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FORMULATION AND *INVITRO* EVALUATION OF EFFERVESCENT FLOATING TABLETS OF DOMPERIDONE

Nandam Uma Maheswara Subbarao*[1], Mrs. Raj Khiani[1], Mrs M.Vineela[1]

[1]Department of Pharmaceutics, Pydah College of Pharmacy Patavala, Andhra University, Kakinada, Andhra Pradesh.

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Abstract:

The present study was aimed to formulate and evaluate floating tablets of Domperidone by direct compression method. Domperidone is a dopamine antagonist medication which is used to treat nausea and vomiting and certain gastrointestinal problems like gastroparesis (delayed gastric emptying). In this study, excipients like Eudragit RSPO, HPMC, Carbopol 974P, sodium bicarbonate and Citric acid were incorporated in a nine different concentrations (F1-F9) along with other excipients (Magnesium Stearate, Talc and Micro crystalline cellulose) to formulate floating tablets by direct compression method. Then all the nine formulations were evaluated for uniformity of weight, hardness, thickness, friability test, floating lag time, drug content and dissolution studies. The dissolution profile of trial-7 (formulation 7) was observed to be better than other formulations. In trial-7 Domperidone was formulated as a floating tablet by using Carbopol 974P (32.5 mg) as a matrix forming polymer and sodium bicarbonate (10 mg) as a gas generating agent. Trial-7 formulation showed a good dissolution profile for a controlled period of time which was noticed to be as 99.29 % at the end of 12th hour. Thus, it can be concluded that the floating drug delivery system of Domperidone using the appropriate polymers in right amount may enhance the activity of the drug by prolonging the gastric residence time or reducing the floating lag time.

Key words: *Domperidone, Eudragit RSPO, HPMC, Carbopol 974P and Floating Tablets.*

Corresponding author:

Nandam Uma Maheswara Subbarao,

Department of Pharmaceutics,

Pydah College of Pharmacy

Kakinada, Andhra Pradesh

Email Id- subbusubbu1456@gmail.com

QR code

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INTRODUCTION:

The aim of drug delivery system is to afford a therapeutic amount of drug to the prope site in the body to attain promptly and then maintain desired drug concentration. The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance. More than 50% of the drug delivery systems available in the market are oral drug delivery systems [1-4].

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. The relatively brief gastric emptying time (GET) in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose. Sustained releases are dosage forms that provide medication over an extended period of time. Controlled release denotes that the system is able to provide some actual therapeutic control [5]. Controlled release (modified release) dosage forms are growing in popularity. These more sophisticated systems can be used as a means of altering the pharmacokinetic behavior of drugs in order to provide twice or once a day dosage. This is achieved by obtaining a zero-order release from the dosage form. Zero-order release includes drug release from the dosage form that is independent of the amount of drug in the delivery system [6].

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion , flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents, that delay gastric emptying. Oral controlled drug release dosage forms should not be developed unless the recommended dosage interval for the controlled release dosage form is longer than that for immediate release dosage form or unless significant clinical advantages for the controlled release dosage form can be justified like the decreased side effects resulting from a lower C max with the controlled release Form as compared to the immediate release or conventional dosage form. In vivo/in vitro evaluation of FDDS has been discussed by scientists to assess the efficiency and application of such systems. Several recent examples have been reported showing the efficiency of such systems for drugs with bioavailability problems.[7,8,9].

The concept of floating tablets is mainly based on the matrix type drug delivery system such that the drug remains embedded in the matrix which after coming in contact with the gastric fluid swells up and the slow erosion of the drug without disintegration of the tablet takes place. Sometimes for generating a floating system we even need to add some effervescent or gas generating agent which will also ultimately reduce the density of the system and serve the goal of achieving a floating system. These systems have a particular advantage that they can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the GIT. These systems continuously release the drug before it reaches the absorption window, thus ensuring optimal bioavailability. Different approaches are currently used to prolong the gastric retention time, like hydro dynamically balanced systems, swelling and expanding systems, polymeric bio-adhesive systems, modified shape systems, high density systems and other delayed gastric emptying devices. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release [10].

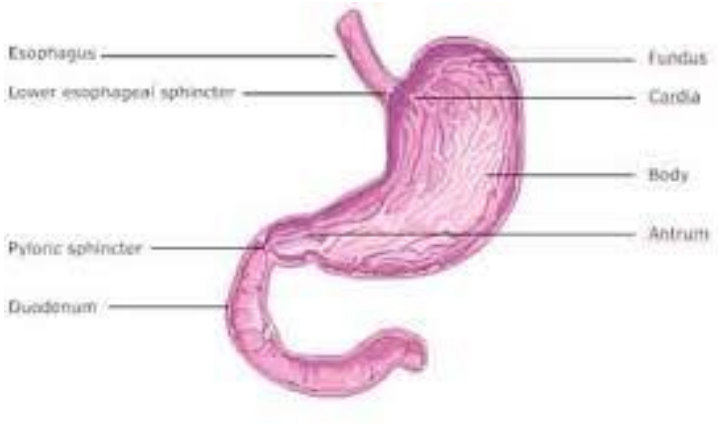

Figure 1: Anatomy of stomach

Physiology of stomach:

The stomach is divided into four major regions: fundus, body, antrum, and pylorus. Its functions are mainly:

• reservoir function: achieved through the flexible volume of the stomach

• emptying function: achieved through low sustained pressure produced by the stomach body

• Mixing and homogenizing function: achieved through stomach contraction that produces grinding.

• Size restriction function: the particle sizes of food emptied through the pylorus is less than 1 millimeter during the fed state.

The stomach is an organ with a capacity for storage and mixing. Its fundus and body region are capable of displaying a large expansion to accommodate food without much increase in the intragastric pressure. Whereas, the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions [11]. Under fasting conditions the stomach is a collapsed bag with a residual volume of 50 ml and contains a small amount of gastric fluid (pH 1-3) and air. Under physiological condition, the gastric absorption of most drugs is insignificant as a result of its limited surface area (0.1-0.2 m2) covered by a thick layer of mucous coating, the lack of villi on the mucosal surface, and the short residence time of most drug in the stomach. Rapid gastric emptying, also called dumping syndrome, occurs when undigested food empties too quickly into the small intestine. Stomach emptying is a coordinated function by intense peristaltic contractions in the antrum. At the same time, the emptying is opposed by varying degrees of resistance to passage of chyme at the pylorus. Rate depends on pressure generated by antrum against pylorus resistance. Chyme = food in stomach which has been thoroughly mixed with stomach secretions. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 - 3 hours [12]. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington [13]. PHASE I the quiescent period, lasts from 30 to 60 mins and is characterized by a lack of secretary, electrical and contractile activity. PHASE II, exhibits intermittent activity for 20-40 min, during which the contractile motions increase in frequency and size. Bile enters the duodenum during this phase, whereas gastric mucus discharge occurs during the latter part of phase II and throughout phase III. PHASE III is a short period of intense large regular contractions, termed "housekeeper waves" that sweep off undigested food and last 10-20 min. PHASE IV is the transition period of 0-5 mins between Phase III & I [14].

MATERIALS:

Domperidone Procured From Mylan Laboratories, Hyderabad, India. Provided by SURA LABS, Dilsukhnagar, Hyderabad. ,Eudragit RSPO Degussa India Ltd. (Mumbai, India). ,HPMCArvind Remedies Ltd, Tamil nadu, India. ,Carbopol 974P Merck Specialities Pvt Ltd, Mumbai, India ,Citric acid Laser Chemicals, Ahmedabad, India. ,Sodium bicarbonate Merck Specialities Pvt Ltd, Mumbai, India ,Micro crystalline cellulose Merck Specialities Pvt Ltd, Mumbai, India ,Magnesium Stearate Apex Chemicals, Ahmedabad, India. ,Talc S.D. Fine Chem., Mumbai, India.

METHODOLOGY:

Analytical method development:

a) Determination of absorption maxima:
A solution containing the concentration 10 µg/ mL drug was prepared in 0.1N HCL UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

b) Preparation calibration curve:
10mg Domperidone pure drug was dissolved in 10ml of methanol (stock solution1) from stock solution 1ml of solution was taken and made up with10ml of 0.1N HCL (100µg/ml). From this 1ml was taken and made up with 10 ml of 0.1N HCL (10µg/ml). The above solution was subsequently diluted with 0.1N HCL to obtain series of dilutions Containing 2, 4, 6, 8, 10 µg /ml of per ml of solution. The absorbance of the above dilutions was measured at 215 nm by using UV-Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis.

Preformulation parameters
The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:
The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$\tan \theta = h / r$ $\tan \theta$ = Angle of repose

h = Height of the cone , r = Radius of the cone base

INGREDIENTS (MG)	FORMULATION CODE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Domperidone	10	10	10	10	10	10	10	10	10
Eudragit RSPO	32.5	65	130	-	-	-	-	-	-
HPMC	-	-	-	32.5	65	130	-	-	-
Carbopol 974P	-	-	-	-	-	-	32.5	65	130
Citric acid	5	5	5	5	5	5	5	5	5
Sodium bicarbonate	10	10	10	10	10	10	10	10	10
Micro crystalline cellulose	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4
Total Weight	200	200	200	200	200	200	200	200	200

Table 1: Formulation composition for Floating tablets

All the quantities were in mg

RESULTS AND DISCUSSION:

Analytical Method

a. Determination of absorption maxima
The standard curve is based on the spectrophotometry. The maximum absorption was observed at 215 nm.

b. Calibration curve
Graphs of Domperidone was taken in 0.1N HCL (pH 1.2)

Table no 2: Observations for graph of Domperidone in 0.1N HCL

Conc. [µg/mL]	Abs
0	0
2	0.125
4	0.248
6	0.364
8	0.475
10	0.586

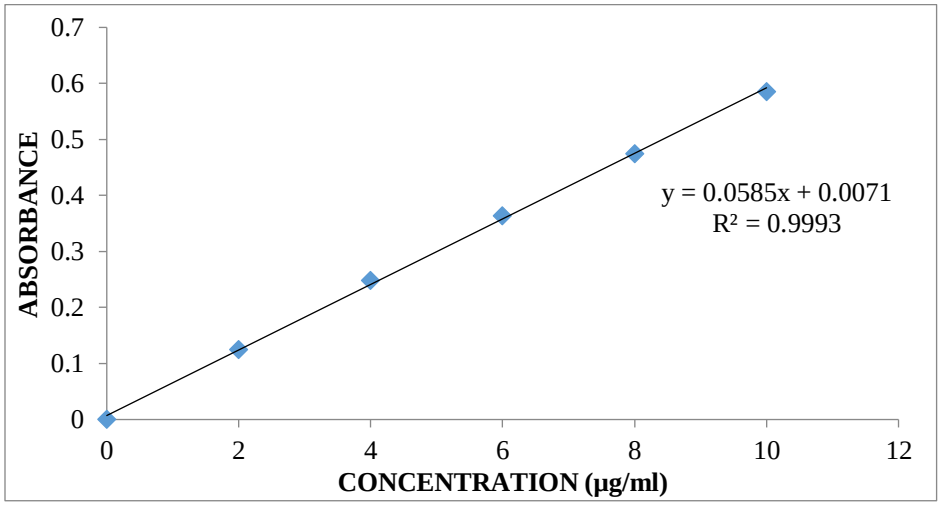

Fig 2: Standard graph of Domperidone in 0.1N HCL

Preformulation parameters of blend

TAble3: Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's Ratio
F1	33º01'±1.18	0.22 ± 0.02	0.25 ± 0.25	13.10±1.14	1.15± 0.15
F2	30º01'±1.37	0.25 ± 0.02	0.29 ± 0.04	13.32±5.22	1.15 ± 0.07
F3	31º09'±2.12	0.26 ± 0..03	0.29 ± 0.02	10.44±3.94	1.11 ± 0.05
F4	34º06'±0.53	0.27± 0.06	0.31 ± 0.07	11.83±2.85	1.13 ± 0.03
F5	34º17'±1.07	0.23 ± 0.01	0.28 ± 0.01	17.04±2.82	1.20 ± 0.04
F6	32º29'±0.91	0.29 ± 0.01	0.33 ± 0.01	7.09 ± 2.82	1.13 ± 0.03
F7	33º21'±0.83	0.24 ± 0.03	0.27 ± 0.03	11.22±4.21	1.12 ± 0.05
F8	33º28'±0.83	0.28 ± 0.01	0.31 ± 0.05	11.55±3.52	1.13 ± 0.04
F9	32º47'±0.62	0.25 ± 0.01	0.27 ± 0.01	10.41±0.27	1.08 ± 0.03

Quality control parameters for tablets:

Table4 : *In vitro* quality control parameters

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (sec)	Total Floating Time(Hrs)
F1	199.50	4.9	0.39	5.62	98.14	56	10
F2	198.32	5.6	0.15	5.51	97.24	42	12
F3	195.20	4.1	0.48	5.14	99.51	61	11
F4	198.75	4.8	0.55	5.75	97.21	34	11
F5	196.86	5.6	0.62	5.89	99.56	52	12
F6	197.21	5.2	0.21	5.12	97.35	48	10
F7	199.36	4.8	0.40	5.32	99.22	15	12
F8	200.03	5.4	0.31	5.20	96.36	30	9
F9	197.89	4.2	0.28	5.72	98.57	24	10

***In Vitro* Drug Release Studies**

Table5: Dissolution data of Floating Tablets

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	13.58	9.17	8.92	10.80	12.51	19.10	14.21	20.11	11.15
1	18.69	18.25	14.03	15.37	17.92	25.49	20.36	25.34	17.94
2	22.12	24.39	20.62	19.29	22.19	29.82	27.48	30.40	21.67
3	36.34	37.75	26.47	26.40	28.62	37.87	33.24	33.89	25.56
4	44.11	40.28	35.89	33.67	36.51	46.73	48.82	39.90	34.40
5	51.86	47.56	44.56	39.12	43.86	53.87	50.31	45.90	37.58
6	58.27	54.12	49.84	50.74	54.98	62.31	66.17	56.88	41.10
7	67.14	63.29	56.47	57.56	62.26	69.12	73.99	59.34	52.67
8	75.26	68.76	62.35	63.58	68.32	77.58	77.61	67.51	57.25
9	79.98	75.92	68.13	71.75	74.57	81.73	84.50	76.56	65.32
10	83.29	84.27	73.58	75.96	83.34	88.17	89.72	78.49	74.15
11	92.42	90.63	76.21	81.36	86.95	92.52	93.31	80.20	80.52
12	99.16	95.79	82.18	87.24	90.11	98.21	99.29	85.15	90.19

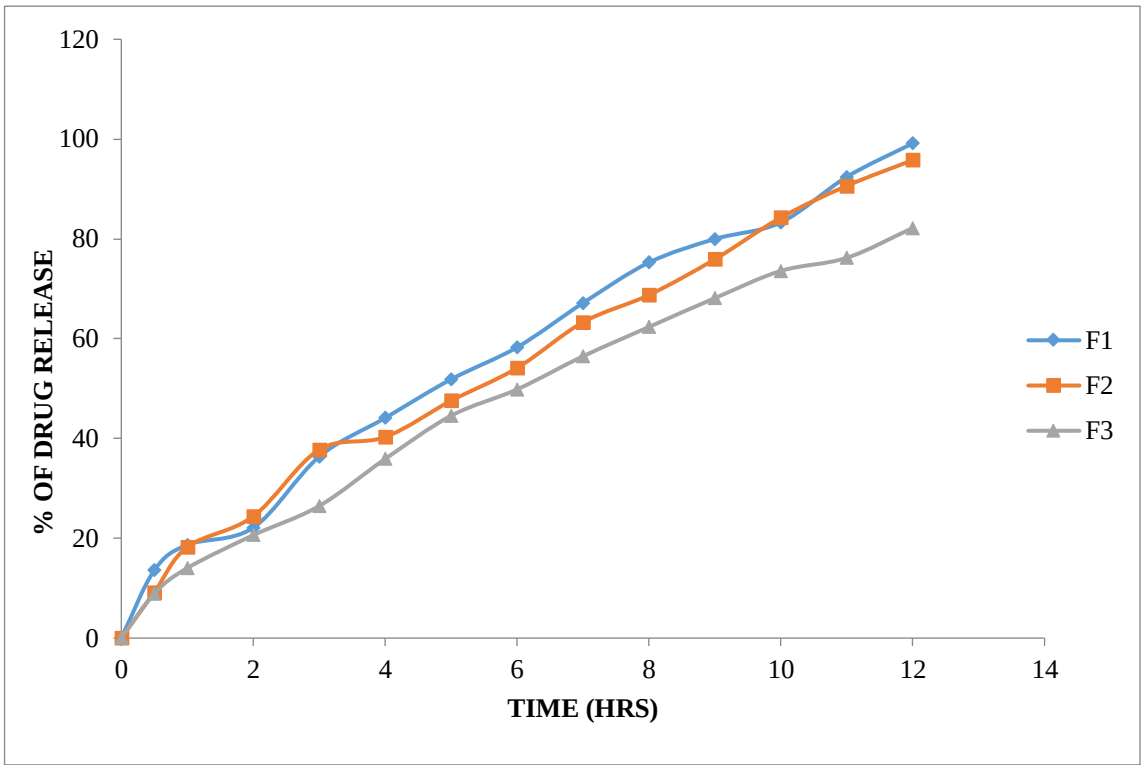

Fig 3: Dissolution data of Domperidone Floating tablets containing Eudragit RSPO

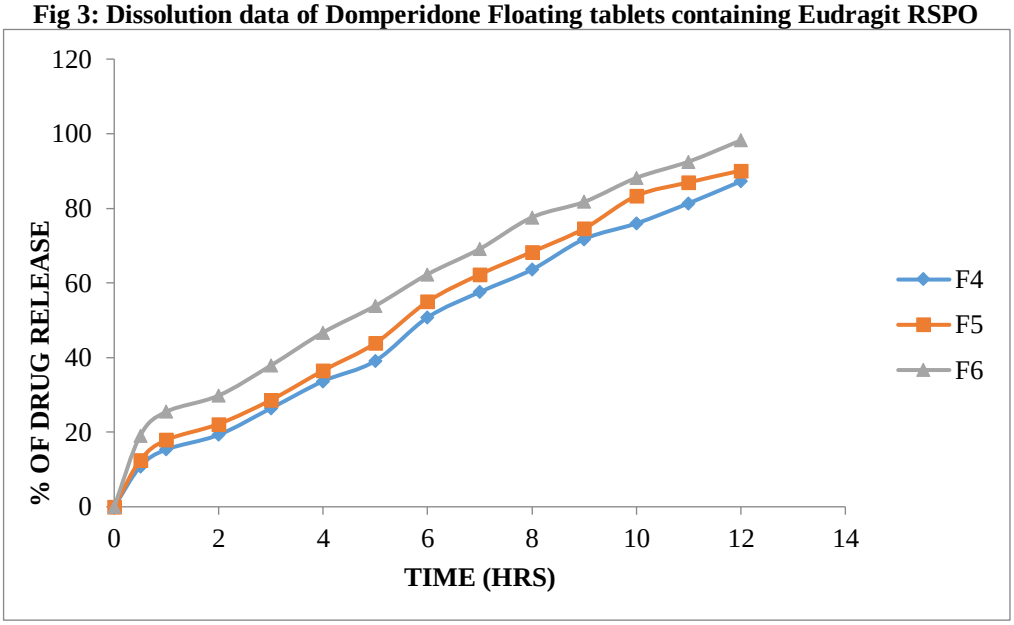

Fig: 4 Dissolution data of Domperidone Floating tablets containing HPMC

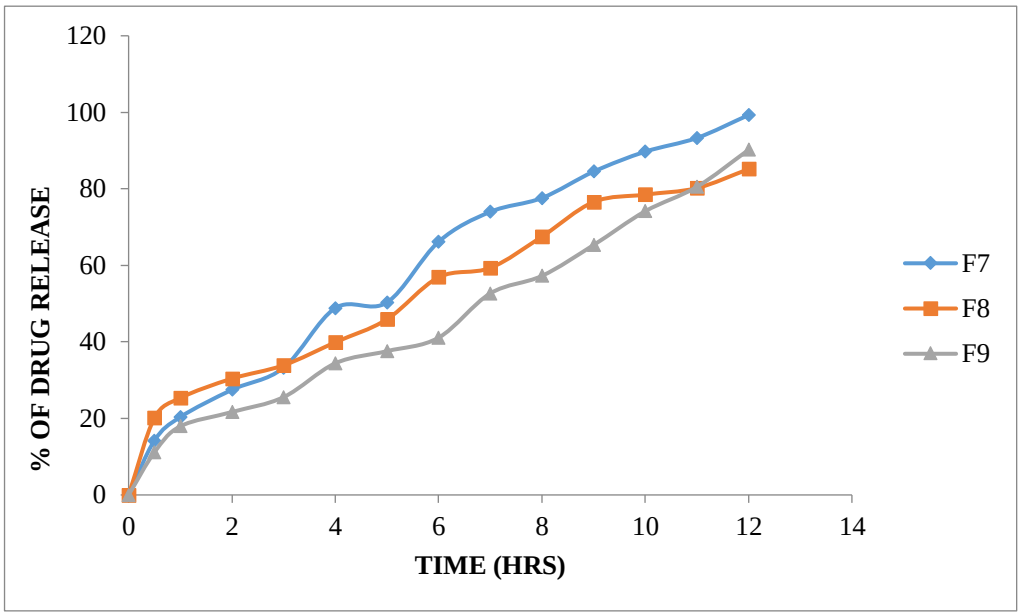

Fig: 5 Dissolution data of Domperidone Floating tablets containing Carbopol 974P

Table 6 :Application kinetics for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
14.21	0.5	0.707	1.153	-0.301	1.933	28.420	0.0704	-0.847	85.79	4.642	4.410	0.231
20.36	1	1.000	1.309	0.000	1.901	20.360	0.0491	-0.691	79.64	4.642	4.302	0.339
27.48	2	1.414	1.439	0.301	1.860	13.740	0.0364	-0.561	72.52	4.642	4.170	0.471
33.24	3	1.732	1.522	0.477	1.825	11.080	0.0301	-0.478	66.76	4.642	4.057	0.585
48.82	4	2.000	1.689	0.602	1.709	12.205	0.0205	-0.311	51.18	4.642	3.713	0.929
50.31	5	2.236	1.702	0.699	1.696	10.062	0.0199	-0.298	49.69	4.642	3.676	0.965
66.17	6	2.449	1.821	0.778	1.529	11.028	0.0151	-0.179	33.83	4.642	3.234	1.407
73.99	7	2.646	1.869	0.845	1.415	10.570	0.0135	-0.131	26.01	4.642	2.963	1.679
77.61	8	2.828	1.890	0.903	1.350	9.701	0.0129	-0.110	22.39	4.642	2.818	1.823
84.5	9	3.000	1.927	0.954	1.190	9.389	0.0118	-0.073	15.5	4.642	2.493	2.148
89.72	10	3.162	1.953	1.000	1.012	8.972	0.0111	-0.047	10.28	4.642	2.174	2.467
93.31	11	3.317	1.970	1.041	0.825	8.483	0.0107	-0.030	6.69	4.642	1.884	2.757
99.29	12	3.464	1.997	1.079	-0.149	8.274	0.0101	-0.003	0.71	4.642	0.892	3.749

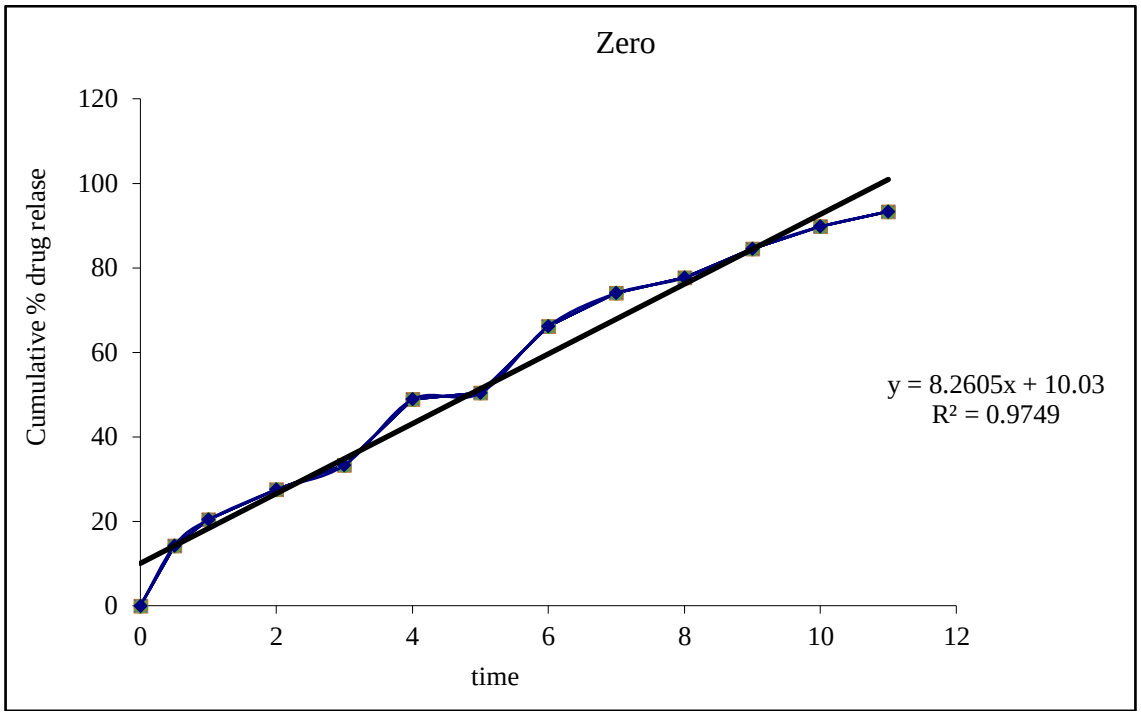

Fig no 7 : Zero order release kinetics

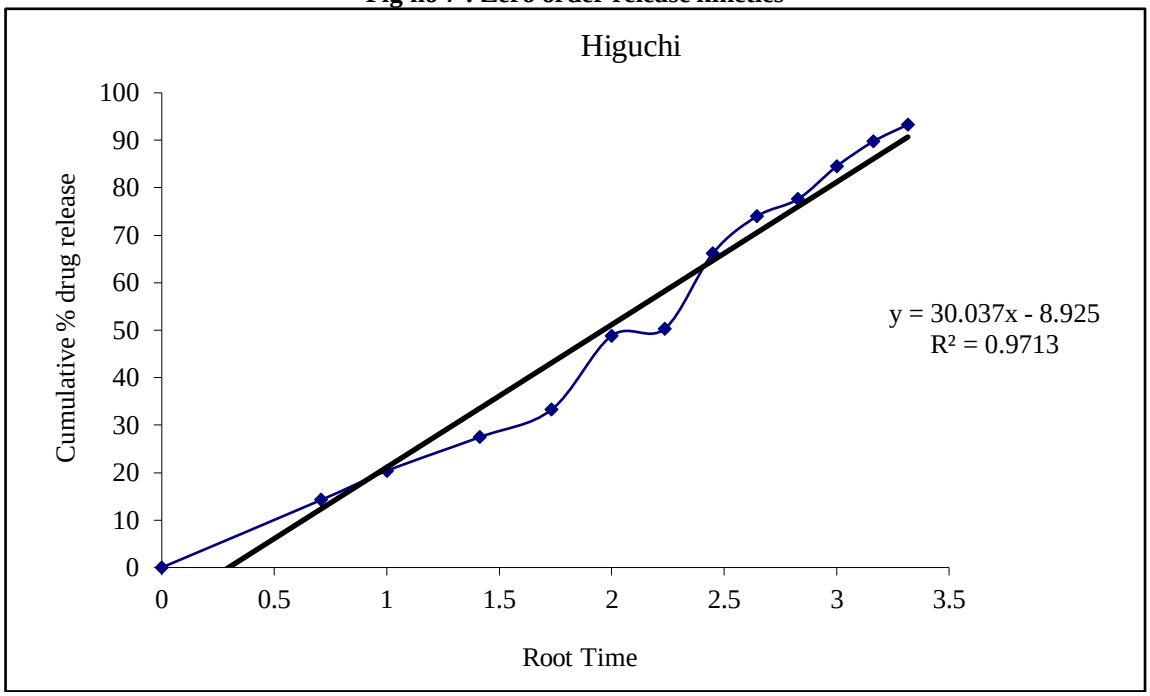

Fig no 8: Higuchi release kinetics

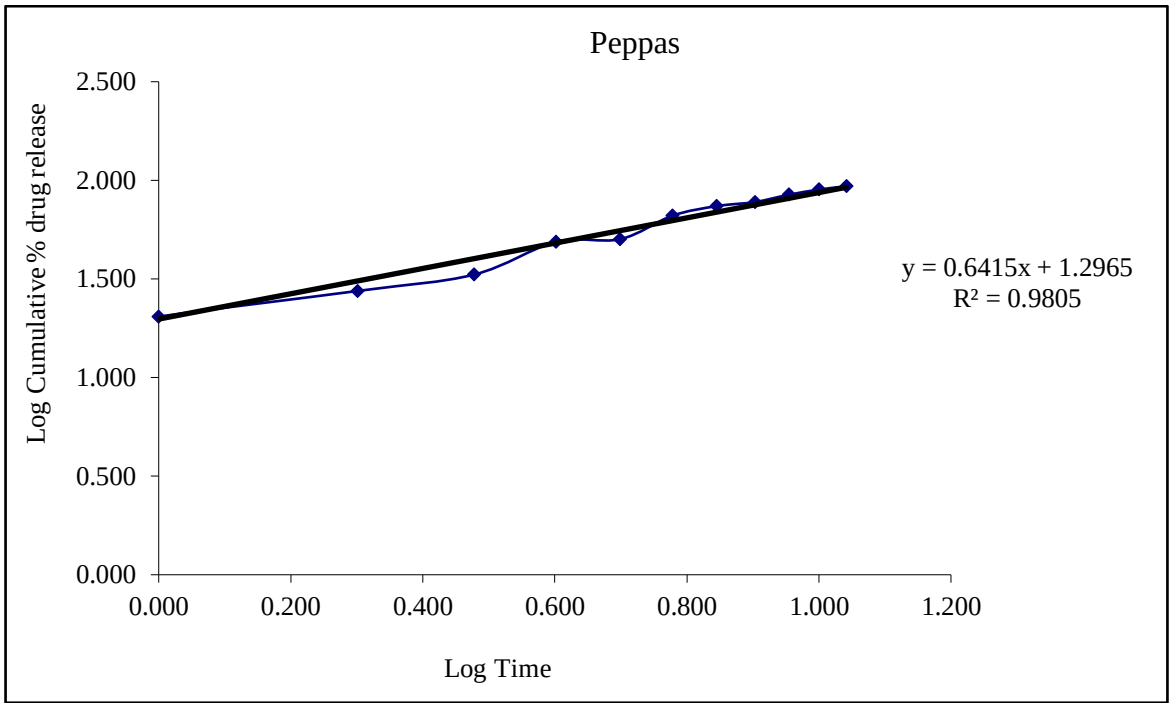

Fig9 : Kors mayer peppas release kinetics

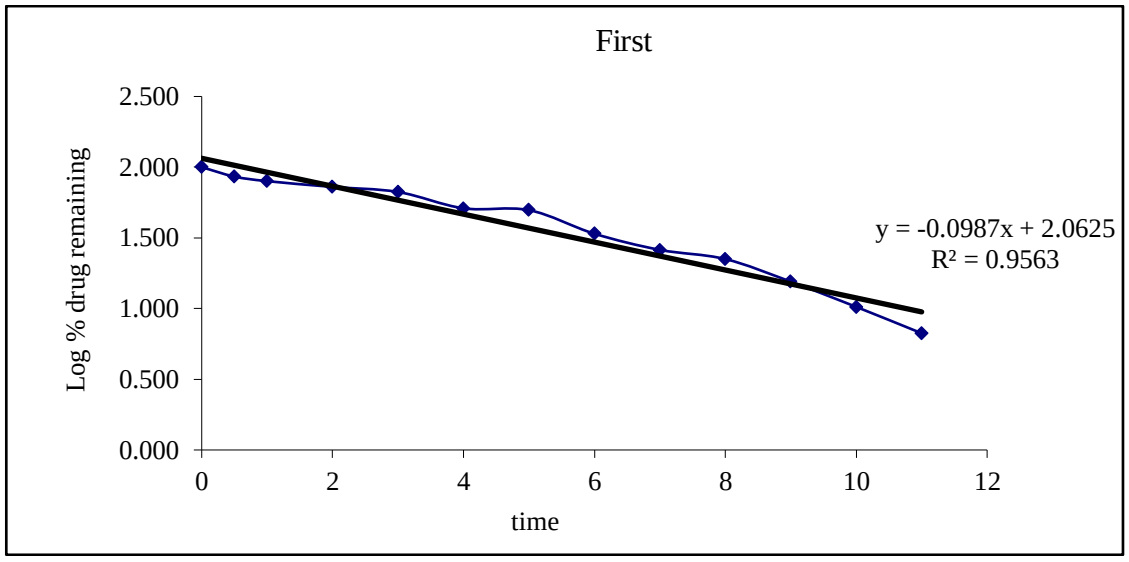

Fig10: First order release kinetics

Drug – Excipient compatibility studies

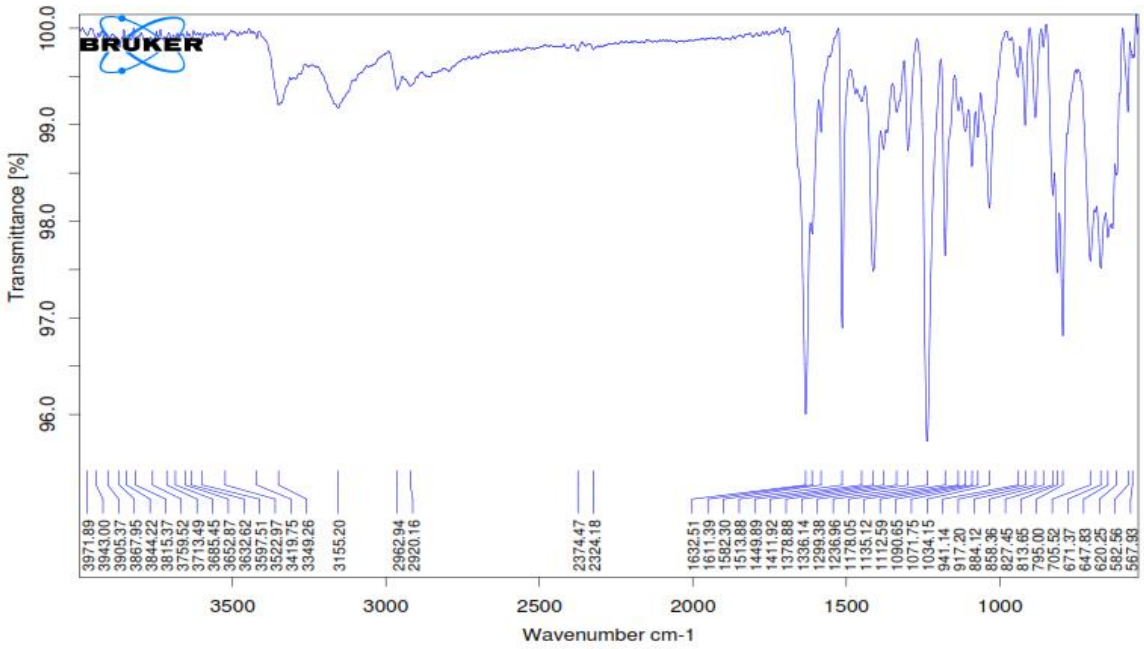

Figure 11: FTIR Spectrum of pure drug

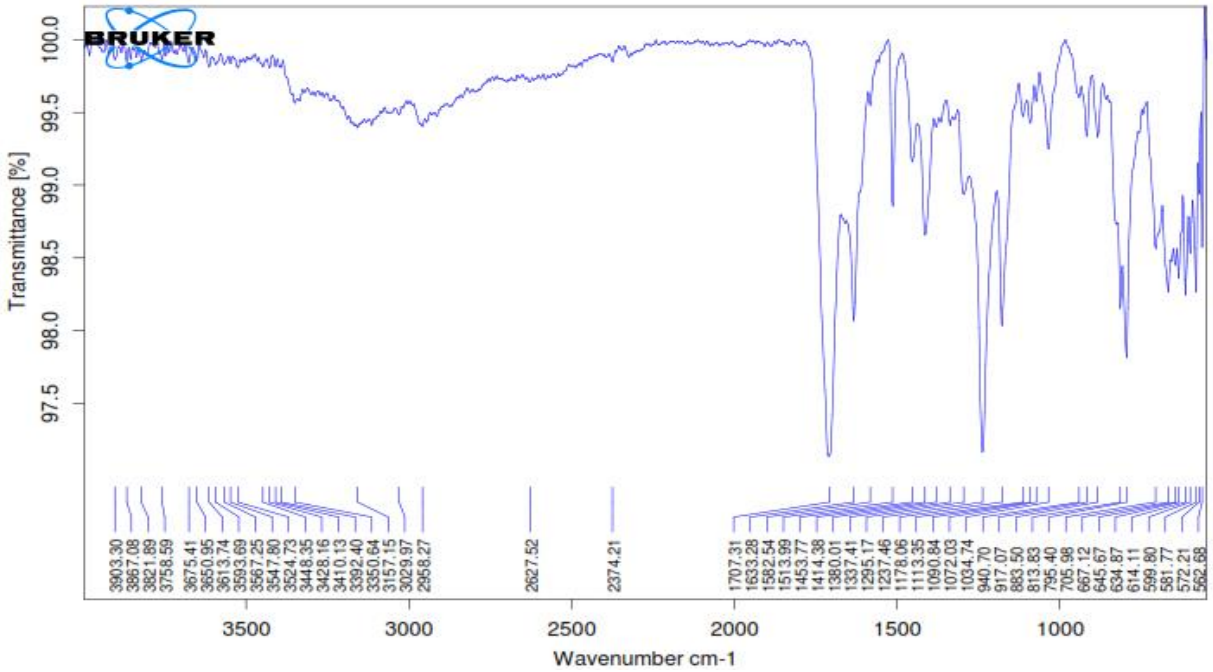

Fig 12 FTIR Spectrum of optimised formulation

CONCLUSION:

The floating tablets for Domperidone (F1-F9) were successfully prepared using Eudragit RSPO, HPMC and Carbopol 974P matrix forming polymer and Sodium bi carbonate and Citric acid as gas generating agent by direct compression method. All the pre compression and post compression parameters are in its limits. The optimized formulation F7 has shown better sustained drug release and which has good floating properties. The release profile of optimized formula, fitted best to korsemeyer peppas model mechanism.

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