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FORMULATION AND EVALUATION OF BI-LAYER DOMPERIDONE FLOATING TABLETS

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ABSTRACT

The present work was carried out to design the floating drug delivery system to minimize the side effect, improve the prolongation of action, to reduce the frequency of administration. The objective of the present investigation was to develop a bilayer-floating tablet (BFT) and evaluate for domperidone maleate using wet granulation technology. HPMC, K-grade and effervescent sodium bicarbonate formed the floating layer. The release layer contained domperidone and various ratios of polymers such as HPMC-K100M.The floating behavior and *in vitro* dissolution studies were carried out in a USP paddle apparatus 2 in simulated gastric fluid. Final formulation released approximately 104% drug in 12 h *in vitro*, while the floating lag time was 4 min and the tablet remained floatable throughout all studies. Statistically significant differences were found among the drug release profile from different formulations Final formulation followed the Higuchi release model and showed no significant change in physical appearance, drug content, floatability or *in vitro* dissolution pattern after storage at 45°C/75% RH for three months. The release mechanism was explored and explained with zero order, first order equation. The results generated in this study showed that the profile and kinetics of drug release were functions of polymer type, polymer level and physico-chemical properties of the drug.

INTRODUCTION: Oral drug delivery has been known for decades as the almost widely used route of administration among all the routes that have been explode for systematic delivery of drug via various pharmaceutical products of different dosage form. Sustained are formulated in such manner as to make the contained drug available over an extended period of time following administration. Floating drug delivery have the property of retaining the dosage units in the stomach for prolonged period of time and are useful for drugs acting locally in the gastro intestinal tract drugs which are poorly soluble and unstable in intestinal fluids. These systems are advantageous in improving GIT absorption of drug with controlled release due to specific site absorption limitations.

The main objective of developing these systems is to increase the safety of a product to extend its duration of action and decrease side effects of drugs. These systems have more flexibility in dosage form design than conventional dosage form. Several approaches have recently been developed to extend gastrointestinal transit time by prolonging residence time of drug delivery system in the GIT. Basic of this drug delivery system is to optimize biopharmaceutical, pharmacokinetic and pharmacodynamic properties of drugs in such a way that to reduce dosing frequency to an extent that once daily dose sufficient for therapeutic management through uniform plasma concentration providing maximum utility of drug through reduction in local and systematic side effects

and cure or controlled condition in shortest possible time by smallest quantity of drug to assure greater patient compliance [6, 7].

Need for developing bi-layer tablets currently variety of reasons: patent extension, therapeutic, marketing to name a few. To reduce capital investment, quite often existing but modified tablet presses are used to develop and produce such tablets. This article explains why the development and production of quality bi-layer tablets needs to be carried out on purpose-built tablet presses to overcome common bi-layer problems, such as layer-separation, insufficient hardness, inaccurate individual layer weight control, cross-contamination between the layers, reduced yield, etc. Using a modified tablet press may therefore not be your best approach to producing a quality bi-layer tablet under GMP-conditions. Especially when in addition high production output is required [8].

Emesis occurs due to the stimulation of emetic centre situated in medulla oblongata. The chemoreceptor trigger zone located in the area of nucleus tractus solitarious are the important for afferent impulses arising in GIT, throat and viscera CTZ accessible to blood borne drugs hormones and toxins etc. Nausea is accompanied by reduced gastric tone and peristalsis. In the emetic response fundus and body of stomach, esophageal sphincterrelax while duodenum and pyloric stomach contract in a retrograde manner. Rhythmic contraction of diaphragm and abdominal muscles then compress the stomach and evacuate its contents via the mouth. Nausea and vomiting are the symptoms of many conditions but not the diseases.

These conditions are related to the following systems like digestive tract: gastritis, bowel obstruction, and pancreatitis, hepatitis, brain: cerebral hemorrhage, brain tumor, alcohol, intoxication, and hypertension. The objective of the present study is to develop fast bilayer floating tablets of Domperidone Hydrochloride and to study the effect of functionality differences of superdisintegrants on the tablet properties as well as to improve the patient compliance without compromising the therapeutic efficacy. Domperidone was chosen as model drug because Domperidone blocks the dopamine action. It has strong affinities for the D2 and D3 dopamine receptors, which are found in the chemoreceptor trigger zone, located just outside the blood brain barrier, which - among others - regulates nausea and vomiting. Domperidone is white colorless powder; it's not soluble in water, and completely soluble in N, N- Dimethylformamide. The protein binding of domperidone is 91- 93% and elimination half life 7 hours. It is chemically described as 5- chloro-1- (1- [3- (2- oxo-2, 3- dihydro-1H-benzo [d] imidazol- 1-yl) propyl]piperidin- 4- yl)- 1H-benzo[d]imidazol- 2 (3H) - one. To maintain the therapeutic range the drug should be administered 3-4 times a day, which leads to saw tooth kinetic and resulting in ineffective therapy. Tablet dosage form was selected because of its fast moving and acceptable dosage form to design newly improved bilayer floating delivery system Therefore, the development of domperidone bilayer floating released dosage form is of therapeutic relevance and can be used to provide a consistent dosage through sustaining an appropriate level of the drug over time [4, 5].

MATERIALS AND METHODS: Domperidone maleate was obtained as gift sample from Dr. Reddy's Laboratories Ltd., Hyderabad. HPMC K100M, Crosscarmellose sodium, microcrystalline cellulose, PVPK30, Starch, Magnesium stearate, Talc were procured from Tablets India Ltd Chennai, and all other chemicals/ Solvents used were of AR grade.

Preparation of Bilayer Tablets [12]: Granules were prepared using wet granulation method as per formulae given in **(Table 1)**. Domperidone bilayer floating tablets contained two layers i.e. an immediate release (IM.R) layer and a sustained release floating (SR) layer. All ingredients were passed through a sieve (20#) and mixed well in a mortar. Granules were prepared using starch and isopropyl alcohol solution. Prepared granules dry with tray drier at temperature of 60^{o}C for 30 minutes. After the granules are dried, pass through a sieve (30#) a screen of smaller size than the one used for the wet mass select granules of uniform size to allow even fill in the die cavity. The selected granules lubricated with magnesium stearate and talc. Weighed quantities of the SR layer equivalent to 100 mg were subjected to mild compression. Weighed granules of the immediate layer equivalent to 100 mg were added to the compressed SR layer.

Both the layers were compressed into using 10/32 inch tablet shaped standard concave punch with 27 station double rotator rimek compression machine and where one cam was removed and air disgusting unit was fitted for sucking of excess powder to the overlap of powder. Firstly compression was done for color part, and adjusts 100mg, after this, white part was compressed with color part, keeping average weight 200 mg. After compression weight variation, friability, dissolution and assay test were carried out.

Physical characterization floating bilayer tablets: The formulations were evaluated for weight variation, thickness, friability, hardness, disintegration time, content uniformity, drug content (assay) [The data is presented in **Table 2 & 3**] and *in vitro* dissolution study [9-18].

Weight variation: Weight variation was done by selecting 20 tablets randomly and weighing individually. Average weight was calculated and the weight of individual tablet was compared with it.

Thickness: The thickness was measured using Vernier Caliper and expressed in mm.

Friability: Friability test was performed using a Roche friability testing apparatus. It is performed 100 to access the effect of friction and shocks which may often cause tablet to chip, cap or break. This device subjects a number of tablets to the combine effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm, dropping the tablets at a distance of 6 inches with each revolution. Pre-weighed tablet sample is placed in friabilator which is then operated for 100 revolutions. The tablets are then dusted and re-weighed. The % friability was measured using following formula:

$$\% F = [(W-W0)/W0] X 100$$

Where; %F = Friability in percentage, W = Initial weight of tablet, W0= Weight of tablet after test

Hardness: The strength of tablet is expressed as tensile strength (Kg/cm^2). The tablet crushing load, which is the force required to break a tablet into halves by compression. It was measured using a tablet hardness tester (Monsanto hardness tester).

Disintegration time: One tablet was placed in each of six tubes of disintegration test apparatus. The test was carried out at 37±2˚C according to USP XXII. Disintegration test apparatus was used without disc. Time required for complete disintegration of tablet fragments through sieve (#10) was considered as a disintegration time of tablet.

Content uniformity: The same procedure was followed for content uniformity testing as described under assay procedure for 10 dosage units.

Flow properties: A funnel was kept vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom is closed and 10 gm of sample powder is filled in funnel. Then funnel was opened to release the powder on the paper to form a smooth conical heap, is found by measuring in different direction.

The height of the heap was measured by using scale. The value of angle of repose is calculated by using the following formula;

$$\tan \theta = h/r$$

Compressibility index = Mass of the granules (w)/initial volume of the granules (vo)

Hausner's Ratio = Mass of the granules (w)/tapped volume of granules (vf)

Estimation of drug content in bilayer floating tablet: Domperidone maleate is assayed by non-aqueous titration method**.** Dissolve 0.400gm in 500ml of anhydrous glacial acetic acid R using 0.2 ml napthalobenzene as indicator. Resulting solution titrate with 0.1 perchloric acid until the color change from orange yellow to green. The formula is following;

$$\text{Amount present} = \frac{\text{Sample Area x Standard Wt. x Dilution Factor of Sample}}{\text{Standard Area x Sample Wt x Dilution Factor of Standard}} \text{ x Potency x Avg. weight}$$

***In-vitro* disintegration time:** *In- Vitro* disintegration time was performed by apparatus specified in USP at 50 rpm. 0.1N HCl, pH 1.2, 900 ml was used as disintegration medium, and the temperature of which maintained at 37±2^{o}C and the time in second taken for complete disintegration of the tablet with no palpable

mass remaining in the apparatus was measured in seconds.

Procedure for standard curve: The first stock solution was prepared by dissolving 100 mg of Domperidone maleate in 100 ml of 0.1N HCl (1mg/ml). From this the second solution was prepared by diluting 5 ml to 50ml of mixed 0.1N HCl (100µg/ml). From the second stock solution 2, 4, 6, 8 and 10µg/ml dilution were prepared. The absorbance of each sample was measured at 284 nm. Standard curve of concentration vs. absorbance was plotted.

***In vitro*- drug release Studies:** The *in vitro* study of domperidone bilayer tablets for a period of 12 hours was studied. The values obtained are shown in table. It is evident that an increase in amount of and HPMC K100M causes increase and depending on the concentration the drug release will vary. The *in vitro* dissolution study of domperidone tablets was performed according to British Pharmacopoeia [22] using USP apparatus II (model TDT-06T, Electrolab, Mumbai, India) fitted with paddles (50 rpm) at 37 ÌC ± 0.5 ÌC and using hydrochloric acid (pH 1.2, 900 ml) as a dissolution medium [22]. At the predetermined time interval, 5-ml samples were withdrawn filtered through a 0.45 µm membrane filter diluted, and assayed at 284 nm using a Shimadzu UV/Vis double-beam spectrophotometer (Shimadzu Kyoto, Japan). Cumulative percentage drug release was calculated using an equation obtained from a calibration curve. The experiments were conducted in triplicate **(table 4 & fig. 2**).

***In vitro* buoyancy studies:** The *in vitro* buoyancy was determined by floating Lag time as per the method described by Rosa *et al*. The tablets were placed in a 100-ml glass beaker Containing simulated 0.1N hydrochloric acid, as per USP. The time required for the tablet to rise to the surface and float was determined as floating lag time (**table 5**).

IR studies: Accurately, the Fourier-transform infrared spectra of domperidone hydrochloride and mixture domperidone hydrochloride with other excipients were obtained by using FTIR spectroscopy- 5300 (JASCO Japan). Samples were prepared by Potassium bromide pressed pellet technique. The scanning range was 400-4600 cm^{-1} and the resolution was 4 cm^{-1}. The spectra are shown in **Fig. 3 to 6.**

RESULT AND DISCUSSION: Domperidone maleate were prepared with varying concentration three superdisintegrants: Sodium starch glycolate, Crosspovidone, Crosscarmellose Sodium, and Starch, Microcrystalline cellulose and Magnesium stearate, talc were used as lubricants (**Table 1**).

TABLE 1: COMPOSITION

Ingredients (gm)	IR1	IR2	IR3	SR1	SR2	SR3
Domperidone maleate	10	10	10	20	20	**20**
PVPK30	3	3	3	5	5	**5**
HPMC K100M	-	-	-	15	20	**25**
Magnesium stearate	1	1	1	1	1	**1**
Talc	1	1	1	1	1	**1**
Starch	25	25	25	25	20	**15**
Microcrystalline cellulose	50	50	50	23	23	**23**
Sodium starch glycolate	10	-	-	-	-	**-**
Crosscarmellose sodium	-	10	-	-	-	**-**
Sodium bicarbonate	-	-	-	10	10	**10**
Crosspovidone	-	-	10	-	-	**-**
Color Erythrosine	-	-	-	0.1	-	**-**
Brilliant Blue	-	-	-	-	0.1	
Tartarazine's Yellow	-	-	-	-		**0.1**
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	**q.s**
TOTAL QUANTITY	**100**	**100**	**100**	**100**	**100**	**100**

IR – Immediate release layer SSG – sodium starch glycolate CP – crosspovidone; SR – Sustained Release layer CCS – crosscarmellose sodium; HPMC – hydroxyl propyl methyl cellulose. BDFT- Bilayer domperidone floating tablet

For each formulation, blend of drug and excipients were prepared and evaluated for various parameters as explained earlier. The powder blend was compressed using wet granulation technique. Bulk density, was found in the range of 0.500-0.580g/ml and the tapped density between 0.580- 0.640 g/ml. The Hausner's ratio and Compressibility index was calculated using bulk and tapped density data.

Hausner's ratio for prepared formulation was found to be <1.19 which indicates good flow property. The compressibility index was found to be between 9.3% - 15.12% which indicates good flow property of the powder blend. The excellent flow property of the powder blend was also evidenced with angle of repose (ranging from 29.31˚- 31.84˚) which is near to 30˚, indicating excellent flow property (**Table 2**). Tablets were prepared using wet granulation technique. Since the powder material was free flowing, tablets were obtained of uniform weight due of uniform die fill, with acceptable weight variations as per B.P.

TABLE 2: RESULTS OF PRECOMPRESSION PARAMETER

PROPERTIES	IR1	IR2	IR3	SR1	SR2	SR3
Tapped density	0.62	0.58	0.64	0.60	0.64	0.62
Bulk density	0.54	0.52	0.56	0.54	0.58	0.56
Hausner's ratio	1.14	1.11	1.14	1.11	1.10	1.10
Compressibility index	12.90	10.34	12.5	10.00	9.37	9.67
Angle of repose	29.31	29.88	30.26	31.26	31.84	31.46

The drug content was found in the range of 98.5 % - 101.1% (acceptable limit). Friability of the tablets was found below 0.5% and hardness was found between 9.0-9.2kg/cm^2, indicating a good mechanical resistance of the tablets, and the parameters were found well within the specified limit for uncoated tablets **(Table 3)**. The standard curve of domperidone maleate is excellent linearity and R^2=0.999 (**fig. 1**).

TABLE 3: RESULTS OF POST COMPRESSION PARAMETER

PROPERTIES	BDFT 1	BDFT 2	BDFT 3
Weight variation (mg)	198±2	200±1	199±1
Hardness (kg/cm^2)	9.2±0.2	9.1±0. 1	9.0±0.1
Thickness (mm ± S.D)	3.3±0.03	3.1±0.01	3.2±0.02
% Friability	0.21	0.31	0.28
Disintegration time (sec)	50	35	54
Assay(w/v)	99.2	99.8	99.12

IR1+SR1 = BDFT 1; IR2+SR2 = BDFT 2; IR3+SR3 = BDF

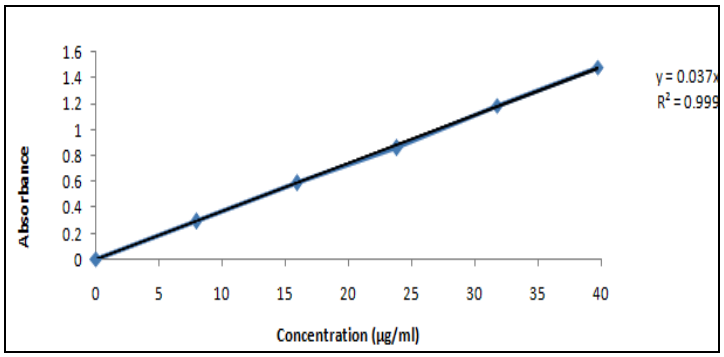

FIG. 1: STANDARD CURVE OF DOMPERIDONE MALEATE

The *in- vitro* disintegration time (DT) of the tablets was found to less than 60 sec. Tablets containing 15% Sodium starch glycolate and 25% Crosspovidone had disintegration time of 54 and 50 sec respectively. While rest of the tablets 20% Crosscarmellose sodium had disintegration time 35sec. From the results of the dissolution rate of all the formulations, it is demonstrated that although functionality differences existed between the superdisintegrants, the bilayer domperidone bilayer tablets could be prepared by using any of the superdisintegrants used. Three formulations BDFT 1, BDFT 2, BDFT 3 were studied by drugs SSG with 15%HPMCK100M, 20%CCS with HPMCK100M, and 25%CP with HPMCK100M. The maximum increase in the dissolution rate was observed with 20% HPMC with Crosscarmellose sodium amongst the super- disintegrants (**Table 4 & fig. 2**).

TABLE 4: *IN-VITRO* PERCENTAGE DRUG RELEASE OF BILAYER DOMPERIDONE FLOATING TABLET

Time (hours)	FORMULATION CODE		
	BDFT 1 SSG 15%	BDFT 2 CCS 20%	BDFT 3 CP 25%
0.5	15.21	29.40	33.30
1	28.30	35.90	39.65
3	34.30	42.90	49.65
6	56.87	60.80	75.30
9	69.56	80.00	101.45
12	95.25	104.30	

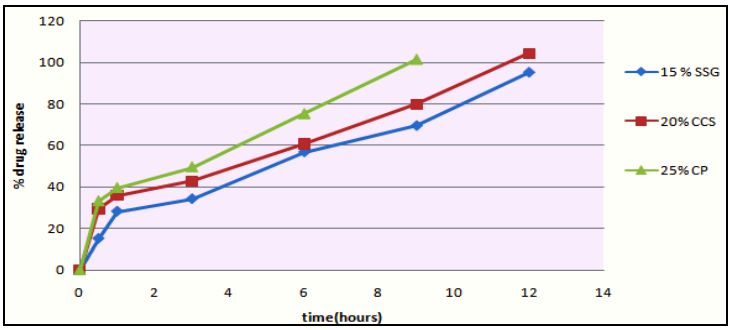

FIG. 2: COMPARATIVE *IN-VITRO* DRUG RELEASE OF VARIOUS POLYMER RATIOS WITH SUPERDISINTEGRANTS

From the above data we can conclude that drug with 20% HPMC K 100M (BDFT 2 104.3%) is an excellent formulation as it released the drug sustained in 12 hours high percentage of drug released, when compare to the other formulations released the drug quickly within 9 hours (BDFT 3 104.1%) and low percentage drug released in 12 hours (BDFT 1 95.5%). FTIR spectrum of tablet reveals that there is no interaction of the polymer and tablet excipients with the drug **(fig. 3, fig. 4, fig. 5, fig. 6).**

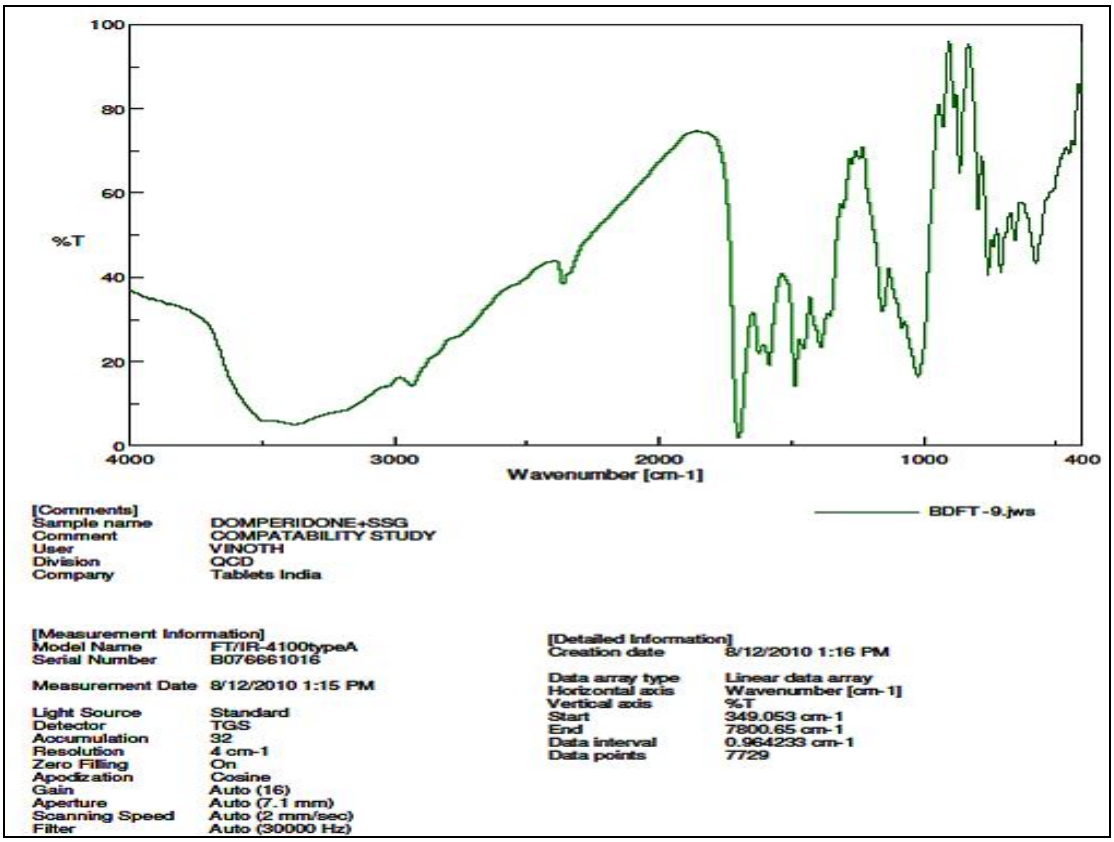

FIG. 3: IR SPECTRUM OF DOMPERIDONE + CROSSCARMELLOSE SODIUM

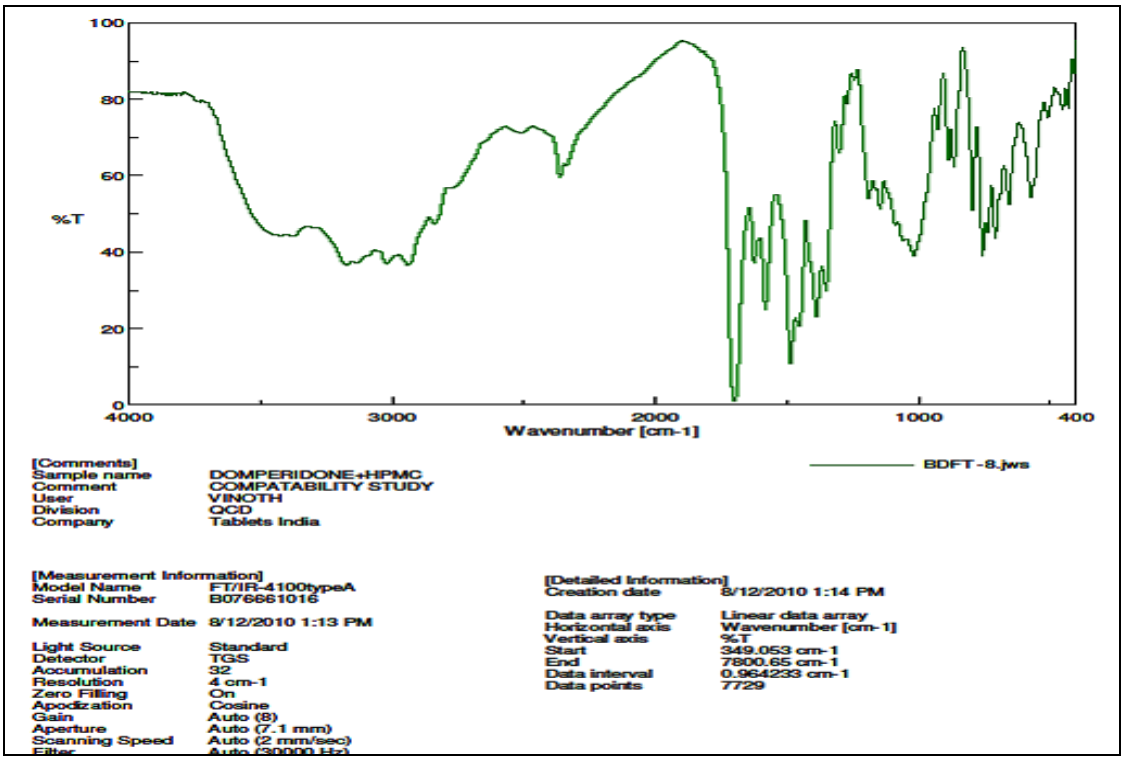

FIG. 4: IR SPECTRUM OF DOMPERIDONE + HPMC POLYMER

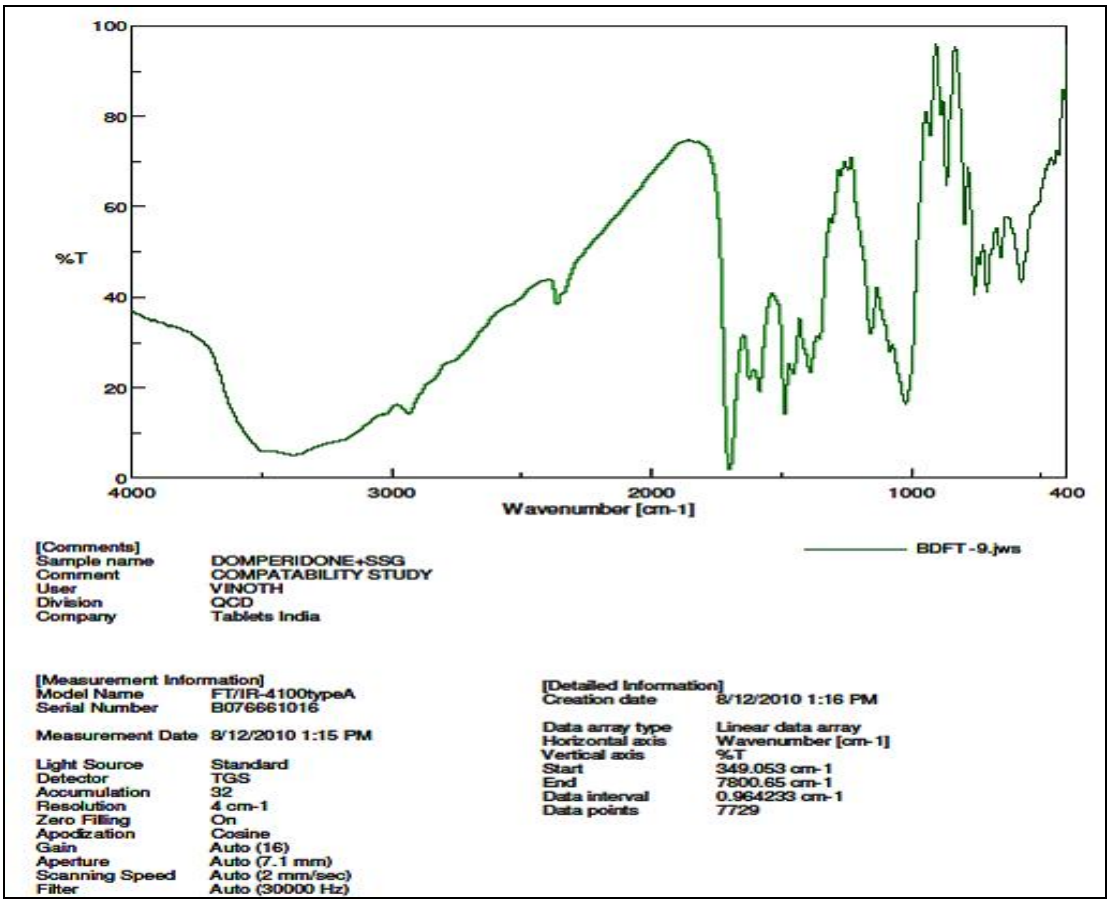

FIG. 5: IR SPECTRUM OF DOMPERIDONE + SODIUM STARCH GLYCOLATE

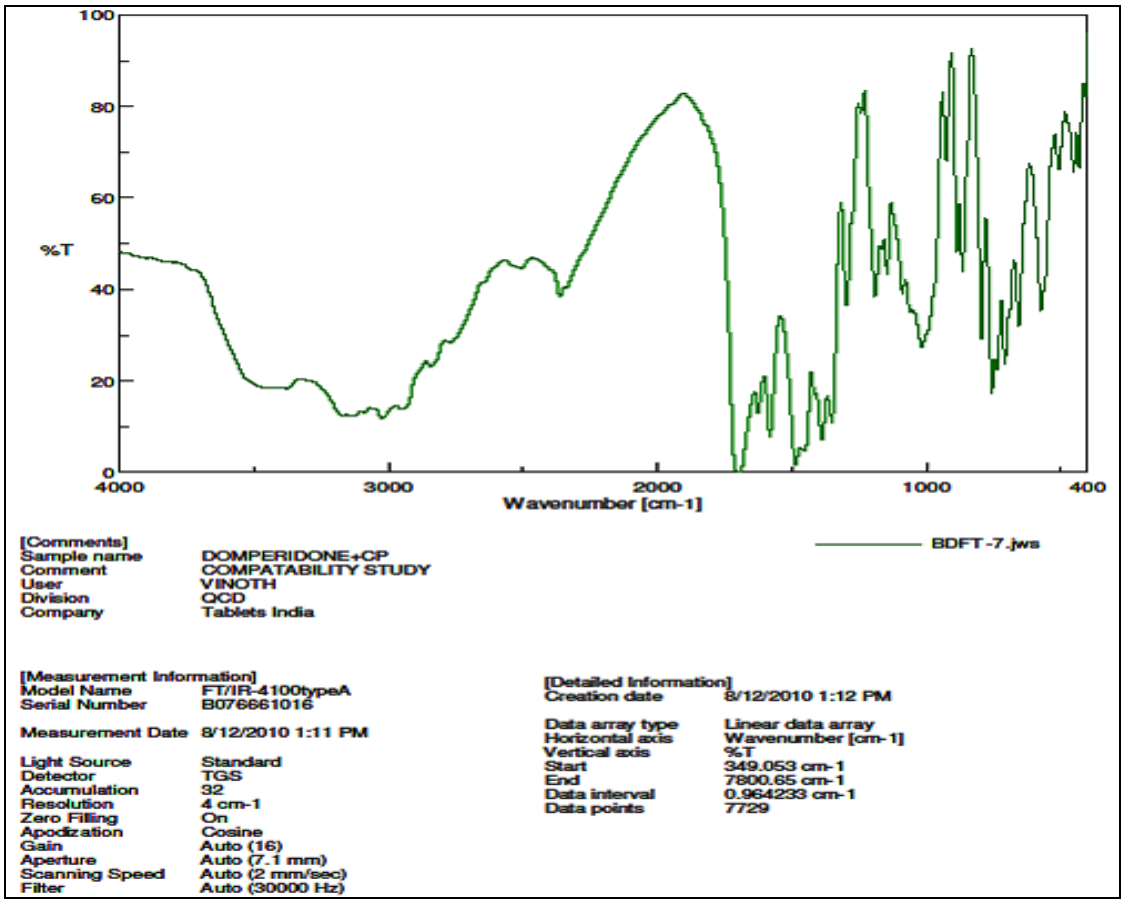

FIG. 6: SHOWING IR SPECTRUM OF DOMPERIDONE + CROSSPOVIDONE

In-vitro buoyancy study indicates Optimized formulation BDFT 2 remained floatable in the stomach for 12 hours and give the maximum released 104.30% at 12th hours. It is thus concluded that bilayer floating tablet containing domperidone (BDFT 2 formulation) is slow and complete drug release spread over 12 hours compared with other formulation is very low (**Table 5)**.

TABLE 5: RESULTS OF IN-VITRO BUOYANCY STUDY

FORMULATION CODE	FLOATING LAG TIME	FLOATING DURATION
BDFT 1	4 min 30 sec	12 hours
BDFT 2	3 min 25 sec	12 hours
BDFT 3	5 min 15 sec	09 hours

Optimized formulation BDFT 2 was subjected to curve fitting analysis, zero order, and first order, % drug release log cumulative kinetics model **(Table 6).**

TABLE 6: RESULTS OF KINETIC DRUG RELEASE

Time	% Cumulative drug release	% to be released	Log % Cumulative drug release
0	0	100	2
0.5	29.40	70.60	1.8488
1	35.90	64.10	1.80686
3	42.90	57.10	1.75664
6	60.80	39.20	1.59329
9	80.00	20.00	1.30103
12	104.30	6.606	- 0.8202

All kinetic drug release complies within limit

The slope and R^2 are shown in (**fig. 7, 8 & 9**). Optimized Formulation BDFT 2 fitted best kinetics releases high linearity with R^2 value of 0.92. Stability study of the optimized formulation BDFT 2 is shown in (**Table 7**). All the parameters within the limits and formulated tablets no color change and better in-vitro release after 3 months (90 days).

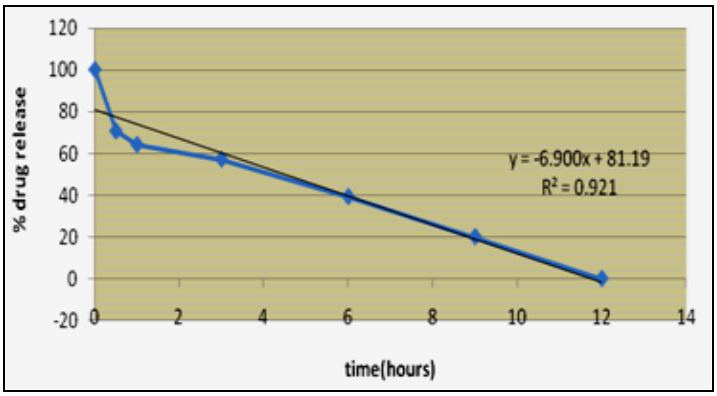

FIG. 7: FIRST ORDER % DRUG RELEASE OF BILAYER FLOATING TABLET

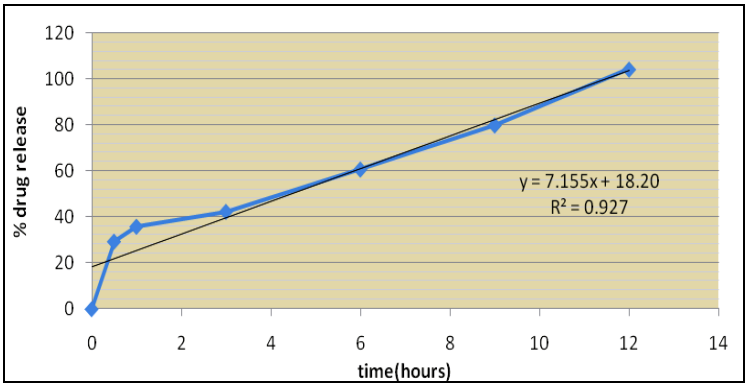

FIG. 8: ZERO ORDER % DRUG RELEASE OF BILAYER FLOATING TABLET

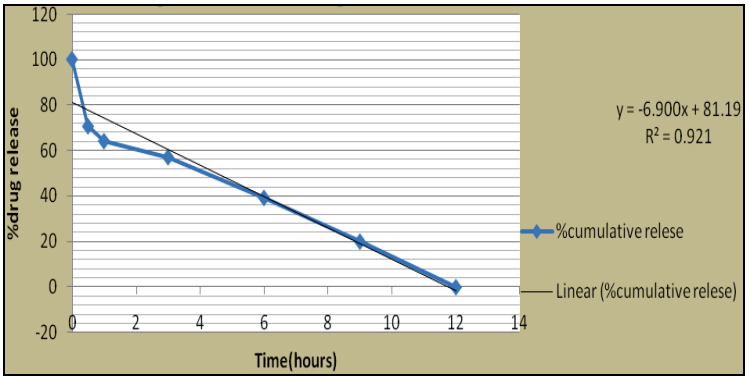

FIG. 9: LOG CUMULATIVE % DRUG RELEASE KINETICS

TABLE 7: STABILITY STUDY OF SELECTED FORMULATION BDFT 2

Properties	Formulation code	30 days	45 Days	60 days	90 days
Weight variation (mg)	BDFT 2	201	201	201	200
%Friability	BDFT 2	0.287	0.287	0.286	0.286
Hardness (kg/cm^2)	BDFT 2	9.2.	9.2	9.1	9.1
Thickness (mm)	BDFT 2	3.1	3.1	3.1	3.0

CONCLUSION: In the present study obtained the data concluded that 200 mg of Domperidone bilayer floating tablet once in a day which can provide effective drug release 12 hours. In-vitro buoyancy studies shows that excellent floating drug release and it provides effective prolongation of GI retention \time. *In-vitro* drug release study showed batch trail BDFT-2 (20% HPMC + CCS) 200 mg label claimed tablet was very excellent release formulation. *In- vitro* buoyancy all shows good floating time and 20% polymer ratio

shows best floating lag time so the drug effective prolongation of GI retention time. FTIR spectrum of tablet reveals that there is no interaction of the polymer and tablet excipients with the drug. Stability study and kinetic study is passed as per IP limits.

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