As can be seen from Table 2, n values of formulations C1, C3, B1 and B3 lying between 0.43–0.85 indicated non-fickian transport controlled both by diffusion and relaxation of the polymer. On the other hand, the n values of C2, B2 and B4 were greater than 0.85, the mechanism of drug release was determined as Case II transport indicating zero order release kinetics. The n value of formulation B4 was 1.00. The release was controlled by relaxation of the polymer. It was difficult to establish any relation between the release mechanism and the type of the formulations.

In conclusion, Ca^{2+} was the most effective agent to obtain extended release from the NC alginate beads and various polymers did not show any influence to prolong the NC release.

3. Experimental

3.1. Materials

Nicardipine HCl was kindly supplied by Novartis Co, Turkey. Sodium alginate (Manugel A7B618) was donated from Kelco Co, England. Carbopol 941 was from Sumitomo Seika, Japan. Hydroxypropylmethylcellulose was from Sigma, USA and Eudragit RS 30 was from Rhöm Pharma; Germany. All other chemicals and solvents were of analytical grade.

3.2. Preparation of the alginate gel beads

Gel beads were prepared using the method described previously [13]. The codes and content of the formulations were shown in Table 1. The concentration of sodium alginate solution was 2.5%. A concentration of 0.1 M crosslinking agent ($CaCl_2$, $BaCl_2$ or $SrCl_2$) was used. Carbopol 941 was added to the alginate-nicardipine dispersion (B1) whereas HPMC or Eudragit RS solutions were added to the $CaCl_2$ solutions (B2–B4).

3.3 Particle size determination

The particle size of 50 beads were measured with a micrometer and the mean particle size was determined.

3.4. Swelling studies

Alginate beads were placed in various buffer solutions and water at 37 °C. Beads were removed at selected time intervals and were weighted. Changes in their weight were measured during the swelling, then the swelling ratio was calculated.

3.5. Drug content determination

After disintegration of the beads in pH 7.5 phosphate buffer, NC was extracted with dichloromethane. The organic phase was evaporated and the drug was assayed spectrophotometrically at 240 nm.

3.6. Target profile

The target profile was plotted as described elsewhere [11].

3.7. Drug release studies

The release of NC from alginate gel microparticles was investigated by a flow-through cell apparatus (Sotax, USA). The flow rate was 4 ml/min. The gel microparticles equivalent to 10 mg NC were subject to pH 1.2, 2.5, 4.5, 7 and 7.5 dissolution media for 1, 1, 1.5, 1.5 and 3 h, respectively. The collected samples were assayed spectrophotometrically at 240 nm.

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Formulation and *in vitro/in vivo* investigation of carbamazepine controlled-release matrix tablets

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Carbamazepine controlled-release tablet formulations containing hydroxypropyl methylcellulose (HPMC) as matrix material at different concentrations were developed and evaluated *in vitro* and *in vivo*. The formulation containing 10% HPMC (HPMC-10) showed a controlled-release profile comparable to that of a commercially available, controlled-release carbamazepine preparation (Tegretol® CR 200). The kinetics of controlled-release carbamazepine tablets was examined in eight healthy volunteers. The peak plasma concentration of $1.99 \pm 0.56\ \mu g \cdot ml^{-1}$ was obtained for HPMC-10 at 15.0 ± 9.0 h, and $1.33 \pm 0.35\ \mu g \cdot ml^{-1}$ for Tegretol® CR 200 at 15.2 ± 8.9 h, and $AUC_{0-\infty}$ values of $85.2 \pm 30.8\ \mu g \cdot h \cdot ml^{-1}$ and $76.9 \pm 20.7\ \mu g \cdot h \cdot ml^{-1}$, respectively. Developed formulation (HPMC-10) was found to be bioequivalent to Tegretol® CR 200 and, controlled release was obtained with smoother concentration-time curve resulting in less fluctuations.

1. Introduction

Carbamazepine is a widely prescribed drug for the treatment of epilepsy [1]. It is characterized by a slow and irregular gastro-intestinal absorption due to its low water solubility [2]. During repeated administration, elimination half-life is strongly decreased due to auto-induction of the microsomal enzyme system. Its initial half-life is about 24 h, while on chronic dosing it is lowered to 12 h under monotherapy and 8 h in those patients who take other

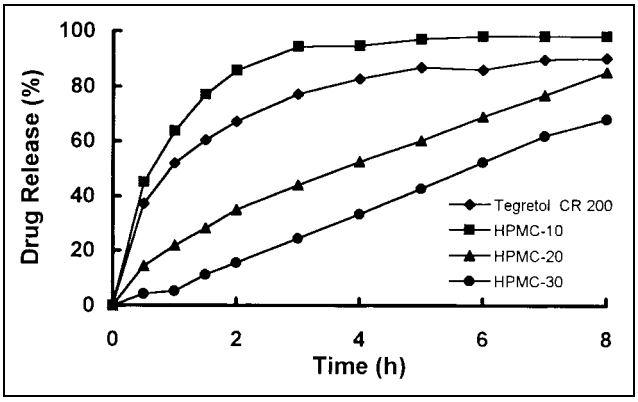

Fig. 1: Carbamazepine release profiles from controlled release tablets

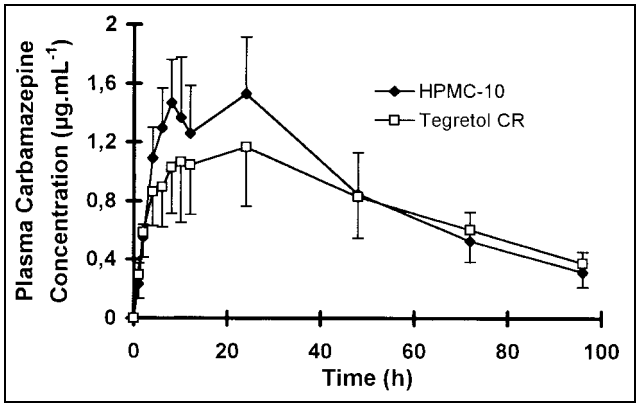

Fig. 2: Mean plasma concentration of carbamazepine after a single 200 mg dose (n = 8)

enzyme-inducing drugs [3, 4]. Moreover, the daily carbamazepine dose very often must be divided into 3 or 4 doses, which could cause plasma fluctuations and side effects.

A controlled-release preparation of carbamazepine may "smooth out" this fluctuation and thus be useful in diminishing side-effects, as well as increasing the drug's potential for seizure control by permitting higher steady-state concentrations. Such a formulation might also be expected to improve compliance in patients currently receiving 3 or 4 daily doses.

In this study, a controlled-release tablet formulation was developed using HPMC and the release of carbamazepine from the tablet was examined *in vitro*. Furthermore, the absorption of carbamazepine after administration of the formulated and a commercially available controlled-release tablet (Tegretol® CR 200) was investigated in humans.

2. Investigations, results and discussion

2.1. In vitro study

Fig. 1 shows release profiles of carbamazepine from Tegretol® CR 200 and controlled release tablets containing HPMC at 10 (HPMC-10), 20 (HPMC-20) and 30% (HPMC-30) concentrations. As expected, the drug was released more slowly from the tablets with increasing polymer content. When 10, 20 and 30% of HPMC was incorporated into the formulations, the amount of carbamazepine released in 8 h was 98, 85, and 68%, respectively. The main factor controlling drug release was the concentration of HPMC. With commercially available controlled-release carbamazepine tablets (Tegretol® CR 200) the amount released in 8 h was 90% (Fig. 1). In order to investigate the mechanism of release, the percentage release versus time profile was evaluated applying the goodness-of-fit method. The details of this statistical technique are given by Bamba et al. [5]. For the formulations investigated, Higuchi's square-root equation $(100 - W = k_d \sqrt{t})$ [6] showed a significantly better fit than first-order $(\ln W = -k_f t + i)$ and cube-root $(\sqrt[3]{100} - \sqrt[3]{W} = k_c t)$ equations, determined by the F test. The release rate constants determined from the slopes of the linear square-root plots are given in Table 1. The HPMC-10 tablets gave similar release rate constants as Tegretol® CR 200 which were evaluated further *in vivo*.

Table 1: *In vitro* release rate constants ($mg \cdot h^{-1/2}$) of controlled-release tablets

Formulation	Release rate constant ($mg \cdot h^{-1/2}$) Mean ± SD (n = 6)	r^2
HPMC-10	38.9 ± 0.4	0.938
HPMC-20	33.1 ± 1.4	0.994
HPMC-30	31.5 ± 2.6	0.968
Tegretol® CR 200	37.1 ± 1.2	0.982

Table 2: Pharmacokinetic parameters in healthy volunteers following administration of 200 mg carbamazepine (mean ± SD)

Parmeter	HPMC-10	Tegretol® CR 200
C_{max} ($\mu g \cdot ml^{-1}$)	1.99 ± 0.56	1.33 ± 0.35
t_{max} (h)	13.5 ± 8.17	14.75 ± 7.77
$AUC_{0-\infty}$ ($\mu g \cdot h \cdot ml^{-1}$)	85.2 ± 30.8	76.9 ± 20.7

Water penetration is visualized as hydrating the polymer and dissolving carbamazepine, which then diffuses through the swollen matrix. Decrease in HPMC concentration increases the release rate, which is most likely due to chances in the porosity and tortuosity of the matrix after dissolution of lactose at a higher concentration. As lactose dissolves, it diffuses outward and decreases the tortuosity of the diffusion path carbamazepine. Similar results were also obtained in our previous studies [7–10].

Moreover, decrease in the amount of the matrix material causes a decrease in the embedding capacity of the matrix tablets thus resulting in a higher release at lower concentrations. Giunchedi et al. [11] developed an extended-release formulation of carbamazepine using cross-linked sodium carboxymethylcellulose (CMC-XL) and HPMC, and showed that the release rate was dependent on the concentration of HPMC. Presence of HPMC at 30% concentration was found to cause a slower release rate with respect to 20% concentration.

2.2. In vivo study

Mean plasma carbamazepine concentrations resulting from the administration of Tegretol® CR 200 and HPMC-10 tablets are presented in Fig. 2. Mean pharmacokinetic parameters determined from analysis of the single-dose data are presented in Table 2. The AUC values for HPMC-10 and Tegretol® CR 200 tablets are $85.2 \pm 30.8\ \mu g \cdot h \cdot ml^{-1}$ and $76.9 \pm 20.7\ \mu g \cdot h \cdot ml^{-1}$, respectively. The statistical analysis indicated no significant differences among the C_{max}, t_{max} and $AUC_{0-\infty}$ values of HPMC-10 and Tegretol® CR 200 tablets $(p > 0.05)$. A considerable intersubject variability was observed in this study. This is also consistent with published reports on highly variable bioavailabilities of carbamazepine tablets between individuals and products [12]. Up to authors knowledge no study is available showing pharmacokinetic parameters for single-

dose controlled release tablets containing 200 mg carbamazepine. Chan et al. [13] reported that the C_{max} for 2×200 mg conventional or 4×100 mg chewable tablets were $3.24 \pm 0.49\ \mu g \cdot ml^{-1}$ and $3.72 \pm 0.61\ \mu g \cdot ml^{-1}$ respectively. The $AUC_{0-\infty}$ values for conventional and chewable tablets were $215.0 \pm 25.5\ \mu g \cdot h \cdot ml^{-1}$ and $225.0 \pm 28.8\ \mu g \cdot h \cdot ml^{-1}$.

Our results confirm a controlled-release profile for the carbamazepine (formulated and commercially available) formulations, with a slow rise in carbamazepine concentration and a plateau from 4 to 48 h following a single dose. Macphee et al. [14] observed that many patients complain of maximum drowsiness and diplopia 30–120 min after ingestion of carbamazepine i.e. before the peak drug concentration is achieved. A rapid increase in concentration may be important in initiating the mild neurotoxic side-effects associated with the drug. If this is the case, the smaller increments achieved with carbamazepine controlled-release tablets may be as relevant as the reduction in peak drug concentration or in overall fluctuation.

It can be concluded that the formulation developed in this study is indeed a controlled-release preparation of carbamazepine, with "smoother" concentration-time curves resulting in a less fluctuation of blood levels.

3. Experimental

3.1. Materials

The following materials were used: carbamazepine (Abdi İbrahim, Turkey), HPMC, viscosity 12000 to 18000 cps (Metholose 90SH 15000, Shinetsu Chemical Co., Japan), lactose (Fast Flo, Foremost Food Co., USA), magnesium stearate (E. Merck, D-Darmstadt).

3.2. Preparation of tablets

HPMC was used a matrix material in formulations. The powders were mixed and directly compressed with 1.5% of magnesium stearate, incorporated prior to compression. Tablets were compressed on a single punch-tablet machine Korsch EK/O at a tablet weight of 400 mg using flat non-beveled punch of 12 mm diameter.

Controlled-release matrix tablets were formulated to contain 200 mg (50%) carbamazepine, 10, 20 and 30% matrix material of total tablet weight. In order to obtain constant tablet weights, different percentages of the filler excipient, lactose was added at different percentages.

3.3. In vitro release of carbamazepine from tablets

To study the *in vitro* release of carbamazepine from controlled-release tablets, a Prolabo-Paris type dissolution tester (USP XXIII) was used at 75 rpm paddle speed in 900 ml of water containing 1% sodium lauryl sulfate. Samples were collected at appropriate time intervals, filtered and assayed for carbamazepine using UV spectrophotometer at 285 nm.

3.4. In vivo studies

Eight healthy volunteers, seven females and one male, after the explanation of the experimental protocol, agreed to participate in the study and written informed consent was obtained from each subject. Their age ranged from 21 to 28 years (23 ± 2) and their weight from 53 to 60 kg (57 ± 3). The subjects received no medication for at least two weeks before the study. All subjects were judged to be healthy on the basis of the story, physical examination, serum chemistry profile, complete blood count and urine analysis. Approval was obtained from the Ethic Committee of the Hospital of Hacettepe University.

3.5. Study design

The study followed an open, randomized, balanced, cross-over design. The treatments were:

a) one 200 mg formulated controlled-release tablet (HPMC-10)
b) one 200 mg commercially available controlled-release tablet (Tegretol® CR 200).

Half the subject received treatment (a) first and the other half treatment (b) according to a randomization plan. After one week, the subjects were crossed over to the alternative treatment. All subjects abstained from medications, smoking, and alcohol for one week prior to and throughout the study. Subjects fasted for 10 h before each drug administration and 4 h thereafter. Carbamazepine tablets were administered with 100 ml of water.

3.6. Collection of samples

Blood samples were collected (5 ml via an indwelling heparinized scalp-vein needle) before medication and at 1, 2, 4, 6, 8, 10, 12, 24, 43, 72 and 96 h postdose and placed in citrated tubes. Following centrifugation, the plasma were stored in the deep-freeze until analyzed.

3.7. Plasma assay

The determination of plasma carbamazepine concentrations was based on modifications of the HPLC method of MacKichan [15]. A 0.5 ml plasma sample was added to 0.5 ml of aqueous saturated tribasic sodium phosphate solution, extracted with 7 ml of chloroform. The organic layer was transferred to a conical glass tube and evaporated at 40 °C under a gentle stream of nitrogen. The residue was dissolved in 0.5 ml of mobile phase, vortex-mixed for 30 s and 20 µl of the extract was injected into the chromatograph.

3.8. Apparatus

The modular HPLC consisted of Waters Assoc. Model 510 constant flow pump, a Waters Assoc. 717 autosampler and IBM Modal (pc/2, 80/386) chromatography workstation. Samples were analyzed on a Waters Assoc. Bondapak CN (particle size 10 µm) column and carbamazepine was quantitated in a Waters Assoc. Model 490 E ultraviolet detector. The mobile phase consisted of 30% acetonitrile in distilled deionized water. The flowrate was $1.2\ ml \cdot min^{-1}$. Column effluent was monitored by UV-absorption measurement at 254 nm. Experiments in which plasma prior to analysis showed an average recovery of $102.9 \pm 0.9\%$ in the rage $0.5–10\ \mu g \cdot ml^{-1}$. The limit of sensitivity was $0.1\ \mu g \cdot ml^{-1}$ based on the reproducibility of the assay.

3.9. Data analysis

The peak plasma level (C_{max}) is the highest observed concentration, and t_{max} is the corresponding time of this concentration. The terminal half-life ($t_{1/2}$) ws determined by least-squares regression analysis of the log-linear phase of the plasma level versus time data. The area under plasma versus time curves from time zero to infinity ($AUC_{0-\infty}$) was calculated according to the linear trapezoidal rule up to the last measurable level, Cp, residual area, calculated by Cp. last. $t_{1/2}$/0.693. Comparisons of formulations between subjects were done in terms of 95% confidence limits using a two-way ANOVA.

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