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Research Article

FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY OF INDOMETHACIN USING MODIFIED PULSINCAP TECHNOLOGY

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A R T I C L E I N F O

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A B S T R A C T

Indomethacin is used as a NSAID. The objective of the present study was to design and evaluate a modified pulsincap drug delivery system of Indomethacin for treatment of rheumatoid arthritis. Capsule body was made water insoluble by cross linking with formaldehyde. The modified capsule was filled with drug and with polymers such as HPMC K100, CCS, Magnesium sterate to expel the drug after pre-determined lag time. A hydrogel plug made of HPMC K100 was placed in the capsule body to achieve desired drug release after lag time for chronotherapy of rheumatoid arthritis. Untreated cap was fitted to the treated body was sealed. The drug was subjected to pre-compression parameters such as angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio. The capsules were subjected to post formulation evaluation studies such as %weight variation, %drug content, in¬¬ vitro dissolution studies respectively. The pre and post formulation parameters are within acceptable limits. The compatibility of the drug, polymers& excipients were determined by FTIR spectroscopy. The results showed that the drug was compatible with polymers and other excipients. Invitro dissolution studies were carried out using pH 7.2 buffer for 4hrs.Based on the results f5 formulation showed good dissolution profile. The release data was fitted to various mathematical methods such as zero order, first order, Higuchi, Hixson-Crowell and Korsemeyerr-peppas to evaluate the kinetics and drug release. The drug release follows first-order kinetics and the mechanism was found to be Anomalous (Non-Fickian) diffusion.

INTRODUCTION

The Pulsatile drug delivery systems (PDDS) are designed according to the circadian rhythm of the body. The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is not desired[1]. There are many conditions and diseases where sustained release formulations do not show good efficacy, so these conditions demand the release of drug after a lag time Many body functions follow circadian rhythm, i.e., their activity increases or decreases with time. A number of hormones like rennin, aldosterone, and cortisol show daily as well as timely fluctuations in their blood levels. Circadian effects are also observed in case of pH and acid secretion in stomach, gastric emptying, and gastro-intestinal blood transfusion. Severity of diseases like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension is time dependent A drug delivery system administered at bed time but releasing drug as a burst after the time of administration (during morning hours), would be ideal in this case.Modified pulsincap is a single-unit capsular PDDS. The capsule consists of a insoluble capsule body and soluble cap along with hydrogel plug[2].The plug is removed after predetermined lag time is reached due to its swelling and erosion. Upon contact with the gastro-intestinal fluid, the plug swells, pushing itself outside from the capsule.

The approach is based on the principle of delaying the time of drug release until the system transmits from mouth to colon[3,4]. Alag time of 5 hours is usually considered sufficient since small intestine transit is about 3- 4 hours, which is relatively constant and hardly affected by the nature of formulation administrated.

Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties used for remedy of arthritis, fever. The study aims attention at developing pulsatile capsules of indomethacin which are the single unit systems where the lag time is controlled by a plug. Polymers used for designing of the plug are hydroxyl propyl methyl cellulose (K100M, K4M) which are erodible compressed polymers. The main constituent of capsule is gelatin, formaldehyde is used to retard the rate of hydrolysis.

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In the present investigation capsule body was hardened by formaldehyde vapours to prevent dissolution of capsule body. The main intention of this work was to formulate a single unit pulsatile capsules of indomethacin which releases the drug after a definite lag time and provides required concentration of drug at regular intervals of time[5,6] The pulsincap drug delivery system of Indomethacin to the colon provides minimal toxic concentrations as this system, the drug to absorb in the colon.

MATERIALS AND METHODS

Materials

Indomethacin was gift sample from Veras Pharmaceutical Pvt Ltd, Andhra Pradesh, India. All other excipients used were of analytical grade.

Method

Preparation of formaldehyde treated empty gelatin capsule[7,8,9]

The selected 0 size hard gelatin capsules 100 (brown coloured both cap and body) were taken, their bodies and caps are separated. The bodies were placed on a wire mesh and spread as a single layer. They are placed in a desiccator, containing formaldehyde liquid at bottom, which is equilibrated with its vapour. The body of capsule was made to react with formaldehyde vapours for a period of 2 hours. The reaction time was optimized by taking 20 samples of capsule bodies at 15-, 30-, 45-, 60- and 120-mins interval. Then they were removed and kept on filter paper and dried for 48 hrs at room temperature to ensure the completion of reaction between formaldehyde and gelatin. Afterwards the capsules were kept in open atmosphere to facilitate the removal of residual formaldehyde. These capsule bodies were capped with untreated caps and stored in polythene bag

Preparation of Indomethacin granules: Indomethacin granules were prepared by wet granulation method. The composition of different formulations was prepared by using excipients such as HPMC K100M, were sieved (no.60) separately and mixed with indomethacin. The powders were blended and granulated with CCS. Isopropyl alcohol was used as granulating agents. The wet mass was passed through a mesh and granules were dried at 50^0C for 1 hour. Then talc and magnesium stearate were added.

***Preparation of Hydrogel plug[10]*:** Hydroxy propyl methyl cellulose (HPMC k_{100}M), spray dried Lactose were mixed for 10minutes. Magnesium stearate (1%) was added to the previous mixture and further blended for 5 minutes and compressed using single punch tablet machine.

Sealing and coating of capsules[11,6]

The joint of the treated body and cap of the capsule was sealed with a small amount of the 5% w/v ethyl cellulose ethanolic solution, and the filled and sealed capsules were then coated with CAP to ensure that drug release occurred in the colon rather than in the stomach. The various parameters of coating conditions were standardized, such as dipping time (5 s), coating solution concentration, temperature (25±10 °C) and drying time (5 min) at 50°C. Coating was repeated until a 6–8% increase in weight was obtained. The percentage weight gain of the capsules before and after coating was determined using the Equation1.

Where W_t is the weight of the capsules after coating, Wo is the initial weight of capsules. The capsules were dried in an oven at 50 °C for 12 h.

$$\% \text{ weight gain} = \left(\frac{W_t - W_o}{W_o}\right) \times 100 \qquad \text{Equation 1}$$

Physico chemical characterization of formaldehyde treated empty gelatin capsules

Length of the capsule, external diameter of the capsule, thickness of the capsule was determined.

Physico chemical characterization of Indomethacin granules

- Physical appearance of the drug, Determination of melting point
- Solubility, physical properties, angle of repose, bulk density[12], tapped density[13], carr's index and Hausner's ratio[14], drug-excipient compatibility studies: FTIR.

Physico Chemical Characterization of Hydrogel Plug: Shape and appearance

Hydrogel plug s were examined under a lens for the shape of the tablet, colour was observed by keeping the tablets in light.

Weight Uniformity

Ten tablets were weighed individually on electric balance from which the mean was calculated, and the percentage deviations were determined.

Thickness

The thicknesses of ten tablets were determined using a Vernier calliper and the mean of these readings was taken as the mean of the tablet thickness.

Friability

The friability of the tablets was determined using the Roche friabilator. Five tablets were weighed and put into the friabilator and set to rotate at 25 rounds per minute for about four minutes. The tablets were then removed and weighed again. The friability (F) is given by the formula;

$\mathbf{F} = \mathbf{W}_i - W_{f/}\, W_f$
$\mathbf{W}_i = W_{initial}$
$W_f = W_{final}$

Hardness

The tablets to be tested are held between a fixed and a moving jaw of hardness test apparatus (Monsanto) and reading of the indicator is adjusted to zero. The screw knob was moved forward until the tablet breaks and the force required breaking the tablet was noted.

Lag time test for Hydrogel plug

The prepared HPMC plugs were plugged to the capsule bodies containing formulated granules, and the cap was closed. The lag time test was conducted using USP XXII dissolution testing apparatus using 7.2 pH phosphate buffer as a medium. Then drug release was observed

Physico chemical characterization of modified pulsincap: In-Vitro drug release study

In Vitro drug release study was performed for Indomethacin capsules according to the USP Dissolution for 4 hours.

Dissolution was done at 37±5°C at 50rpm in type-I apparatus. For the 4 hours, 900ml of pH 7.2 Buffer media was used in the dissolution vessels. Samples withdrawn were replaced with an equal amount of fresh dissolution medium at time intervals, samples were immediately filtered through filter paper. The absorbances of these samples were noted at maximum wavelength 318 nm using UV-Visible Spectrophotometer. The amount of drug present in the samples was calculated using the calibration curve constructed from reference standards.

Analysis of Dissolution Data

The dissolution data obtained was fitted to zero order, firstorder, Higuchi and Hixson- crowell[19] to understand the order and mechanism of drug release from the pulsincap.

Zero order kinetics[14]

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

$Q = Kot$

First order kinetics[15,16]

The release of the drug which followed first order kinetics can be expressed by the equation:

$dc/dt = - Kc$

Where K is first order rate constant expressed in units of time-1.

Higuchi equation[17]

It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time.

$Q = K_2 t^{1/2}$

Where, K_2 is the release rate constant. A plot of the fraction of the drug released against square root of time will be linear if the release obeys Higuchi equation.

Korsemeyer-Peppas model[19]

Korsemeyer derived a simple relationship which described drug release from a polymeric system equation

$Mt / M^x = Kt^n$

Where Mt / M* is a fraction of drug released at time t, k is the release rate constant and n is the release exponent. The n value is used to characterize different Release for cylindrical shaped matrices.

Table 1 Composition of Hydrogel plug

Composition	Ingredients	Quantity(mg)
Hydrogel pug	HPMC-K100M Lactose	100mg

Table 2 Composition of Indomethacin modified capsules

S.NO	Name of the ingredient	F1 (mg)	F2 (mg)	F3 (mg)	F4	F5	F6	Purpose
1	Indomethacin	25	25	25	25	25	25	Drug
2	Hpmc k4m	25	50	75	-	-	-	Polymer
3	Hpmc k100m	-	-	-	100	125	150	Polymer
4	Ccs	20	20	20	20	20	20	Super disintegrant
5	Talc	2.5	2.5	2.5	2.5	2.5	2.5	Lubricant
6	Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	Glidant

RESULTS AND DISCUSSIONS

Evaluation of formulation treated empty capsules

Table 3 Physical characteristics of empty gelatin capsule with or without treatment (mean±SD)

Physical characteristics	Untreated cap	Untreated body	Formalin treated body
Length(mm)	8.9±0.1	16.9±0.4	18.7±0.1
External Diameter(mm)	7.3±0.2	6.5	6.7
Thickness (mm)	0.25±0.1	0.1±0.0	0.1±0.0

Weight of the empty capsule =94.1±2.2
Weight of the formalin treated capsule =95.22±2.1

Table 4 Evaluation of Hydrogel plug:(mean±SD)

Hydrogel plug	Weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Lag time(hrs)
H	100	3.16±0.75	4.5±0.08	0.8±0.09	3.5±0.98

The weight uniformity, thickness, hardness, friability to be in within the limits. So, the indicated plug possesses good mechanical strength.

Drug-excipient compatibility studies

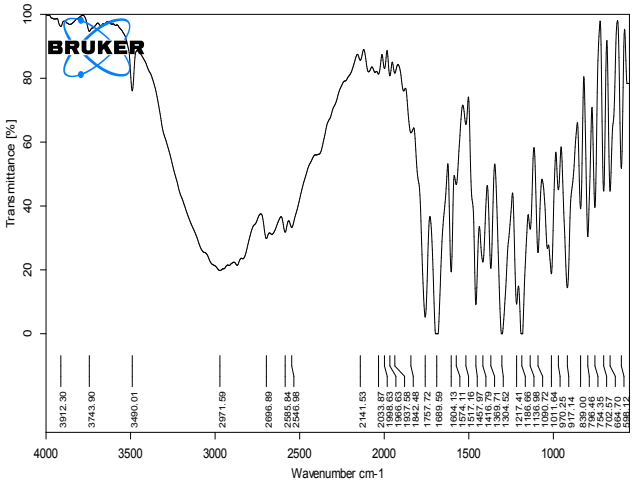

Fig 1 IR spectrum of pure drug Indomethacin

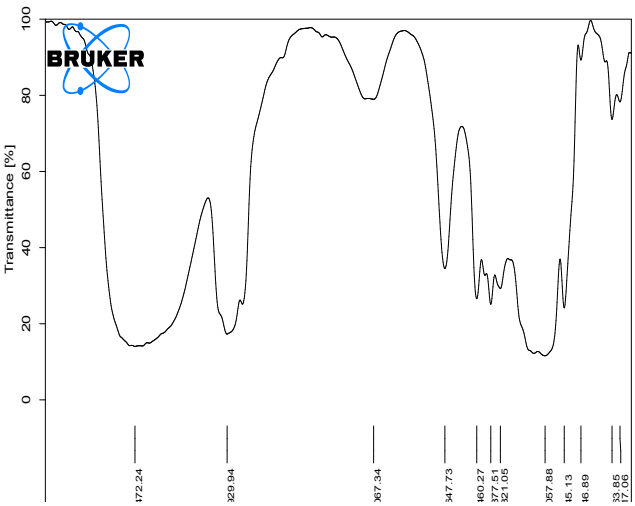

FIG 2 Ir Spectrum of Hpmc-K100m

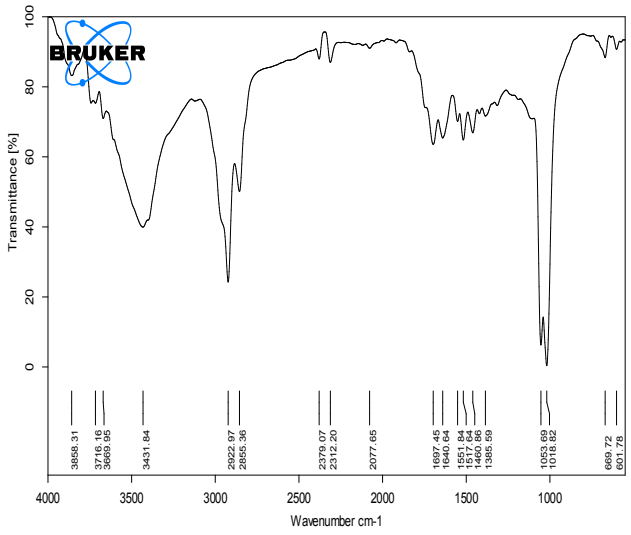

Fig 3 Ir Spectrum of F5 Formulation

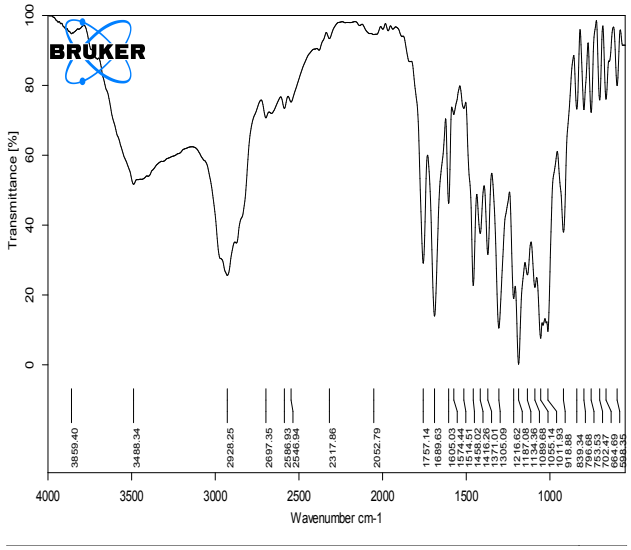

Fig 4 Ir Spectrum of Drug Indomethacin & Hpmc-K100m

Inference

The FTIR spectra of the pure drug and drug with HPMC-K100M, (polymer in the optimized formula) are shown in fig:4. The drug shows intense peaks at 1305cm^{-1} and1605cm^{-1} .The reports of FTIR studies indicates that there is no chemical reaction between drug and the excipients and they are compatible

Table 5 Data of pre-formulations studies of the blends (mean±SD)

Formulation code	Angle of Repose (degree)	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's ratio
F_1	26.94±0.48	0.276±0.06	0.314±0.002	12.10±0.61	1.137± 0.01
F_2	25.6±1.33	0.350±0.05	0.408±0.001	14.21±0.98	1.161± 0.04
F_3	25.42±0.84	0.320±0.03	0.370±0.003	14.240±0.26	1.134± 0.13
F_4	26.40±0.51	0.271±0.67	0.316±0.008	14.207±0.04	1.166± 0.01
F_5	27.32±0.60	0.353±0.08	0.400±0.007	11.89±0.70	1.165± 0.02
F_6	28.54±0.62	0.354±0.04	0.466±0.001	11.95±0.33	1.173± 0.05

The prepared blends were evaluated for pre-formulation parameters -Angle of repose, bulkdensity, tappeddensity, compressibility index, Hausner'sratio.The results were mentioned in table 5. All the parameters were in accepted limits (table-5) showing the blends has good flow.

Table 6 Data for post formulation studies of the prepared capsules (mean±SD)

Formulation code	Weight variation (%)	Assay (%) n=3
F1	1.54±0.38	96.22±1.09
F2	1.22±0.59	97.25±1.822
F3	1.53±0.94	96.77±1.90
F4	1.43±0.01	95.42±0.96
F5	1.7±0.03	98.73±1.051
F 6	1.65±0.13	98.65±0.77

The post formulation parameters were given in table.6. The prepared capsules were evaluated for post formulation parameters-Weight variation (%), &assay (%). All the parameters were in acceptable limits showing that capsules prepared were good.

Table 7 In-Vitro Drug Release Data (Mean±Sd)

Time (mins)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)
0	0	0	0	0	0	0
15	5.99±0.49	10.09±0.01	11.18±0.87	5.10±0.06	4.78±0.35	5.08±0.51
30	10.84±0.22	23.22±0.15	20.20±0.81	10.97±0.48	6.30±0.45	15.41±0.42
45	16.41±0.03	34.43±2.7	25.80±0.80	10.11±0.44	16.51±0.71	23.32±0.84
60	21.22±0.43	35.82±0.1	32.37±0.84	21.50±0.48	38.65±1.47	26.48±0.72
90	42.01±0.21	61.30±0.85	47.75±0.87	41.80±0.50	72.71±1.07	62.51±0.55
120	52.84±0.21	69.33±1.14	61.85±0.83	54.58±0.77	84.66±0.69	75.43±0.91
180	86.23±0.02	77.22±1.70	86.00±1.54	82.40±0.82	92.82±1.13	82.10±1.24
240	89.03±0.36	85.31±1.68	86.67±0.40	91.03±0.82	96.05±1.24	86.78±0.78

All the 6 formulationsof the prepared modified pulsincap capsules of Indomethacin were subjected to in-vitro using USP dissolution apparatus-I (basket). The results were evaluated for 4 hours. The results were shown in table no-7 of dissolution study.

According to the results obtained.

Formulation F6 prepared by using HPMC-K100M, of 150mg shows drug release and the formulations shows highest drug release i.e.,86.78% respectively at 4thhour.

Formulation F5 prepared by using HPMC-K100M of 125mg shows drug release i.e,96.05% respectively at 4thhour.

Formulation F4 prepared by using HPMC-K100M of 100mg shows drug release i.e,91.03%respectively at 4thhour.

Formulation F3 prepared by using HPMC-K100M of 75mg shows drug release i.e,86.67%respectively at 4thhour.

Formulation F2&F1 prepared by using HPMC-K100M of 50mg & 25mg shows drug release i.e,85.3% & 89.03 respectively at 4thhour .

Among all the 6 formulations, formulation-F5 shows good drug release profile throughout the study. It also shows highest drug release of 96.05% at 4thhour and also other parameters like drug content, % weight variation and assay for this formulation were within the acceptable range. Hence F5 formulation is selected as optimized formulation.

In-Vitro Drug Dissolution Graphs of the Prepared Formulations F1-F6

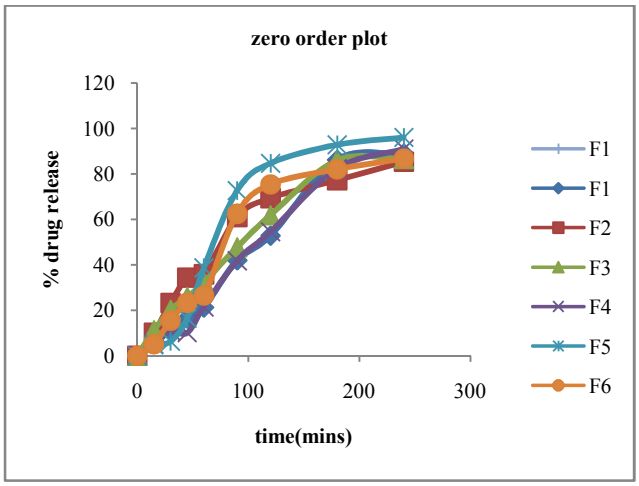

Fig 5 Zero order plot of formulations F1-F6

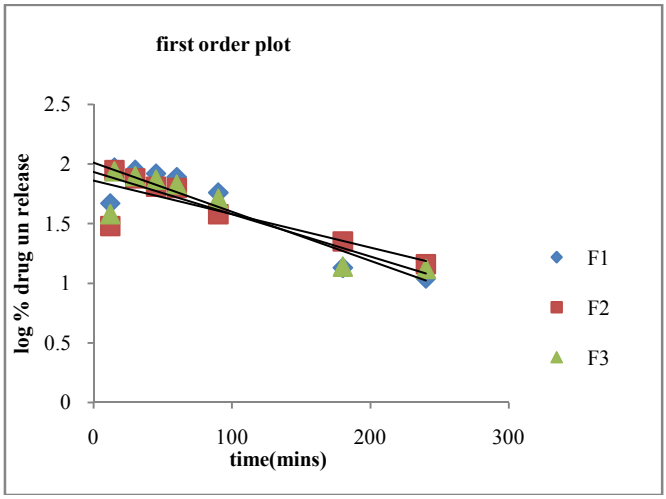

Fig 6 First order plot formulations f1-f3

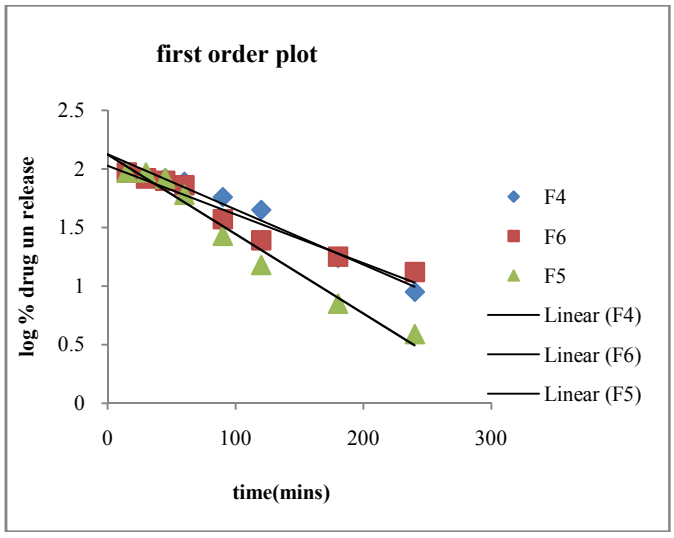

Fig 7 First order plot of formulations f4-f6

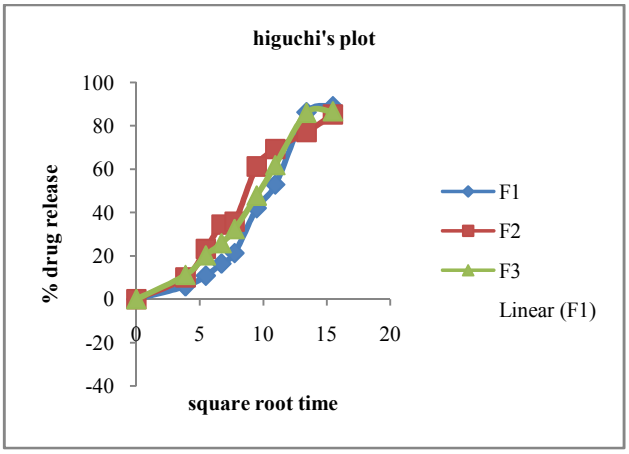

Fig 8 Higuchi plot of formulations f1-f3

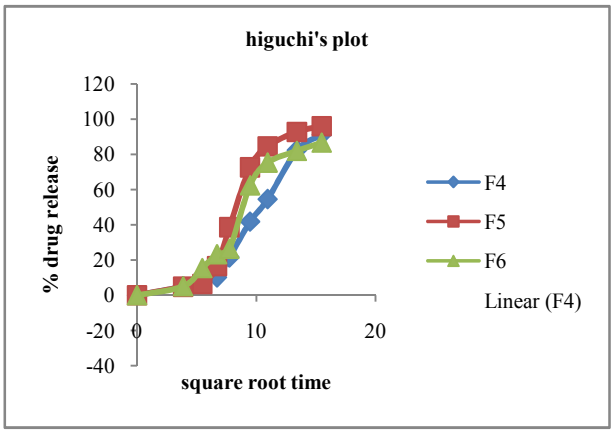

Fig 9 Higuchi plot of formulations f4-f6

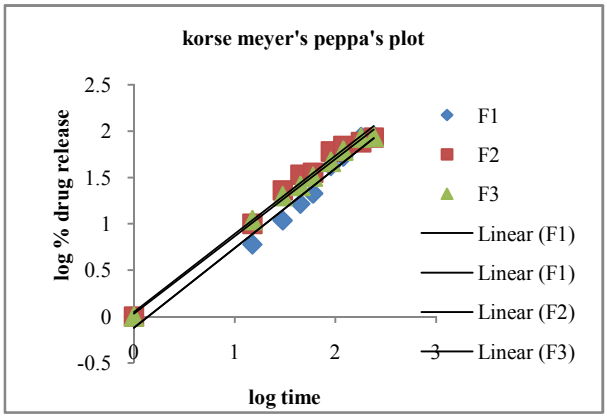

Fig 10 Korsemeyer -Peppas plot of formulations f1-f3

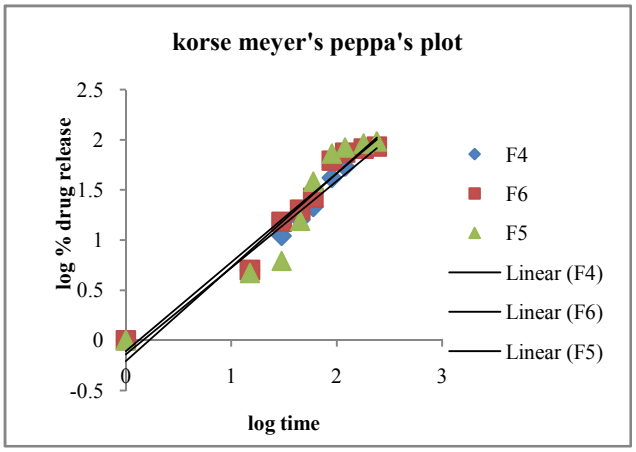

Fig 11 Korsemeyer -Peppas plot of formulations f4-f6

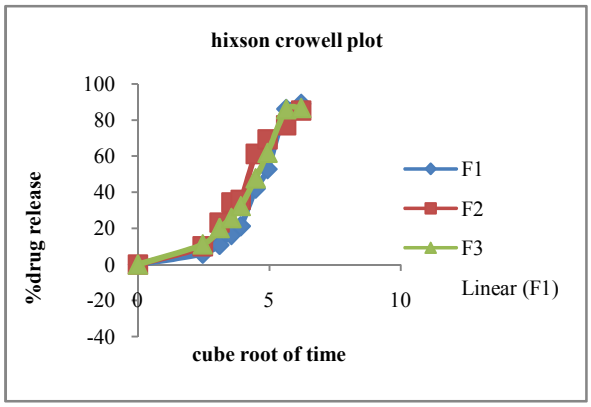

Fig 12 Hixson-Crowell plot of formulations f1 -f3

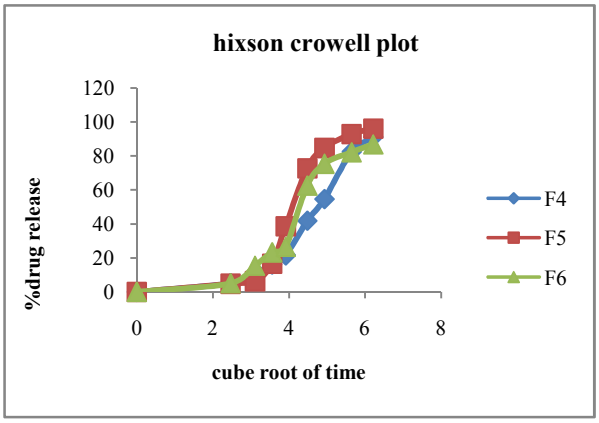

Fig 13 Hixson-Crowell plot of formulations f4 -f6

In-Vitro Drug Release Kinetics of the Prepared Formulations

Table 8 In-vitro drug release kinetics of the prepared formulations

Brand name	Zero – order	First Order	Higuchi	Hixson Crowell	Korsemeyer-	Peppas
	R^2	R^2	R^2	R^2	R^2	Diffusion Component(n)
F1	0.9674	0.9491	0.9015	0.9451	0.9759	0.8586
F2	0.9125	0.9739	0.9583	0.9696	0.9844	0.8437
F3	0.9943	0.9536	0.9555	0.9693	0.9953	0.834
F4	0.9937	0.9733	0.910	0.95810	0.9712	0.8665
F5	0.9032	0.9731	0.9000	0.9139	0.9105	0.8870
F6	0.9224	0.9422	0.9021	0.9329	0.9640	0.8386

Drug Release Mechanism

Different models like In-vitro drug release kinetics of the prepared formulations Zero-order, first order, Higuchi, Hixson -Crowell, Korsemeyer-Peppas plots were drawn. The regression coefficient (R^2) values for Zero-order, first order, Higuchi, Hixson – Crowell, Korsemeyer-Peppas plots (fig:5-13& table no-8) for all the formulations were shown. TheKorsemeyer-Peppas plot is also calculated (fig 10,11& table no.8).Among all the formulations F5 showed best release of Indomethacin over a period of 4 hours. Hence these formulations are considered further work.The regression co-efficient (R^2) values of the optimized formulations F5 for all Zero-order, Firstorder, Higuchi, Hixson – Crowell, Korsemeyer-Peppas were found to be 0.9731,0.90,0.9139,0.9105respectively.The slope of Korsemeyer-Peppas plot for F5 is Y=0.8876-0.201.The highest R^2 values for , Firstorder,Hixson – Crowell plots of F5,indicates formulation F5 follows First-order drug release, where release rate is dependent of concentration of drug in the formulation, whereasthe 'n'values i.e,0.8870 of Korsemeyer-Peppas plot confirms that the drug release through non-fickians diffusion mechanism.

CONCLUSION

On studying all the experimental results of the prepared formulations, it can be concluded that modified pulsincap of indomethacin can be successfully prepared using hydrophilic polymers like HPMC. From results HPMC K100M of 125mg showed better solubility and dissolution enhancement for indomethacin. It is observed that release of indomethacin from different formulation was spread over a period of 240mins. And the release of the drug from the formulation was found to follow first order kinetics.

Among various formulations studied F5 containing 125mg of HPMCk100M which showed 96.05% drug release at the end of 240 mins was selected as the best formulation due to its dissolution profile was same with innovator.

Indomethacin given in form of modified pulsincap should be advantageous for patients suffering from rheumatoid arthritis, and it provides better patient compliance and effective mode of treatment in a disguised manner.

Formulation F5 appears suitable for further pharmacodynamic and pharmacokinetic to evaluate clinical safety of these modified pulsincapof indomethacin in suitable animal and human models.

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