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FORMULATION AND EVALUTION OF FLOATING TABLETS FOR INDOMETHACIN

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ABSTRACT
Indometacin, or indomethacin, is a non-steroidal anti-inflammatory medicine (NSAID with anti-inflammatory, analgesic, as well as antipyretic residential or commercial properties. Gastric transit time is beneficial possession for dosage kinds, which stay in the stomach for a long period of time than traditional dose form. The preformulation parameters like organoleptic properties, angle of repose, bulk density, tapped density, Hausner's ratio, carr's index and compressibility index of pure drug was evaluvated and complied with the pharmacopoeial specifications. FTIR studies showed there was no interaction between drug and polymer. Gastro retentive floating matrix tablets of Indomethacin were successfully prepared with hydrophilic polymers like HPMC K4M, HPMC K15M.,HPMC 100M. The formulated batches were evaluated for physicochemical parameters, floating properties and dissolution profiles. From the evaluation results, it was observed that the tablets contain the higher viscosity HPMC showed long floating lag time when compared to tablets prepared with lower viscosity HPMC. The physical properties like hardness, weight variation and friability of majority of the batches complied with the pharmacopoeial specifications. The drug content of all tablets was in the range of 95 – 100%.In vitro dissolution study of all the formulations was done in 0.1 N HCL. 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. The tablets containing HPMC K4M (F2) showed satisfactory results with short floating lag time (68 sec) total buoyancy time more than 12 h, cumulative % drug release (99.33) and controlled drug release up to 12 h. So F2 was taken for kinetic studies. The kinetic studies were carried for formulation F2 showed high regression value of 0.9877 for zero order, 0.981 for Higuchi order (conforms non- Fickian sustained release) and N value greater than 5 (conformsdiffusion controlled) with complete release in 12 hrs made it to select as an optimized formulation compared with other formulations. The accelerated stability was carried for F2 formulation and shown no much change in physical parameters and cumulative % drug release. Hence formulation F2 conformed as stable.Hence it was concluded that formulation F2 choosen as optimum formulation.

KEYWORDS: Indomethacin, floating tablets, HPMC K4M, HPMC K15M, HPMC 100M.

INTRODUCTION
Gastric transit time is beneficial possession for dosage kinds, which stay in the stomach for a long period of time than traditional dose form. Traditional dental dose forms (such as tablets, capsules) give specific medication concentration in systemic blood circulation without supplying any type of control over medicine shipment as well as additionally cause excellent changes in plasma medicine levels.[1,2] Several attempts have been made to develop sustained release preparations with prolonged scientific results as well as decreased application regularity.[3,4] Among the such method can be drifting systems which are reduced density systems that have enough buoyancy to float over the gastric contents as well as remain in the belly for a long term duration. While the system floats over the gastric materials, the medicine is launched slowly at the preferred price, which results in increased gastro-retention time as well as decreases fluctuation.[5,6] Floating medicine distribution systems have an advantage to reduce the dose frequency and boosts patient conformity. It therefore boosts the treatment.[7] The variations in plasma medicine concentration are minimized, and also hence concentration-dependent unfavorable impacts that are related to peak focus can be prevented. This function is of special importance for medicines with a narrow therapeutic index. That makes it feasible to acquire particular selectivity in the elicited pharmacological result of drugs that trigger different kinds of receptors at different focus.[8,9] Floating medication delivery systems lowers the drug concentration change over an essential concentration and also hence improves the

pharmacological effects and improves the scientific results.[10]

Indometacin, or indomethacin, is a non-steroidal anti-inflammatory medicine (NSAID with anti-inflammatory, analgesic, as well as antipyretic residential or commercial properties. NSAIDs include representatives that are structurally unrelated; the NSAID chemical classification of indometacin is an indole acetic acid by-product. The pharmacological impact of indometacin is not completely understood, nevertheless, it is thought to be mediated through powerful and also nonselective inhibition of the enzyme cyclooxygenase (COX), which is the primary enzyme in charge of catalyzes the rate-limiting action in prostaglandin and thromboxane biosynthesis via the arachidonic acid (AA) path. IUPAC name of Indomethacin is 2- [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl] acetic acid. Molecular weight is 357.78 g/mol. indomethacin was made use of as a design poorly-aqueous soluble drug because the amorphous-form has boosted dissolution residential properties over its crystalline forms. ASDs of indomethacin/polyethylene glycol (PEG) and also indomethacin/hydroxypropyl methylcellulose (HPMC) in a 1:3 wt proportion were compared.[11]

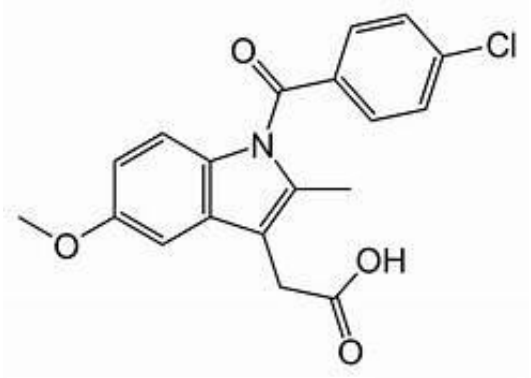

Figure 1: Chemical structure of Indometacin.

Materials

Indomethacin was purchased from Aurobindo Pharma Limited, Hyderabad, India, Hydroxypropyl methyl cellulose K4M,K15M,K100M are from Aurobindo Pharma Limited , Magnesium Stearate from Taurus Chemicals (P) Ltd. Secunderabad, Standard chemical reagents from SD fine chemical Ltd, Hyderabad. Methanol was of high performance liquid chromatography (HPLC) grade. All other reagents and solvents were of analytical reagent grade

Methodology

Pre-formulation studies

The following pre-formulation studies were performed:

- Study of organoleptic properties
- Solubility analysis
- Melting point of drug
- Drug powder characterization
- Physical compatibility studies
- Identification of drug-excipients compatibility study by FT-IR

Organoleptic properties

The Organoleptic character of the drug like colour, odour, taste and appearance play an important role in the identification of the sample and hence they should be recorded in an descriptive terminology.

Solubility Studies

It is important to know about solubility characteristics of a drug in aqueous systems, since they must posses some limited aqueous solubility to elicit a therapeutic response.

Melting point

The melting point of Indomethacin was determined by capillary method, using small quantity of Indomethacin is taken and placed in apparatus and determined the melting point and matched with standards.

Loss on drying

Determined 1.000 g by drying in an oven at 100°C to 105°C for 3 hours. Accurately weighed the substance to be tested. If the sample was in the form of large crystals, reduce the particle size to about 2 mm by quickly crushing.

The loss on drying is calculated by the formula:

$$\% \text{ LOD} = \frac{(W2-W3)}{100\ (W2-W1)} X$$

Where, W1 = Weight of empty weighing bottle
W2 = Weight of weighing bottle + sample
W3 = Weight of weighing bottle + dried sample

Drug powder characterization

Angle of repose: Angle of repose is the maximum angle of a stable slope determined by friction, cohesion and the shapes of the particles.

$\Theta = \tan^{-1} (h/r)$

Where, h = height of heap, r = radius of heap, Θ = angle of repose.

Bulk density: Bulk density is defined as the mass of the powder divided by the bulk volume.

Bulk Density = Bulk Mass / Bulk Volume

Tapped density: Tapped density is achieved by mechanically tapping a measuring cylinder containing a powder sample.

Cylinder dropping distance: 14± 2mm at a normal rate of 300 drops / minute.

Measurement of Powder Compressibility

The compressibility Index and Hausner's ratio are measures of the propensity of a powder to be compressed.

Indomethacin was mixed well with the excipients according to the formula selected for the tabletting and kept small portion of this mixed powder in cleaned and dried vials in stability chamber at 40°C±2° C / 75±5RH and room temperature. Physical observations have been carried out visually for 7 days

Drug-Excipient Compatability Studies

Fourier Transform Infrared (FTIR) Spectroscopy

The Infrared spectra of samples were obtained using by infrared spectrophotometer. Pure drug, excipients, physical mixture of drug and excipients were subjected to FTIR study. The IR spectra were obtained using KBr disk method

Construction of calibration curve

Standard graph of Indomethacin in 0.1N HCl

The stock solutions were freshly prepared by dissolving 100mg of Losartan in a 100ml volumetric flask and then made up the solution up to the mark using 0.1N HCl for obtaining the solution of strength 1000 µg/ml (stock I). 10ml of this solution was diluted to 100ml with 0.1N HCl to obtain a solution of strength 100 µg/ml (stock II). From this secondary stock required concentrations 2, 4, 6, 8, 10, 12 and 14 µg/ml is prepared. The absorbance was measured at 224 nm using a UV Spectrophotometer.

Formulation of floating matrix tablets of Indomethacin

Accurately weighed quantities of polymer and lactose were taken in a mortar and mixed geometrically to this required quantity of Indomethacin was added and mixed with the pestle. Accurately weighed quantity of sodium bicarbonate was then mixed with the drug blend. The powder blend was then lubricated with magnesium stearate and talc mixed for about 3 minutes. Finally this mixture was compressed on a 16-station rotary tablet machine using 10-mm standard flat-face punches.

Table 1: Composition of floating matrix tablets of Indomethacin.

Ingredient (mg)	Composition(mg)											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Indomethacin	50	50	50	50	50	50	50	50	50	50	50	50
HPMC K4M	75	100	125	-	-	-	-	-	-	50	-	50
HPMC K15M	-	-	-	75	100	125	-	-	-	50	50	-
HPMC K100M	-	-	-	-	-	-	75	100	125	-	50	50
$NaHCO_3$	50	50	50	50	50	50	50	50	50	50	50	50
Lactose	172	147	122	172	147	122	172	147	122	147	147	147
Mg. Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Evaluation of floating matrix tablets of Indomethacin

Tablet thickness and Diameter

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using vernier callipers.

Hardness

This test is used to check the hardness of a tablet which may undergo chipping or breakage during storage, transportation and handling. In this six tablets were selected at random and the hardness of each tablet was measured with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm^2.

Friability

The friability test was carried out to evaluate the hardness and stability instantly in Roche Friabilator. Here twenty tablets were weighed (Wo) initially and put in a tumbling and rotating apparatus drum. Then, they are subjected to fall from 6 inches height. After completion of 100 rotations i.e., 25 rpm for 4 minutes, the tablets were again weighed (w). The percent loss in weight or friability (F) is calculated by the formula

F= (1-W/Wo) x 100

F= friability

Wo= initial weight

Weight variation

This test was performed to maintain the uniformity of weight of each tablet which should be in the prescribed range. This was done by sampling randomly and weighing 20 tablets and average weight is calculated.

Content Uniformity

This test was performed to maintain the uniformity of weight of active ingredient in each tablet which should be in the prescribed range according to the Indian Pharmacopoeia.

In vitro buoyancy determination

The floating characteristics of the GFDDS are essential, since they influence the in vivo behaviours of the drug delivery system. However there seemed to be no threshold value for the floating system to remain a float under a physiological condition due to the latter's complication.

Floating Lag Time: The time taken by the tablet to emerge onto the surface of the liquid after adding to the dissolution medium at pH 1.2, temperature 37 ± 0.5˚C, paddle rotation at 50 rpm.

Total Floating Time: The time taken by the tablet to float constantly on the surface of the gastric fluid, at pH 1.2, temperature 37 ± 0.5˚C, paddle rotation at 50 rpm.

Buoyancy / Floating Test

The in vitro buoyancy was determined by floating lag time, as per the method described by a Rosa et al.,1994. Here, the tablets were placed in a 100-mL beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

Water uptake studies

The swelling behaviour of dosage unit can be measured either by studying its dimensional changes, weight gain or water uptake. The water uptake study of the dosage form was conducted by using USP dissolution apparatus-II in a 900ml of distilled water which was maintained at $37^{o}\pm$ 0.5^{o}c, rotated at 50 rpm. At selected regular intervals the tablet is withdrawn and weighed. Percentage swelling of the tablet was expressed as percentage water uptake (%WU)(Chavanpatil et al., 2006).

%WU = (Wt - Wo) * 100 / Wo

Where Wt is the weight of the swollen tablet and Wo is the initial weight of the tablet.

In vitro dissolution studies

Dissolution studies were carried out using USP II dissolution apparatus. The stirring speed was 50 rpm. 0.1 N hydrochloric acid is used as dissolution medium (900ml). It was maintained at 37 ± 1˚C. Samples of 5ml were withdrawn at predetermined time intervals, filtered and replaced with 5ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid wherever necessary and were analyzed at 224 nm by using a double beam UV spectrophotometer. Each dissolution study is performed three times and the mean values were taken.

Kinetic model fitting

To analyze the in vitro release data and to determine the release mechanism various kinetic models were used.

There are several linear and non-linear kinetic models to describe release mechanisms (Higuchi, Peppas model) and order of release (Zero and First order).

- Zero order kinetics
- First order kinetics
- Korsmeyer-Peppas model
- Higuchi model

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 in this way, a graphic of the drug-dissolved fraction versus time will be linear if the previously established conditions were filled.

Korsmeyer Peppas model (power law)

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

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.

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. For purpose of data treatment, the above equation is usually reduced to:

$Q = Kt^{1/2}$

Stability protocol

The storage conditions used for stability studies were accelerated conditions (40°C±2°C/75%±5% RH).Stability study was carried out for the optimized formulation. Tablets of optimized formulation were striped packed and kept in stability chamber for 3 months on above mention temperature.

Test Performed

- Test for other physical parameters.
- Dissolution profile.

RESULTS AND DISCUSSIONS

Pre-Formulation Studies

Organoleptic properties

Table 2: Observation of organoleptic properties.

TEST	SPECIFICATION	OBSERVATION
Colour	White or almost white powder	White powder
Odour	---	Odourless

Solubility analysis

Indomethacin samples are examined and it was found to be soluble in water and phosphate buffer pH 1.2, 6.8and 7.4.

Melting point of drug

The melting point of Indomethacin was determined by capillary method, melting point of Indomethacin was found to be 184°C. Melting point compared with USP standards that showed that drug was pure.

Loss of Drying

It was determined as per procedure given in methodology. The results were as follows

Table 3: Observations for loss on drying

Test	Loss on drying	Observation
Loss on drying	Not more than 0.5%	0.41%

The loss drying of drug was founded as0.41 which was within the limit.

Drug powder characterization

Angle of repose

It was determined as per procedure given in material and methodology section.

Table 4: Determinations of Angle of repose.

Material	Angle of repose
Indomethacin Raw material	24°56"

The results indicating that the raw material has good flow property.

Flow properties

The method to determine the flow properties are given in methodology.

Table 5: Flow properties of pure drug.

Material	Bulk density	Tapped density	Carr's index (%)	Hausner's ratio (%)
Indomethacin raw material	0.347±0.04	0.391±0.07	15.52±0.01	1.19±0.06

The results are clearly indicating that the Indomethacin raw material has good flow and cohesive nature.

FTIR Studies

Potential chemical interactions between the drug and polymer may change the therapeutic efficacy of the drug. To investigate the possibilities of chemical interaction between drug and excipients. FTIR spectra of pure drug and optimized formulations were analyzed over the range 400-4000cm-1. (shown in Figure 10 to 15) the IR spectrum of pure Indomethacin showed strong absorption bands at wave numbers of 3195, 2957, 1460, 1423, 1260, 995.8,and763.7cm-1. Due to hydroxyl stretching--- OH, C—H, C=0 stretching, N-H bending, C-H bend in plane and C-C stretching respectively in optimized formulations also these peaks were well preserved with additional peaks which correspond to the excipients used in the formulation. This indicates no drug-excipient interaction.

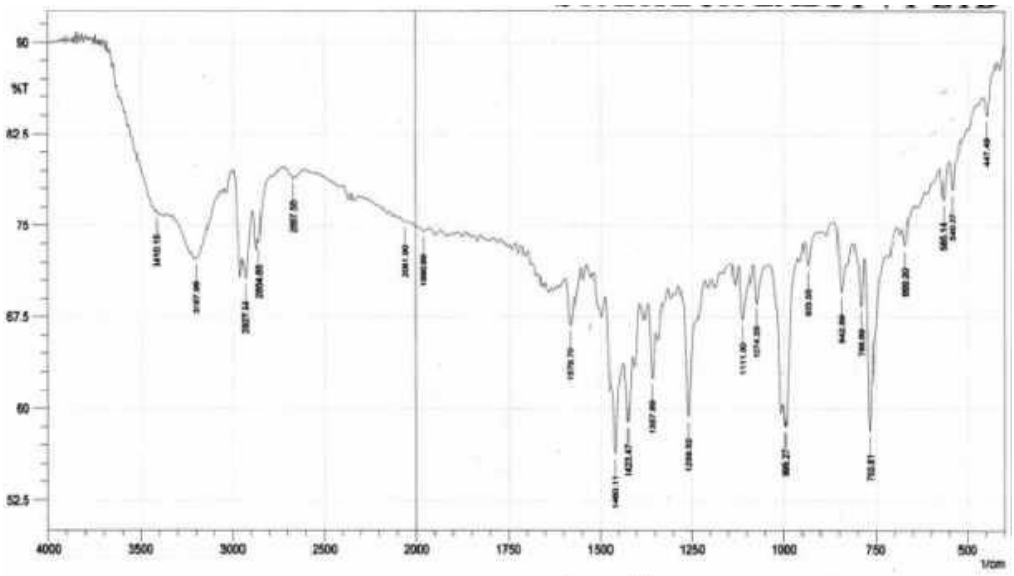

Figure 2: FTIR spectra of pure drug, Indomethacin.

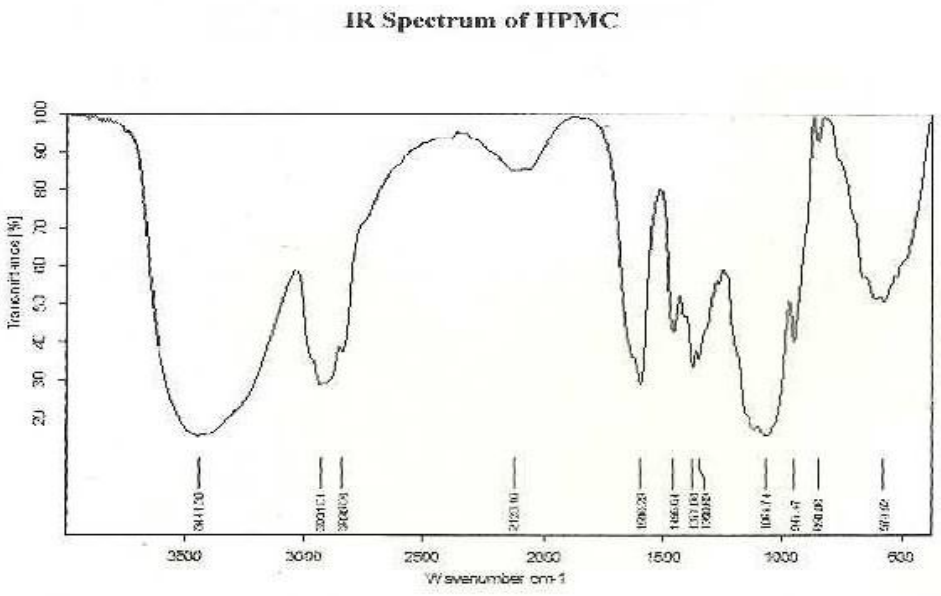

Figure 3: FTIR spectra of HPMC *wave number cm-*.

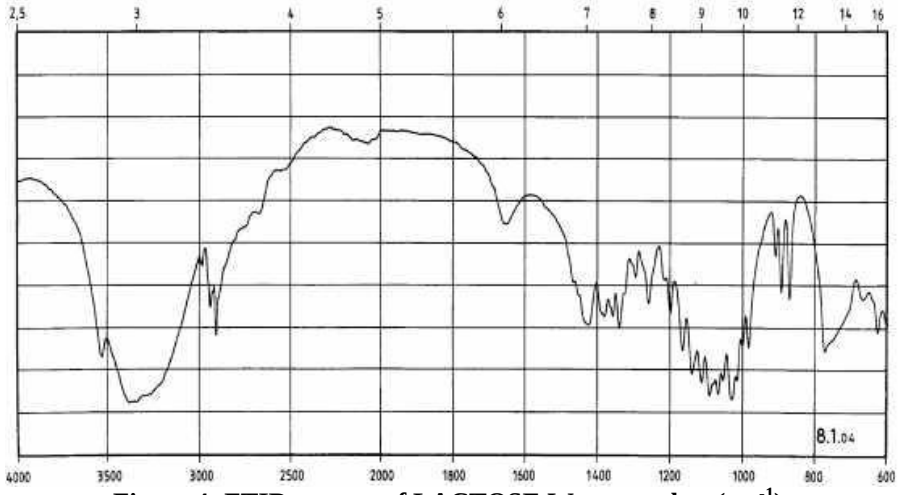

Figure 4: FTIR spectra of LACTOSE Wave number (cm^{-1}).

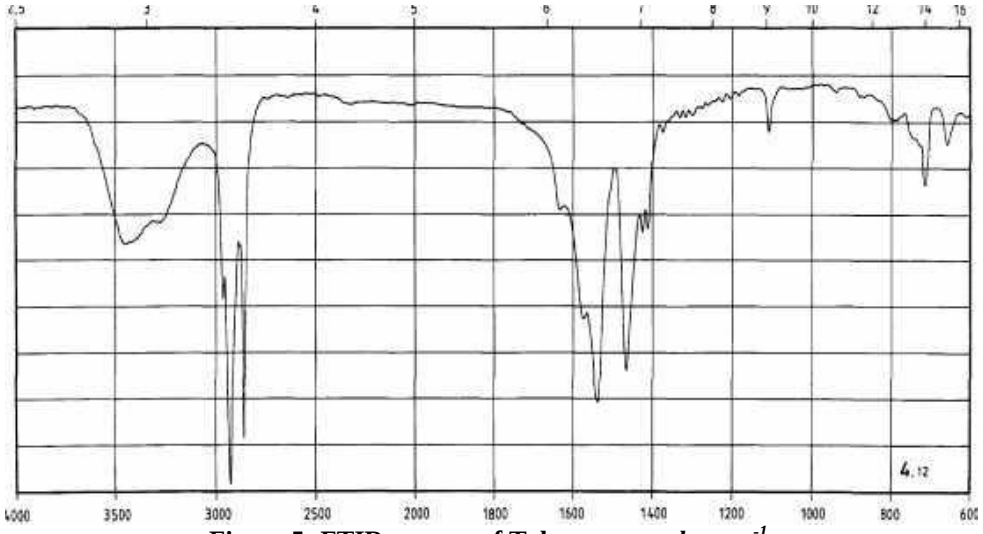

Figure 5: FTIR spectra of Talc *wave number cm^{-1}*.

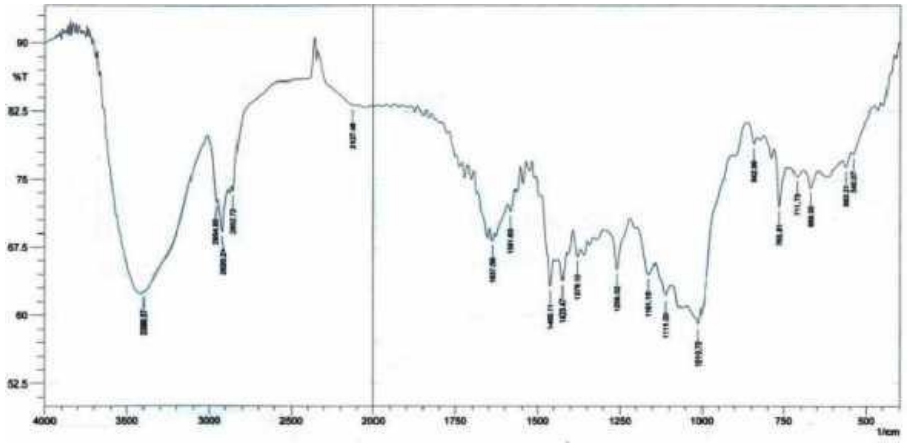

Figure 6: FTIR spectra of pure drug and polymers wave number cm^{-1}.

Table 6: Observed Value of functional groups.

S. No	Functional Group	Observed Value (cm^{-1})	Theoretical value (cm^{-1})
1	C-H stretching	763.05	1000-675
2	O-H stretching	995.29	1050-1150
3	C-N stretching	1260.47	1340-1020
4	C-O stretching	1423.10	1250-1350
5	C=C stretching	1460.23	1450-1600
6	N-H bending	2957.64	2500-3000
7	C-H bending	3195.36	3500-4000

Peaks were well preserved with additional peaks which correspond to the excipients used in the formulation. This indicates no drug-excipient interaction

Standard graph of Losartan in 0.1N HCL

The scanning of the volumetric solution of Losartan in the ultraviolet range (200-400nm) against 0.1 N HCL blank gave the λ_{max} as 224 nm. The standard concentrations of Indomethaacin (2-14 µg/ml) prepared in 0.1N HCL showed good linearity with R^2 value of 0.9989, which suggests that it obeys the Beer-Lamberts law.

Table 7: Absorbance of Indomethacin of different concentrations at λ_{max} (224nm).

Concentration(µg/ml)	Absorbance
0	0
2	0.1158
4	0.2535
6	0.3458
8	0.4819
10	0.619
12	0.7436
14	0.867

Evaluvation of Preconpression Parameters

The following parameters were carried out by the procedure The results were illustrated in the below table.

Table 8: Evaluvation of preconpression parameters.

Formulation code	Angle of repose (degree± SD)	BD (gm/ml± SD)	TD (gm/ml± SD)	Carr's index (%± SD)	Hausner's ratio (%± SD)
F1	24.12±0.04	0.317±0.01	0.367±0.02	14.65±0.06	1.08±0.05
F2	23.07±0.01	0.327±0.03	0.389±0.04	15.21±0.07	1.09±0.04
F3	26.04±0.03	0.337±0.06	0.381±0.01	13.63±0.04	1.11±0.02
F4	25.0i±0.07	0.347±0.04	0.391±0.07	16.52±0.01	1.19±0.06
F5	22.97±0.09	0.296±0.03	0.320±0.03	13.12±0.03	1.16±0.03
F6	25.71±0.06	0.260±0.01	0.336±0.01	15.27±0.01	1.15±0.01
F7	24.16±0.03	0.266±0.04	0.372±0.02	14.56±0.04	1.16±0.03

F8	21.11±0.09	0.307±0.05	0.332±0.03	13.41±0.07	1.17±0.05
F9	26.16±0.04	0.312±0.02	0.356±0.01	16.31±0.05	1.18±0.04
F10	26.04±0.03	0.347±0.04	0.381±0.01	13.63±0.04	1.11±0.02
F11	25.0i±0.07	0.296±0.03	0.391±0.07	16.52±0.01	1.19±0.06
F12	22.97±0.09	0.260±0.01	0.320±0.03	13.12±0.03	1.16±0.03

Physical compatibility test

The method for determination of physical compatibility test was given in methodology.

Table 9: Observation for physical compatibility test.

Test	Observation	Inference
Description	No colour change was observed	Complies with the condition

The physical compatibility evaluation was performed in visual basis. The study implies that the drug, polymer and other excipients were physically compatible with each other as there was no change of physical description.

Evaluation of physical parameters of floating matrix tablets of Indomethacin

All the prepared formulations were tested for physical parameters like Hardness, Thickness, Weight variation, Friability, Total floating time, Floating lag time are fond to be within pharmacopeias limits. The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicates that prepared formulations were good.

Table 10: Physical parameters of floating matrix tablets of Indomethacin.

Batch No	Tablet Thickness (mm)	Weight Variation(mg)	Hardness Kg/cm^2	Drug content (%)	Friability (%)	Lag time (sec)	Total floating time(sec)
F1	3.52±0.05	350±7.2	4.0±0.4	98.78±1.2	0.44	65	>12
F2	3.53±0.07	350±8.3	4.1±0.3	97.6±0.98	0.45	68	>12
F3	3.55±0.06	352±7.1	4.06±0.6	96.6±0.43	0.36	70	>12
F4	3.53±0.03	352±9.4	4.02±0.4	93.3±1.43	0.51	80	>12
F5	3.51±0.08	351±7.8	4±0.2	86.6±0.56	0.52	73	>12
F6	3.52±0.04	350±9.4	4.3±0.2	99.9±1.43	0.27	70	>12
F7	3.56±0.07	351±8.6	4.0±0.2	98.1±0.97	0.37	52	>12
F8	3.55±0.05	349±11.6	4.3±0.3	101±1.03	0.38	45	>12
F9	3.51±0.05	349±10.5	4.0±0.2	99.3±1.02	0.42	45	>12
F10	3.59±0.05	349±9.2	4.2±0.5	99.3±1.32	0.45	75	>12
F11	3.53±0.08	352±1.4	4.2±0.2	97.37±2.6	0.45	55	>12
F12	3.58±0.05	351±8.6	4.1±0.5	97.5±2.31	0.43	70	>12

All values represent mean ± standard deviation (SD) n=3.

Swelling Studies

Table 11: Percent swelling of formulations with HPMC K4M and K15M.

Sampling time(hr)	F1	F2	F3	F4	F5	F6
1	15.41	21.83	23.53	16.97	22.87	22.45
2	19.96	34.33	37.65	22.47	35.73	36.42
3	42.19	52.33	56.63	48.34	53.68	54.66
4	60.22	71.26	75.64	69.19	72.34	78.76
6	79.89	84.74	88.78	81.83	90.42	99.38
8	68.26	79.28	80.27	79.59	82.69	88.14
10	61.15	72.36	76.85	76.02	76.93	82.64
12	59.35	68.48	71.36	70.99	73.29	78.54

All values represent mean ± standard deviation (SD) n=3.

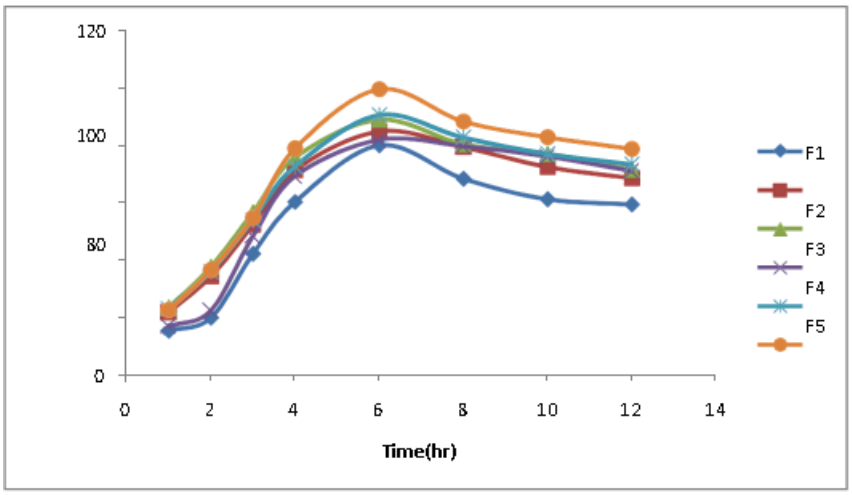

Figure 7: Percent swelling of formulations with HPMC K4M&K15M

Table 13: Percent swelling of formulations with HPMC K100M and polymer combinations.

Sampling time(hr)	F7	F8	F9	F10	F11	F12
1	22.56	24.45	24.48	21.27	22.26	22.47
2	34.73	39.57	38.46	33.76	36.38	35.64
3	56.26	60.84	56.37	49.27	54.18	50.15
4	74.28	79.36	76.72	70.56	76.45	70.84
6	89.27	92.34	99.64	90.36	99.48	95.42
8	84.38	88.34	92.27	81.16	91.65	85.37
10	75.74	78.38	82.64	75.64	86.24	80.25
12	68.34	70.37	78.84	73.34	82.56	75.32

All values represent mean ± standard deviation (SD)

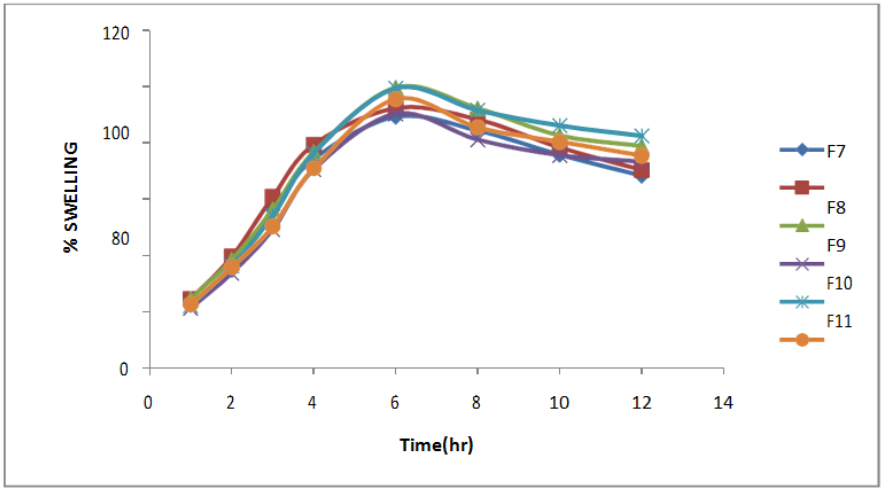

Figure 8: Percent swelling of formulations with HPMC K100M& combination of polymers.

The percentage swelling obtained from the water uptake studies of the formulations was shown in tables 12 and 13. The floating tablets containing HPMC K4 , K15M and K100m showed higher percent swelling up to the first 6th hour but could not maintain their matrix integrity up to 12 h. The floating tablets containing HPMC K4M (F1 to F3) showed less percentage of swelling when compared with HPMC K15M and HPMC K100M. The floating tablets containing HPMC K15M showed less amount of swelling when compared with HPMC K100M This was due to increase in the viscosity of polymer, the swelling increases more and the drug release will be decreased. So formulations containing HPMC K100M showed more amount of swelling when compared with the other formulations. From the above figures we can observe that formulations containing HPMC K100M has more swelling properties from the other two polymers.

In Vitro Drug Release Study

Table 14: Cumulative Percentage drug release of formulations with HPMC K4M (F1, F2, F3).

S. No	Time(hrs)	F1	F2	F3
1	0	0	0	0
2	1	21.22	19.97	18.50
3	2	33.13	29.13	26.70
4	4	50.56	47.00	40.36
5	6	73.18	64.46	62.83
6	8	99.91	73.61	75.07
7	12	-	99.33	92.88

All values represent mean ± standard deviation (SD) n=3.

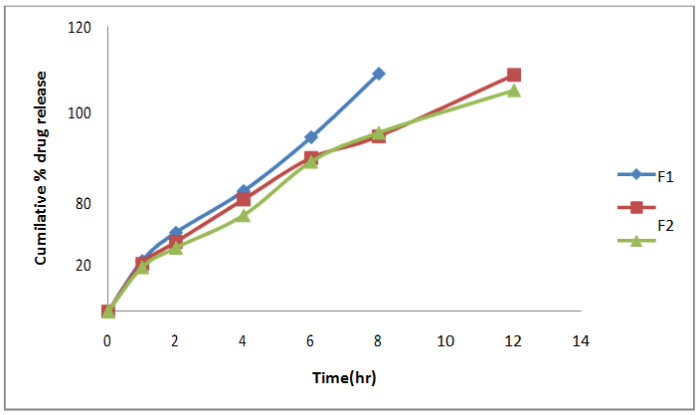

Figure 9: Cumulative percentage drug release of formulations containing HPMC K4M

From the above figure it can be observed that the polymer HPMC K4M has controlled effect on the release of drug from the floating matrix tablet. The percentage of drug release from formulations F1, F2 and F3 was 99.91, 99.33, 92.88 respectively and difference in the drug release profile of various formulations was due to the presences of different concentrations of polymer. Formulations F1 failed to release the drug within the desired time. Formulation F2 and F3 release drug from floating matrix above 12 hr. Formulation F2 was considered as best formulation among all three formulations it showed good buoyancy properties (floating lag time: 78 sec & floating time > 12 hrs) and controlled the drug release for desired period of time (12hrs).

Table 15: Cumulative percentage drug release of formulations with HPMC K15M.

S. No	Time(hrs)	F4	F5	F6
1	0	0	0	0
2	1	17.98	15.17	14.83
3	2	29.98	24.41	20.57
4	4	47.55	41.41	36.70
5	6	63.52	55.66	50.41
6	8	76.57	69.32	61.12
7	12	95.84	85.33	83.81

All values represent mean ± standard deviation (SD) n=3.

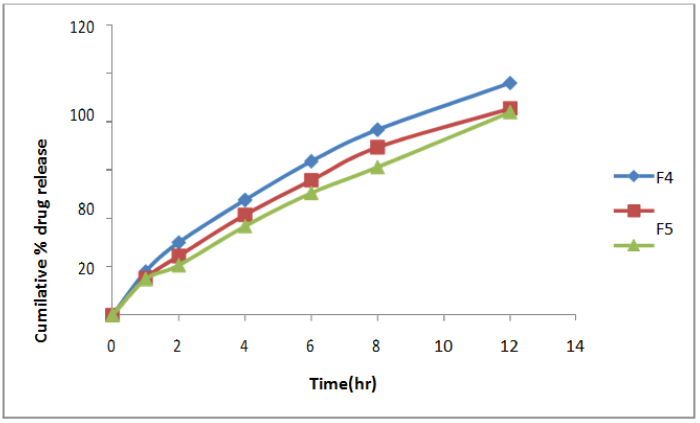

Figure 10: Cumulative percentage drug release of formulations containing HPMC K100M

From the above figure it can be observed that the polymer HPMC K15M has controlled effect on the release of drug from the floating matrix tablet. The percentage of drug release from formulations F4, F5, and F6 95.84, 85.33 and 83.81 in 12 h respectively. Formulations F6, F7 and F8 failed to release the drug within the desired time. The difference in the drug release profile of various formulations was due to the presences of different concentrations of polymer. All these three formulations floated for 12h. Formulation F4 was considered as best formulation among all four formulations it showed good buoyancy properties (floating lag time: 80 sec & floating time > 12 hrs) and controlled the drug release for desired period of time (12hrs).

Table 17: Cumulative percentage drug release of formulations with HPMC K100M.

S. No	Time(hrs)	F7	F8	F9
1	0	0	0	0
2	1	11.99	10.10	9.29
3	2	23.71	15.17	14.89
4	4	40.68	29.87	23.71
5	6	57.02	47.52	44.52
6	8	72.97	60.95	57.72
7	12	90.47	74.01	61.55

All values represent mean ± standard deviation (SD) n=3.

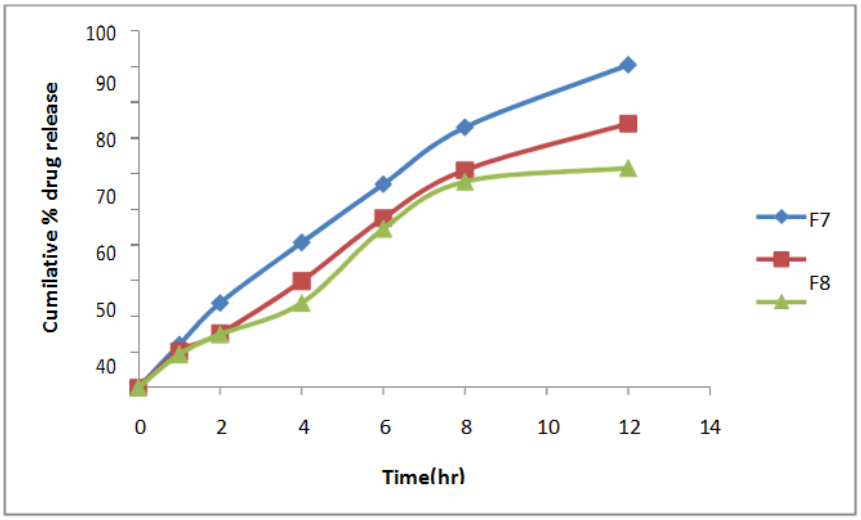

Figure 11: Cumulative percentage drug release of formulations containing HPMC K100M.

From the above figure it can be observed that the polymer HPMC K100M has controlled effect on the release of drug from the floating matrix tablet. The percentage of drug release from formulations F7, F8 and F9 are 90.47, 74.01 and 61.55 in 12 h respectively. Formulations F8 and F9 failed to release the drug within the desired time. The difference in the drug release profile of various formulations was due to the presences of different concentrations of polymer. All these three formulations floated for 12h. Formulation F7 was considered as best formulation among all three formulations it showed good buoyancy properties (floating lag time: 52 sec & floating time > 12 hrs) and controlled the drug release for desired period of time (12hrs).

Table 18: Percent drug release of formulations with combination of polymers.

S. No	Time(hrs)	F10	F11	F12
1	0	0	0	0
2	1	15.20	10.94	12.69
3	2	24.43	16.79	21.26
4	4	33.11	24.29	33.08
5	6	46.56	34.07	44.13
6	8	58.53	47.18	55.57
7	12	80.36	68.84	75.86

All values represent mean ± standard deviation (SD) n=3.

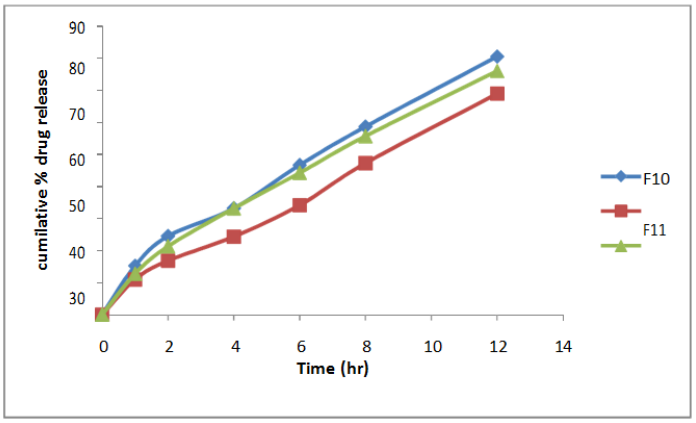

Figure 12: Cumulative % drug release of formulations containing combination of polymers

From the above figure it can be observed that the polymer HPMC K4M, K15M and K100M has controlled effect on the release of drug from the floating matrix tablet. The percentage of drug release from formulations F10, F11, and F12 was 80.36, 68.84, and 75.86 in 12 h respectively. These are the formulations done by combination of polymers. Formulations F11,and, F12, failed to release the drug within the desired time and difference in the drug release profile of various formulations was due to the presences of different concentrations of polymer and due to the high viscosity of the polymers. The cumulative percent of drug release from various formulations and release coefficients values of the various models for respective formulation were represented in tables Formulation F10 was considered as best formulation among all three formulations it showed good buoyancy properties (floating lag time: 75 sec & floating time > 12 hrs) and controlled the drug release for desired period of time (12hrs).The cumulative percent of drug release from various formulations and release coefficients values of the various models for respective formulation were represented in tables 23 to 26 respectively. Fomulation F2 showed good drug release and buoyancy time than all other formulations. The formulation F2 showed a constant release in a controlled manner with 99.33%. Hence F2 was chosen for kinetics studies.

Drug Release Mechanism

Release Kinetics

Table 19: Release kinetics of the optimum formulation F2.

S. no.	Time (hr)	√T	Log T	Cumulative %drug dissolved	Cumulative %drug un dissolved	Log Cumulative %drug dissolved	Log Cumulative %drug un dissolved
1	0	0	0	0	100	0	2.0
2	1	1.0	0	19.97	80.03	1.03	1.903
3	2	1.414	0.30	29.13	70.87	1.46	1.85
4	4	2.0	0.60	47.00	53.00	1.67	1.72
5	6	2.4	0.778	64.46	35.54	1.809	1.55
6	8	2.8	0.90	73.61	26.39	1.867	1.42

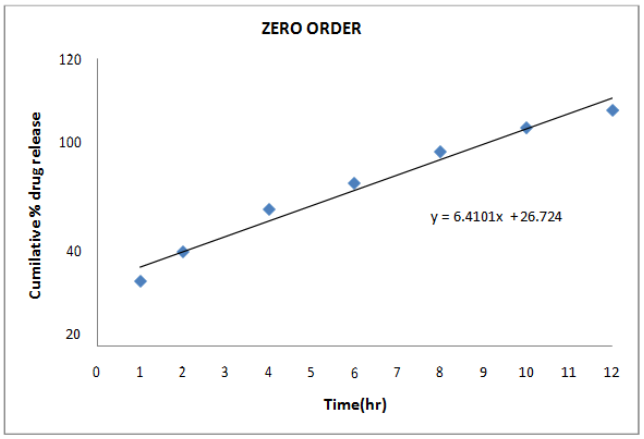

Figure 13: Zero order plot (F2) Formulation.

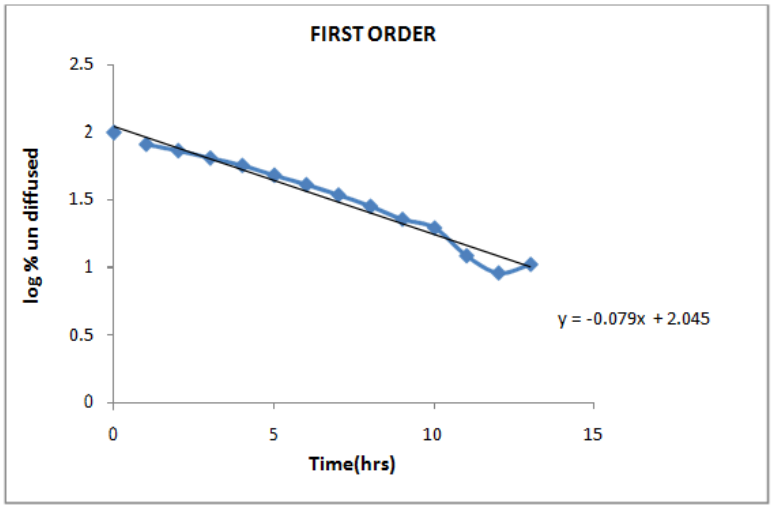

Figure 14: First order plot (F2).

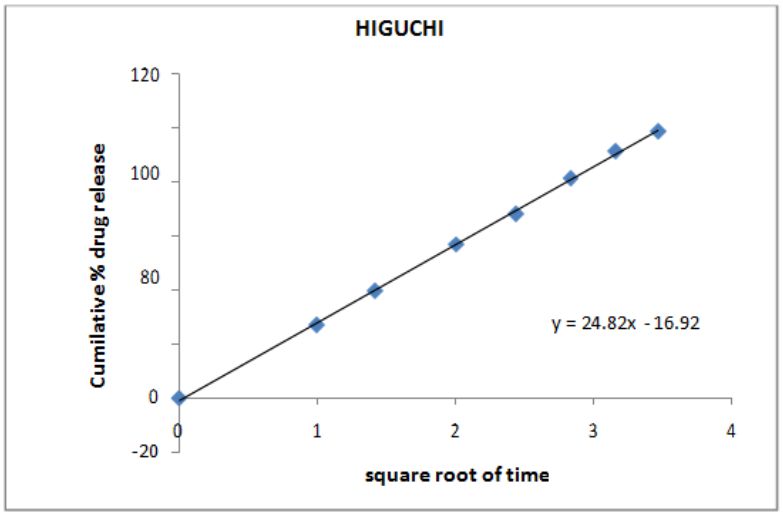

Figure 15: Higuchi Plot (F2).

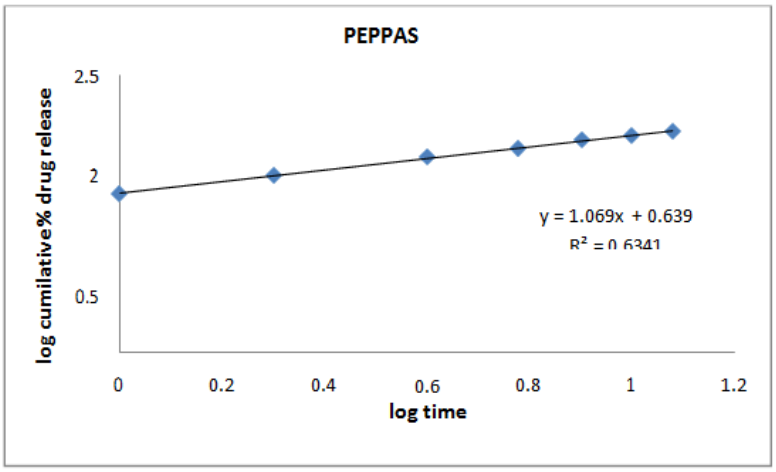

Figure 16: Korsemeyer Peppas Model (F2).

Kinetics of drug release

Table 20: Drug release kinrtics.

Formulation	Zero-order	First-order	Higuchi	Krosmeyer peppas	
				2R	N
F2	0.9877	0.8245	0.9818	0.6341	0.5062

The results of R^2 for zero order and first order were obtained as 0.9877 and 0.8245. Based on that we confirmed that the optimised formulation followed zero order release. The drug release was diffusion controlled as the plot of optimized formulation F2 was found 0.9818 as regression coefficient in Higuchi plot. From Korsemeyer- peppas's plot the release exponent value N was found as 0.506 and it was confirmed as the release of drug from formulation was founded as anomalous non-fickian transport of diffusion.

Accelerated Stability Studies

In any rationale design and evaluation of dosage forms for drugs, the stability of the active component must be major criteria in determining their acceptance or rejection.

During the stability studies the product was exposed to normal conditions of temperature and humidity. However the studies will take a longer time and hence it would be convenient to carry out the accelerated stability studies where the product was stored under extreme conditions of temperature. In the present study, stability studies were carried out on formulation F2.The tablets were stored at 40 ± 2^0 C 75 ± 5 % RH for a duration of three months.

The selected formulation was evaluated for stability studies. The formulation were stored at 40°C at 75%RH for 3 months and analysed for their physical parameters, drug content and friability after 3rd month the data were showed in table no 21.

Table 21: Physical parameters studies.

	Drug content (%)	Hardness (kg/cm^2)	Friability (%)
After 1 month	99.33±0.17	4.1±0.3	0.45
After 2 months	99.12±0.15	4.0±0.42	0.46
After 3 months	99.12±0.15	4.0±0.42	0.46

Table 22: In Vitro Dissolution Studies

Time(hr)	Initial	1st month	2nd month	Rd 3 month
0	0	0	0	0
2	19.97	19.71	19.64	19.52
4	29.13	29.01	28.97	28.65
6	47.00	46.87	46.53	46.37
8	64.46	64.26	64.15	64.07
10	73.61	73.44	73.35	73.30
12	99.33	99.20	99.15	99.12

From the above tables (table no 21 & 22) it was observed there is no much change in its physical properties and %drug release. Hence formulation(F2) conformed stable.

SUMMARY AND CONCLUSION

The preformulation parameters like organoleptic properties, angle of repose, bulk density, tapped density, Hausner's ratio, carr's index and compressibility index of pure drug was evaluvated and complied with the pharmacopoeial specifications.FTIR studies showed there was no interaction between drug and polymer. Gastro retentive floating matrix tablets of Indomethacin were successfully prepared with hydrophilic polymers like HPMC K4M, HPMC K15M.,HPMC 100M. The formulated batches were evaluated for physicochemical parameters, floating properties and dissolution profiles. From the evaluation results, it was observed that the tablets contain the higher viscosity HPMC showed long floating lag time when compared to tablets prepared with lower viscosity HPMC. The physical properties like hardness, weight variation and friability of majority of the batches complied with the pharmacopoeial specifications. The drug content of all tablets was in the range of 95 – 100%.In vitro dissolution study of all the formulations was done in 0.1 N HCL. 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. The tablets containing HPMC K4M (F2) showed satisfactory results with short floating lag time (68 sec) total buoyancy time more than 12 h, cumulative % drug release (99.33) and controlled drug release up to 12 h. So F2 was taken for kinetic studies.The kinetic studies were carried for formulation F2 showed high regression value of 0.9877 for zero order, 0.981 for Higuchi order (conforms non-Fickian sustained release) and N value greater than 5 (conformsdiffusion controlled) with complete release in 12 hrs made it to select as an optimized formulation

compared with other formulations. The accelerated stability was carried for F2 formulation and shown no much change in physical parameters and cumulative % drug release. Hence formulation F2 conformed as stable. Hence it was concluded that formulation F2 choosen as optimum formulation. However In vivo studies and development of suitable packaging material are made for future continuation of this experimental work.

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