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FORMULATION OF REGIOSELECTIVE FLOATING MATRIX TABLETS OF DEXTRO-METHORPHAN USING GAS FORMING TECHNIQUE AND EVALUATION

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ABSTRACT: The present study deals with the formulation and evaluation of gastroretentive floating tablets of dextromethorphan. Dextromethorphan is a highly potent and commonly used antitussive agent. It has no narcotic, analgesic or addictive properties and its potency as an antitussive agent is almost equal to that of codeine. The purpose of this research is to increase the gastric residence time by preparing gastroretentive floating tablets whereby making it available at its site of absorption and to achieve an extended action for a time period of 12 hrs. Dextromethorphan floating tablets were prepared by direct compression method using various grades of METHOCEL, POLYOX and CARBOPOL with three different concentrations. Preformulation studies were carried out and the compatibility of the drug with the excipients was confirmed through differential scanning calorimetry studies. The prepared gastroretentive floating tablets were evaluated for uniformity of weight, hardness, friability, density, drug content, floating lag time, floating time, swelling index and *in vitro* dissolution studies. The optimized formulations F3, F5 and F11 showed a floating time more than 12hrs with matrix integrity in pH 1.2. The *in vitro* release studies revealed that the drug release was sustained upto 12hrs. Optimized formulations showed no significant change in physical appearance, pre and post compression parameters and drug dissolution studies after storage at 40° C ± 2° C and 75% ± 5% relative humidity in a humidity chamber for 1 month. Using Higuchi's Model and the Korsmeyer equation, the drug release mechanism from the floating sustained release tablets was found to be Anomalous (non-Fickian) diffusion.

INTRODUCTION: Oral drug delivery is the most widely used route of administration due to its ease of administration, patient compliance and flexibility in formulation etc. From immediate release to site specific delivery, oral dosage forms have really progressed.

All controlled release drug delivery systems have limited applications if the systems cannot remain in the vicinity of the absorption site [1, 2]. A gastric floating drug delivery system (GFDDS) can overcome some of these problems and is particularly useful for drugs that;

(i) Are locally active in the stomach,
(ii) Have an absorption window in the stomach or in the upper small intestine,
(iii) Are unstable in the intestinal or colonic environment,
(iv) Exhibit low solubility at high pH values [3].

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Many approaches have been reported in literature for prolonging gastric retention time which include mucoadhesion [4], floatation [5], high-density systems [6] and modified shape systems [7, 8] or by the simultaneous administration of agents which delay gastric emptying.

Dextromethorphan hydrobromide (DXM) is an antitussive drug, which has similar effect to codeine and has no analgesic or addictive action. DXM has central action on the cough center in the medulla and it is also used in the treatment of respiratory disorders. It is generally used as an ingredient in cough and cold remedies [9].

Adult dose of DXM is 10-30 mg. DXM has a short biological half-life of 2-4 hr and it is orally administered for three to four times a day. Multiple dosing may lead to fluctuations of drug in the systemic circulation and often dose related adverse effects, in turn poor compliance and inefficient therapy [10].

Therefore, sustained release dosage forms are developed to avoid repeated administration. Hence, floating sustained release tablets are formulated to increase the gastric residence time by preparing gastroretentive floating tablets whereby making it available in the upper gastrointestinal tract and to achieve an extended action for a time period of 12 hrs.

The objective of present investigation is to prepare and evaluate region selective floating matrix tablets of DXM based on gel forming polymers using hydroxypropylmethyl cellulose (K4M, K15M and K100m), carbopol (971P), polyethylene oxide which will help to retain the dosage form in the stomach. The optimized formulations were used for stability studies for three months.

MATERIALS AND METHOD:

Materials: Dextromethorphan hydrobromide was obtained from Mylan Labs, Hyderabad. Hydroxy propyl methyl cellulose (HPMC K100 M, HPMC K15 M, HPMC K4 M), Polyox WSR 303 and Carbopol 971P was obtained from Colorcon, Goa. Sodium bicarbonate and citric acid were obtained from SD Fine Chemicals, Mumbai. Avicel PH 102 (MCC) was obtained from FMC Bio Polymer, Mumbai and Magnesium stearate was obtained from Evonik, India.

METHODS:

Drug-Excipient Compatibility studies:

Differential Scanning Calorimetry: Differential scanning calorimetry is used to determine drug excipient compatibility studies and also used to observe more phase changes, such as glass transitions, crystallization, amorphous forms of drugs and polymers.

DXM, Physical mixtures of drug and excipients were analyzed by differential scanning calorimeter (Mettler Toledo, USA).The thermo grams of DXM, physical mixture of DXM with excipients were obtained at scanning rate of 20^0C/min conducted over 25-250^0C.

Preparation of DXM floating tablets: DXM floating tablets were prepared by direct compression method using hydrophilic polymer (different grades of HPMC), Polyox and Carbopol, gas generating agent (sodium bicarbonate and citric acid), MCC and magnesium stearate was used as lubricant.

All the ingredients except magnesium stearate were passed through sieve No. 40 mesh were mixed uniformly for 10 min and mixed with magnesium stearate which was previously passed through sieve No. 80.

The resultant mixture was then compressed into tablets using a sixteen station tablet compression machine (Cadmach) with 10.50mm diameter concave punches. The amount of DXM in floating tablets was kept constant at 60mg while the amount of other excipients was varied **(as shown in Table 1)**.

Determination of λ max of DXM: The UV absorption spectrum of DXM in 0.1N HCl is shown in **fig. 1**. A solution of DXM containing concentration 50µg/ml was prepared in 0.1N HCl and UV Spectrum was taken using a Shimadzu spectrophotometer and scanned between 200 to 400 nm. The maxima obtained in the graph were considered as λ_{max} for the drug. The DXM exhibited maximum at 278nm [11].

TABLE 1: FORMULATION OF DXM GASTRORETENTIVE FLOATING TABLETS (Weight in mg)

Batch	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Drug	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60
HPMC K4 M	80	100	120	…...	…...	…...	…...	…...	…...	…...	…...	…...	…...	…...	…...
HPMC K15 M	…...	…...	…...	80	100	120	…...	…...	…...	…...	…...	…...	…...	…...	…...
HPMC K100 M	…...	…...	…...	…...	…...	…...	80	100	120	…...	…...	…...	…...	…...	…...
Polyox WSR 303	…...	…...	…...	…...	…...	…...	…...	…...	…...	80	100	120	…...	…...	…...
Carbopol 971P	…...	…...	…...	…...	…...	…...	…...	…...	…...	…...	…...	…...	80	100	120
Sodium bicarbonate	35	35	35	35	35	35	35	35	35	35	35	35	35	35	35
Citric acid	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Avicel PH 102	164.5	144.5	124.5	164.5	144.5	124.5	164.5	144.5	124.5	164.5	144.5	124.5	164.5	144.5	124.5
Magnesium stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Total	350	350	350	350	350	350	350	350	350	350	350	350	350	350	350

Note: HPMC: Hydroxy methyl cellulose

Characterization of Floating tablets:

Assay of Drug Content: Ten tablets from each formulation were powdered. The powdered sample equivalent to 60mg of drug was transferred to a 100ml volumetric flask. Required amount of media was added, mixed and filtered; the filtrate was suitably diluted with media and analyzed against blank by UV spectrophotometer at 278nm for DXM (Shimadzu UV-1700).

Hardness of the tablets: Ten tablets were measured in the hardness examination. The hardness was examined using a Schleuniger hardness tester, Switzerland

Friability of the tablets: Twenty tablets of the formulation were weighed and measured in a Roche type friabilator (Electrolab, Mumbai). The tablets were rotated at 25rpm for 4min, and the samples were then reweighed. The percentage friability was calculated using the equation:

$$\%\text{Friability} = [(W_1-W_2)/W_1] \times 100$$

Where, W_1= weight of tablets before test, W_2 = weight of tablets after test

Where %Friability represents the percentage weight loss, and W1 and W2 are the initial and final tablets weights, respectively.

***In vitro* buoyancy studies:**

Floating lag time and floating time: The floating lag time and the floating time were determined in dissolution apparatus II (Electrolab, Mumbai) in an acid environment (i.e. 0.1N Hydrochloric acid). The time interval between the introduction of the tablet into the dissolution medium and its buoyancy to the top of dissolution medium was taken as floating time and the duration for which the system was floating was observed visually [12].

Matrix integrity: The swollen mass of the tablets remained intact or not was checked [13]. Matrix integrity was observed throughout *in vitro* dissolution studies.

Swelling index: The swelling behavior of dosage forms can be measured by studying its dimensional changes, weight gain, or water uptake. The swelling property of the formulation was determined by various techniques. The study is performed by immersing the tablets in 0.1 N HCl at 37±5°C and determining these factors at regular interval [14]. Water uptake (Q) is measured in terms of percent weight gain and it calculated using the formula given below,

$$Q = \frac{100(W_w - W_i)}{W_i}$$

Where, W_w is the mass of the hydrated sample and W_i is the initial dry sample weight.

Tablets were removed at intervals of 2, 4, 6, and 8 h, excess water was blotted, and tablets were weighed. Water uptake is measured in terms of percent weight gain.

***In vitro* Drug release:** The *in vitro* drug release was studied by performing dissolution test for the tablets. The dissolution studies for the prepared formulation were conducted for a period of 12 hrs using an Electro lab model dissolution tester USP Type-2 apparatus (rotating paddle) set at 50 rpm and a temperature of 37± 0.5°C formulation was placed in the 500ml of the medium. At specified intervals 5ml samples were withdrawn from the dissolution medium and replaced with fresh medium to keep the volume constant. The absorbance of the sample solution was analyzed at 278 nm[15] for the presence of DXM, using a UV-visible spectrophotometer. Three replicates for each experiment were obtained.

Kinetic modeling of Drug Release: The dissolution of all the batches of floating tablets of DXM was carried out. Kinetic model has described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release from the tablets, drug release data was analyzed according to zero order, first order, Higuchi square root, Korsmeyer's- Pappas model. The criteria for selecting the most appropriate model were chosen on the basis of goodness of fit test [16, 17, 18].

Stability Studies: To assess the physical and chemical stability of the floating tablets, stability studies were conducted for 3 month under different storage conditions mentioned in ICH guidelines. The sample containing optimized formulation were placed in vials and stored at 40°C/75%RH. After 90 days the formulations was checked for physical appearance and drug content [19].

Fourier Transform Infrared Spectroscopy (FTIR) studies: DXM, physical mixtures and optimized formulations were subjected for FTIR analysis. The samples were prepared on KBr-press (Startech Lab, India). The samples were scanned over a range of 4000-400 cm^{-1} using Fourier transformer infrared spectrophotometer. Spectra were analyzed for drug polymer interactions [20].

RESULTS AND DISCUSSION:

Drug-Excipient Compatibility studies: The DSC endotherms of drug with various excipients such as HPMC K4 M, HPMC K15 M, HPMC K100 M, PEO WSR 303, Carbopol 971P, Sodium bicarbonate, Citric acid, Avicel PH 102, Magnesium stearate showed no change in melting point of the drug and no additional peaks were observed indicating compatibility of drug with the excipients **(as indicated in fig. 1 to fig. 10)**. However, sharp melting peaks were observed for the drug indicating the crystalline nature of drug. Based on the visual observation of drug excipient compatibility studies and DSC studies, it can be presumed that all the excipients were compatible with the drug. The observed onset, peak and endset values obtained from endotherms were tabulated in **table 2**.

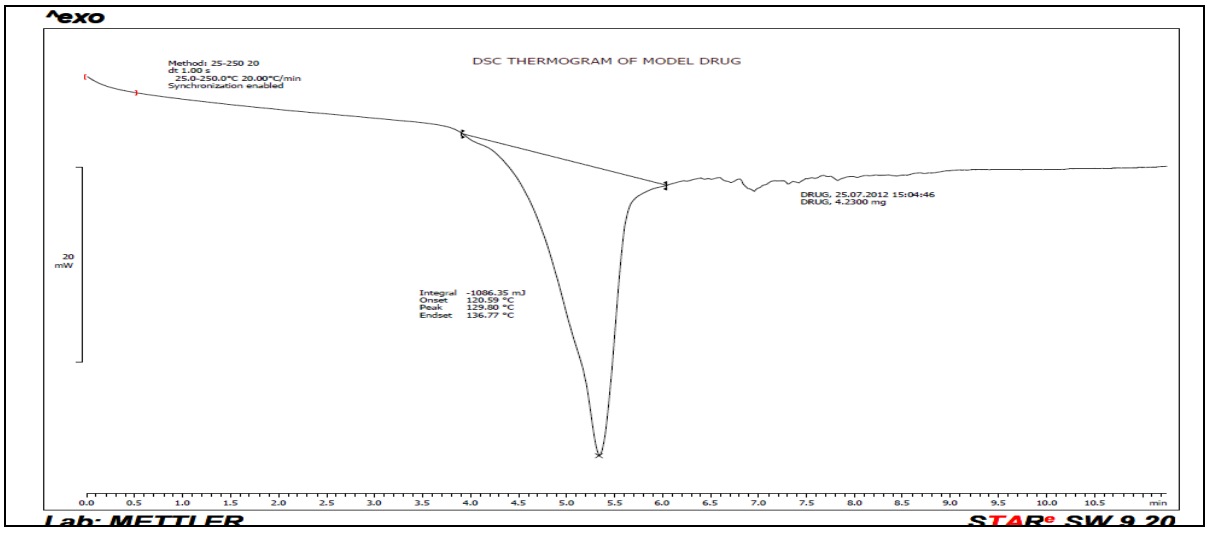


FIG. 1: DSC THERMOGRAM OF DXM

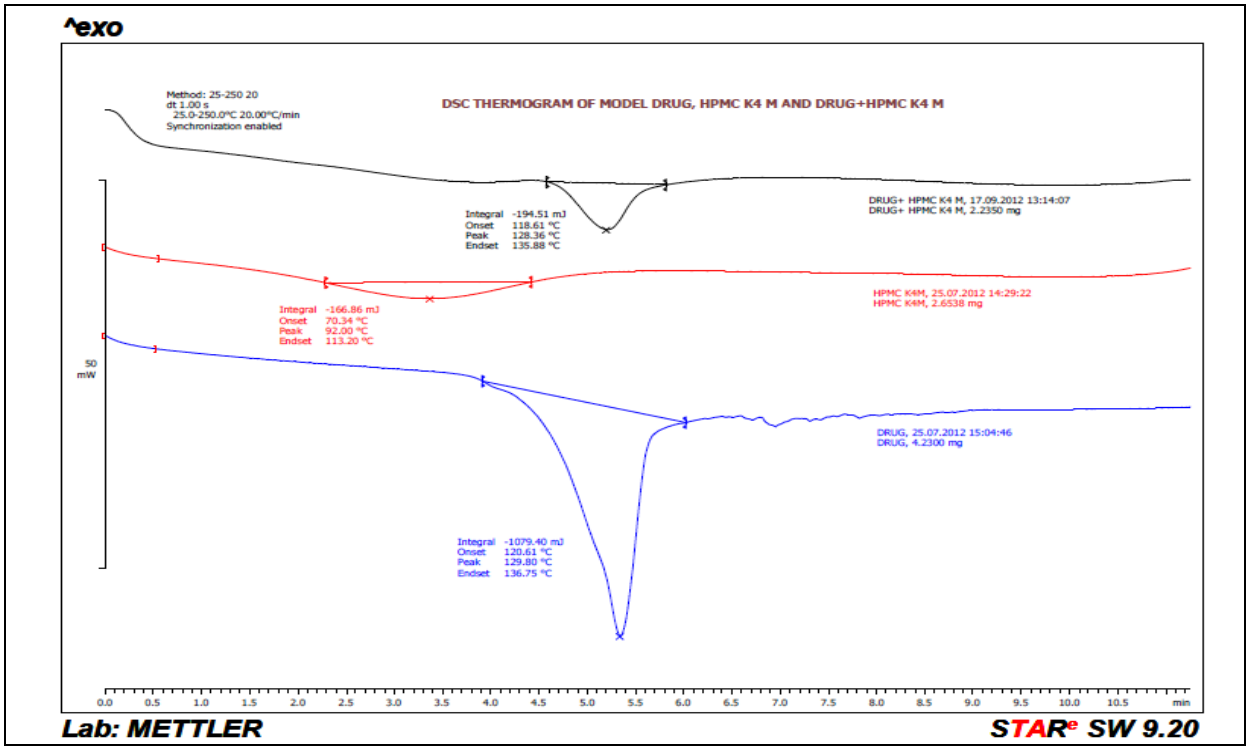


FIG. 2: DSC THERMOGRAM OF DXM, HPMC K4 M & DXM+ HPMC K4 M

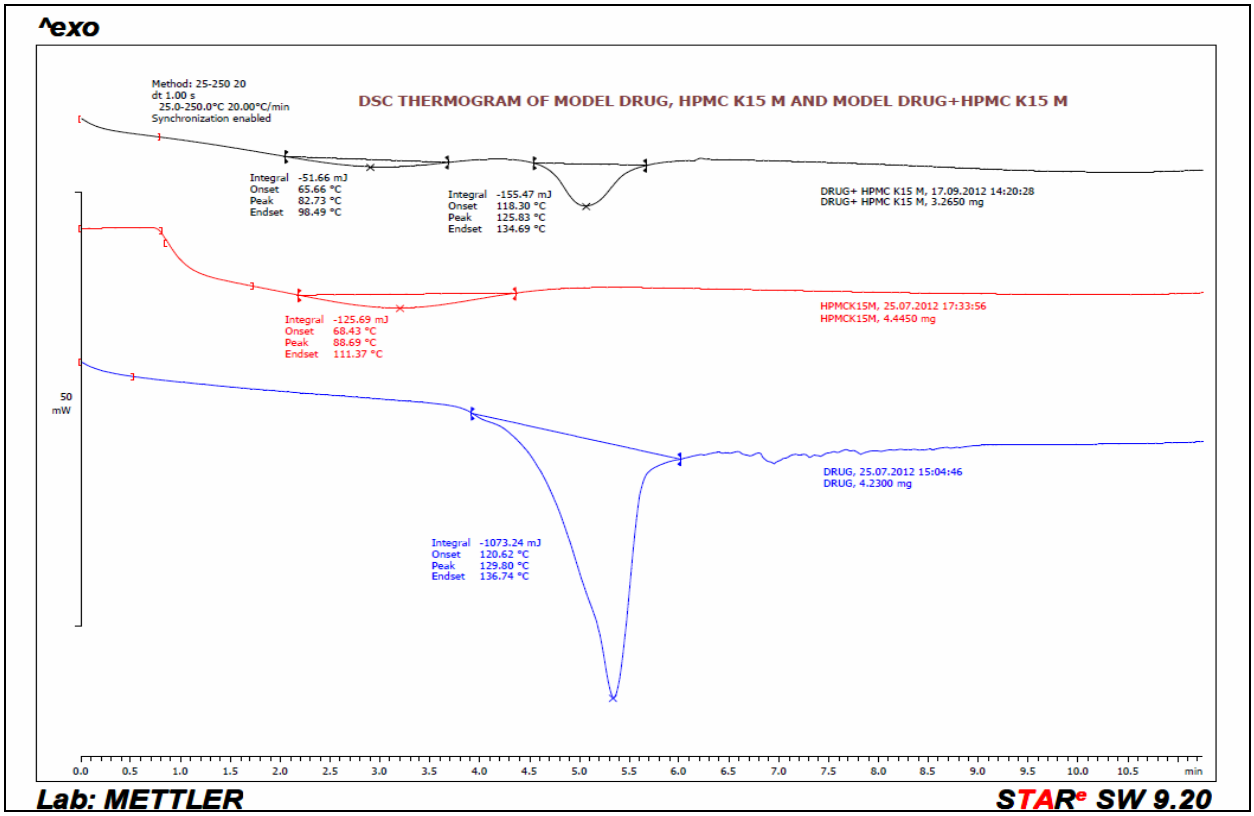


FIG. 3: DSC THERMOGRAM OF DXM, HPMC K15 M & DXM+ HPMC K15 M

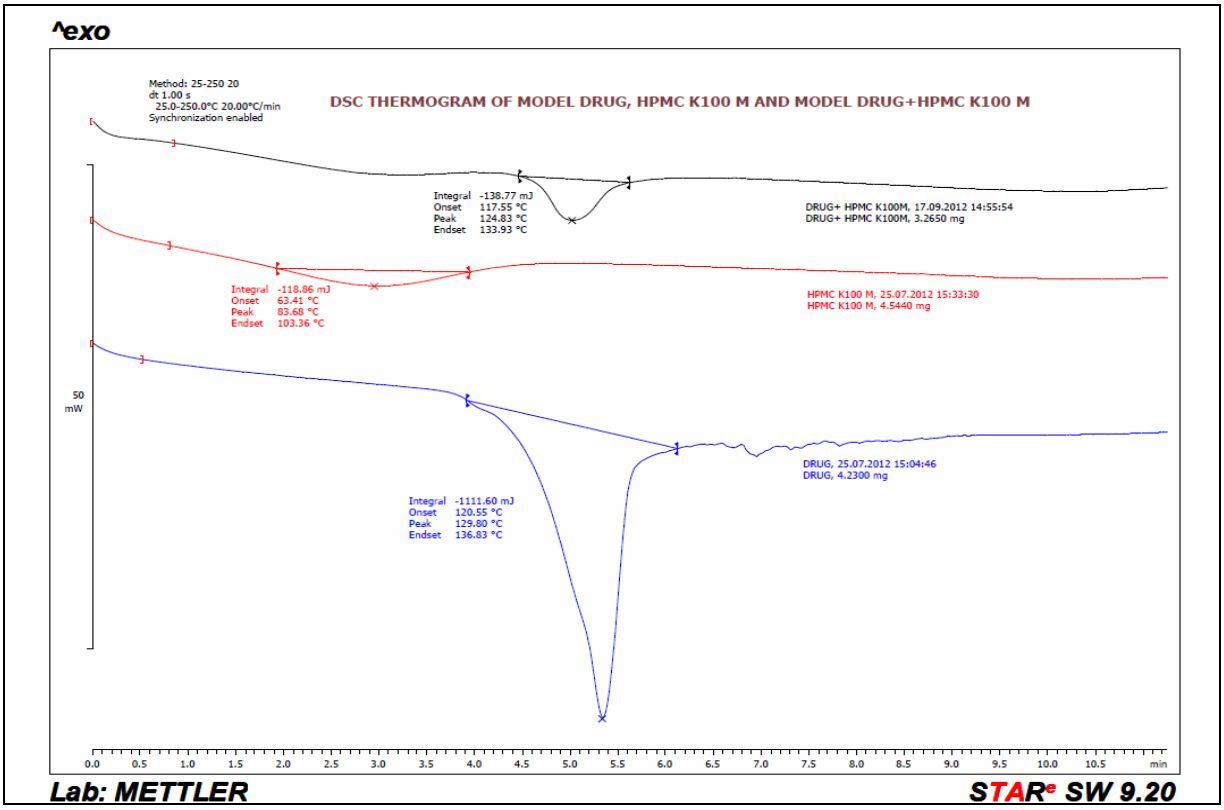


FIG. 4: DSC THERMOGRAM OF DXM, HPMC K100 M & DXM+ HPMC K100 M

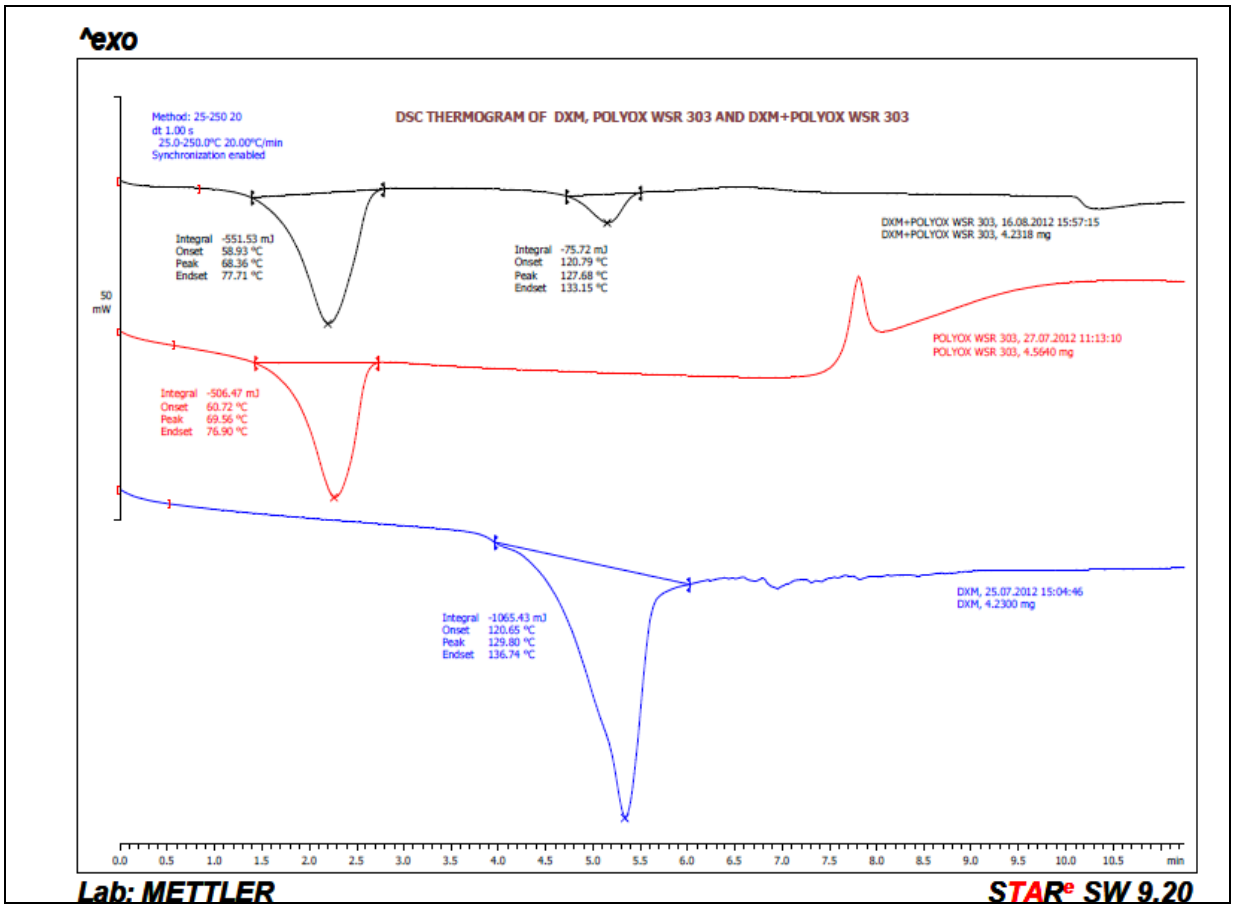


FIG. 5: DSC THERMOGRAM OF DXM, POLYOX WSR 303 & DXM+ POLYOX WSR 303

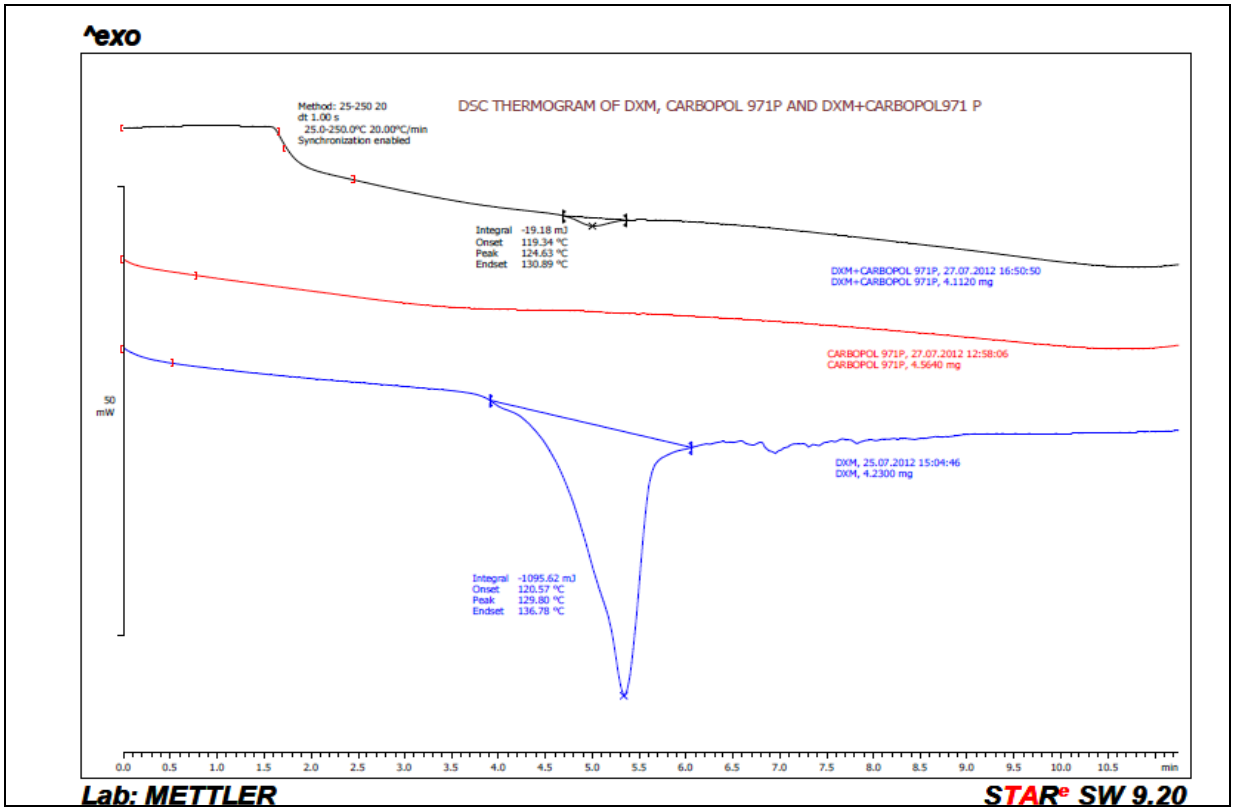


FIG. 6: DSC THERMOGRAM OF DXM, CARBOPOL 971P & DXM+ CARBOPOL 971P

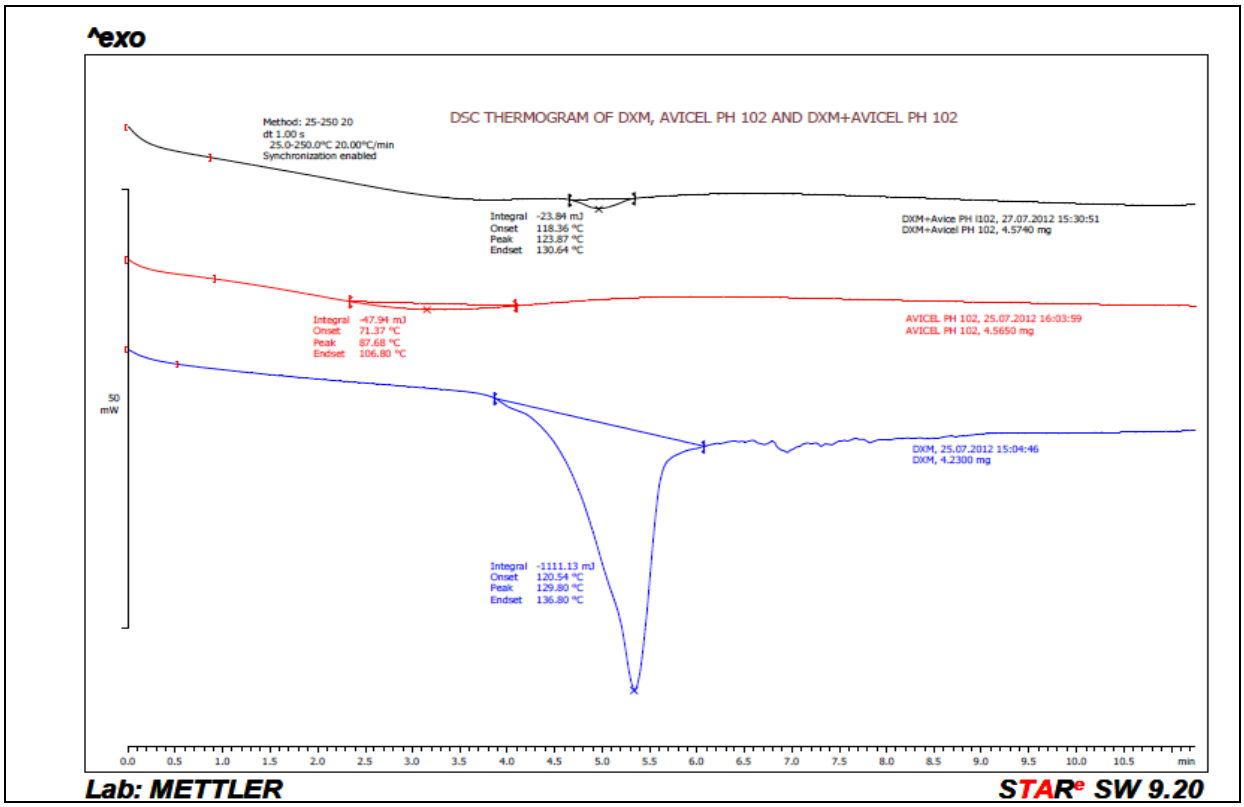


FIG. 7: DSC THERMOGRAM OF DXM, AVICEL PH 102 & DXM+ AVICEL PH 102

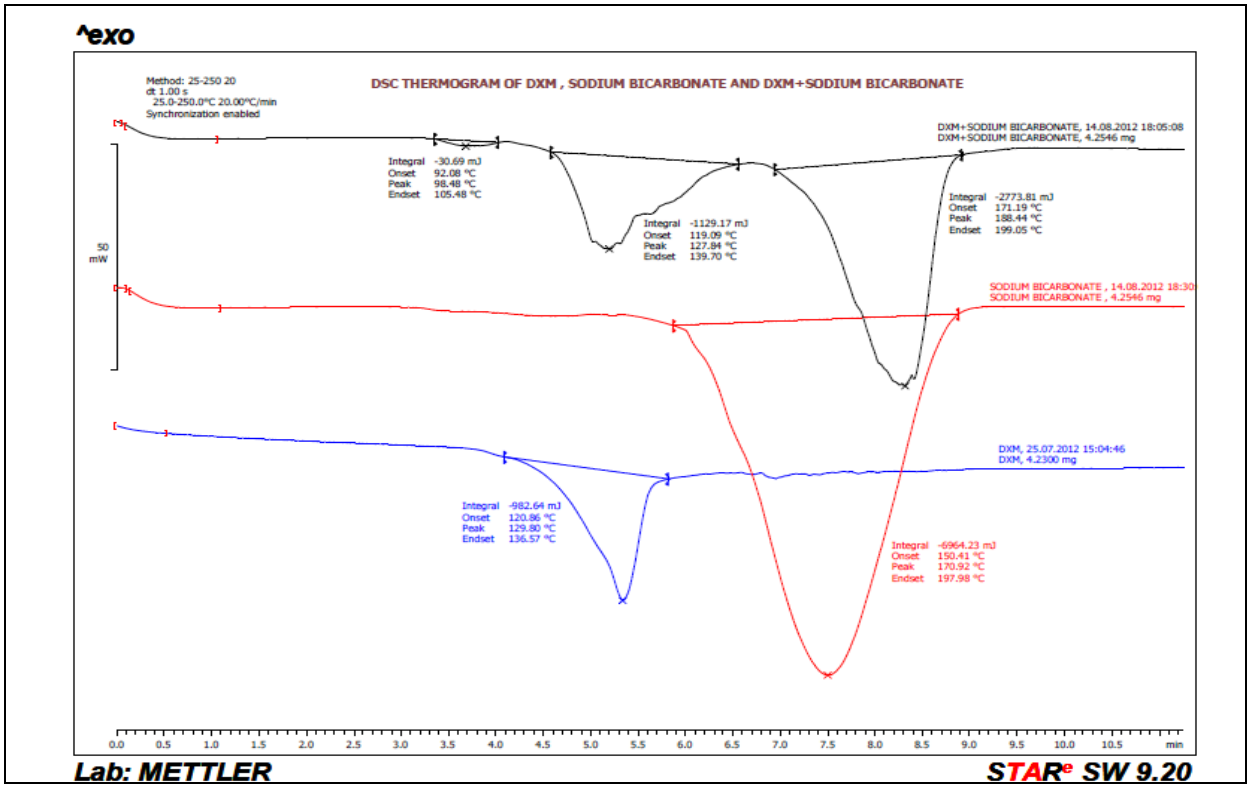


FIG. 8: DSC THERMOGRAM OF DXM, SODIUM BICARDONATE & DXM+ SODIUM BICARBONATE

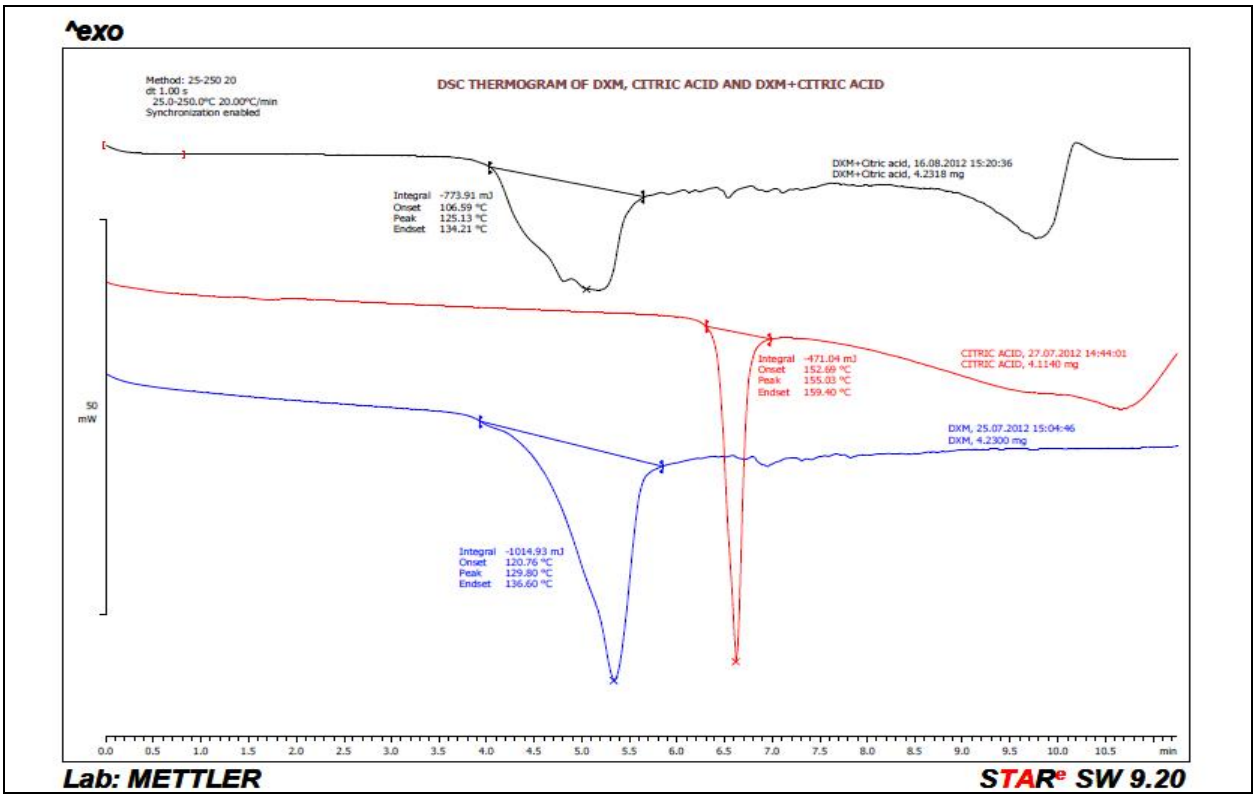


FIG. 9: DSC THERMOGRAM OF DXM, CITRIC ACID & DXM+ CITRIC ACID

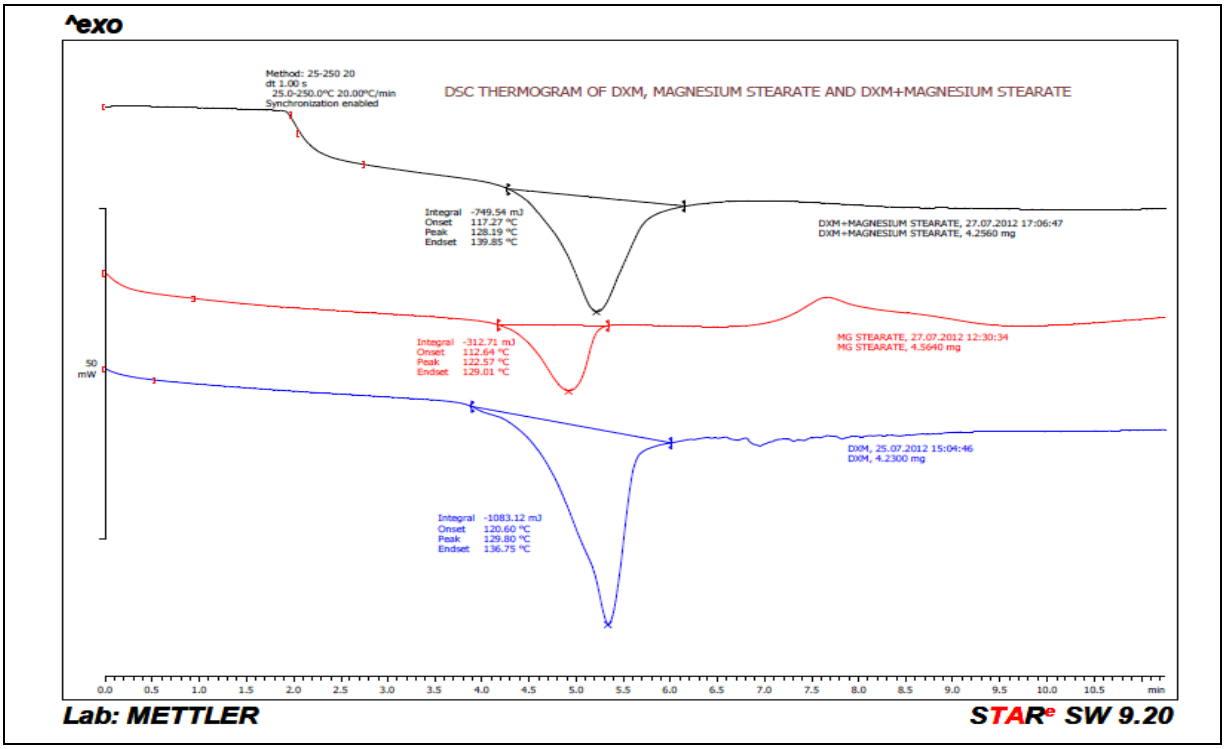


FIG. 10: DSC THERMOGRAM OF DXM, MAGNESIUM STEARATE & DXM+ MAGNESIUM STEARATE

TABEL 2: ONSET, PEAK AND ENDSET VALUES OBTAINED FROM VARIOUS THERMOGRAMS

S. No.	Ingredients	Onset values	Peak values	Endset values
1	Dextromethorphan	120.59	129.8	136.77
2	Dextromethorphan + Methocel K4 M	118.61	128.36	135.88
3	Dextromethorphan + Methocel K15 M	118.30	125.83	134.69
4	Dextromethorphan + Methocel K100 M	117.55	124.83	133.93
5	Dextromethorphan + Polyox WSR 303	120.79	127.68	133.15
6	Dextromethorphan + Carbopol 971P	119.34	124.83	130.89
7	Dextromethorphan + Sodium bicarbonate	119.09	127.04	139.70
8	Dextromethorphan + Citric acid	106.59	125.13	134.21
9	Dextromethorphan + Avicel PH 102	118.36	128.87	130.64
10	Dextromethorphan + Magnesium stearate	117.24	128.19	139.85

Formulation optimization:

Effect of viscosity of HPMC: HPMC is a hydrocolloid gelling agent. Upon contact with gastric fluid, HPMC takes up water and swell, which retarded the drug release. As the increase in volume is greater than the increase in mass during swelling, the density decreases and the systems start to float.

The effect of viscosity of HPMC was studied using drug release pattern and it is represented in **fig. 11.** The viscosity studies of HPMC (K4M, K15M, K100M) were done at a fixed quantity of 120mg/tablet.

As the viscosity was increased from K4M to K100M the drug release decreased and the drug release at the end of 12th hour was 100.1±0.97, 94.8±1.20 and 71.3±1.02. This observation was also reported in other works [11].

The release rate was faster with lower viscosity grades of HPMC, probably owing to less polymer entanglement and less gel strength and also to the larger effective molecular diffusion area at lower viscosity as compared with higher viscosity grades of HPMC. Moreover, the tablets formed by the higher viscosity grade HPMC would have more gel strength than the one formed by the lower viscosity grade because of which, the erosion would be less.

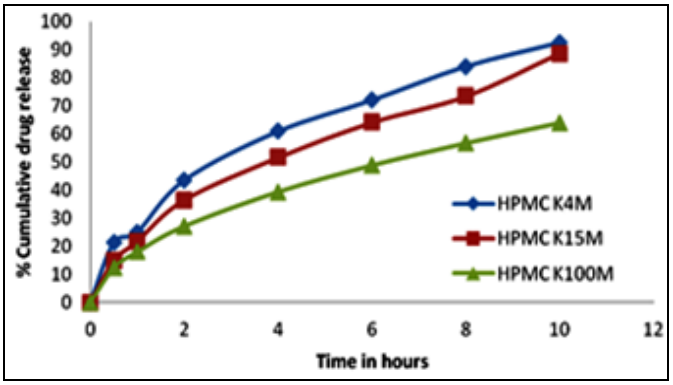


FIG. 11: EFFECT OF VISCOSITY OF HPMC ON *IN VITRO* DRUG RELEASE (n = 3). Standard deviation less than 3% in the drug release profiles

Effect of Sodium bicarbonate: Sodium bicarbonate and citric acid were employed as gas forming agent to improve *in vitro* buoyancy. The influence of sodium bicarbonate on buoyancy was noticed. When sodium bicarbonate concentration was 5%w/w, the tablets could not float at all. This might be due to the gas generated was not sufficient to keep the formulation floating.

The presence of carbon dioxide bubbles, produced after reaction of sodium bicarbonate with the acidic release medium, was protected within the gel formed by HPMC, decreasing the density of the tablet below 1 g/cm^3 and the tablet becomes buoyant. When amount of sodium bicarbonate was increased above 20%, the tablets could not retain its physical integrity. This was due to excess carbon dioxide disturbing the monolithic tablet and hence, the floating tablets were formulated using 10% w/w concentration of sodium bicarbonate.

Effect of citric acid: The pH of stomach is elevated under fed condition (~3.5). In this pH condition the floating lag time increases or sometimes the tablet cant float, hence to improve the buoyancy citric acid was added in the formulation to provide an acidic medium to sodium bicarbonate. When the concentration of citric acid was 1%w/w, the tablets could not float at all. It was observed that as the concentration of citric acid was increased up to 2% the floating lag time decreased. When the concentration of citric was above 2%w/w tablet disintegrated, thus there was no significant matrix to entrap the gas generated by effervescent mixture due to decrease in matrix integrity of the tablet. So, Floating tablets were formulated using 2%w/w concentration of citric acid.

Characteristics of DXM Floating Tablets:

Physical characteristics of DXM Floating Tablets: The floating tablets of DXM were formulated by using HPMC (K4M, K15M and K100M), PEO and Carbopol 971P as retardant polymers. Sodium bicarbonate and citric acid were used as the effervescent mixture. The floating tablets were prepared using direct compression method and prepared tablets were evaluated for physical parameters like weight variation, hardness, friability, drug content.

The weight of the tablet was 350mg and the standard deviation value (0.5) was low. The variation in weight was within the range of ±7.5% complying with pharmacopoeial specifications, indicating uniformity of weight. The hardness of different formulations was found to be in between 4.4 kg/cm^2 -5.6kg/cm^2. The friability of the floating tablet was found to be in the acceptable limits (below 1%, w/w), which was an indication of good mechanical resistance of the tablets. The drug content was in between 99.5-100.9% in different batches with low coefficient of variation (C.V. < 1.0%), indicating content uniformity in the prepared batches. All the values are tabulated in **table 3**. All the parameters lie within the limits.

The floating lag time and the total floating time: All the tablets were prepared by effervescent approach. Sodium bicarbonate was used as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium (0.1 N hydrochloric acid). The pH of the stomach is elevated under fed condition (~3.5); therefore citric acid was incorporated in the formulation to provide an acidic medium for sodium bicarbonate.

Hence, the combination of sodium bicarbonate and citric acid provided desired floating ability and therefore this combination was selected for the formulation of the floating tablets. It was observed that the gas generated is trapped and protected within the gel, formed by hydration of polymer (methocel), thus decreasing the density of the tablet below 1gm/cm^3 and tablet becomes buoyant. The tablet swelled radially and axially during *in vitro* buoyancy studies. All the batches of tablets were found to exhibit short floating lag times in the artificial gastric fluid and the floating time of all

the formulation was more than 12h except for formulations F1, F4 and F10 (showed a floating time of 4h, 8h and 7h respectively). Formulations F13, F14 and F15 (Carbopol 971P) showed lesser floating time than 8h.

Matrix integrity of all the formulations was more than 12hours except for formulations F1 and F4 this may be due to insufficient polymer concentration to entrap the carbon dioxide produced (**table 4**).

TABLE 3: PHYSICO-CHEMICAL CHARACTERIZATION OF DXM FLOATING TABLETS

Formulae	Weight of Tablet (mg) ±SD	Thickness (mm) ±SD	Density (g/cc)	Hardness (kp) ±SD	Friability (%)	Drug content (%) ±SD
F1	350.9±0.5	4.75±0.05	0.897	4.5±0.03	0.390	100.54±0.73
F2	350.89±0.2	4.71±0.02	0.897	4.8±0.01	0.415	99.54±0.78
F3	349.9±0.5	4.69±0.03	0.88	4.4±0.12	0.426	99.68±0.58
F4	349.2±0.3	4.62±0.04	0.897	4.4±0.09	0.524	99.77±0.51
F5	350.3±0.8	4.66±0.05	0.872	4.9±0.01	0.541	100.9±0.78
F6	351.2±0.1	4.62±0.04	0.895	4.8±0.19	0.390	99.95±0.68
F7	349.7±0.8	4.62±0.08	0.884	4.5±0.06	0.344	99.98±0.91
F8	350.2±0.3	4.75±0.02	0.888	4.7±0.05	0.314	100.09±0.38
F9	351.6±0.3	4.61±0.06	0.865	4.5±0.05	0.325	100.5±0.56
F10	350.4±0.2	4.68±0.04	0.844	4.3±0.09	0.076	100.5±0.28
F11	349.9±0.5	4.69±0.02	0.858	4.5±0.08	0.072	100.9±0.69
F12	349.3±0.5	4.67±0.05	0.872	4.2±0.22	0.066	99.54±0.89
F13	350.6±0.3	5.54±0.05	0.765	5.6±0.19	0.050	100.67±0.12
F14	350.4±0.3	5.53±0.02	0.745	5.4±0.23	0.040	100.56±0.94
F15	349.6±0.2	5.56±0.05	0.726	5.6±0.06	0.060	99.64±0.91

n= ±3

TABLE 4: FLOATING PROPERTIES OF FORMULATIONS

Formula	Floating lag time (sec's)	Floating time (hrs)	Matrix integrity
F1	15±0.11	4	-
F2	56±0.21	10	+
F3	72±0.41	12	+
F4	69±0.51	8	-
F5	88±0.59	12	+
F6	180±0.23	12	+
F7	68±0.08	12	+
F8	90±0.56	12	+
F9	200±0.51	12	+
F10	30±0.09	7	+
F11	96±0.15	12	+
F12	182±0.51	12	+
F13	2±0.11	4h 30min	+
F14	2±0.15	5 h 48min	+
F15	3±0.16	8	+

n= ±3

Swelling studies: The swelling studies were performed in 0.1N Hydrochloric acid. The percent swelling of the tablet was determined by the method described in Section 2.6.3 at different time intervals. The complete swelling was achieved by the end of 8h, so percent swelling was determined at the end of 8 h for all the developed formulations. As the concentration of polymer increased in the tablet the rate of swelling also increased. The swelling studies for HPMC polymers (K4M, K15M, K100M) inferred that the formulations F7, F8 and F9 showed highest amount of swelling, this may be due to high viscosity of the HPMC K 100M. The formulations containing less amount of polymer concentration such as F1 and F4 showed erosion and this may be due to inability of the polymer to withstand the carbon dioxide produced with effervescent mixture. Among all the formulations F12 showed highest amount of swelling, this may be due to the high swelling ability of polyethylene oxide compared to HPMC and Carbopol. A graph was plotted using %swelling index and formulation code as shown in **fig. 12**.

In all the set of formulations the percentage swelling index increased with increase in the polymer concentration.

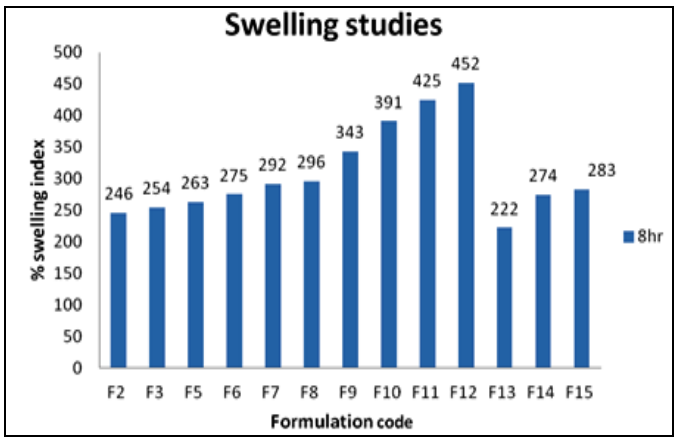


FIG. 12: SWELLING INDEX VALUES OF STABLE FORMULATIONS

***In vitro* release data:** From the *in vitro* release data of the batches F1 to F15, it was concluded that release from the matrix is largely dependent on the polymer swelling, drug diffusion and matrix erosion. The drug release study was carried out up to 12 hrs. The formulations low concentration of polymers in F1 & F4 could not sustain the release upto 12h.

The percentage drug release from batches F1 to F15 vary from 71.3 to 100.2%. Large concentration of high viscosity polymer (HPMC K100M) induces the formation of strong viscous gel layer that slowed down the rate of water diffusion into the tablet matrix, which may result in the retardation or decreases the drug release (F7-F9). The formulation F13-F15 (Carbopol 971P) could sustain the drug release but failed to remain in floating condition. The drug release data from the dissolution profiles for all batches were shown in (**Figure 13 & 14**) and *in vitro* dissolution data is tabulated in **table 5**.

TABLE 5: *IN VITRO* DRUG RELEASE FOR FORMULATIONS

S. No.	% Drug release								
	0 hr	0.5hr	1hr	2hr	4hr	6hr	8hr	10hr	12hr
F1	0	68.7±1.02	80.6±0.95	91.6±2.86	**99.9**±1.11	……	…..	…	….
F2	0	24.6±1.06	28.5±1.08	36.7±20.5	59.7±0.86	66.3±1.56	86.7±1.22	**99.8**±1.05	…..
F3	0	21.4±1.55	25.1±.086	43.5±0.84	60.9±2.62	66.0±2.84	84.0±2.01	92.5±1.22	**100.1±0.97**
F4	0	38.8±2.45	59.3±1.54	68.6±1.44	80.5±0.95	88.5±1.26	**99.8±.096**	…….	……
F5	0	19.7±0.96	29.7±1.11	48.3±1.56	58.9±0.84	68.2±2.56	86.2±1.11	95.9±2.06	**100.2±1.44**
F6	0	14.9±2.11	21.8±.096	44.5±1.56	51.6±1.34	64.1±2.59	83.4±1.95	88.7±1.59	94.8±1.20
F7	0	24.5±1.44	32.5±1.42	41.8±1.23	52.9±1.86	62.6±1.44	70.5±2.54	77.9±1.25	83.4±2.44
F8	0	18.1±1.02	21.1±1.56	30.5±2.22	43.1±1.26	52.9±2.05	61.7±2.84	69.8±1.95	77.1±2.56
F9	0	12.33±1.84	18.0±1.56	27.1±2.07	39.3±2.26	48.7±2.69	56.6±1.59	63.8±2.09	71.3±1.02
F10	0	21.4±1.02	24.2±1.44	57.3±1.86	76.0±2.34	87.8±0.95	**99.9±1.84**	……	…..
F11	0	18.8±1.35	20.8±2.06	29.4±2.45	52.9±1.44	73.2±1.08	83.7±0.84	93.1±2.45	**100.2±0.91**
F12	0	15.7±0.84	18.5±2.45	28.8±1.84	45.2±1.65	59.7±2.44	73.8±1.59	82.5±2.07	92.7±2.22
F13	0	26.1±2.01	36.3±0.86	52.2±1.34	72.8±1.43	81.0±1.75	94.4±1.11	**100.2±0.81**	…….
F14	0	22.0±1.95	24.3±2.01	43.0±2.59	61.8±2.84	73.2±1.37	84.4±2.24	93.3±2.03	**100.1±1.11**
F15	0	18.6±0.95	21.2±1.62	33.9±2.44	58.3±1.44	67.0±1.92	79.0±0.97	84.6±1.56	91.9±2.10

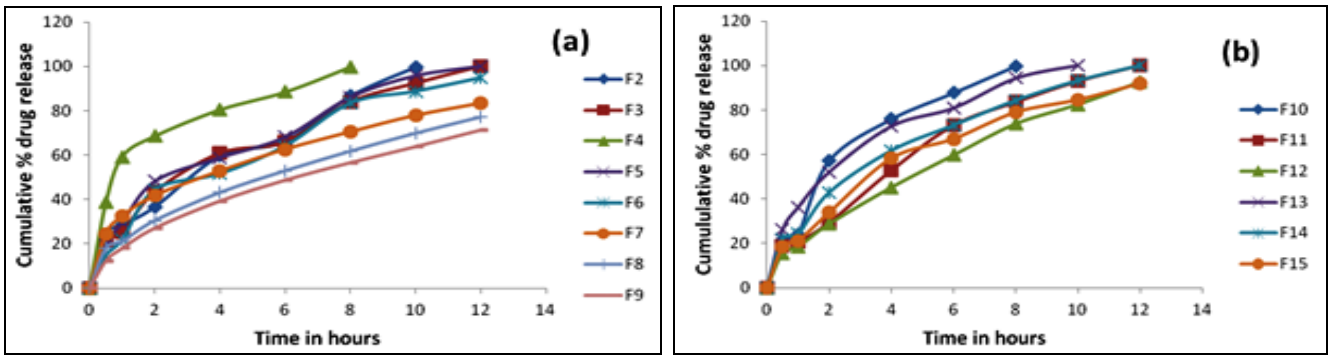


FIG. 13 AND 14: COMPARATIVE DISSOLUTION PROFILES. (A) FROM FORMULATION F2 TO F9, (B) FROM FORMULATION F10 TO F15

The optimized formulations were evaluated for drug release kinetics using zero order, first order, higuchi, Korsemeyer-Peppas and R^2 values of all the formulations were tabulated in **table 6**.

TABLE 6: EVALUATION OF DRUG RELEASE KINETICS

Batch No	R^2 values (Correlation coefficient)				
	Zero order	First order	Higuchi	Korsmeyer's- Peppas	
				R^2 value	n value
F3	0.9267	0.9559	0.9937	0.9859	0.5059
F5	0.9161	0.9163	0.9925	0.9884	0.5045
F11	0.9535	0.9713	0.9853	0.972	0.5869

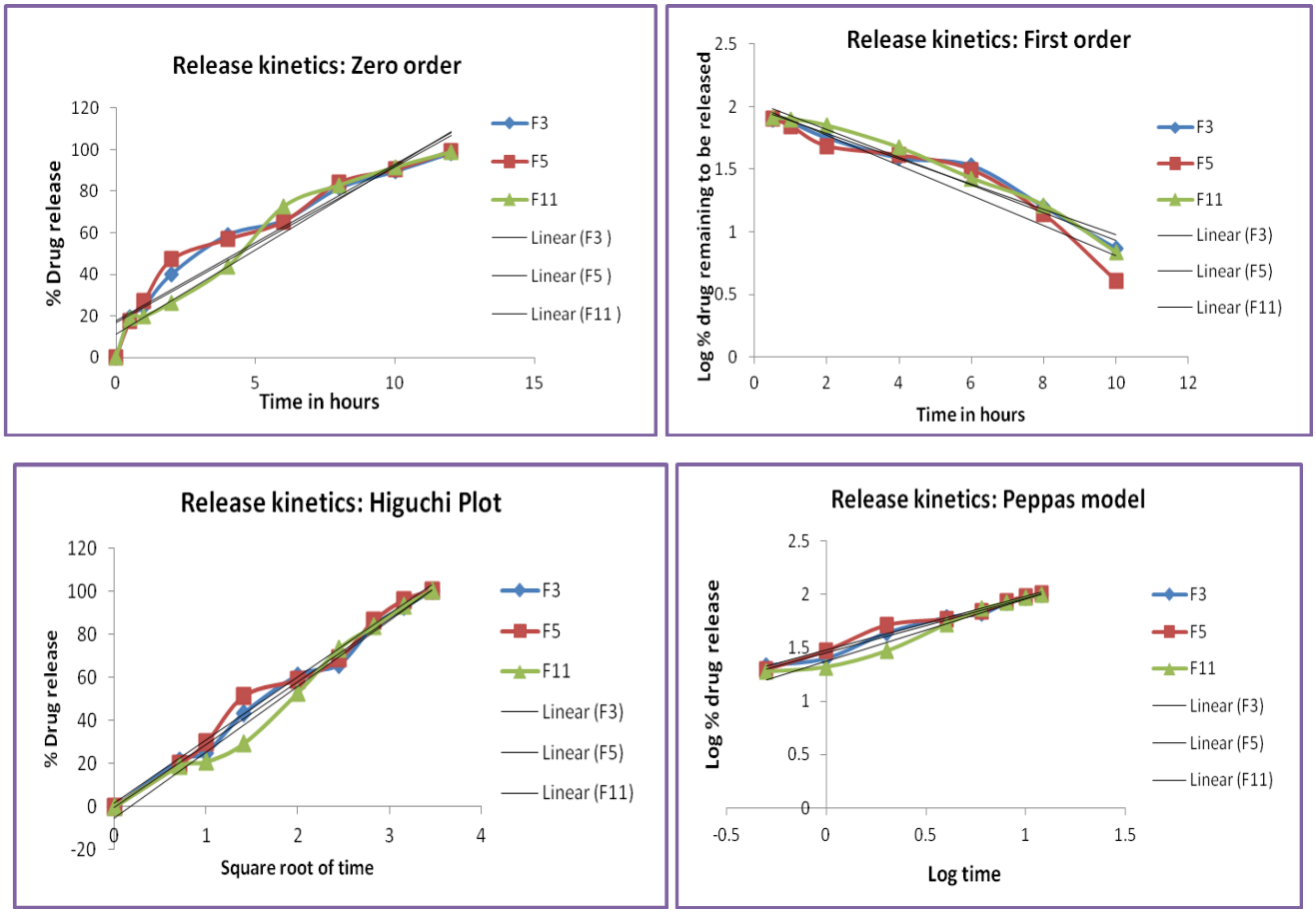


FIG. 15, 16, 17 & 18: RELEASE KINETICS OF OPTIMISED FORMULATIONS

Release kinetics of optimized formulations are shown in **figures 15-18**. F3 and, F3 and F5 were best explained by both Higuchi and Korsmeyer's-Peppas model. The release kinetics was explained by Higuchi's equation (R^2 = 0.9937, 0.9925) indicating that the release from the tablets was via diffusion. The diffusion co-efficient values obtained by Korsemeyer-Peppas model was 0.5059 and 0.5045 indicating anomalous diffusion or non-Fickian i.e. both diffusion and erosion controlled rate release and formulation F11 was best explained by both Higuchi and Korsmeyer's-Peppas model. The release kinetics was explained by Higuchi's equation (R^2 = 0.9853) indicating that the release from the tablets was via diffusion.

The diffusion coefficient values obtained by Korsemeyer-Peppas model was 0.5869 indicating anomalous diffusion or non-Fickian i.e. both diffusion and erosion controlled rate release. Stability study of optimized batches was conducted and it indicated no change in physical appearance in the dosage forms of optimized batches over a period of three months in accelerated conditions (40°C/75 % RH). The results of stability study after three months are reported in the **table 7**. The floating tablets did not show any significant change in physicochemical parameters and other tests. Thus, it was found that the floating tablets of DXM were stable under these storage conditions for at least 3 months.

TABLE 7: STABILITY STUDIES OF OPTIMIZED FORMULATIONS

Parameters	F3		F5		F11	
	Initial	3 months	Initial	3 months	Initial	3 months
Physical appearance	White color	White color	White color	White color	White color	White color
Weight of tablet (mg)	349.9±0.5	349.8	350.3±0.8	349.8±0.5	349.5±0.60	348.2±0.9
Hardness (kp)	4.5±0.103	4.5±0.100	4.9±0.23	4.85±0.11	4.56±0.10	4.23±0.12
Thickness (mm)	4.69±0.04	4.54±0.06	4.66±0.05	4.56±0.05	4.69±0.02	4.56±0.02
Drug Content (%)	99.8±0.80	99.7±0.59	100.9±0.78	100.6±0.56	100.2±0.62	99.9±0.56
Floating lag time (sec)	72±0.41	76±0.56	88±0.59	90±0.65	96±0.16	98±0.23
Floating time (h)	> 12h	>12h	> 12h	>12h	> 12h	>12h
In vitro drug release at 12h	100.1±1.44	99±1.36	100.2±1.23	100.1±0.99	100.12±1.22	100.00±1.09

FTIR Studies: The FTIR spectra of optimized formulation showed characteristic peaks same as that of the pure drug at characteristic wave numbers. This indicates that there was no interaction between drug and polymer during accelerated stability conditions.

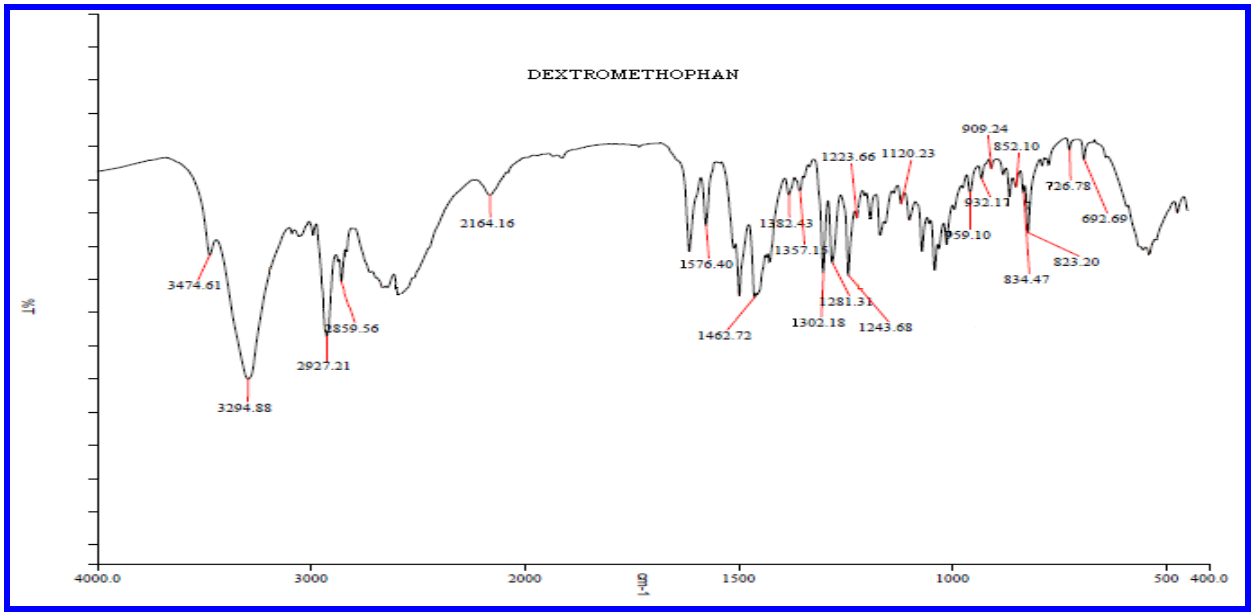


FIG. 15: FTIR SPECTRUM OF DEXTROMETHORPHAN HYDROBROMIDE

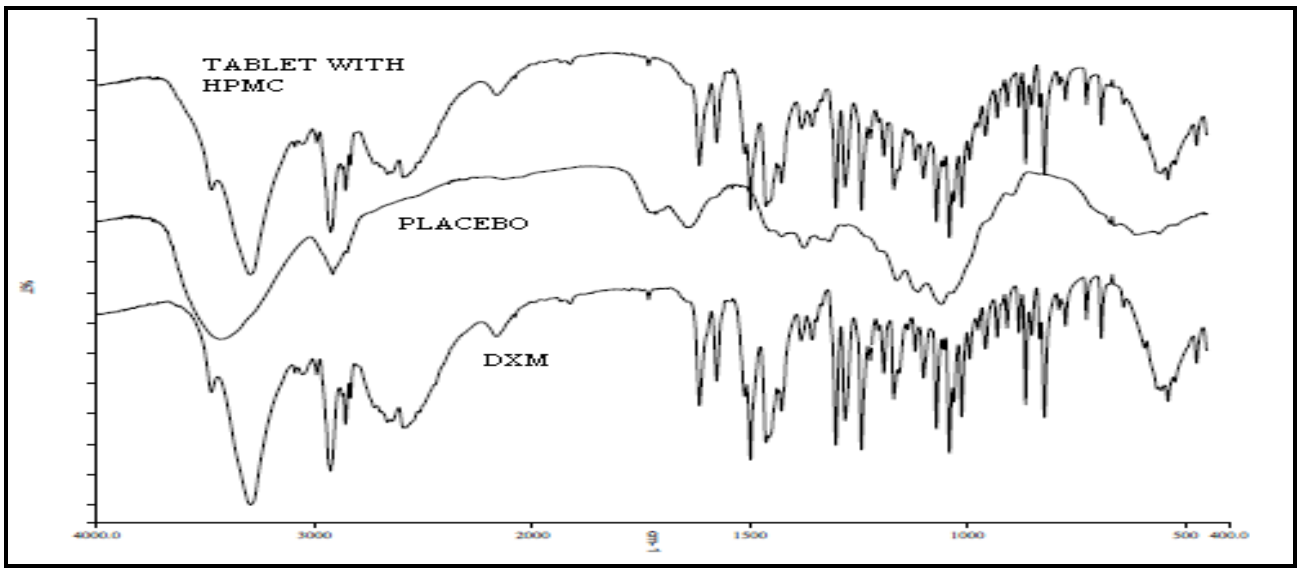


FIG. 16: IR SPECTRA OF DRUG, PLACEBO AND OPTIMIZED FORMULATION WITH HPMC

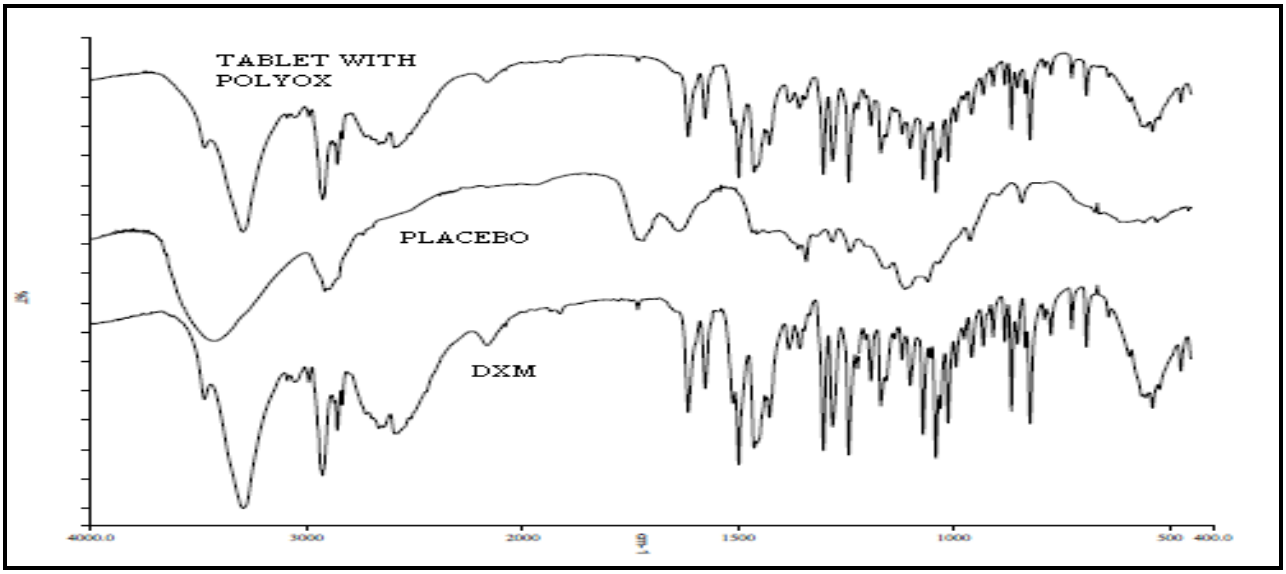
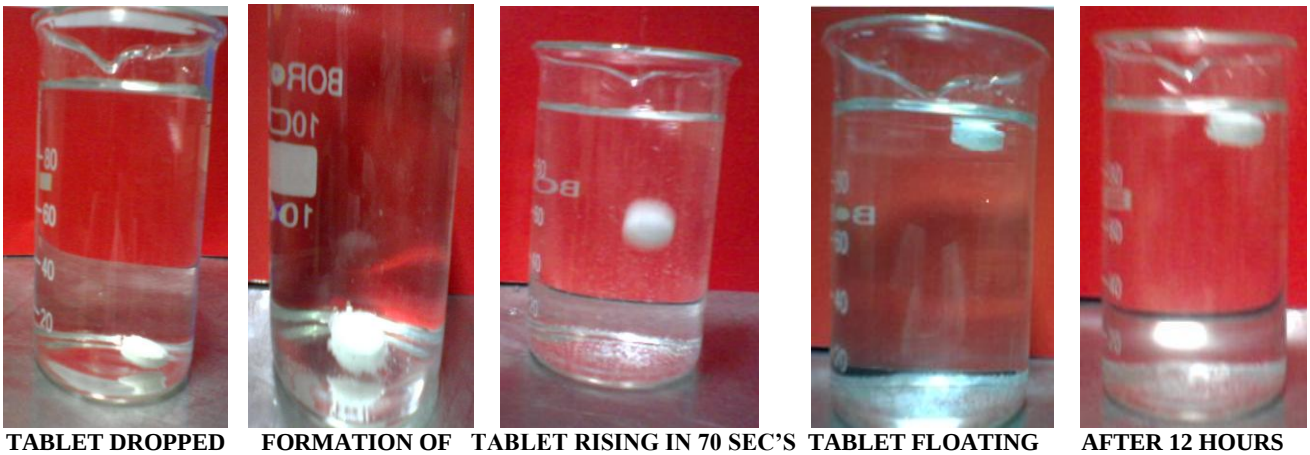


FIG. 17: IR SPECTRA OF DRUG, PLACEBO AND OPTIMIZED FORMULATION WITH POLYOX



TABLET DROPPED **FORMATION OF EFFERVESCENCE** **TABLET RISING IN 70 SEC'S** **TABLET FLOATING** **AFTER 12 HOURS**

FIG. 18: PICTURES OF OPTIMIZED FORMULATION

CONCLUSION: The region selective floating tablets of DXM were successfully formulated by effervescent technique. The Floating tablets containing HPMC K4M (F3) and HPMC K15M (F5) and PEO (F11) showed satisfactory results with short buoyancy lag time, total buoyancy time more than 12 h and controlled drug released up to 12 h. The tablets were stable at 40°C/75% RH up to 3 months. Among all the optimized formulation F3 is considered as the best formulation based on short buoyancy and release kinetics values.

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