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Investigation of certain varieties of carbopol in ketorolac tromethamine hydrophilic matrix tablet formulations and evaluation of the kinetics of its in vitro release

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Abstract

Matrix tablets of ketorolac tromethamine (KT) were prepared by direct compression technique and Carbopol 934, 940 and 1342 have been used as polymers in different concentrations (5-15 %). For the quality control of tablets; physical tests as crushing strength, diameter-height ratio and friability, KT amount assay and *in vitro* dissolution techniques were performed and dissolution profiles were plotted and evaluated kinetically. The *in vitro* release kinetics of ten different formulations of KT matrix tablet were studied at pH 1.2 and pH 7.0 using the USP dissolution technique and apparatus with basket assembly. Dissolution results were evaluated kinetically and statistically. According to our results, different types and concentrations of carbopol to tablet formulations may effect in controlled drug release.

Key words: Hydrophilic matrix tablet, Carbopol, Ketorolac tromethamine, *In vitro* release kinetics, Sustained release

1. Introduction

Hydrophilic matrices became extremely popular in controlling the release of drugs. When designing an oral sustained release formulation, the hydrophilic matrices present an alternative to other pharmaceutical dosage forms. They have several advantages such as; ease of manufacture, low production cost, the possibility of introducing large proportions of the drug and the wide range of release profiles, and the manufacturing processes are relatively straight forward. In the formulation of hydrophilic matrices, a wide range of polymers can be employed among which the group of acrylic acid derivatives, known officially as Carbomers or by their commercial name Carbopol® were included (1).

Malamataris and Ganderton (2) showed that the combination of diffusion and erosion release mechanisms in a matrix systems comprising an insoluble hydrophobic and a hydrophilic gel-forming part depends greatly on the wettability of the added drug. They used

Carbopol 934 to be a hydrophilic gel-forming element. Malley et al. (3), prepared controlled release matrix tablet of sodium salicylate using Carbopol 934. Their studies carried out with thin sheets of various concentrations of sodium salicylate pressed into Carbopol matrix in synthetic gastric liquid have got insight into the phenomenon of matter transfers, both transfers of liquid and drug take place with a swelling of the matrix and drug release in the liquid ad the result. Şenel et al. (4), studied factors affecting the formulation of sustained release potassium chloride tablets. Polyvinyl chloride, carbomer, methylcellulose and glycerol palmitostearate were used as matrix materials in their investigation. Hardness had no marked effect on release characteristics except for wax matrices. With hydrophilic matrices, for methylcellulose, increased matrix material concentration did not effect the release profile, but for carbomer, as the concentration increased, a significant decrease in released amount was obtained.

The release of lithium carbonate incorporated into polymethylmethacrylate, polyvinyl chloride, hydrogenated vegetable oil and carbomer (carbopol 934) was studied in vitro by Çiftçi et al. (5). The formulation containing 10% carbomer showed a sustained release profile comparable to that of a standard.

Three different sustained release agents, i.e., Compritol 888 (glyceryl behenate), Klucel HXF (hydroxypropylcellulose) and Carbopol 934 P (carbomer) had been used to prepare theophylline tablets with a desired release rate of approximately 50% in 6h by El-Sayed et al.(6). The effect of incorporating different excipients with different water and acid solubility on drug release was investigated. The release profiles of glyceryl behenate tablets were best described by the linear square root of time dependence, indicating a diffusion controlled mechanism. They studied that comparative bioavailability of theophylline tablets with different sustained release kinetics in their second study (7). The sustained release agents were Compritol, glyceryl behenate, Klucel HXF, hydroxypropyl cellulose, and carbopol 934. These polymers containing tablets provided much slower drug release in vivo than the respective control tablets.

KT was absorbed rapidly (Tmax <hr) and efficiently (>87%) following oral and intramuscular doses. Its plasma half-life ranged from 1.1 to 6.0 hr and its single dose was 10-30 mg. (8). KT was 36 times more potent than phenylbutazone, approximately twice as potent as indomethacin and 3 times more potent than naproxen in systemic anti-inflammatory activity. Its analgesic activity was stronger than aspirin. Clinical studies indicated that single dose efficacy of KT was greater than that of morphine, pethidine and pentazocine in moderate to severe postoperative pains (9). For this reason, KT was used in our study.

Matrix tablets of KT were prepared by direct compression techniques and to achieve this, Carbopol 934, 940 and 1342 have been used as polymers in varying concentrations in the present work. For the quality control of tablets, physical control and in vitro dissolution techniques were performed. Dissolution profiles of each tablet were plotted and evaluated kinetically and statistically. The effect of polymer types and their concentrations on release behaviour and physical properties of matrix tablets were also investigated.

2. Materials and Methods

2.1. Materials

Ketorolac tromethamine; Dr. Reddy's laboratories (TD), Carbopol; Goodrich. All the other chemicals were of analytical grade. Tablet machine; Erweka, granulator; Erweka, friabilator; Roche, hardness apparatus; Monsanto, dissolution apparatus; Aymes, pH meter; Bilmar model 101, UV spectrophotometer; Shimadzu UV-visible recording spectrophotometer 160 A.

2.2. Methods

2.2.1. Preparation of tablets

Ten formulations were prepared on an instrumented single-punch tablet machine by direct compression technique. Magnesium stearat was used as the lubricant (2.5 % w/w) and Carbopol 934, 940 and 1342 were the polymers in different concentrations (5-15 % w/w). Contents of matrix tablet formulations are given in Table 1.

Table 1. Content of matrix tablet formulations

	Tablet Code No									
Contents	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
KT (mg)	14	14	14	14	14	14	14	14	14	14
Amylum(mg)	26	26	26	26	26	26	26	26	26	26
Carbopol 934(%w/w)	-	5	10	15	-	-	-	-	-	-
Carbopol 940(%w/w)	-	-	-	-	5	10	15	-	-	-
Carbopol 1342(%w/w)	-	-	-	-	-	-	-	5	10	15
PVP (mg)	10	10	10	10	10	10	10	10	10	10
Lactose (mg)	50	50	50	50	50	50	50	50	50	50
Mg Stearat (%w/w)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

2.2.2. Physical tests

The following tests were applied to the tablets; Amount of KT, crushing strength, diameter-height ratio and friability. Tablet weight uniformity was calculated according to USP XXIV and tablet thickness was determined using a micrometer. Tablet hardness tests were carried out using a Monsanto hardness tester. For friability tests, twenty tablets were weighed (W_1) and rotated at one hundred revolutions for 4 min in a Roche friabilator. The tablets were weighed again (W_2) and the percentage friability (%F) was calculated using Equation 1.

$$\%F = [(W_1 - W_2) / W_1] 100 \quad \text{Eq. 1}$$

2.2.3. Amount of KT

Spectrophotometric method was used for KT assay (10). For this purpose 15.0 mg KT was weighed accurately and dissolved in simulated gastric medium (SGM, pH 1.2) and the volume adjusted to 100 ml. Six samples of 1-6 ml were taken from this stock solution and diluted to 50 ml with the same medium. Absorbances of these samples were measured at 323.0 nm and the quantitative assay results were plotted therefrom. Regression equation and regression coefficients were then calculated. The same procedure was repeated with pH 2.5, 4.5, 7.0 and simulated intestinal medium (SIM, pH 7.5).

2.2.4. In vitro dissolution test

Dissolution tests were performed according to the basket method described in USP XXIV, Apparatus II. The rotating paddle was 50 rpm and the temperature was 37±0.5°C. Dissolution studies were carried out in 600 ml of dissolution medium prepared from SGM and SIM without enzymes and changed at certain times and the pH values of the fluids were; 0-1 h: pH=1.2, 1-2 h: pH=2.5, 2-3.5 h: pH=4.5, 3.5-5 h: pH=7.0 and 5-8 h: pH=7.5.

5 ml of samples were taken from the dissolution media at appropriate time intervals with the aid of an injector fitted with a Schleicher-Schuell filter paper. An equal volume of the same medium was returned to the system after each withdrawal. Absorbances of the samples were measured at 323.0 nm against blank by using an UV spectrophotometer. Placebo tablets corresponding to each formulation were used as blank. The amounts of KT released were evaluated by using the standard calibration curve equation. Six tablets were used for each test.

2.2.5. Evaluation of release kinetics

The results thus obtained were evaluated kinetically by zero, first - order, Hixson Crowell, RRSBW, Q Square Root of Time, Higuchi equation, Spherical, Cylindrical and Slab Erosion (the rate constant k', k" and k"' were obtained according to Hopfenberg). The release

rate constants (k), correlation coefficients (r) and determination coefficients (r^2) were calculated by means of a computer program (11).

The in vitro release profiles (percentage of drug released versus time) obtained from the KT matrix tablet formulations were fitted to the main models which have been proposed to describe drug release kinetics from tablets and other polymer matrices. A polynomial mathematical equation was also explained for describing release profiles. Three different models were used to evaluate release profiles. Model equations used for the evaluations are given in Table 2.

Table 2. Model equations

MODELS	EQUATIONS
Model 1	$\sqrt[3]{100} - \sqrt[3]{w} = k.t$
Model 2	$w = a + bt + ct^2$
Model 3	$\log w = \log w_o - kt$

SPSS-6 statistical programme was used for statistical evaluations.

2.2.6. Statistical Analysis

In order to demonstrate any change of the drug release from KT tablets which mainly results from modifications of tablet formulations, the presence of different types and concentrations of polymers in tablet formulations were evaluated statistically. Statistical analysis were performed for each group of formulation using regression and co-variance analysis.

3. Results and Discussion

The physical characteristics of the KT tablets are given in Table 3 (n=10). These tablets provided good weight uniformity and friability (F< 0.5%). These results were in accordance with the pharmacopoeia limits.

Drug release profiles are given in Figures 1-3. The drug release from matrix tablets depended upon the concentration of Carbopol. When F1 matrix tablets (without carbopol) were investigated for their release behaviour, KT release was 76% in the first sixty mins. The release of KT from matrix tablets was significantly slower than that of control tablets (F1).

On the other hand, as observed in F2-10 formulated tablets, the amount of Carbopol has an important effect on the release rate of the drug. An increase in Carbopol content resulted with a slow release rate of drug as was expected. Therefore, the ratio of drug to polymer was

Table 3. Tablet specifications (n=10).

Tablet Specifications	Tablet Code No									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
KT amount(mg)	14.07 ±0.39	14.01 ±0.27	13.87 ±0.11	14.00 ±0.09	13.89 ±0.55	14.10 ±0.51	14.08 ±0.66	14.18 ±0.41	13.91 ±0.26	14.15 ±0.34
Hardness (kg)	1.0	1.5	2.7	3.0	1.7	2.5	3.2	1.5	2.7	3.2
Friability (%)	0.01	0.46	0.32	0.25	0.35	0.34	0.22	0.33	0.30	0.13
Diameter-height ratio	4.76	4.76	4.63	4.38	4.76	4.50	4.15	4.76	4.63	4.50
Tablet weight (mg)	102.0 ±0.51	107.6 ±0.15	112.7 ±0.12	117.7 ±0.12	107.6 ±0.06	112.6 ±0.15	117.9 ±0.24	107.6 ±0.14	112.8 ±0.10	117.7 ±0.11

observed to be an important factor in the release rate of drug. The drug release from Carbopol tablets with different concentrations was approximately 28 to 100% over 6 h. According to these results, tablets prepared with 5% Carbopol 1342 (F8) were found to be the most suitable formulation for KT followed by 15% Carbopol 934 (F4) and 15 % Carbopol 940 (F7). The effects of drug /matrix ratio on the release of KT from matrix tablets are shown in Figs 1-3. These results showed that variables, associated with the type and proportion of Carbopol, play an important role in the release characteristics of the active compound.

In the present investigation, controlled release tablet forms containing different types of polymers were developed. Using different types and concentrations of polymers, it was planned to prolonged the drug release and compared the effect of polymer type and concentrations.

3.1. Results of release profiles

Figs 1-3 show KT release profiles (n=6) from the tablets. Percentage of drug released from tablet formulations were examined and it was observed that KT tablets formulated with different types of Carbopol showed slower release of KT than the control (F1). It was also observed that complete KT release from polymer containing tablet formulations lasted for 8 hrs. From these results it appears that polymer type and concentrations are the main factors for improving the formulation and also effecting time-dependent characteristic changes such as the drug release rate from dosage forms. Carbopols are high molecular weight polymers of acrylic acid cross-linked with polyalkenyl ethers of sugars or polyalcohols. They have different molecular weight and viscosity. These properties may effect in controlled release formulations. For this reason, the different carbopols gave different release profiles.

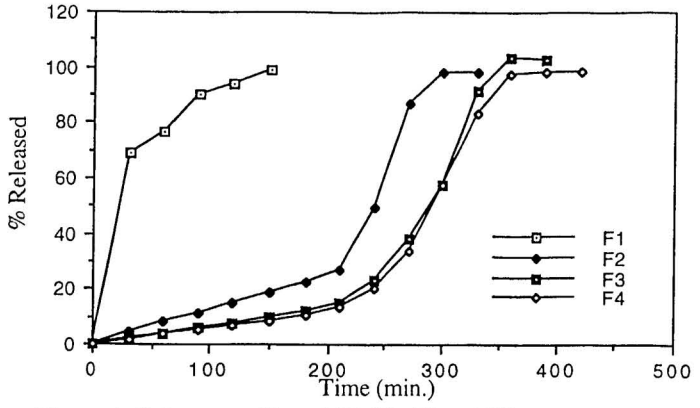

Figure 1. Release profiles of F1, F2, F3 and F4.

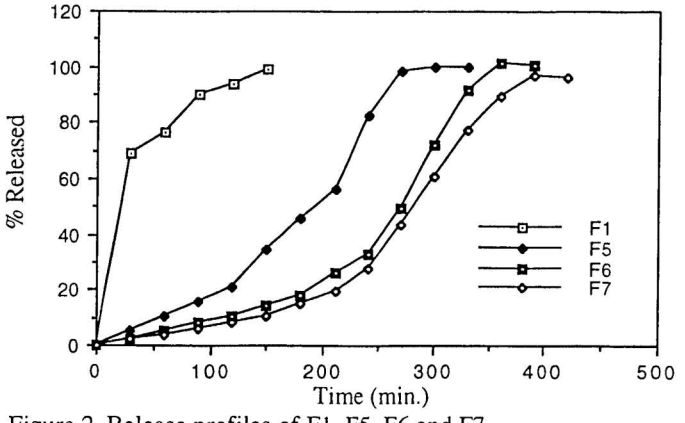

Figure 2. Release profiles of F1, F5, F6 and F7.

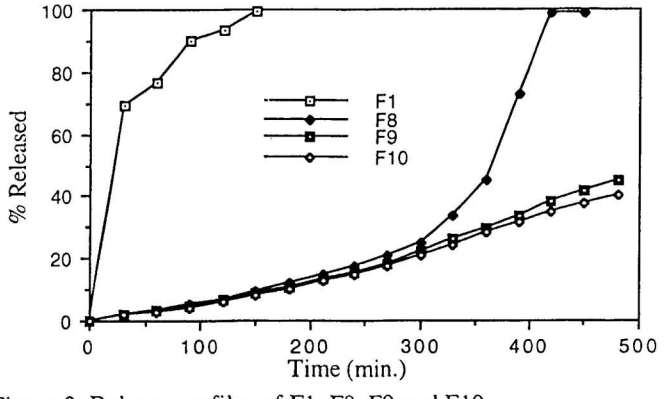

Figure 3. Release profiles of F1, F8, F9 and F10.

The matrix tablets prepared with Carbopol 1342 (5%) (F8) showed the best fit to zero-order kinetic according to the Akaike's Information Criteria (AIC), Weighted Sum of Squared Deviations (WSSD) and R square (r^2) results. The kinetic assessment of dissolution rate of F8 is given in Table 4. The best three kinetics according to r^2, WSSD and AIC were zero-order, Modified Hixson-Crowell and RRSBW Kinetics. As for the kinetic evaluations the highest determination coefficient and the best linear relation were observed for matrix tablet (F8) by the zero-order kinetic. Graphically zero-order distribution gave a straight line (Fig 4).

Table 4. Kinetic Assessment of Release Data for Formulation F8

KINETICS		
Modified Hixson-Crowel	r^2	0.9709
	A	1.9357
	B	$1.8044 \cdot 10^{-3}$
	AIC	-22.8865
	WSSD	0.1054
First order	r^2 0.5929	
	Kr^1	$0.8107\ h^{-1}$
	AIC	5.3271
	WSSD 0.2912	
Zero order	r^2	0.9780
	Kr^0	2.2408 mg/h
	AIC	-13.9789
	WSSD	0.1857
Hixson-Crowel (Sink)	r^2	0.7882
	Slope	$1.3127 \cdot 10^{-3}$
	Rate	$5.4937 \cdot 10^{-2}$ mg/h/cm^2
	AIC	-6.3828
	WSSD	0.8453
RRSBW	r^2	0.9172
	T%63.2	269.9063 min
	B	2.2330
	AIC	-17.0222
	WSSD	0.1901
Q $\sqrt{t}$	r^2	0.9266
	K	0.1043
	AIC	-7.2674
	WSSD	0.6200
Higuchi	r^2	0.6916
	Slope	$1.2155 \cdot 10^{3}$

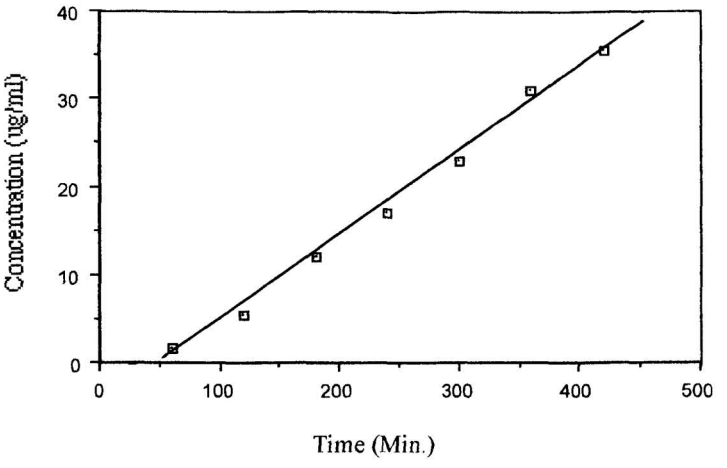

Figure 4. Release of KT from matrix tablet (F8) according to the zero-order kinetic

3.2. Results of statistical analysis

Both control and prepared tablet formulations were evaluated statistically for three different models. The significance of slope values for three models were controlled for all formulations. Tests for significant differences between model slopes were carried out by analysis of co-variance (ANCOVA). The differences between the control group and Carbopol containing formulations were found statistically significant. From the results of ANCOVA between each concentration and type of polymer and control group the significance of slope values were different for each model ($p<0.001$). There was a statistically significant difference between the release profiles of Carbopol containing formulations and the profile corresponding to the control ($p<0.05$).

4. Conclusion

In conclusion, it was shown that the addition of different types and concentrations of polymer to tablet formulations could result in controlled drug release and thus different release profiles obtained could best explain the effects of different types and concentrations of the polymer in matrix tablet formulations.

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