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Design and invitro evaluation of gastro retentive oral matrix tablet formulations of ketorolac tromethamine

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Abstract---Ketorolac Tromethamine floating tablets were prepared by using combination of hydrophilic polymers such as Hydroxy Propyl Methyl Cellulose 4000 cps grade and 100000 cps grade. Eight set of formulations were prepared by gradual increasing and decreasing concentrations of above two polymers. The floating pattern was found to be instant for all the formulations and best controlled release profile was achieved for few set of formulations. The drug content, tablet weight, friability and weight variation were found to be within the limits. Validated UV spectrophotometric method was developed and standard linear regression was used to determine the concentration of

released drug during the course of dissolution. The release studies were subjected to zero order, first order, Higuchi and Ritger-Peppas kinetics and the parameters for controlled release were calculated.

Keywords---ketorolac tromethamine, floating tablets, gastro retentive, drug delivery, hydroxypropyl methylcellulose, UV method.

Introduction

Floating drug delivery was used to increase the gastric retention time and they remain float in the stomach for longer duration without affecting the gastric emptying rate. A floating formulation is for those drugs that act locally in gastrointestinal tract (GIT) and unstable in lower parts of GIT, or are poorly absorbed in the intestine [1]. Hydroxy methyl cellulose (HPMC) matrices hydrate rapidly only at the surface, retaining their original air bubbles and extending floatation beyond 8 h [2]. The formulation floating is associated with intrinsic density lower than that of the gastric content, which is reported as 1.004–1.010 g/cm³, or due to the formation of a gas inside the system after contact with gastric fluid [3]. Floating matrix systems containing HPMC as excipient begin to swell and form a gel layer with entrapped gas around the tablet core after contact with gastric fluid, whereas this gel layer controls the drug release [4-7]. Ketorolac is a non steroidal anti-inflammatory drug (NSAID) with strong analgesic activity (Figure 1) [8]. The minimum dose of ketorolac tromethamine is 10 mg, medium dose is 20 mg and does not exceed the dose of 40 mg per day. The aim of present study was to develop floating matrix tablets of ketorolac tromethamine and useful in avoiding the side effects associated with conventional dosage forms having the minimum and maximum strengths.

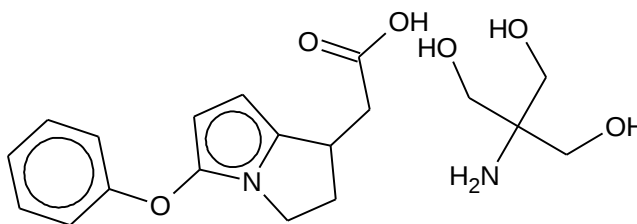


Figure 1. Ketorolac Tromethamine

Materials and methods:

Materials

Ketorolac tromethamine, Hydroxy Propyl Methyl Cellulose 4000 cps and 100000 cps were purchased from Laser Chemicals, Ahmedabad, India. Talc and all other ingredients used were of analytical grade and were used as received.

Analytical Method

A validated UV spectrophotometric method was performed by using single beam Analytical Technologies loaded with UVWin software with 1-cm matching quartz cells, using methanol 20 % (v/v) - pH 1.2, Hydrochloric acid at 315 nm was used for the estimation of drug in bulk, formulations, and dissolution samples. The results of the analysis and overlay Spectra were shown in the Table 1 and Figure 2.

Table 1: Calibration data of the validated method

Conc. (mcg/mL)	Mean Abs	Std. Deviation¥	RSD†	Std. Error
4	0.222	0.003	1.34	0.001
8	0.433	0.007	1.79	0.002
12	0.654	0.006	1.02	0.002
16	0.855	0.01	1.22	0.003
20	1.114	0.018	1.62	0.006

¥ Standard deviation, series of (n=9) determinations

† Relative standard deviation, (<3% indicates the reproducibility of the method)

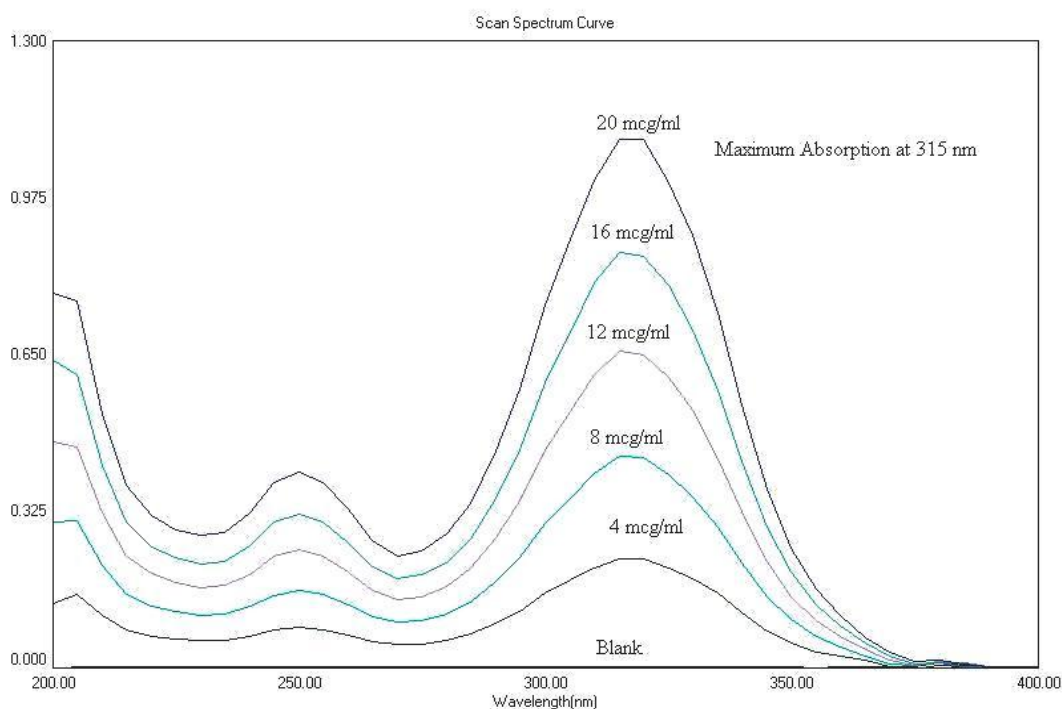


Figure 2: Overlay spectra of each concentration in the range of 4 to 20 (mcg/mL)

Characterization of Bulk Drug and Effect of Formulation Excipients

The active pharmaceutical ingredient was characterized by using FT-IR spectra and certificate of analysis. The infrared (IR) spectrum obtained from Bruker alpha FTIR instrument and calibrated with polystyrene (IR Standard) was compared with that of the standard. To determine the compatibility of excipients with drug, solid samples were prepared by combining the drug with each excipient individually in the ratio of 1:20 and then stored in airtight containers at $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$ with 65% relative humidity (RH) $\pm 5\%$ RH for a period of six months. The prepared solid samples were characterized and given in Figure: 3.

Preparation & Physical characterization of Tablets

Ketorolac tromethamine floating matrix tablets were prepared by taking 20 mg of drug per tablet (number of tablets per batch = 20), were passed through mesh # 80 separately. The drug was mixed with the polymers as mentioned in Table 2. The powder blend was then lubricated with talc (2% w/w), and this lubricated blend was compressed into tablets using 6 mm flat-face round tooling on a single punch tablet machine (Rimek Ahmedabad, India) 10 station compression machine. The compression force was adjusted to obtain tablets with hardness in range of 5 to 6 kg/cm². The formulations are shown in Table 2.

The tablet hardness, friability, weight variation, and drug content uniformity of all tablet formulations were found to be satisfactory and reproducible as observed from the data in Table 2. Tablet hardness was found to be good (between 5 and 6 kg/cm²) and friability was less than 0.5% (w/w).

Table 2: Tablet Formulations*†

Formulations	F1	F2	F3	F4	F5	F6	F7	F8
Ketorolac (%)	20	20	20	20	20	20	20	20
HPMC 4000 cps (%)‡	85	75	65	55	45	35	25	15
HPMC 100000 cps (%)‡	5	15	25	35	45	55	65	75
Drug content (mg/tablet)	98% to 103% was observed. (Mean of triplicate with Relative Standard Deviation <3% indicates reproducibility of the assay)							
Weight variation (%)	Weight variation was found to be 3 to 5 %							
Hardness (kg/cm ²)	Hardness was fixed in the range of 5 to 6 kg/cm ²							
Friability % (w/w)	The formulations was fall in the rage of 0.32 to 0.5 %							

* n=20 (Each formulation was consisting of 20 tablets)

† (2% of talc was added to each formulation)

‡ (HPMC 4000 cps & HPMC 100000 cps were of directly compressible grades)

In Vitro Dissolution Studies

The dissolution study (n=6) was performed using USP apparatus (model TDT-06T, Electrolab, Mumbai, India) attached with paddles (50 rpm) at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ using 900 mL of Hydrochloric acid having pH of 1.2; as a dissolution medium. At the

predetermined time interval, 10 mL samples were withdrawn, filtered through a 0.45 μm membrane filter, diluted, and assayed at 315 nm using a Analytical Technologies, UV-Visible single-beam spectrophotometer. Cumulative percentage drug release was calculated using linear regression equation {Absorbance = 0.055 (Concentration) – 0.006} obtained from a calibration curve.

Kinetic Modelling of Drug Release

Dissolution of polymers plays an important role in regulating the release of drug in the case of lower viscosity grades of HPMC and for water-insoluble drugs [9]. Several drug release kinetic models have been proposed to describe the release pattern of a drug from a controlled release polymer matrix. The following equations are generally used, because of their simplicity and applicability [10], [11]: Equation 1, the zero-order; Equation 2, Higuchi's square-root; and Equation 3, the Ritger-Peppas.

$$M_t/M_\infty = K_0 t \quad \text{Equation (1)}$$

$$M_t/M_\infty = K_H t^{1/2} \quad \text{Equation (2)}$$

$$M_t/M_\infty = K t^n \quad \text{Equation (3)}$$

where M_t/M_∞ is the fraction of drug released at any time t ; and K_0 , K_H , and K are release rate constants for Equations 1, 2, and 3, respectively. In Equation 1, n is the diffusion exponent indicates mechanism of drug release. In the case of cylindrical tablets, a value of $n = 0.45$ indicates Fickian or case I release; $0.45 < n < 0.89$ indicates non-Fickian or anomalous release; $n = 0.89$ indicates case II release; and $n > 0.89$ indicates super case II release.

Characterization of Release Kinetics

The order and mechanism of ketorolac tromethamine release from the floating matrix tablets were determined by fitting the data in the Equations 1, 2, and 3. The values of K_0 , K_H , and K , n , and r (correlation coefficient) were determined. Based on the value of n obtained by fitting the data into Equation 3, is helpful in describing the mechanism of drug release from the formulation [12]. In case of the Fickian release, the rate of drug release is less than that of polymer relaxation. So the drug release is chiefly depends on the diffusion through the matrix. In the non-Fickian (anomalous) case, the rate of drug release is due to the both drug diffusion and polymer relaxation. Case II release refers to the polymer relaxation [10].

Results and Discussion

Characterization of Bulk Drug and Effect of Various Formulation Excipients

FTIR spectra of pure drug and solid samples of ketorolac tromethamine with various excipients used in the preparation of floating matrix tablet formulations, characterized after six months of storage, are given in Figure 3. The spectrum indicates the s of drug with various excipients

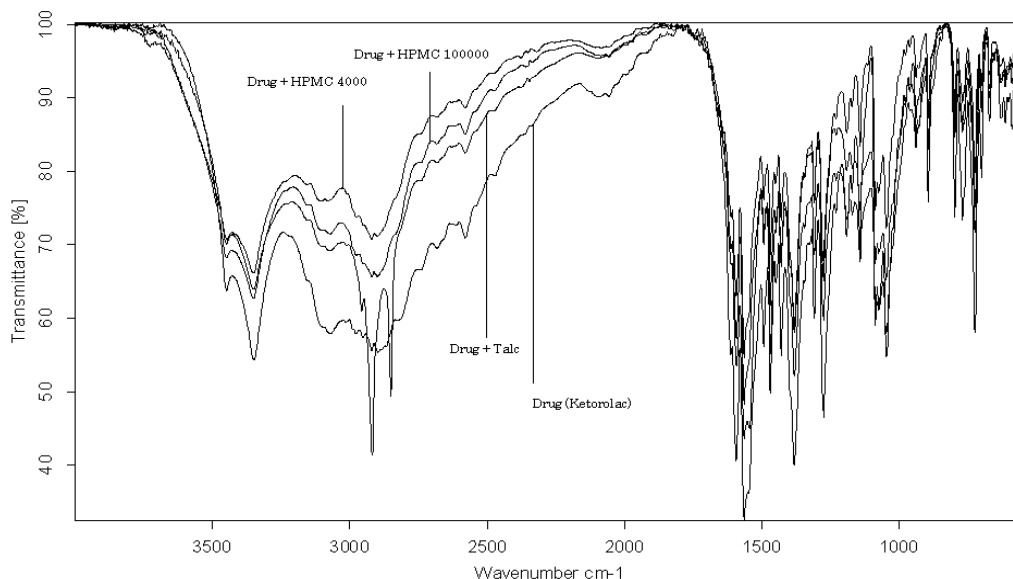


Figure 3. FTIR Spectra of drug and inert excipients

Release Rate Studies

The kinetic parameters for all the formulations are given in Table 3. A plot of cumulative percentage released vs time for floating matrix tablets of ketorolac tromethamine prepared using different proportions of HPMC 4000 cps and HPMC 100000 cps, with hardness 5 to 6 kg/cm², is shown in Figure 4. The initial percentage released for the first thirty minutes varied between 24 to 5% for all the formulations. However, in the later stages, the release was found to be slower and more controlled in the tablets with a higher proportion of the polymer. The release of the drug from the tablets extended as the polymer proportion was increased from 35% to 75%. The release extended from 12 hours in the case of 25% (F3) to more than 24 hours in the case of 75% (F6 to F8) polymer proportion. In the case of F7 and F8, 100% drug release was not observed after 24 hours of dissolution because of the high polymer proportion used in the formulation. The release rate was dependent on the proportion of polymer.

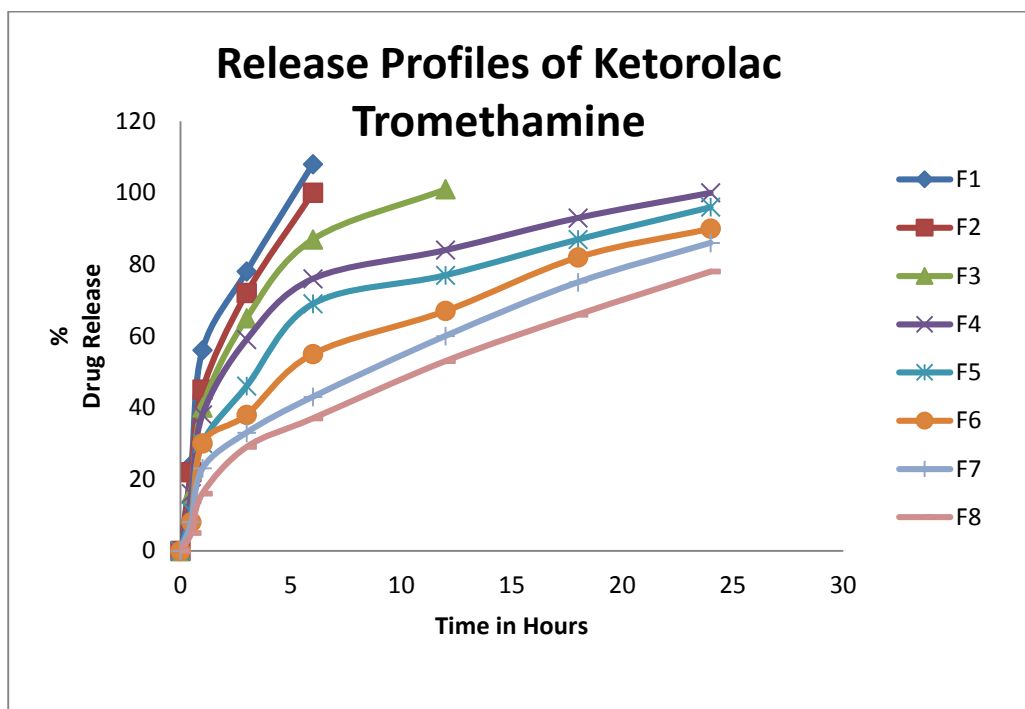


Figure 4. Release profiles of Ketorolac Tromethamine

Table 3. Release characterization of Ketorolac Tromethamine

Release Kinetics	Parameter	F1	F2	F3	F4	F5	F6	F7	F8
Zero order	r *	0.899	0.93	0.9	0.759	0.807	0.873	0.933	0.93
	K	13.47	13.09	11.71	3.69	3.8	3.603	3.406	3.15
First order	r *	0.977	0.992	0.908	0.958	0.967	0.985	0.988	0.989
	K	0.169	0.141	0.059	0.056	0.05	0.037	0.032	0.024
Higuchi Square Root Eqn.	r *	0.95	0.982	0.931	0.901	0.935	0.963	0.988	0.992
	KH	44.25	42.8	29.74	18.02	18.77	17.87	17.38	16.35
Ritger Peppas Eqn.	r *	0.908	0.958	0.91	0.894	0.909	0.878	0.938	0.938
	K †	3.76	4.62	6.29	17.21	19.31	23.25	28.81	30.93
	n ‡	0.501	0.425	0.51	0.42	0.64	0.532	0.54	0.63

* Correlation coefficients

† Release rate constant for Ritger-Peppas equation.

‡ Diffusional exponent indicative of release mechanism in Ritger-Peppas equation.

Conclusions

Floating matrix tablets of ketorolac tromethamine were conforming to good quality was prepared using HPMC by the direct compression method. Release of the drug from the matrix tablets was depending on amount as well as viscosity of HPMC

used. The designed tablets, which release 5% to 24% of drug in the first thirty minutes and extend the release up to 12 to 24 hours, can overcome the disadvantages associated with conventional tablet formulations.

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