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SUSTAINED RELEASE WAX MATRIX FORMULATIONS OF KETOROLAC TROMETHAMINE WITH COMPRITOL 888 ATO AND HD 5 ATO

KETOROLAK TROMETAMIN'İN COMPRITOL 888 ATO VE HD 5 ATO'LU SÜREKLİ ETKİLİ MUM MATRİKS FORMÜLASYONLARI

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Sustained release wax matrix tablets of ketorolac tromethamine (KT) were prepared with different concentrations of Compritol 888 ATO (Glyceryl behenate) and HD 5 ATO (Glyceryl and Polyethylene glycol behenate). Tablet matrix systems containing Compritol have extensively been used in oral sustained-release drug delivery system formulations. Direct compression tecnique was used to prepare the tablets and the effect release of excipients and their concentrations on drug were investigated. Physical controls and in vitro dissolution techniques were performed for quality assesment. Dissolution profiles of the tablets were plotted and evaluated kinetically.

Farklı konsantrasyonlardaki Compritol 888 ATO (Gliseril behenat) ve HD 5 ATO (Gliseril ve polietilen glikol behenat) ile ketorolak trometamin'in sürekli etkili mum matriks tabletleri hazırlanmıştır. Compritol içeren matriks sistemler, peroral sürekli etkili ilaç salıveren sistemleri geliştirmek için deneysel formülasyonlarda yaygın olarak kullanılmaktadır. Tabletleri hazırlamak için direkt basım tekniği kullanılmıştır. Eksipientlerin ve konsantrasyonlarının ilaç salımına etkisi araştırılmış, tabletlerin kalite kontrolu için , fiziksel yöntemler yanında in vitro dissolüsyon çalışmaları yapılmıştır. Her tabletin dissolüsyon profili çizilmiş ve kinetik olarak değerlendirilmiştir.

Keywords : *Sustained release; Wax matrix; Ketorolac tromethamine; Compritol 888 ATO; HD 5 ATO*

Anahtar kelimeler Sürekli etki; Mum matriks; Ketorolak trometamin; Compritol 888 ATO; HD 5 ATO

Introduction

Wax matrix dosage forms are utilized to incorporate drugs into inert water insoluble matrix materials. Many types of matrix forms, including granules and tablets, in an attempt to obtain effective sustained release systems have been used. In order to examine the function of a wax matrix system as a barrier for the controlled release of oral dosage forms, reservoir devices were prepared and dissolution tests were carried out. It was reported that after dissolution of the active or water-soluble ingredients in a wax matrix, the wax matrix system becomes porous without disintegrating and this porous structure is used as a barrier for control of the drug dissolution rate, as is the insoluble polymer membrane (1, 2).

Tablet matrix systems containing Compritol have extensively been used in formulations for developing oral sustained release drug delivery systems. Compritol 888 ATO has good compressibility and binding properties to build matrices when it is used at appropiriate levels in tablets. It can be used as lubricant in tablets and hard shell capsules. Tablets which were prepared with Compritol 888 ATO can provide good mechanical properties (3-5).

Concerning the mechanism of drug release from a homogenous matrix system, Higuchi was the first to theoretically treat the matrix model and to show that the amount of a drug released per unit surface area was proportional to the square root of the

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time. The amount of total drug released from such a system into a bathing medium acting essentially as a perfect sink would be determined by the relationship,

$$Q = \sqrt{Dt}\,(2A - Cs)\,Cs, \qquad \text{(Eq. 1)}$$

where Q=the amount of drug released after time (t) per unit exposed area, D= the diffusitivity of the drug in the matrix media, A= the total amount of drug present in the matrix per unit volume, and Cs= the solubility of the drug in the matrix substances (6).

Ishino and Sunada (7) carried on studies to evaluate the effect of the solubility of the drug and the matrix structure on the drug release rate. They examined the releationship between porosity and tortuosity representing the matrix structure using modified Higuchi equation. They found that the tortuosity formed in the matrix tablets varied with the drug even though the porosity was the same, and also the dependency of tortuosity on porosity varied.

The *in vitro* release kinetics of eight commercially available controlled-release preparations were studied at pH 1.0-7.5 using the USP dissolution apparatus. The kinetics of the dissolution process were determined by using four kinetic equations, namely; zero-order, first-order Higuchi's square root equations and Hixson-Crowell cube root law. The results were found to obey both the first order and the Higuchi square root equations showing that the dissolution process is diffusion and dissolution-controlled (8).

Xu and Sunada (9) studied the influence of formulation on drug release kinetics from hydroxypropylmethyl-cellulose (HPMC) matrix tablets and found that the release mechanism varied accordingly with formulation. HPMC content was the predominant controlling factor

Velasco et al. (10) investigated the *in vitro* evaluation of sustained release matrix tablets prepared with new modified polymeric carbohydrates. The study of the rheological and compressional properties of sustained release matrix tablets prepared with new polymers obtained by graft copoly-merization of methyl methacrylate on various carbohydrates was the main purpose of their work. All the mixtures had good flow properties, but mixtures of cellulose derivatives gave the best values.

Bain et al. (11) studied the comparison of the in vitro release characteristics of a wax matrix and a hydrogel sustained release diclofenac sodium tablet. Wax matrix tablets exhibit classic diffusion-controlled release of drug down tortuous pores release is relatively independent of rotation speed, except when unprotected from abrasion. Hydrogel tablets exhibited zero-order release which is a dynamic equilibrium existing between rate of gel swelling and erosion.

Ketorolac tromethamine (KT) is a non-steroidal drug with potent analgesic and anti-inflammatory activity and is absorbed rapidly (Tmax < 1.0h) with a bioavailability of >87% following oral and intramuscular administration (12-17) and Kamath et al. (18) studied the spectro-photometric determination of KT.

Wax matrix tablets of KT were prepared by direct compression technique in the present work. To achieve this compritol 888 ATO and HD 5 ATO were used as wax matrix excipients in different concentrations (10-50 %).The formulations of all matrix tablets are given in Table 1. The effect of excipient concentration on drug release was investigated. For the quality control of tablets physical controls and *in vitro* dissolution techniques were performed. Dissolution profile of each tablet was plotted and evaluated kinetically.

Materials

KT was obtained from Dr. Reddy's Laboratories Ltd., India. Compritol 888 ATO (GRAS/NF/)SFA) and Compritol HD5 ATO (DMF)(Gattefossé, Saint Priest, France). Amylum (E. Merck D-6100 Darmstadt, F.R. Germany). All other chemicals were of analytical grade. UV Spectrophotometer (UV-visible Recording spectrophotometer, UV-160 A, Shimadzu, Japan), dissolution apparatus (Aymes, Turkey), pH meter (Bilmar Model 101, Turkey), cubic mixer (Erweka AR 400), tablet machine (Korsch, Erweka AR 400), friabilator (Roche), hardness apparatus (Monsanto), thickness tester (Micrometer, Czechoslovakia).

Methods

1.Preparation of tablets

The powders were mixed in a rotating cubic mixer for ten minutes. Tablets were prepared on an instrumented single-punch tableting machine by direct compression technique (DCT) according to the ratioes given in Table 1.

2. Physical tests

Tablets were physically analyzed by: KT amount, crushing strength (hardness), diameter-height ratio, friability,weight uniformity and *in vitro* dissolution test according to USP XXII.. For the content uniformity; tablets were selected randomly from each type and the amounts of KT were determined spectrophometrically. The tablet weight uniformity was calculated from the weight of the tablets

3. Amount of KT

Spectrophotometric method was used for KT assay (18). 15.0 mg KT was accurately weighed and dissolved in simulated gastric medium (SGM) (pH 1.2) and diluted to 50 ml with SGM. Absorbances of these samples were measured at 323.0 nm. Regression equation and regression coefficients were calculated (Table 2). The same procedure were repeated with pH 2.5, 4.5, 7.0 and simulated intestinal medium (SIM) (pH 7.5).

4. In vitro dissolution test

Dissolution tests were performed according to the basket method described in USP XXII,

Table 1. Contents of wax matrix tormulations

Content	Tablet Code No						
	F1	F2	F3	F4	F5	F6	F7
KT (mg)	14.0	14.0	14.0	14.0	14.0	14.0	14.0
Amylum (mg)	76	56	36	76	56	36	86
Compritol 888 ATO (%w/w)	10	30	50	-	-	-	-
Compritol HD 5 ATO (%w/w)	-	-	-	10	30	50	-

Table 2. Regression equation, regression coefficient, λmax of KT in each medium (n = 10).

Medium	Regression equation	Regression coefficient	λmax
pH 1.2	y = 0.0614 x + 0.0081	r = 0.9998	318
pH 2.5	y = 0.0505 x + 0.0053	r = 0.9999	318
pH 4.5	y = 0.0529 x + 0.0083	r = 0.9998	323
pH 7.0	y = 0.0555 x + 0.0085	r = 0.9998	323
pH 7.5	y = 0.0528 x + 0.0023	r = 0.9997	323

apparatus I. The rotating speed was 50 rpm and temperature was 37±0.5°C. Dissolution studies were carried out in 400 ml of dissolution medium prepared from SGM and SIM without enzymes and changed at certain times and the pH values of 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. An equal volume of the same medium was returned to the system after each withdrawal. Absorbances of the samples were measured by using UV spectrophotometer at 323.0 nm against blank which consisted of placebo tablets corresponding to each formulation. The amounts of KT released were calculated by using the standart calibration curve equation. Six tablets were used for each test.

Results and Discussion

All the tablets prepared were found to fit the USP XXII requirements for weight uniformity , thickness and friability test (F<0.5%), disintegration, The hardness of the tablets ranged from 0.5 to 1.5 Kg. Hardness of tablets increased with increasing amounts of compritol. Even with a high percentage of Compritol (50%), tablets without any problem of capping or sticking were compressed Table 3 shows the physical characteristics of the prepared KT wax matrices. The results were in accordance with the pharmacopoeia limits except dissolution rate. Contents uniformity tests were performed and the analysis of each type of tablet gave approximately the same amount of active ingredient.

Many researches have been carried on using simulated gastric fluid (pH 1.2) without enzyme as the dissolution media. With respect to the pH of intestinal fluids, we studied the dissolution rate in simulated intestinal fluid at pH 7.5. Dissolution rate studies were made by using different pH media. Seven different types of tablet formulations were used to evaluate the effect of polymer ratio on drug release rate. Drug releases from wax matrices results showed in Table 4. Drug release from tablets with 10% compritol 888 ATO was approximately 98% in the first five hours. Tablets with 30% of wax shoved a 96% drug release while tablets with 50% wax released 90% of the drug after five hours. As the wax level increased in the formula, release of drug decreased. 96-97% drug release was observed in F2 and F5 tablets in the first five hours. KT release was 78.5% in the first sixty minutes (F7, without Compritol). The release of KT from wax matrix tablets was slower than normal tablet.

Table 3. Wax matrix tablet specifications (n = 5)

Tablet Specifications	Tablet Code No						
	F1	F2	F3	F4	F5	F6	F7
KT (mg)	13.735 ±0.110	13.960 ±0.380	13.901 ±0.242	13.866 ±0.309	14.055 ±0.133	13.771 ±0.241	13.990 ±0.384
Hardness (kg)	0.50 ±0.176	0.75 ±0.111	1.00 ±0.155	0.50 ±0.055	0.75 ±0.108	1.50 ±0.169	0.50 ±0.064
Friability (%)	0.44 ±0.070	0.25 ±0.060	0.17 ±0.025	0.52 ±0.060	0.27 ±0.023	0.15 ±0.014	0.45 ±0.029
Diameter-height ratio	3.23 ±0.220	3.09 ±0.150	2.96 ±0.145	3.23 ±0.173	3.08 ±0.177	2.96 ±0.213	3.02 ±0.281
Tablet weight (mg)	100.6 ±0.699	99.80 ±0.829	100.10 ±0.737	99.50 ±0.972	99.55 ±0.882	100.10 ±0.994	99.83 ±0.876

Dissolution profiles of matrix tablets are shown in Figs 1, 2.

In real systems, however , a number of other factors may have influence on the modification of the total behavior. The models employed assume that the systems are neither surface coated, nor that their matrices undergo significant alteration in the presence of moisture. Since in real systems these varying roles in modifiying the release pattern of sustained-action dosage forms, any attempt to apply Higuchi equations must be made with this in mind (6). The results indicated that the infiltration of medium into interspace of matrix tablet obeyed the square root law described by Higuchi. The drug release from Compritol matrices follow the Higuchi diffusion model with a linear relationship between the percent drug release and the square root of time. As sufficient quantities of Compritol are incorporated in the formulations to get a prolonged release of the drug, the tablets remained intact through out the in vitro dissolution test. The drug release follows the Higuchi square root equation up to eight hours (Figs 3,4). The release profiles of Compritol tablets were described by the linear square root of time dependence, indicating a diffusion controlled mechanism.

By direct compression, Compritol was a very efficient sustained release agent. It could be used at concentrations of 10 to 50 % and the amount of Compritol is the key parameter for the control of the drug release. The formulations tested with Compritol 888 ATO were very effective in providing slow drug release (3-5). The data indicates that the dissolution of the drug was diffusion controlled, also Compritol HD 5 ATO was more sersitive to changes in concentrations.

Table 4. Dissolution results of wax matrix tablets (n =6)

Time (min)	pH	Released %						
		F1	F2	F3	F4	F5	F6	F7
30	1.2	44.75 ±2.09	34.38 ±2.63	29.36 ±1.77	43.91 ±0.98	41.86 ±3.22	12.99 ±1.63	70.34 ±4.58
60	1.2	50.30 ±2.18	44.28 ±3.58	39.12 ±8.62	50.71 ±4.72	45.48 ±1.69	29.38 ±2.85	78.56 ±12.40
90	2.5	57.22 ±3.45	53.93 ±4.67	47.07 ±5.94	56.92 ±3.45	53.69 ±6.01	37.81 ±4.06	91.67 ±1.89
120	2.5	63.95 ±1.20	58.59 ±1.58	52.16 ±4.09	67.36 ±6.37	59.23 ±3.46	45.17 ±2.68	97.88 ±3.42
150	4.5	69.72 ±7.26	64.34 ±1.22	61.90 ±3.21	70.87 ±9.06	69.58 ±5.79	52.62 ±4.01	97.56 ±2.88
180	4.5	77.20 ±9.07	73.04 ±3.84	69.04 ±2.67	82.07 ±5.31	72.15 ±10.43	60.29 ±6.42	-
210	4.5	87.81 ±4.23	82.57 ±7.25	71.13 ±8.04	89.03 ±1.74	80.22 ±8.99	67.51 ±3.65	-
240	7.0	92.04 ±4.89	87.75 ±6.72	84.00 ±1.85	95.69 ±3.48	85.69 ±1.09	78.83 ±2.36	-
270	7.0	95.75 ±11.09	92.79 ±4.44	87.99 ±6.89	94.98 ±2.39	90.71 ±2.69	88.37 ±5.70	-
300	7.0	98.86 ±3.76	96.12 ±2.87	90.84 ±4.50	-	96.43 ±7.84	90.57 ±6.44	-
330	7.5	-	96.04 ±6.71	95.72 ±2.92	-	96.40 ±0.78	94.31 ±1.68	-
360	7.5	-	-	95.36 ±3.58	-	-	95.28 ±2.79	-

In conclucion, to wax matrix a water soluble drug with different types and concentrations of Compritol might be a suitable system. It was shown that the addition of a wax matrix excipient to the tablet formulations could result in sustained release. Different release profiles thus obtained could best explain the effect of different types and concentrations of wax matrix excipients in tablet formulations.

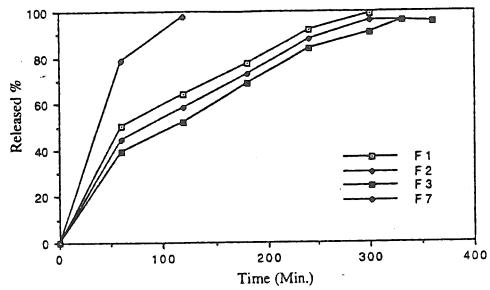

Fig.1. Dissolution profiles of F1, F2, F3 and F7

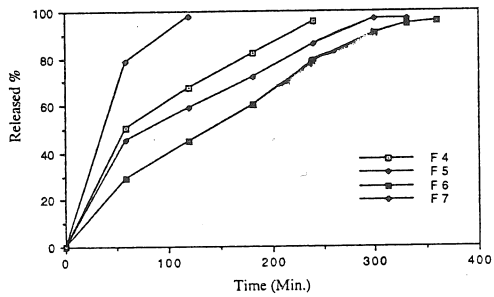

Fig.2. Dissolution profiles of F4, F5, F6 and F7.

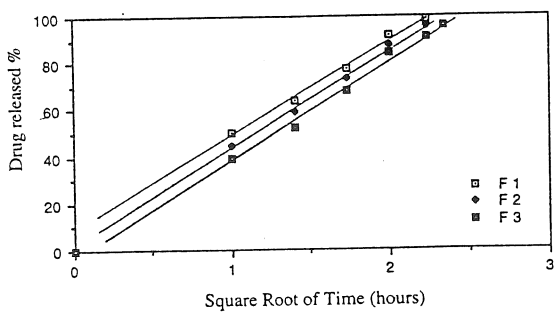

Fig.3. Square Root of Time plots for tablets F1, F2 and F3.

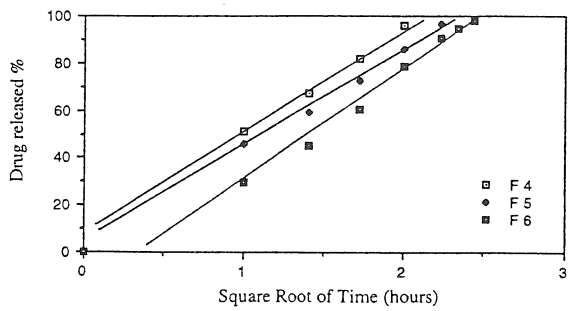

Fig.4. Square root of time plots for tablets F4, F5 and F6.

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