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PREPARATION OF SUSTAINED-RELEASE TIAPROFENIC ACID BEADS

A. YILDIZ, D. ŞENSOY, A. BAYTOKOVA, Y. ÖZSOY*, A. ARAMAN

SUMMARY

Tiaprofenic acid (TA), has analgesic, anti-inflammatory and antipyretic properties; it is an inhibitor of prostaglandin synthetase. The usual oral dose by mouth is 600 mg daily; this may be given in 2 or 3 divided doses or once daily as a sustained-release preparation. TA is readily absorbed from the gastrointestinal tract. It has a short half-life of about 2 hours.

Sodium alginate is a natural, biodegradable and biocompatible polymer used as suspending and gelling agent in pharmaceutical technology. Recently, the alginate gel beads has received much attention in sustained-release preparation.

The aim of the present study was to formulate sustained-release TA beads based on sodium alginate in order to reduce daily dose and to minimize gastrointestinal disturbance caused by the drug.

Key words: Tiaprofenic acid, sustained-release beads, sodium alginate.

ÖZET

Tiaprofenik asit, prostaglandin sentezini inhibe eden ağrı kesici, enflamasyon giderici ve ateş düşürücü bir ilaçtır. Oral yoldan günlük dozu 600 mg olup bu doz 2 veya

(*) Correspondence
University of Istanbul, Faculty of Pharmacy, Department of Pharmaceutical Technology 344-52-Beyazıt/Istanbul

3'e bölünmüş halde veya günlük sürekli etkili preparat halinde verilebilir. Tiaprofenik asit yaklaşık 2 saat gibi kısa yarılanma ömrüne sahiptir.

Sodyum aljinat, farmasötik teknolojide süspansiyon ve jel ajanı olarak kullanılan doğal, vücutta parçalanabilen ve organizma ile uyumlu bir polimerdir. Son yıllarda, sürekli etkili preparatların hazırlanmasında kullanılmaktadır.

Bu çalışmanın amacı; tiaprofenik asidin günlük dozunu azaltmak ve gastrointestinal sisteme olan yan etkilerini gidermek için, sodyum aljinat ile sürekli etkili boncuklarını oluşturmaktır.

Anahtar kelimeler: Tiaprofenik asit, sürekli etkili boncuk, sodyum aljinat.

INTRODUCTION

Tiaprofenic acid (TA), 2-(5-benzoyl-2-thienyl) propionic acid, has analgesic, anti-inflammatory and antipyretic properties; it is an inhibitor of prostaglandin synthetase. The usual oral dose by mouth is 600 mg daily; this may be given in 2 or 3 divided doses or once daily as a sustained-release preparation. TA is readily absorbed from the gastrointestinal tract. It has a short half-life of about 2 hours [1].

Natural polymers (e.g. pectin, chitosan, gellan and carregeenan) subjected as barriers to delay the drug release is one of the main objectives of researchers dealing with long acting dosage forms [2-8]. Alginates naturall polysaccharides obtained from brown algae, have been widely employed in food and pharmaceutical industries for various purposes namely suspending or gelling agent, emulsion stabilzier etc. [9]. Alginates form tough gels through reactions with curing solutions containing various cations as H^+, Ca^{++} and some other divalent ions [10]. The gelation procedure of alginates can be carried out in one single-step process under very mild conditions. Recently, spherical gel beads of alginate, loaded with different substances have been prepared by gelation of the polymer with calcium cations, and release characteristics of the subjected substances from alginate gel beads have been investigated [11-15]. There is no data in literature about TA beads with sodium alginate.

In this study, a number of parameters such as polymer/drug ratio, dropping rate and distance, maintenance period of the beads in calcium chloride solution were investigated for optimizing bead formations and sustained-release TA beads based on sodium alginate were formulated.

RESULTS AND DISCUSSION

The results indicated that the dropping speed and distance of TA dispersion into calcium chloride solution affected the shape of the beads. The faster dropping rate and longer distance resulted shapeless, nonspherical beads. 35 drops/min and 4 cm of distance were found as optimum values. 24 h of maintenance in calcium chloride solution was found to be sufficient for instantly occured spherical beads. Average diameter of beads were found as 0.99±0.02, 1.07±0.08, 0.98±0.01, 1.12±0.03, 0.96±0.03 mm for 1:1, 1:1.5, 1.5:1, 2:1 and 1:2 polymer/drug ratios, respectively. According to these results, diameter of the beads were observed to increase with the increase in the amount of TA (Table 1).

Table 1: *Average diameter of beads and encapsulation efficiency of the tiaprofenic acid beads*

Polymer/drug ratio	Average diameter of beads (mm)*	Encapsulation efficiency (%) **
1:1	0.99±0.02	88.56±1.63
1:1.5	1.07±0.08	87.15±3.05
1.5:1	0.98±0.01	82.97±1.91
1:2	1.12±0.03	84.55±1.07
2:1	0.96±0.03	85.45±2.37

* data were the average±standard deviation of 10 beads
** data were the average±standard deviation of 3 batches

The equation of standard curve of TA is given below:

$y=15.979\ x - 0.220$ $r^2=0.998$ [y= concentration (mcg/ml), x=absorbance, r^2=determination coefficient].

The encapsulation efficiency of beads was found to be >80% in all the examined polymer/drug ratios (Table 1).

In vitro release of TA from the beads at the end of 2 h was 70.13±2.31%, 85.63±1.49%, 71.50±3.24%, 48.59±2.10%, 48.00±1.99% for 1:1, 1:1.5, 1:2, 1.5:1 and 2:1 polymer/drug ratios respectively (Figure 1).

The release of pure TA was found as 84.68±2.74% after 2 h. Therefore, the 1:1, 1:1.5, 1:2 of polymer/drug ratios gave almost the same release profile exhibiting no sig-

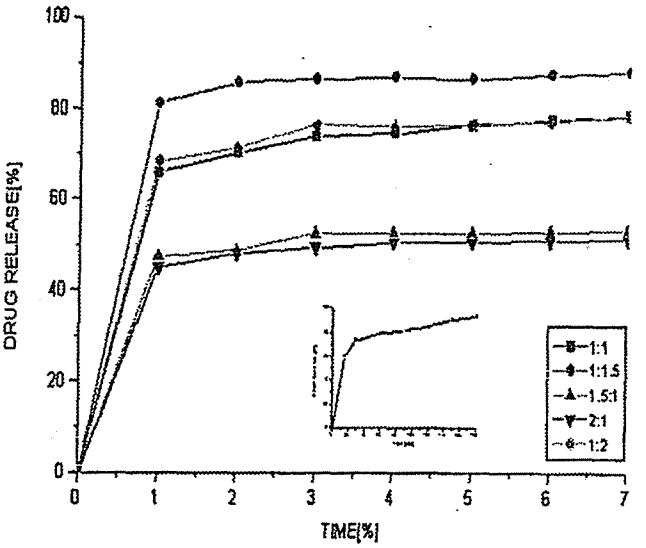

Figure 1: *In vitro* release profiles of tiaprofenic acid in the beads (insert represents the release of pure drug)

nificant effect of delayed action ($p>0.05$) while increase in polymer ratio (1.5:1 and 2:1) significantly decreased the released amount TA ($p<0.05$). This delay in release continued up to 7 h. After 7 h, drug release from 1.5:1 and 2:1 polymer/drug ratios were 53.20±1.50% and 51.10±1.99%, respectively. There was no significant difference between these values ($p>0.05$).

Kinetical evaluation showed that 1.5:1 and 2:1 polymer/drug ratio is in good agreement with Higuchi model, $r^2=0.953$ and $r^2=0.942$ respectively (Table 2). Hence, the release process was controlled by a diffusion-type mechanism [16].

Table 2 : Kinetic data of tiaprofenic acid from the beads

Polymer/drug ratio	Zero order kinetic	First order kinetic	Higuchi kinetic
1.5:1	k_0= 47.601	k_1=1.678	k_h= 44.348
	r_2 = 0.867	r_2= 0.865	r_2 = 0.953
2:1	k_0 = 45.632	k_1= 1.659	k_h= 42.390
	r_2 = 0.891	r_2 = 0.884	r_2 = 0.942

k= release rate (k_0= mg.h^{-1} k_1= h^{-1} k_h= mg. h$^{-0.5}$)
r^2=determination coefficient

Results suggest that 1.5:1 and 2:1 polymer-drug ratio can succesfully be used as a carrier for TA gel beads based sodium alginate. The proposed method for beads formation is proved to be simple and reproducible.

EXPERIMENTAL

Materials

Tiaprofenic acid (Hoechst Pharm. Comp.), Sodium alginate (A-2033, Sigma) (1% w/v 260±35 cps) and other materials were of analytical grade.

Methods

Preparation of beads

A weighed quantity of TA powder was dispersed in polymer solutions (1% w/v) to obtain 1:1, 1:1.5, 1.5:1, 2:1, and 1:2 polymer/drug ratios. The bubble-free dispersions were dropped into 100 ml of 0.1 M calcium chloride solution at room temperature using 21 gauge needle. The droplets instantaneously formed gelled spheres by iontoropic gelation of sodium alginate with Ca^{++} cations. The gelled spheres were then allowed to stand for sometime to form fully-cured beads retaining their spherical shape. Beads were separated, washed with 100 ml of distilled water for the removal of excess Ca^{++} cations and dried at room temperature. A number of variables such as polymer/drug ratio, dropping rate and distance, maintenance period of the beads into calcium chloride solution were investigated to optimize the bead properties.

Measurement of bead size

The diameter of dried beads were measured by using micrometer (Mitutoyo) and average diameter was calculated by means of 10 beads of each batch.

Standard curve of tiaprofenic acid

For the standard curve, accurately weighed 100 mg of TA was dissolved in 100 ml phosphate buffer (pH 7.4). Using this stock solution, the solutions were prepared at 1-10 mcg/ml concentrations. Absorbances of this solutions were measured spectrophotometrically (Shimadzu UV-1601) at 316 nm. The standard curve was plotted and the equation for the standard curve of TA was calculated.

Drug content and encapsulation efficiency

25 mg TA beads were extracted with 100 ml phosphate buffer (pH 7.4) and the absorbances of filtered extracts were measured at 316 nm. The TA contents of beads were calculated using standard curve. Preliminary studies have shown that the presence of the polymer has no interference with the spectrophotometric method. The measurements were carried out in triplicate. The encapsulation efficiency of beads at 1:1, 1:1.5, 1.5:1, 2:1 and 1:2 polymer/drug ratios was calculated as follows:

$$\text{Encapsulation efficiency (\%)} = \frac{\text{Found amount of drug}}{\text{Theoretical amount of drug}} \times 100$$

In vitro release studies

The dissolution behavior of TA beads were examined by using USP XXIII basket method [17]. Appropriate amount of beads were suspended at 50 rpm in 300 ml of phosphate buffer (pH 7.4, 37±0.5°C). Sample solution (1 ml) withdrawn periodically at 1-7 h from dissolution medium was diluted to 10 ml with the same buffer solution. TA content of each sample was assayed as above and the cumulative percentage of released drug was calculated. Release studies were done in triplicate and the average values were calculated. Taking into consideration the in vitro release profile, only sustained-release formulations were evaluated kinetically using the zero order, first order and Higuchi kinetic model.

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