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BIOPHARMACEUTICAL ASSESSMENT OF A POLYCOMPLEX MATRIX SYSTEM BASED ON CARBOMER 940 AND EUDRAGIT® EPO FOR COLON-SPECIFIC DRUG DELIVERY

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The biopharmaceutical properties of a new drug carrier based on an interpolyelectrolyte complex (IPEC) between Carbomer 940 and Eudragit® EPO have been studied in the form of a polycomplex matrix system (PMS) intended to be a potential carrier for peroral drug delivery systems. The release profiles of diclofenac sodium from the proposed PMS and Voltaren® retard in model gastroitestial tract medium belong to the intestine-soluble and sustained-release types, respectively. Evaluation of the pharmacokinetic parameters of the PMS revealed a close *in vitro*/*in vivo* correlation. The proposed PMS, in contrast to the parent drug, provides targeted drug delivery to the colon region and is comparable with Voltaren® retard with respect to the bioavailability and the main pharmacokinetic parameters.

Key words: interpolyelectrolyte complex, Carbomer 940, Eudragit® EPO, polycomplex matrix system (PMS), Voltaren® retard, *in vitro*/*in vivo* correlation.

Many strategic approaches are currently employed to deliver drugs to various sections of the gastrointestinal (GI) tract, the most significant section of which is the colon [1 – 3].

Ideally a peroral system created for targeted delivery into the colon should not only ensure that the drug is released at pH > 7 (pH-dependent, pharmaceutical component) but also guarantee that it is completely released by a certain time point (time-dependent, chronopharmacological component) [2]. The lag-time for drug release should be 3 ± 1 h. This corresponds to the time for the delivery system to pass through the small intestine and provides targeted release of the drug in the colon. In other words, the system should have a combination structure with both pH-sensitive and matrix-forming excipients. As a result, drug release is controlled either by erosion processes occurring gradually in the matrix that lead to drug elution or by swelling of polymers incorporated into the system that provide diffusion-type transport [3].

Obviously the desired effect can be achieved by combining pH-sensitive, pH-dependent, and gel-forming copolymers of both natural and synthetic origin. The copolymers that are used most often for this purpose are (meth)acrylates manufactured under the trade name Eudragit® and Carbopol® (Carbomer) [4].

We have previously reported on the physicochemical properties and diffusion-transport characteristics of a new carrier based on an interpolyelectrolyte complex (IPEC) between loosely linked polyacrylic acid (PAA) manufactured under the brand Carbomer 940 and a tertiary polymer based on cationic dimethylaminoethylmethacrylate (DMAEMA) and neutral esters of methacrylic acid (Eudragit® EPO) [5 – 10]. The studied properties of the Carbomer 940/Eudragit® EPO IPEC enabled it to be recommended for further biopharmaceutical tests in order to study the possibility of using it as a promising polymeric drug carrier, the optimum assimilation range of which was various sections of the intestines. It is well known that a conclusion about the potential of a developed system can be made only after a pharmacokinetic study in animal experiments and a compari-

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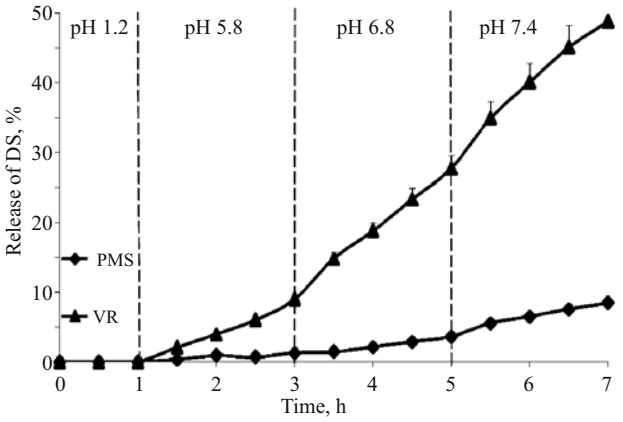

Fig. 1. Release profiles of diclofenac sodium (DS) from the polycomplex matrix system (PMS) and Voltaren® retard (VR) tablets under conditions imitating movement through the GI tract.

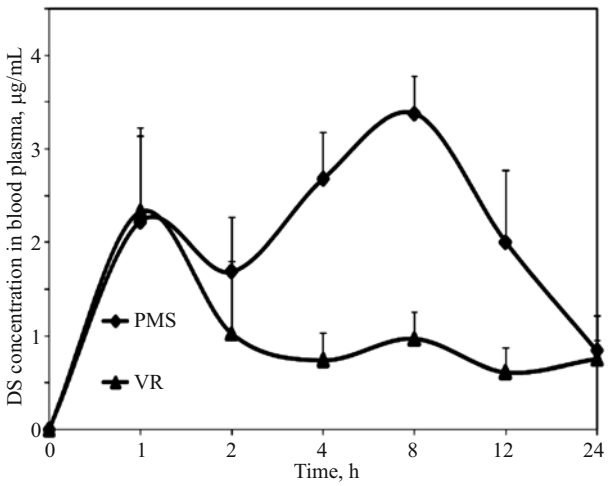

Fig. 2. Pharmacokinetic profiles of diclofenac sodium (DS) in rabbit blood plasma after administration of the polycomplex matrix system (PMS) and Voltaren® retard (VR) tablets.

son with the original drug taken as a standard in bioequivalency tests [11 – 13].

The goal of the present work was to compare the pharmacokinetic parameters of diclofenac sodium (DS) incorporated into the studied polycomplex matrix system (PMS) for delivery to the colon with those of the original tableted preparation Voltaren® retard and to establish correlations between *in vitro* release and *in vivo* assimilation.

EXPERIMENTAL PART

We used Eudragit® EPO (EPO) from Evonik Rohm GmbH (Germany) of average molecular weight 150,000 and Carbomer 940 (C940) from Federa (Belgium) of average molecular weight 1,500,000. Solutions of the polyelectrolytes were prepared based on the molecular weight of the copolymer monomer. DS (Sigma, Belgium) was used in the developed PMS as a model drug with the optimum assimilation range in the colon [14, 15]. The reference drug containing DS was Voltaren® retard (VR) produced by Novartis (Switzerland).

The synthesis and purification of the IPEC and the preparation of the polymer matrices were performed using the published methods [5, 8 – 10].

The release kinetics were studied under conditions modeling movement through the GI tract using the literature method [15]. The first hour was spent in HCl solution (0.1 M, pH 1.2) corresponding to stomach juice. Then, every subsequent two-hour period was spent in phosphate buffers with gradually increasing pH values (5.8, 6.8, and 7.4) imitating various intestinal sections starting with the duodenum (pH > 5.5) and jejunum (pH 6 – 7) to the colon (pH 7) and ileum (pH 7.5). Drug release was assessed using the rotating basket method on an Erweka DT626 instrument (Germany) at rotation rate 100 rpm in 900 mL. The DS concentration in samples taken every 30 min for 7 h was determined by UV spectrophotometry at wavelength 276 nm on a Perkin–Elmer Lambda 25 instrument (USA). The sample volume (3 mL) was replenished with pure buffer solution.

The *in vivo* pharmacokinetic parameters were assessed using a method [16] according to which eight male chinchilla rabbits of average mass 2.70 ± 0.5 kg were fasted overnight for 12 h and given a tablet (PMS or VR). Then, blood was sampled at 1, 2, 4, 8, 12, and 24 h. The obtained blood was centrifuged. The serum was treated with HCl (0.1 M) and $CHCl_3$ and centrifuged again. After this the $CHCl_3$ was separated, treated with NaOH solution (0.1 M), and centrifuged again. The alkaline back-extract was used to determine the DS concentration by HPLC. Measurements were made on a Perkin—Elmer Series 200 chromatograph with a UV detector. We used fractionated EtOH and pharmacopoeial grade acetic and phosphoric acids. The analysis was carried out using a mobile phase of EtOH (96%), aqueous monosodium phosphate (0.15 M), and acetic acid in a 55:40:5 ratio. The chromatographic separation was performed at room temperature (25 ± 2°C) on an analytical column with a grafted C18 phase (4.6 × 250 mm, 10 μm). The detector was an installed Perkin—Elmer Series 200 UV spectrometer at wavelength 280 nm. The elution flow rate was 0.8 mL/min. The chromatographic peak appeared at 7 – 8 min. The DS concentration was calculated using an absolute calibration method. The main pharmacokinetic parameters were calculated using the Thermo Kinetica® applied pharmacokinetics program (Version 5.0, Build 5.00.11; Thermo Fisher Scientific, USA). The results were processed statistically. The significance of differences in the relative bioavailability parameters was estimated using dispersion analysis (ANOVA).

RESULTS AND DISCUSSION

Figure 1 shows the release profiles from the two compared systems under conditions imitating passage through

the GI tract. The DS release kinetics for Voltaren® retard tablets differed considerably from those for the analyzed PMS and showed a constant and smooth increase in the drug concentration as the pH of the dissolution medium increased until the experiment was finished. According to the known classification of controlled release profiles (nine types) given on the Colorcon® website [17], such a profile is characterized by the delayed/sustained concept and is used to create systems with prolonged release (lag-time ≈ 1 h). However, the profile from the PMS with a more delayed release over 3 ± 1 h is placed in the intestinal type. Thus, the differences found in the DS *in vitro* release profiles from the PMS and Voltaren® retard suggested both systems would behave differently during testing *in vivo* in animal experiments. Furthermore, the results were interesting for determining the *in vitro*/*in vivo* correlation between *in vitro* release and *in vivo* assimilation.

Figure 2 plots pharmacokinetic curves for the DS concentration in rabbit blood plasma as a function of time. It can be seen that the results correlate with the aforementioned studies of DS release from the compared systems under conditions imitating passage through the GI tract.

It is noteworthy that the DS concentrations in both systems are comparable at 1 h, the time for the reference drug (VR) to reach the maximum concentration. However, the subsequent statistically significant decrease ($p < 0.05$) of DS concentration up to 8 h does not correspond to the criterion for a colon delivery system. The obtained values are very comparable with the degree of drug release in *in vitro* experiments. The maximum concentrations and their onset time obey a similar principle. The PMS profile is characterized by a significantly greater area under the pharmacokinetic curve (*AUC*). The maximum concentration in blood is observed after 8 h. This produces a bimodal (biphasic) release, i.e., the release of a second larger DS dose from the system directly into the colon, and presupposes the creation of the desired chronopharmacological system with a gradually increasing drug blood concentration over a certain time interval from the time of administration. It is important that both systems provide an initial DS concentration that guarantees simultaneous onset of the therapeutic effect.

Both the added excipients and the construction features resulting in the production of comparable drug forms obviously have an effect on the compared systems that demonstrate different release profiles and DS assimilation. Because our initial goal was not to produce a system analogous to Voltaren® retard, the result achieved during the biopharmaceutical assessment of the developed PMS seemed very interesting.

We recalculated the main pharmacokinetic parameters of the compared systems using a model-independent method in order to obtain a complete picture. Table 1 presents the results. The drug kinetics in rabbit blood were interpreted in terms of a one-compartment model with nonparametric assimilation. The results indicated that DS assimilation in blood occurs at different rates after administering it as a PMS and Voltaren® retard.

Because of the slow release from both drugs, Voltaren® and the PMS, the assimilation and elimination phases occurred in parallel. Therefore, the elimination half-life from plasma was not analyzed and the $AUC_{1\text{-}?}$ was not determined.

Bioavailability is known to be estimated qualitatively for a single dose from the maximum drug concentration in blood plasma (C_{max}), the time to reach the maximum concentration (t_{max}), and the area under the curve of drug concentration vs. time (*AUC*) [18]. Therefore, the two peroral systems were compared by calculating the relative bioavailability (F_{rel}):

$$F_{rel} = \{(AUC_{peros}(PMS))/AUC_{peros}(VR)\times$$
$$\times(C_{peros}(VR)/C_{peros}(PMS))\}100\ \% = 168.63\%.$$

The comparison of the pharmacokinetics of the developed PMS and the known preparation Voltaren® retard showed that the drugs had similar pharmacokinetic parameters whereas the relative DS bioavailability after PMS administration relative to the reference drug was greater than 150%.

The correlation coefficient for PMS relative to the reference drug Voltaren® retard was calculated using a least-squares method ($R^2 = 0.9607$). The result indicates that the degrees of DS release in the *in vitro* tests are closely correlated despite the nature of the drug release profile from the PMS and its degree of assimilation *in vivo*.

Thus, the comparative biopharmaceutical assessment of Voltaren® retard and the PMS showed that the main pharmacokinetic parameters (AUC_{0-1}, C_{max}) of the developed peroral delivery system were comparable to those of Voltaren® retard. The PMS was characterized by a high relative bioavailability (F_{rel}) and provided the required delivery localized in the colon. This confirmed that the new polymeric carrier based on Carbomer 940/Eudragit® EPO that was synthesized by us was promising.

TABLE 1. Main Pharmacokinetic Parameters of the Polycomplex Matrix System Compared with Voltaren® Retard

Pharmacokinetic parameter	PMS	Voltaren® retard
C_{max}, μg/mL	3.378	2.327
t_{max}, h	8	1
$AUC_{0\text{-}\tau}$, μg·h/mL	47.47	19.392
$AUC_{0\text{-}\infty}$, μg·h/mL	57.402	39.207
$AUMC_{0\text{-}\tau}$, μg·h/mL	462, 432	212.566
$AUMC_{0\text{-}\infty}$, μg·h/mL	820.391	1128.55
MRT, h	14.292	34.21
$C_{max}/AUC_{0\text{-}\infty}$ absorption coefficient	0.059	0.059

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