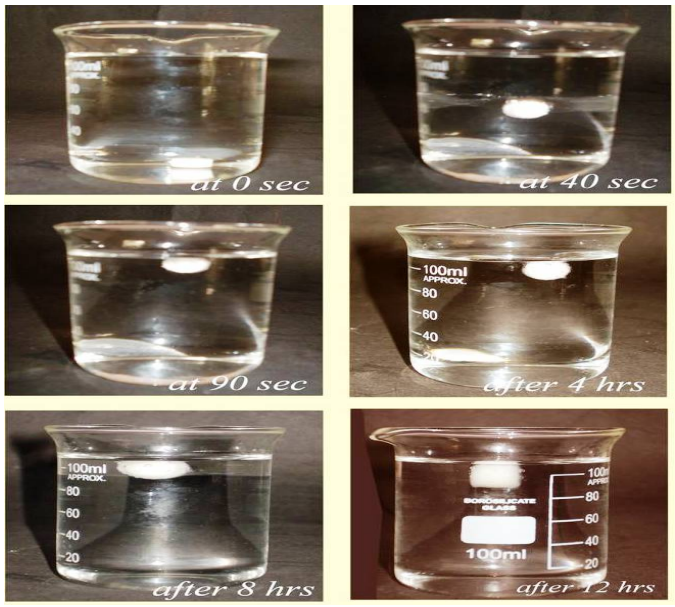


Fig: 2. *In vitro* buoyancy study of Domperidone Maleate floating tablet.

In – vitro drug release data and profiles

The dissolution conditions used for studying the drug release from the matrix tablets of Domperidone Maleate are:

Apparatus : USP Type 2 (paddle)
Agitation speed (rpm) : 50
Medium : 1.2 pH, 0.1 N HCl, 900ml
Temperature : 37.0 ± 0.5 C
Time : 0.5, 1, 2, 3, 4, 6, 8, 10, and 12hr
Wavelength : 284 nm

The samples were withdrawn at predetermined time points and were analyzed spectrophotometrically at 284 nm.

From the figure 3, formulation FH 1 showed rapid burst release within 2-3hrs. FH 2 and FH 3 released the drug only for 6hrs and 8 hrs only. This is due to the low quantity of polymer used, which resulted in the loss of integrity of the tablet Formulation FH 4 sustained the drug release up to 12 hrs. Hence FH 4 was selected as optimized formulation. The mechanism of drug release from FH 4 was found to be fickian diffusion as evident from release exponent (n) value (Table 8).

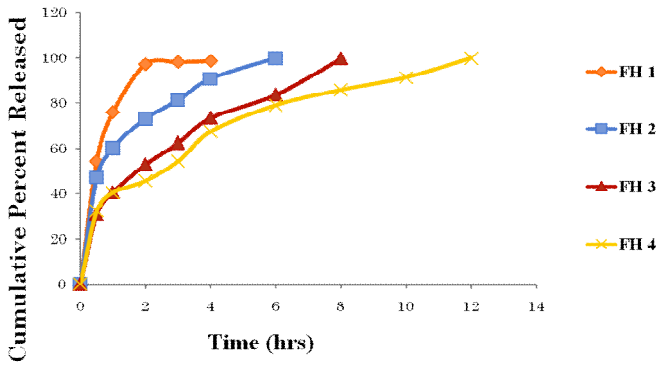


Fig. 3: Drug release profile of Domperidone Maleate floating tablets with HPMC K4M polymer.

Table. 8: Correlation coefficients (r^2) values of different kinetic models.

Formulation	R^2				Peppas (n)
	Zero	First	Higuchi	Peppas	
FH 1	0.65	0.644	0.737	0.858	0.194
FH 2	0.958	0.925	0.93	0.995	0.272
FH 3	0.981	0.931	0.994	0.996	0.43
FH 4	0.951	0.899	0.984	0.974	0.387
FH 5	0.954	0.873	0.989	0.99	0.417
FH 6	0.996	0.969	0.985	0.971	0.403
FH 7	0.987	0.93	0.992	0.981	0.536
FH 8	0.989	0.971	0.969	0.957	0.363
FH 9	0.988	0.956	0.983	0.969	0.424
FH 10	0.961	0.879	0.994	0.994	0.491

From the figure 4, formulation FH 5 released drug completely in 12 hrs. Formulations FH 6 and FH 7 released less than 85 % and 70% of drug in 12 hrs . The drug released from FH 6 and FH 7 was found to be decreasing order (FH5 >FH6 > FH7) due to high quantity of polymer used which retard the drug release. FH 5 formulation was selected as the optimized formulation in HPMC K15 formulation. Drug release from FH 5 follows higuchi model. Release exponent (n) value indicated fickian diffusion (Table 8).

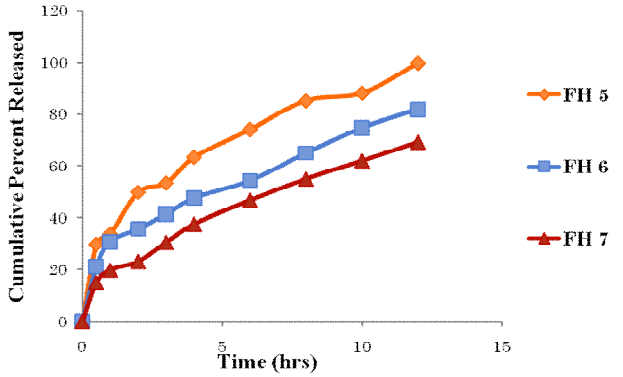


Fig. 4: Drug release profile of Domperidone Maleate floating tablets with HPMC K15M polymer.

From the figure 5, it can be observed that formulations FH8, FH 9 and FH 10 showed the drug release for more than 12 hrs . This is because of improper wetting of the matrix as high viscosity grade polymer was used in the preparation of formulations.

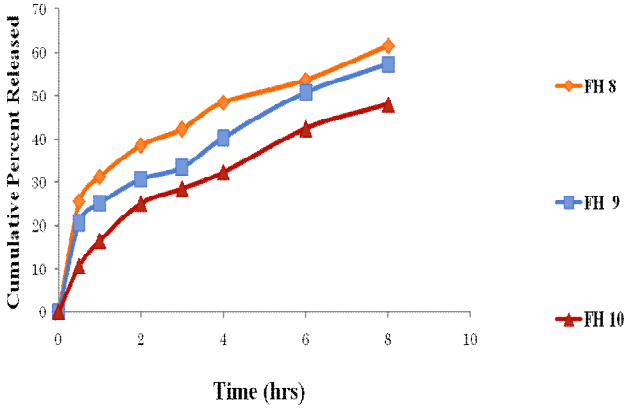


Fig. 5: Drug release profile of Domperidone Maleate floating tablets with HPMC K100M polymer.

In-Vivo evaluation (X-Ray Studies)

Intra-gastric behavior of the floating tablets

The behavior of the floating tablet in the human stomach was observed in real time using a radiographic imaging technique. In radiographic images made 15 min after the administration, the tablets were observed in the stomach. In the next picture taken at 1 hr, the tablet had altered its position and turned round. This provided evidence that the tablets did not adhere to the gastric mucosa, but on the contrary, floated on the gastric fluid. Additionally the swelling of the tablet was visualized very well together with the white dry core and translucent swelling layer around it. As the swelling continued, the glassy core diminished, the swelling layer eroded from the outer surface and a size reduction was seen.

Table. 10: Evaluation of tablets with BaSO4 for *in-vivo* x-ray studies.

Parameters	Optimized batch	Tablets containing BaSO4
Hardness	5-6 kg/cm^3	5-6 kg/cm^3
Thickness	6.0 ± 0.5 mm	6.0 ± 0.5 mm
Density	0.870 g/cm^3	0.884 g/cm^3
Floating Lag time	40 sec	1 min
Floating duration time	More than 12 hrs	More than 12 hrs

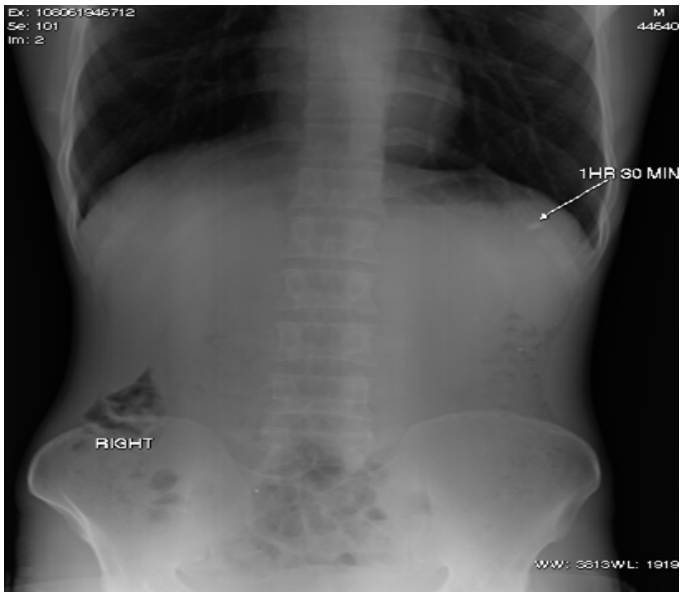
Results of In-vivo X-Ray studies

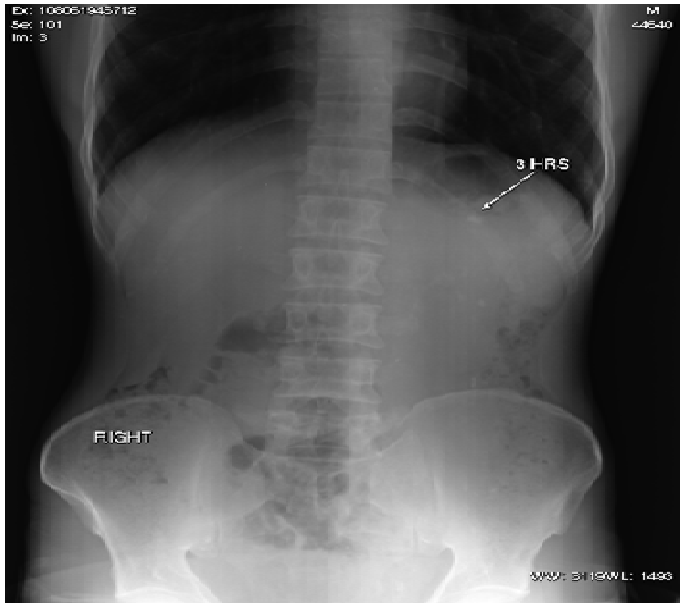
The gastric residence time of optimized Domperidone floating tablets were evaluated by conducting in-vivo X-ray studies in healthy human volunteers. From the radiographic images following results were obtained.

From above results it was observed that the mean gastric residence time for the developed Domperidone floating tablets was 120 min ± 30 in over night fasting state. But in fed state the gastric residence time of floating tablets was observed for 4.5 hrs.

Table 9. Results of in-vivo x-ray studies.

Condition	Gastric residence time (hrs)
Over night fasting state	2 ± 0.5
Fed state	Up to 4.5





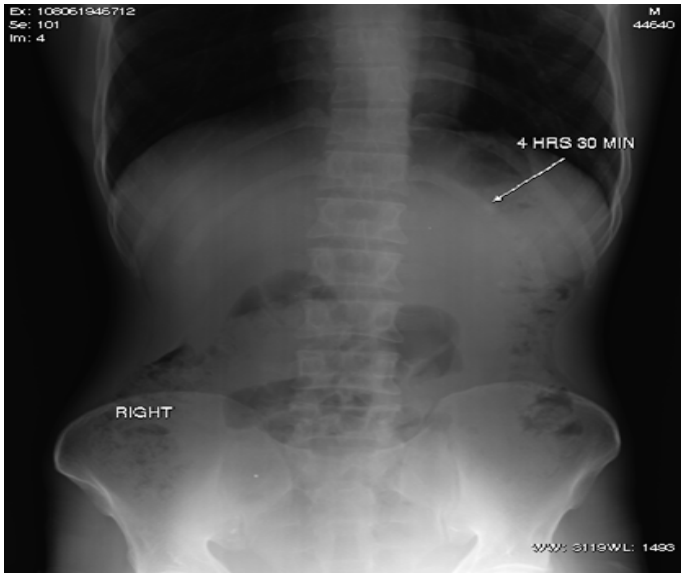


Fig. 6: In *vivo* x-ray studies in fed state.

CONCLUSION

The formulation FH4 prepared with HPMCK4M and FH5 prepared with HPMCK15M showed high regression values of 0.984 and 0.989 for Hguchi order with complete drug release in 12hrs and made it (FH5) to select as optimized formulation compared with other formulations. From the in vivo X-ray studies, conducted in the healthy human volunteers, it was found that the gastric residence time of the developed Domperidone floating tablets dependent on the conditions of the stomach.

In overnight fasting condition the tablets emptied the stomach after 2 hrs of administration. This might be due to rapid gastric motility and insufficient resting volume of the stomach for the tablets to float in the stomach. But in fed condition, the same tablets showed a gastric residence time of more than 4.5 hrs.

In fasting condition the myoelectric migrating contractions force the contents to duodenum from stomach. The forceful house keeping wave will remove all the contents including dosage form to leave stomach. This will not take place in fed state and intake of water after every hour makes the dosage form to float in stomach. After about 4.5 hrs the gastric emptying takes place and thus the dosage form stays in stomach for 4.5-5 hrs. Therefore from these studies, it was clearly observed that the floating tablets should be given to patients after a standard calorific food.

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