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FORMULATION AND *INVITRO* RELEASE STUDIES OF LIPID MATRIX TABLETS OF TOLMETIN SODIUM PREPARED WITH HYDROGENATED CASTOR OIL

HİDROJENE HİNT YAĞI İLE HAZIRLANAN TOLMETİN SODYUM LİPİD MATRİKS TABLETLERİNİN FORMULASYON VE IN VITRO SALIM ÇALIŞMALARI

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The sustained-release preparations of tolmetin sodium were prepared as matrix tablets. The particle size of the substance and the concentration of the matrix agent were changed to investigate the influences on the in vitro release of tolmetin sodium. Direct compression method was used to prepare the tablets and hydrogenated castor oil was used as the matrix agent. The rotating paddle method was applied for the dissolution tests. It was seen that particle size was more effective than the amount of the hydrogenated castor oil on the release rate of tolmetin sodium. Furthermore, the dissolution results of formulas were evaluated kinetically.

Tolmetinin uzatılmış etkili preparasyonu matriks tablet şeklinde hazırlanmıştır. Tolmetin sodyumun in vitro salımı üzerine etkisini göstermek içinmaddenin partikül büyüklüğü ve matriks ayanın konsantrasyonu değiştirilmiştir. Tabletleri hazırlamak için direk basım metodu ve matriks ajan olarak hidrojene hint yağı kullanılmıştır. Dissolusyon testleri için dönen pedal metodu kullanılmıştır. Patrikül büyüklüğünün hidrojene hint yağının miktarından çok daha etkili olduğu görülmüştür. Dissolusyon sonuçları kinetik olarak değerlendirilmiştir.

Keywords: *Tablets, Sustained-release; Tolmetin sodium; Hydrogenated castor oil; Matrix tablets*

Anahtar kelimeler: *Tablet; Sürekli etki; Tolmetin sodyum; Hidrojene hint yağı; Matriks tablet*

Introduction

One method of obtaining a sustained release product is to embed or disperse the solid medicinal compound in a woter insoluble matrix. Insoluble matrices may be prepared by compression of a congealed mixture of the medicinal compound and wax or polymeric material which had been melted, cooled and milled, or a physical mixture of the medicinal compound and waxy or

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polymeric material (1-3). Release of the medicinal compound occurs as the water penetrates the matrix and dissolves the medicinal compounds and the dissolved medicinal compound diffuses out into the bulk solution. The operation of milling and its production of smaller particles of a medicinal compound may affect release of the compound from the matrix (4). Also the matrix material and its ratio affects the dissolution profile (5,6). This study presents the data and description of release of water soluble medicinal compound (tolmetin sodium) from matrix tablets compressed from a physical mixture of tolmetin sodium and hydrogenated castor oil.

Tolmetin sodium has analgesic, anti-inflammatory and antipyretic properties. It is used in rheumatic disorders. The usual doses are 600-1800 mg daily in divided forms. The most frequent adverse reactions are gastrointestinal and nervous system reactions. (7).

Materials and methods

Materials were obtained from various commercial suppliers and used as received.

Tolmetin sodium and hydrogenated castor oil were supplied by Cilag AG. All chemicals were of analytical grade.

Preparation of tablets: Tolmetin sodium was classified by a combined sieve set (Retsch) into <75, 75-125, 125-250 μm size fractions. Tablets corresponding to 200mg tolmetin (245.08 mg tolmetin sodium dihydrate) were prepared using hydrogenated castor oil as the matrix material. The selected size fraction of tolmetin sodium and selected amount of hydrogenated castor oil were blended in a cubic blender (Aymes) for 10 min. 100, 125, 150 mg of hydrogenated castor oil were added for each tablet, respectively. The blends were compressed into tablet forms by Manesty E2 single punch tablet machine using flat-faced punches at a compression pressure of 3 tons. No lubricant was added since there were no technical problems during compaction. Tablet thickness, diameter, hardness and weights, were measured.

Dissolution studies: In vitro dissolution tests were carried out using USP XXII dissolution test apparatus and medium and the method described in official USP monograph for tolmetin sodium tablets (8). All dissolution tests were carried out in 900 ml dissolution medium at pH 4.5 (37°C ± 0.1) a stirring rate of 50 r.pm. Concerning the *in vitro* release tests of the tablets, in order to reduce the variability due to the hydrodynamic conditions of the tests, the tablets were placed in a stationary basket at the bottom of the vessel. The samples were withdrawn at selected times and assayed spectrophotometrically at 322 nm. The dissolution data for different tablets were treated by converting observed drug concentrations at each sampling time to the percentage dissolved. Dissolution studies were performed in triplicate for each batch of the tablets.

Kinetic studies: The results were evaluated kinetically according to zero, first order, Hixon-Crowell, RRSBW,$Q\sqrt{t}$, $(bt)^a$, Higuchi and Hopfenberg equations. The release constants (k), correlation coefficients (r) and determination coefficients (r^2) were calculated by means of a computer programme (9).

Results and discussion

A product development scientist considers formulation and the method of manufacture in designinga product. There have been various studies showing that the milling process, which controls the particle size of a medicinal compound may influence the release of the compound from a solid dosage form (4,10). In addition, there have been many reports concerning the effect of the concentration of the matrix material on the dissolution profile of the drug (11-14).

In our study, we tried to obtain sustained release action for tolmetin sodium using hydrogenated castor oil as the matrix material. Table 1 shows the tablet codes, ingredients and the details concerning the manufacture of the tablets.

Table 1. Physical properties of tolmetin sodium tablets.

Code	Particle size(μm)	Amount of hyd. castor oil(mg)	Diameter (mm)	Height (mm)	Weight (mg)	Hardness (Monsanto)
T1	<75	100	13	2.2	344±0.3	1.8±0.1
T2	75-125	100	13	2.2	345±0.3	2.0±0.2
T3	125-250	100	13	2.3	346±0.5	2.0±0.2
T4	<75	125	13	2.3	370±0.5	2.3±0.1
T5	75-125	125	13	2.4	370±0.4	2.5±0.1
T6	125-250	125	13	2.4	371±0.5	2.5±0.2
T7	<75	150	13	2.5	395±0.5	2.6±0.1
T8	75-125	150	13	2.5	395±0.4	2.6±0.1
T9	125-250	150	13	2.6	395±0.5	2.5±0.1

In our previous study, it was shown that faster release rate was obtained by using the <75 μm particle size of tolmetin sodium than the other particle sizes from the matrix tablets prepared with ethylene maleic acid anhydrides as a matrix material (15). Similarly, the release of tolmetin sodium was the slowest from the tablets prepared with the largest particles. As the particle size reduced, the amount of the drug release increased because dissolution surface area increased. The dissolution profiles of the tablets prepared with different particle sizes are shown in Figs 1-3. In addition, the dissolution profiles of the formulations were compared with the marketed tablet (T). While 47% of tolmetin sodium released within the first minute and the release reached 100% in 8 mins from the commercial tablets, 100% release of tolmetin sodium was reached in nearly 6 hours from the tablets prepared with hydrogenated castor oil. Fig.3 also shows the dissolution profile of marketed tablet of tolmetin sodium.

Matrix agent and its amount are important factors in changing the release of the drug (16-19).It modifies the dissolution profiles. Hydrogenated castor oil was used as the matrix material in different researches (4, 6, 20-22). It also provided sustained release action for tolmetin sodium but the concentration differences in the tablets had no significant effect on the dissolution of the substance.

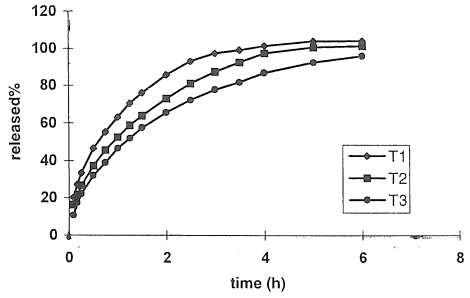

Fig. 1. The release profiles of TS prapared with three different particle sizes from matrix tablets containing 100mg HCO.

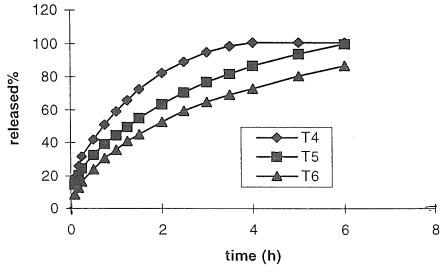

Fig. 2. The release profiles of TS prapared with three different particle sizes from matrix tablets containing 125mg HCO.

Figs 4-6 show the effect of hydrogenated castor oil on the release rate of tolmetin sodium. As shown in Fig. 4, the dissolution profiles of T1, T4 and T7 tablets were found to be

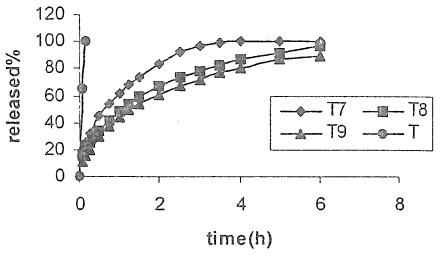

Fig. 3. The release profiles of TS prapared with three different particle sizes from matrix tablets containing 150mg HCO.

practically the same. Despite the amount of hydrogenated castor oil increased, there were no differences in drug release patterns from tablets of differing amounts of the matrix agent. In fact, it was only at the smallest particle size of the drug. In these formulations, the particle size of tolmetin sodium was <75 μm. For the other formulations, the dissolution profiles were similar to each other but not the same. Results indicated slight differences on the release pattern. When the particle size of tolmetin sodium increased, an increase in the amount of hydrogenated castor oil altered little changes on the release rate of the drug.

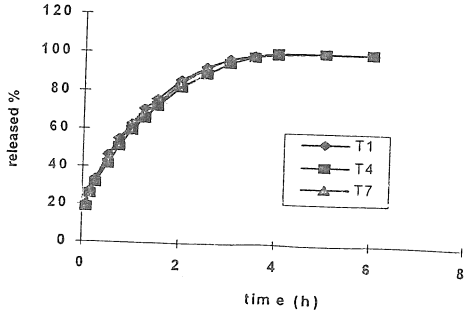

Fig. 4. The release profiles of TS prapared with 75μm of particle size containing three different amounts of HCO.

The dissolution profile of T2 formulation had minor differences from the others but the release of the drug from the T5 and T8 formulations were almost the same (Fig. 5).

On the contrary of our expectations slower release was observed with T6 formulation containing 125 mg of hydrogenated castor oil than T9 formulation with 150 mg of hydrogenated castor oil and 125-250 μm of the particle size of the drug (Fig.6).

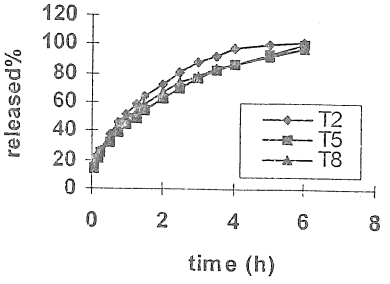

Fig. 5. The release profiles of TS prepared with 75-125μm of particle size containing three different amounts of HCO.

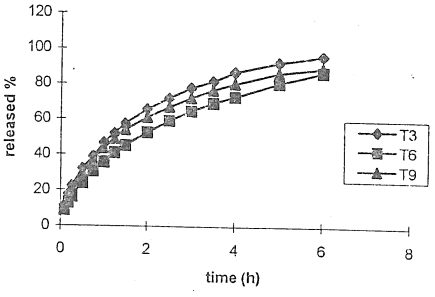

Fig. 6. The release profiles of TS prepared with 125-250μm of particle size containing three different amounts of HCO.

When the dissolution results were evaluated kinetically, it was found that $(bt)^a$ kinetic model was fitted T1, T2, T3 formulations. On the other hand, the data showed better fit to Higuchi heterogeneous pellet, $(bt)^a$, RRSBW, Q versus square root time and Hopfenberg kinetics for other formulations. These results were in agreement with the literature (23) results. The kinetic

models and their kinetic parameters obtained from the dissolution datas of the formulations were shown in Table 2.

A linear relationship was obtained for most of the formulations (except for T1, T4 and T7 formulations prepared with the smallest particle size) when the fraction released was plotted against sqvare root of time (Figs 7-9).

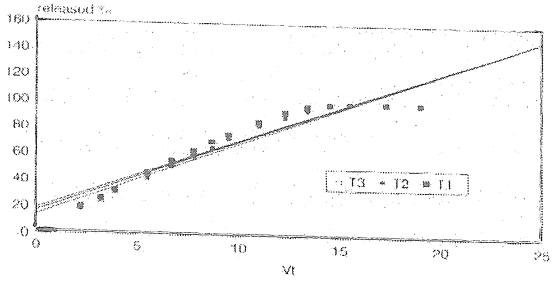

Fig. 7. Relationship between percentage release of tolmetin sodium from the T1, T2, T3 formulations and √t.

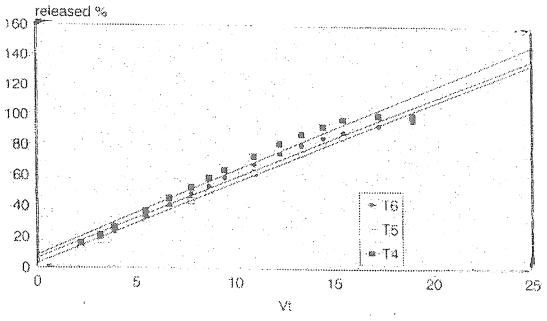

Fig. 8. Relationship between percentage release of tolmetin sodium from the T4, T5, T6 formulations and √t.

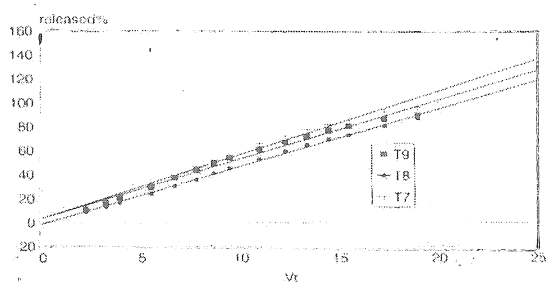

Fig. 9. Relationship between percentage release of tolmetin sodium from the T7, T8, T9 formulations and √t.

Table 2. Kinetic parameter of the dissolution results of tolmetin sodyum tablets prepared with hydrogenated castor oil

	(bt)[a]	Zero order	Hixon-Crowell	RRSBW	Higuchi (het.pel)	Q√t	Hop. finberg (Sph)	Hop. fenberg (Cyl.)	Hop. fenberg (Slab)	First order
T1	A=0.664 B=2.993x10^{-3} r^2=0.985	r^2=0.752	r^2=0.972	r^2=0.871 β=1.040 τ=39.24	r^2=0.927	r^2=0.912	r^2=0.952	r^2=0.917	r^2=0.752	r^2=0.806
T2	A=0.681 B=2.775x10^{-3} r^2=0.980	r^2=0.790	r^2=0.977	r^2=0.851 β=1.049 τ=43.55	r^2=0.931	r^2=0.934	r^2=0.957	r^2=0.931	r^2=0.790	r^2=0.783
T3	A=0.673 B=2.913x10^{-3} r^2=0.984	r^2=0.765	r^2=0.975	r^2=0.864 β=1.045 τ=41.03	r^2=0.934	r^2=0.920	r^2=0.955	r^2=0.916	r^2=0.765	r^2=0.794
T4	A=0.680 B=2.160x10^{-3} r^2=0.976	r^2=0.859	r^2=0.963	r^2=0.832 β=0.978 τ=56.50	r^2=0.980	r^2=0.971	r^2=0.983	r^2=0.979	r^2=0.859	r^2=0.707
T5	A=0.629 B=1.199x10^{-3} r^2=0.987	r^2=0.923	r^2=0.968	r^2=0.977 β=0.726 τ=103.6	r^2=0.985	r^2=0.997	r^2=0.998	r^2=0.991	r^2=0.923	r^2=0.973
T6	A=0.615 B=1.308x10^{-3} r^2=0.993	r^2=0.883	r^2=0.978	r^2=0.980 β=0.715 τ=90.52	r^2=0.997	r^2=0.982	r^2=0.988	r^2=0.969	r^2=0.883	r^2=0.988
T7	A=0.661 B=1.380x10^{-3} r^2=0.997	r^2=0.884	r^2=0.979	r^2=0.991 β=0.757 τ=99.68	r^2=0.997	r^2=0.984	r^2=0.989	r^2=0.971	r^2=0.885	r^2=0.984
T8	A=0.655 B=8.500x10^{-3} r^2=0.998	r^2=0.930	r^2=0.979	r^2=0.994 β=0.717 τ=167.6	r^2=0.992	r^2=0.997	r^2=0.989	r^2=0.979	r^2=0.930	r^2=0.988
T9	A=0.632 B=1.042x10^{-3} r^2=0.998	r^2=0.882	r^2=0.971	r^2=0.997 β=0.706 τ=124.8	r^2=0.998	r^2=0.997	r^2=0.971	r^2=0.953	r^2=0.882	r^2=0.984

Sustained-release tablets tolmetin of sodium were prepared. Using hydrogenated castor oil as a matrix material and their release profiles were evaluated kinetically. The effect of particle size of tolmetin sodium and of the amount of hydrogenated castor oil on the dissolution rate were investigated.

As a result, it might be possible to design sustained-release tablets of tolmetin sodium using hydrogenated castor oil as the matrix material and direct compression method and the biggest particle size of tolmetin sodium would be preferable to obtain the convenient and desired dissolution rates.

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