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FORMULATION AND EVALUATION OF DRUG RELEASE PROFILE OF HYDROPHILIC POLYMER BASED INDOMETHACIN PROLONG RELEASE MATRIX TABLETS

Pharmaceutical

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ABSTRACT

An oral modified release dosage forms have always been more effective therapeutic alternative to conventional dosage forms. The present invention is directed to a modified release pharmaceutical composition of indomethacin by using hydrophilic release retardant polymers like HPMC K15M, Na CMC alone or in combination. Matrix embedded prolong release tablet formulations of Indomethacin were prepared by wet granulation technique and evaluated for tablet properties such as the thickness, hardness, friability, weight variation, drug content, drug release kinetics and in vitro release studies. The influence of drug polymer ratio on drug release was studied by dissolution test. The FTIR studies showed no interactions among drug and polymers. The tablets formulation (F7 and F8) containing combined polymers of HPMC K15M and Na CMC resulted in slower drug release rate form the matrix. So, it can be concluded that Indomethacin prolong release tablets using HPMC K15M and Na CMC as the retardant has successfully extended the release of indomethacin from its formulations. The mixing of two cellulose polymers, ionic and non-ionic, for the formulation of hydrophilic matrices, resulted in a valuable decrease in drug release rate. All the formulations showed Korsmeyer-Peppa's model as a best fit.

KEYWORDS

Indomethacin, prolong release, HPMC K15M, Na CMC

INTRODUCTION

Indomethacin (l-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid) is an anti-inflammatory antipyretic drug commonly used for symptomatic relief of pain and stiffness in rheumatic diseases.[1,2] Indomethacin has been known for years and has been the most successful non-steroidal anti-inflammatory agent available for the treatment of inflammatory diseases such as rheumatoid arthritis and osteoarthritis. The use of indomethacin in the traditional pharmaceutical dosage form such as tablets and capsules has required the ingestion of three or four unit doses per day.[3] Accordingly, it is important for the convenience of the patient and more particularly to ensure compliance by the patient to the particular therapeutic regimen that the number of unit doses per day be kept to a minimum.[4] It is also important to maintain a continuous anti- inflammatory serum concentration of indomethacin. This is particularly difficult to accomplish with the traditional pharmaceutical forms of indomethacin which are rapidly absorbed. These traditional forms result in initial high plasma concentrations of indomethacin which are then slowly metabolized to low blood levels. The length of time that indomethacin blood levels are at effective concentrations is far from optimal.[4,5]

Oral sustained release products provide an advantage over conventional dosage forms by optimizing bio-pharmaceutics, pharmacokinetics and pharmacodynamic properties of drugs in such a way that it reduce dosing frequency to an extent that once daily dose is sufficient for penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion. One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant.[6]

Preparation of sustained release formulation by matrix technique is a commonly employed method because of the ease of preparation, flexibility and cost effectiveness. Hydrophilic polymer matrix systems are widely used for formulating sustained release dosage form.[7,8]

Introduction of matrix tablet as sustained release has given a new breakthrough for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations.[9]

Drug release from hydrophilic matrix tablets is controlled by formation of a hydrated viscous layer around the tablet, which acts as a barrier to drug release by opposing penetration of water into tablet and also movement of dissolved solutes out of the matrix tablets.[10,11,12] The overall drug release process is influenced not only by drug solubility but also by the physical and mechanical properties of the gel barrier that forms around the tablet. The extent of matrix swelling, erosion, and diffusion of drug determine the kinetics as well as the mechanism of drug.[13] Hydroxypropyl methylcellulose (HPMC) is one of the most common hydrophilic polymers used in matrix systems.[14] It is a water-soluble hydrophilic, non-ionic cellulose ether; stable over the pH range 3.0–11.0 and is enzyme resistant.[15]

Controlled release preparations have been reported to reduce the gastro irritant and ulcerogenic effects of non-steroidal anti-inflammatory drugs.[16] It is therefore an object of this invention to formulate the extended release matrix tablets of Indomethacin to minimize or prevent drug release in the acidic environment of upper GIT and start releasing the drug in a controlled manner once it reaches the alkaline environment of small intestine.

MATERIALS AND METHODS

Materials: Indomethacin was obtained from Yarrow Chemicals (Mumbai). Hydroxypropyl methylcellulose (HPMC K15M) was obtained from Cognis, Germany. Sodium carboxy methyl cellulose (Na CMC) was obtained from Mingtai chemical co. LTD. Avicel PH105 MSA Cellulose products obtained from Khadakpur street, Kurnool, Super tab 21AN (Lactose monohydrate) was obtained from ACS chemicals, Sarkhej, Hyderabad. All other chemicals employed were of analytical reagent (AR) grade.

METHODS:

Preformulation Studies: Preformulation study is an investigation of physical and chemical properties of drug substance alone and in combination with excipients. FTIR [Fourier Transformer Infrared Spectroscopy] was used to study the drug-polymer interactions. IR spectrum of Indomethacin, sodium carboxy methyl cellulose, HPMC K15M and its physical mixtures was evaluated.

Formulation of Prolong Release Matrix Tablets: Matrix embedded prolong release tablet formulations of Indomethacin were prepared by wet granulation method. Different formulations (F1-F8) were prepared using various proportions of hydrophilic release retardant polymers like HPMC K15M, Na-CMC. Table 1 shows composition of each formulation. Avicel PH105 and Lactose monohydrate (Supertab 21AN) was used as diluent and filler respectively. The tablets were manufactured by wet granulation process using 1% polyvinyl pyrrolidone (PVP K30) binder in isopropyl alcohol (IPA) as granulating solvent. Accurately weighed quantities of pre-sieved drug and polymer(s) were mixed thoroughly and granulated with PVPK30.

The wet granules were sieved through 20 sieves and the final granules were blended with Alubra PG100, Aerosil 200 and talc and compressed using 9 mm punches on single station tablet press to obtain desirable tablet thickness and hardness.

Table 1: Composition Of The Indomethacin Prolong Release Matrix Tablets

Ingredients	% Composition of tablets							
	F1	F2	F3	F4	F5	F6	F7	F8
Indomethacin	75	75	75	75	75	75	75	75
HPMC K15M	50	100	150	-	-	-	100	50
Na CMC	-	-	-	50	100	150	50	100
Avicel PH 105	50	50	50	50	50	50	50	50
Super tab 21AN (lactose monohydrate)	160	110	60	160	110	60	60	60
Talc	10	10	10	10	10	10	10	10
Aerosil 200	2	2	2	2	2	2	2	2
Alubra PG100	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Average Weight of Tablet(mg)	350	350	350	350	350	350	350	350

Evaluation of Granules

Angle of repose: The flow property of the powder blend was determined by fixed funnel method.

Bulk density: Apparent bulk density was determined by placing granules in to a graduated cylinder and measuring the volume and weight.

Tapped density: Tapped density was determined by USP method II using tapped density tester (Electrolab tap density tester, USP, ETP-1020)

Carr's index and Hausner ratio: This was measured for the flow property of a powder to be compressed; as such they are measured for relative importance of inter-particulate interactions.

Evaluation of Matrix Tablets

Evaluation of physical properties of tablet formulation: All prepared matrix tablets were evaluated for thickness, hardness and loss on drying. Friability was determined using Roche friabilator. Hardness was measured by using Monsanto hardness tester. Weight variation was performed according to IP procedure.

Drug content: The drug content was determined wherein, ten tablets were randomly selected and allowed to equilibrate in 6.2 pH phosphate buffer solution overnight. The solution was filtered and after suitable dilution its absorbance was measured at 323nm by UV visible Spectrophotometer.

In vitro drug release studies: In vitro drug release of Indomethacin Extended release pellets was performed using USP type II apparatus with a stirring speed 50 rpm at 37±0.5°C in 900ml of 6.2 phosphate buffer. Samples of the medium are withdrawn at regular intervals and replaced by fresh medium, and the absorbance of the filtered samples was measured at 323 nm till 24hours and using 6.2pH buffer as blank.[17]

Release kinetics of drugs from matrix formulations: The in vitro release data was analyzed by the zero and first order kinetics equation as well as Higuchi's and Korsmeyer-Peppa's equation to understand the release profile and release mechanism.[18,19,20]

The following four equations hold the special position and are currently in common use due to their simplicity and applicability.

Zero Order Model: $X = K_0 t$……..1
First Order Model: $\text{Log } X = \text{Log } X_0 - K_1 t / 2.303$……..2
Higuchi Model: $Q = K_H t^{1/}$……..3
Korsmeyer-Peppa's Model: $Mt/M\infty = Kt^n$……..4

where, X_0 is initial amount of drug, X is amount of drug released at time t, $Mt/M\infty$ is the fraction of drug released at any time t; and K_0, K_1, K_H, and K are release rate constants for equations 1, 2, 3 & 4 respectively where n is the diffusional exponent, indicative of mechanism of drug release.

RESULTS AND DISCUSSION:

The characteristic peaks of pure Indomethacin showed O-H stretching at 2926.27 cm^{-1}, C=O stretching at 1691.50 cm^{-1}, C=C stretching at 1590.68 cm^{-1}, O-CH_3 stretching at 1432.98 cm^{-1}, O-H stretching at 932.74 cm^{-1} and C-Cl stretching at 751.25 cm^{-1}. IR spectrum of pure drug Indomethacin shows that all the functional groups peaks are present in drug physical mixtures. The absence of possible interaction between drug and polymer was confirmed by the characteristic peaks of functional groups in the IR spectra of drug, polymer and physical mixtures. Hence Indomethacin was compatible with all excipients used as wave numbers are almost similar for pure drug as well as drug excipients mixture IR spectrum of Indomethacin, drug and polymer physical mixtures is shown in figure 1 and 2 respectively.

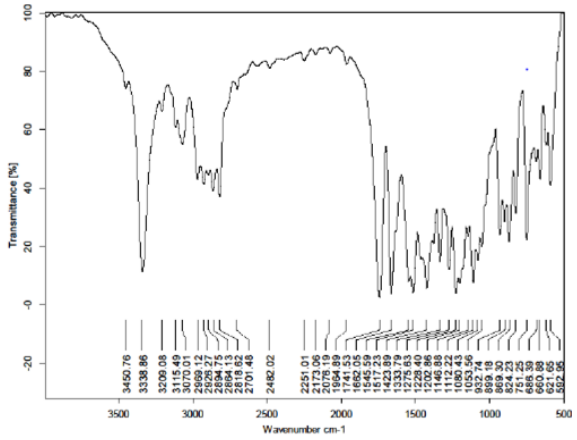

Figure 1: Ftir Spectrum Of Indomethacin

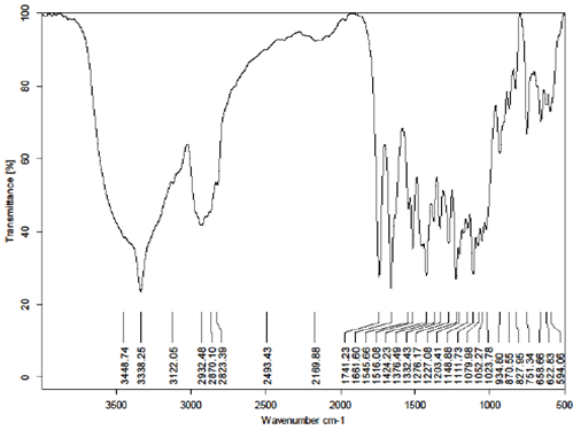

Figure 2: Ftir Spectrum Of Drug Physical Mixture

Evaluation of Granules: The formulated granules of different formulations were evaluated for their rheological properties like angle of repose, bulk density, tap density, Carr's compressibility index and Hausner ratio. The results are mentioned in table 2. The result of angle of repose indicates the good flow properties of all the formulated granules. The bulk density, tapped density, and Carr's index values also suggested that the prepared granules have good property regarding flow ability.

Table 2: Evaluation Of Granules

Formulation	Angle of repose* (^{0})	Bulk density* (g/ml)	Tapped density* (g/ml)	Carr's index* (%)	Hausner ratio*
F1	27.35±1.458	0.39±0.001	0.438±0.005	11.111±1.111	1.13±0.014
F2	28.70±1.436	0.37±0.002	0.418±0.005	12.222±1.123	1.14±0.014
F3	29.01±1.255	0.39±0.004	0.457±0.007	14.821±2.163	1.17±0.029
F4	28.85±0.808	0.44±0.002	0.526±0.011	16.471±1.176	1.16±0.017
F5	25.96±0.442	0.42±0.005	0.485±0.016	12.963±2.796	1.15±0.037
F6	25.78±0.548	0.38±0.004	0.434±0.011	12.959±1.216	1.15±0.016
F7	29.36±0.801	0.38±0.004	0.429±0.003	12.495±1.156	1.14±0.015
F8	28.31±2.005	0.41±0.001	0.479±0.018	14.710±2.823	1.17±0.039

*All the values are expressed as mean ± SD, n=3.

Evaluation of matrix tablets: Physical properties of tablet

formulation: The tablets were evaluated for the various physical properties and the results are mentioned in table 3.

Tablet Hardness: Hardness of the developed formulations F1 to F8 varied from 7.02±0.11 to 7.25±0.09 Kg/cm^2 in all the formulation indicating good mechanical strength with an ability to withstand physical and mechanical stress condition while handling.

Tablet Thickness: Tablets thickness was found to be F1 to F8 in the range 4.89±0.032mm to 5.13±0.018mm in all the formulation and the average thickness are within the range of ± 5%.

Friability: The loss in total weight of the tablets due to friability was in the range of 0.256% to 0.427% in all the formulation and the friability value is less than 1% which ensures that formulated tablets were mechanically stable.

Weight variation: All the formulations showed a deviation of not more than ± 7.5% (I.P. limit) for any of the tablets tested, the prepared formulations comply with the weight variation test, thus it fulfils the I.P. requirements.[21]

Uniformity of drug content: The drug content in different tablet formulations was highly uniform. The maximum drug content for all the formulation was found to be 99.19%. The minimum drug content for all the formulation was found to be 98.28%. It is in the limits specified by IP.[21]

Table 3: Physical Properties Of Tablet

Formulation	Thickness* (mm)	Hardness* (kg/cm^2)	Friability (%)	Weight Variation* (mg)	Drug content (%)
F1	4.97±0.020	7.19±0.08	0.308	±0.441	99.15 ± 2.50
F2	5.06±0.015	7.15±0.11	0.345	±0.31+3	98.35 ± 1.65
F3	5.12±0.020	7.52±0.10	0.364	±0.262	98.50 ± 1.55
F4	4.89±0.032	7.25±0.09	0.399	±0.270	99.19 ± 0.95
F5	4.96±0.020	7.02±0.11	0.420	±0.419	98.30 ± 1.34
F6	5.04±0.024	7.19±0.07	0.427	±0.469	98.80 ± 1.50
F7	4.95±0.025	7.05±0.10	0.347	±0.441	98.28 ± 2.07
F8	5.13±0.018	7.26±0.11	0.256	±0.506	98.49 ± 2.35

*All the values are expressed as mean ± SD, n=3.

***In-Vitro* release Study:** All the tablets formulations (F1- F8) examined, showed a prolonged pattern of drug release up to 24hrs. The results showed release of Indomethacin from sustained release tablets varied according to the types and proportion of matrix forming polymers (Table 4)

Table No 4: % Drug Release From The Formulations F1 To F8

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1	13.869	17.246	12.000	18.151	22.432	10.131	13.508	15.739
2	26.291	26.291	26.714	39.256	34.312	28.281	22.553	21.226
4	37.869	44.744	42.874	54.513	47.879	37.176	29.970	31.538
6	50.111	62.412	49.990	63.317	59.698	49.387	40.884	39.317
8	62.774	70.251	59.940	71.035	70.613	59.578	49.025	48.241
10	77.849	76.462	67.598	78.754	77.005	68.683	63.377	58.432
12	87.980	83.457	75.317	85.266	83.095	80.442	73.025	72.543
24	99.075	89.246	84.724	93.467	92.201	88.704	78.573	83.578

Prolong release matrix tablets prepared with HPMC K15M (formulations F1, F2 and F3 containing 50, 100, 150mg of HPMC K15M respectively) showed decreasing drug release rates as the polymer concentration increased. The % drug release of Matrix containing 150mg HPMC K15M (formulation F3) was found to be ~84%, at the end of 24 hr.

The percentage drug release rate from these formulations is F1 >F2>F3 respectively (figure 3). Similarly in-vitro release studies of formulations F4, F5 and F6 containing 50, 100, 150mg of Na CMC respectively indicated that increasing the concentration of the polymer in the matrix lead to slower drug release as presented in Figure 5. The % drug release of Matrix containing 150mg Na CMC (formulation F6) was found to be ~88%, at the end of 24 hr. The tablets formulation containing combined polymers of HPMC K15M and Na CMC (formulation no F7 and F8) showed slower rate in the drug release compared to other formulations. The release was found to be 83.578 and 78.573% at the end of 24 hour for formulations F7 and F8 respectively.

Interactions between HPMC and Na CMC provide the ability to overpass the burst effect of HPMC systems to the gel, formed on the surface of the tablet and the drug is delivered at a nearly constant rate.[22]The addition of ionic cellulose like Na CMC to a non-ionic cellulose like Hydroxypropyl methylcellulose gives an increase in viscosity. Hydrogen bonding between a carboxyl group of Na CMC and a hydroxyl group of Hydroxypropyl methylcellulose is stronger than between two hydroxyl groups of the same molecule of Hydroxypropyl methylcellulose. Thus blending of Na CMC with HPMC K15M produced increased gel viscosity, prolonging the drug release from the matrix tablets of Indomethacin.

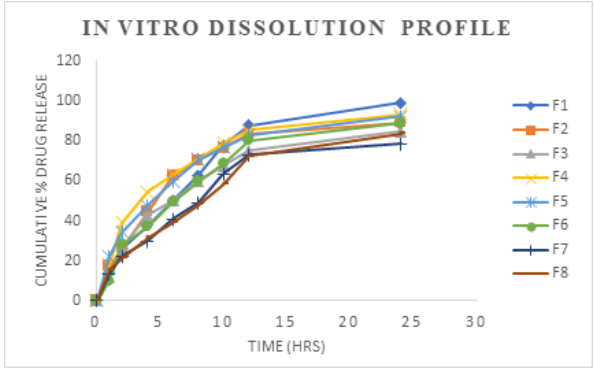

Figure 3: In-vitro Dissolution Profile Of Formulation F1-f8

Kinetics of Drug Release:

In order to understand the mechanism and kinetics of drug release, the results of the in-vitro dissolution study of the batches were fitted with various kinetic release model such as first-order model, zero-order model, Higuchi model, and Korsmeyer-Peppa's model. In Figure 4, the application of zero-order kinetics is presented. The first-order model is illustrated in Figure 5 whereas Figure 6 and 7 present drug release kinetics from Higuchi and Korsmeyer-Peppa's model respectively.

Correlation coefficients of formulation showed higher correlation with Korsmeyer-Peppa's model than zero order, Higuchi and first order. Release of all the formulations was found to fit with Korsmeyer-Peppa's model with regression value 0.9805 for formulation F7 and 0.9682 for formulation F8. The best linear relation were observed for matrix tablets (F7 and F8) by Korsmeyer-Peppa's kinetic. The release was dependent on both drug diffusion of drug through polymeric matrix.

Figure 4: Zero Order Release Kinetics

Figure 5: First Order Release Kinetics

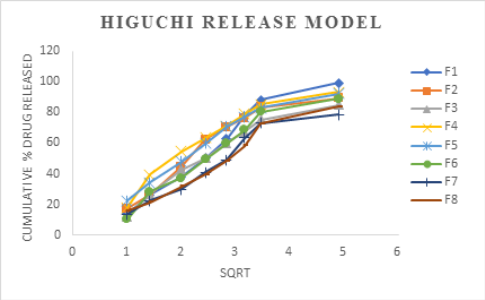

Figure 6: Higuchi Release Kinetics

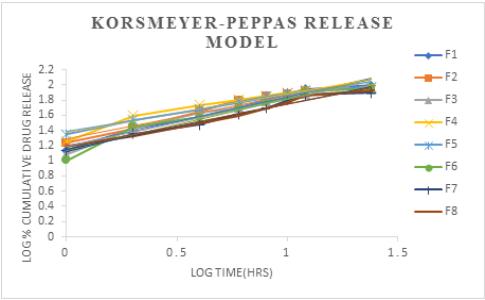

Figure 7: Korsmeyer-peppas Release Kinetics

CONCLUSION:

The study showed that matrix embedding technique using HPMC K15M and Na CMC as the retardant has successfully extended the release of indomethacin from its tablet formulations over a twenty four (24) hour period. The in vitro drug release decreased with increase in the polymer concentration.Analysis of drug release kinetics showed that the drug release from the formulations showed Korsmeyer-Peppa's as a best fit model.

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ABBREVIATION:

HPMC: Hydroxypropyl methyl cellulose
CMC: Carboxy methylcellulose
FT-IR: Fourier Transform Infrared Spectroscopy

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