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# Evaluation of stereoselective dissolution of verapamil hydrochloride from matrix tablets press-coated with chiral excipients

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**Abstract**

In most cases the modulation of the drug delivery rate from modified-release formulations is achieved with polymers also used as chiral stationary phases in liquid chromatography. It is therefore hypothesized that the interaction of the enantiomers with the excipient may lead to differentiated delivery rates from the devices for each enantiomer. This study evaluates the stereoselective dissolution of (±)-verapamil, a model racemic drug and, for this purpose, different matrix compositions, a commercial product and a particular delivery device have been considered. The delivery device, recently proposed for the delayed release of drugs, consists of an active core containing the drug, coated by compression with different types of chiral polymeric materials. The quantitative determination of verapamil enantiomers released by these systems was carried out using a stereospecific HPLC method. Hydroxypropylmethylcellulose, β-cyclodextrin, hydroxypropyl-β-cyclodextrin and cross-linked amylose did not show any stereoselective dissolution properties while pectin, galactomannan and scleroglucan seemed to give a slightly higher dissolution rate of the R, compared with the S enantiomer. It is, however, to be verified whether these small differences in the release rate of the two enantiomers detected 'in vitro' could lead to real 'in vivo' effects.

*Keywords:* Stereoselective dissolution; Verapamil hydrochloride; Delayed release; Polymeric coating; Press-coated tablet

## 1. Introduction

Over the last 10 years a great deal of attention has been paid to the effect of stereochemistry on drug action, metabolism and disposition (Jamali et al., 1989), moreover the development of chiral stationary phases for gas and liquid chromatography has made possible the qualitative and/or quantitative analysis of the enantiomers in bulk substances, biological fluids and pharmaceutical preparations.

Recently, many attempts have been made to investigate the implications of pharmaceutical formulations of chiral drugs (Aubry and Wainer,

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1993; Carr et al., 1993; Duddu et al., 1993; Kunz et al., 1994). In fact, in most cases the modulation of the delivery rate from the dosage form is provided by chiral polymeric materials (also employed as chiral selectors in liquid chromatography) and interactions between drugs with asymmetric carbon and chiral excipients may occur, leading to a different dissolution rate of the two enantiomers from the devices. The studies reported in literature are focused on sustained or prolonged-release formulations rather than conventional fast releasing dosage forms. Indeed, any possible difference in the dissolution rate of the two enantiomers for fast releasing dosage forms could not strongly influence the 'in vivo' behaviour of the drug. In the case of modified-release formulations possible formation of transient diastereoisomers between chiral excipient and chiral drug may lead to differentiated dissolution rates possibly resulting in different pharmacokinetics. Controversial results have been reported on this subject and, although in some cases statistically significant differences were found, these differences were very low (Aubry and Wainer, 1993; Carr et al., 1993; Duddu et al., 1993; Kunz et al., 1994).

In general, the modulation of the delivery rate from a modified-release formulation is provided by hydrophilic polymeric materials in which the drug is dispersed. In the presence of fluids the matrix hydrates and swells progressively and the drug can be released by diffusion through the gel layer, or by matrix erosion. The thickness of the gel layer and, consequently, the diffusion pathlength, as well as the erosion rate, can be extremely variable for each delivery device and the influence on the stereoselective drug-excipient interaction cannot be easily detected. In this study a press-coated tablet recently proposed for the delayed release of drugs, and mainly intended for the therapy of diseases dependent on circadian rhythms (Conte et al., 1993), was chosen in order to evaluate the stereoselective dissolution of a model chiral drug.

To fulfil the specific therapeutic needs of diseases such as asthma, hypertension, gastric ulcer and arthritis, which depend on circadian rhythmicity (Lemmer, 1991, 1992), new drug delivery devices are developed for the time-programmed administration of the active ingredients. Such dosage forms should release the drug both at the best possible rate and at the best possible time. For example, the assumption in the evening of a dosage form able to start releasing the dose some hours after ingestion, could be a suitable therapeutic regimen for all those diseases showing a night symptomatic recrudescence.

The delivery system proposed consists of a matrix core, containing the active ingredient, which is surrounded on the whole surface by a drug-free polymeric shell. This kind of polymeric coating can be applied by a double compression technique (dry-coating), and it is formulated to hydrate and swell in a defined and programmable period of time (a few hours in our case). Only when the shell is completely hydrated does the fluid penetrate into the core and starts dissolving the drug. The release of the active ingredient starts only after this time lag when the drug can diffuse outward; in any case, the active ingredient must always pass through the whole extension of the swollen polymeric layer before leaving the device, and, obviously, this process should enhance any possible interaction of the enantiomers with the chiral excipient (Fig. 1).

The stereoselective dissolution property of a typical retarding polymer hydroxypropylmethylcellulose (HPMC) was verified at first in a plain matrix system, without any coating. HPMC is the most widely used material for the control of drug delivery; in this study, it was used as a component of the core in the dry-coated devices and in combination with other polymers, when an enhancement of the retarding effect was needed. This was the case of the two matrix formulations containing $\beta$-cyclodextrins as chiral excipient. In fact cyclodextrin tends to dissolve quickly and to disintegrate the matrix: for this reason the integrity of the tablet as well as the modulation of the delivery rate from the device can be obtained by including in the formulation a gellable polymer such as HPMC.

For the preparation of the dry-coated devices the following chiral materials were selected: HPMC, amylose, pectin, galattomannan and scleroglucan.

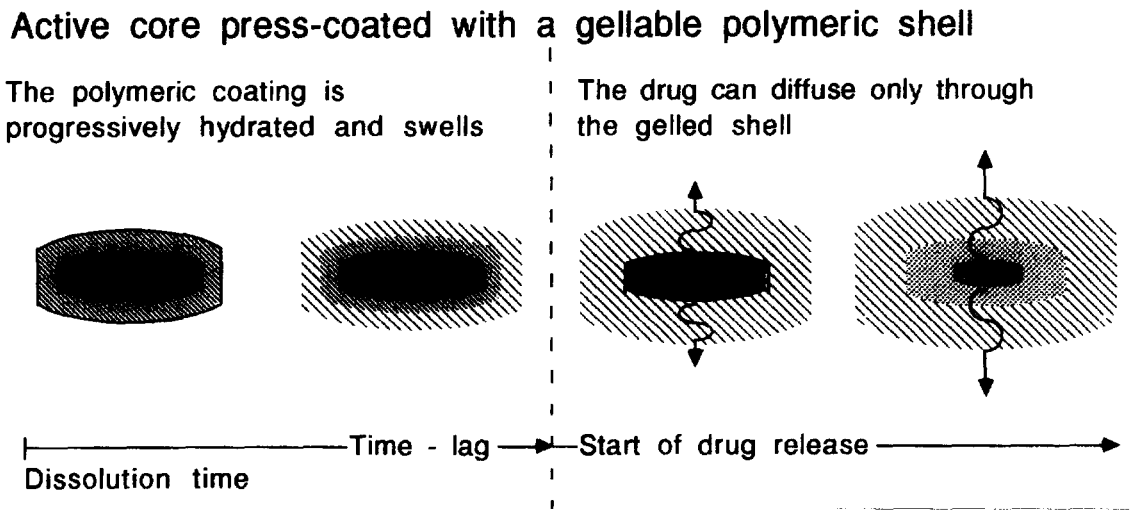


Fig. 1. Typical dissolution behaviour of tablets press-coated with a hydrophilic gellable coating.

(±)-Verapamil (Ver) was chosen as the model. Ver is a calcium channel blocking drug which is used in the treatment of arrythmia, hypertension and angina (Kwon and Triggle, 1991). Although the molecule contains an asymmetric carbon, Ver is routinely administered as a racemate; previous studies have demonstrated that the enantiomers of Ver differ in their pharmacodynamic effect and pharmacokinetic disposition with the (−)-(S)-enantiomer being more pharmacologically active (Chu and Wainer, 1989).

A commercial sustained release product containing racemic Ver, (Calan® SR) which was reported to show stereoselective release (Aubry and Wainer, 1993; Carr et al., 1993), was tested in very mild dissolution conditions that should enhance the chiral interactions among the components. A flow-through-cell apparatus was therefore employed at a very slow flow rate.

## 2. Materials and methods

### 2.1. Materials

The following materials were used: racemic Ver hydrochloride (Recordati SpA, Milan, Italy), β-cyclodextrin (Kleptose®, Roquette, Lille, France), hydroxypropyl-β-cyclodextrin (Encapsin®, Janssen, Olen, Belgium), hydroxypropylmethylcellulose (Methocel® type K, Colorcon, Orpington, UK), of two different viscosity grades: Methocel K15M, viscosity 15000 Cp and Methocel K4M, viscosity 4000 Cp; partially cross-linked amylose (Contramid® CL 8, Rougier Inc., Montréal, Canada), pectin (Cesapectin® LM 32, CESAP S.p.A., Bergamo, Italy), galactomannan (Viscogum® HV 3000 A, Sanofi, Paris, France), scleroglucan (Actigum® CS 6, Sanofi, Paris, France), hydrogenated castor oil (Cutina® HR, Henkel, Düsseldorf, Germany), polyvinylpyrrolidone (Plasdone® K29-32, ISP, Wayne, NY, USA), colloidal silicon dioxide (Syloid 244, Grace, Worms, Germany) magnesium stearate and mannitol, USP grade, were supplied by C. Erba, Milan, Italy. The commercial dosage form Calan® SR was produced by Searle (Skokie, IL, USA). All the solvents employed in the chromatographic experiment were of analytical grade.

### 2.2. Preparation of the delayed-release delivery systems

Two types of matrix tablets, without any coating, were prepared and preliminarily tested. The first composition V1, reported in Table 1, is based on HPMC, the retarding polymer most widely used to control the release rate from solid dosage

Table 1
Matrix formulations (in percentage)

| Formulation | V1 | V$\beta$CD | VHP$\beta$CD | VCore |
|---|---|---|---|---|
| Verapamil HCl | 40.0 | 20.0 | 20.0 | 55.0 |
| $\beta$ cyclodextrin ($\beta$CD) | | 50.0 | | |
| Hydroxypropyl $\beta$CD (HP$\beta$CD) | | | 50.0 | |
| Hydroxypropylmethyl cellulose[a] | 40.0 | 25.0 | 25.0 | 15.0 |
| Mannitol | 15.0 | | | 25.0 |
| Polyvinylpyrrolidone | 3.5 | 3.5 | 3.5 | 3.5 |
| Magnesium stearate | 1.0 | 1.0 | 1.0 | 1.0 |
| Colloidal silicon dioxide | 0.5 | 0.5 | 0.5 | 0.5 |

[a] Methocel K15M.

forms. V1 is designed to verify whether this polymer shows stereoselective dissolution properties, as it would be used combined with other materials to provide the control of drug release when the excipient under test is not able to produce the desired retarding effect by itself.

The second type of matrix formulations V$\beta$CD and VHP$\beta$CD, contains well-known chiral excipients, $\beta$-cyclodextrin ($\beta$CD) and hydroxypropyl-$\beta$-cyclodextrin (HP$\beta$CD), respectively. As these materials tend to disintegrate the tablet, HPMC had to be included in the formulation to maintain the integrity of the matrix system and to produce the needed prolonged-release effect. In the case of the Ver/$\beta$CD composition, equimolecular weights of Ver and $\beta$CD were mixed and ground in a ball mill for 2 h, while the Ver/HP$\beta$CD product was prepared by dissolving equimolecular weights of the raw materials in distilled water; the solution obtained was then freeze-dried (Mini Fast 470, Edwards, Trezzano S/N, Italy) and the lyophilized cake passed through a 710 $\mu$m screen. In both cases the preparations containing the active ingredient and the cyclodextrin were then granulated as detailed below.

The polymers and compositions employed in the shell formulations of the dry-coated systems are designed to delay the core hydration until the coating is completely hydrated and/or gelled, and at the same time, to reduce the release rate of the drug for a prolonged time. To modulate the coating duration and, in many cases, also to improve the technological properties of the compositions, some polymers are used in combination with hydrophilic/hydrophobic excipients. The shell compositions are reported in Table 2 and the core composition is reported in Table 1 and coded VCore.

All the formulations were prepared through a wet granulation process. The active ingredient (or the polymer in the case of the coating formulations) was mixed with the excipients and then wetted with a 10% (w/v) ethanol solution of polyvinylpyrrolidone. The wetted mass was forced through a 710 $\mu$m screen (ATSM series no. 25). The granules obtained were dried in a circulating air oven and calibrated through the same screen. Magnesium stearate and colloidal silicon dioxide were added to the granulate and mixed for 15 min in a Turbula apparatus (type T2A, Basel, Switzerland).

The matrix formulations V1, V$\beta$CD, VHP$\beta$CD and VCore were prepared using a reciprocating tablet machine (Korsh EKO, Berlin, Germany), equipped with punches of 8 mm in diameter. To prepare the press-coated system the machine was then equipped with larger punches, 10 mm in diameter, (for a coating thickness of 1 mm) and

Table 2
Coating compositions (in percentage) and thickness (mm)

| Code | Polymer | Excipient | %Ratio | Coating thickness |
|---|---|---|---|---|
| HPMC | Hydroxypropylmethylcellulose[a] | Mannitol | 50:50 | 1–2 mm |
| CLA | Partially cross-linked amylose | Hydrogenated castor oil | 80:20 | 1–2 mm |
| PEC | Pectin | Hydrogenated castor oil | 50:50 | 2 mm |
| GM | Galattomannan | Mannitol | 50:50 | 2 mm |
| SG | Scleroglucan | Hydrogenated castor oil | 80:20 | 2 mm |

[a] Methocel K4M.

12 mm in diameter (for the thicker coating of 2 mm), respectively. The die was manually filled with half the amount of the coating formulation, the core was placed on the layered powder and centred in the die and then the second charge of barrier powder was carefully added; finally the compression cycle was started. In the case of the first two shell compositions containing HPMC and cross-linked amylose, tablets with two different coating thicknesses of 1 and 2 mm were prepared; for the following three polymers only the thicker coating was applied resulting in tablets of 8/12 mm in diameter.

The shell weight was 250 mg for the 8/10 mm devices and 450 mg for the 8/12 mm dry-coated tablets.

### 2.3. Dissolution tests

The dissolution tests were carried out using two different techniques: the rotating basket (USP Apparatus 1) for the devices prepared in our laboratory and the flow-through-cell method (USP Apparatus 4) for the commercial product Calan SR. In the first case the test was carried out in 1 l of distilled water, at 37°C, at 100 rev./min (six replicates). In the second case the dissolution medium was also distilled water at 37°C and the flow rate was 8 ml/min. The racemic drug concentration was spectrophotometrically determined (Spectracomp 602, Advanced Products srl, Milan, Italy) at 278 nm. A personal computer was connected to the spectrophotometer for data processing. As the results were reproducible ($n = 6$, S.D. $< 3\%$) only the average values were reported in the graph. At proper time intervals a few millilitres of the dissolution medium were sampled for the enantioselective HPLC determination.

### 2.4. Enantioselective chromatography

The quantitative determination of Ver enantiomers in the samples obtained from the dissolution medium was performed using a previously reported stereospecific HPLC method (Hermansson, 1989) with minor modifications. The chromatographic system consisted of a Hewlett Packard HP1050 liquid chromatograph (Palo Alto, CA, USA) with a Rheodyne sample valve (20 $\mu$l loop), equipped with a Hewlett Packard 1050 variable wavelength UV detector connected to an HP Vectra Q5/165 workstation.

A 100 × 4.6 mm I.D. Chiral-AGP column (Chrom Tech AB, Högersten, Sweden) was used with a Chiral-AGP guard column. The mobile phase was composed of 10 mM potassium phosphate (pH 7.0)-acetonitrile (85:15). The wavelength was fixed at 277 nm. The concentration of the two enantiomers was determined by comparison of peak areas from the calibration curves.

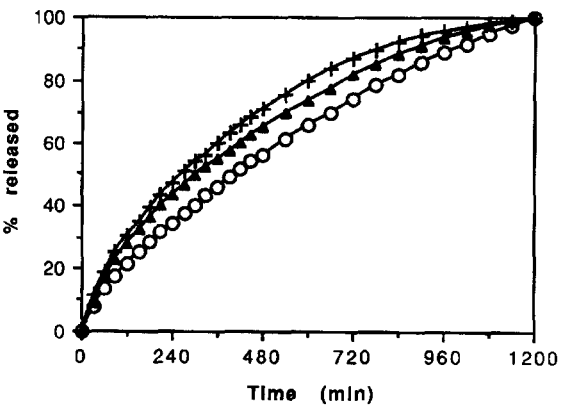


Fig. 2. Dissolution profiles of matrix tablets V1 (○), containing HPMC as retarding polymer, and of the two formulations containing the cyclodextrin derivatives: V$\beta$CD (▲) and VHP$\beta$CD (+).

### 2.5. Statistical analysis

The S/R ratio was determined from the results obtained and the statistical significance was verified using a single-sample $t$-test, considering that a normal distribution of the S/R ratio (population mean) should be around unity.

## 3. Results

The conventional matrix formulation V1, containing HPMC as retarding polymer, shows an extended release of the drug in about 24 h (Fig. 2) and a typical diffusion-dependent dissolution profile. As expected, comparable release trends can be achieved with the two compositions con-

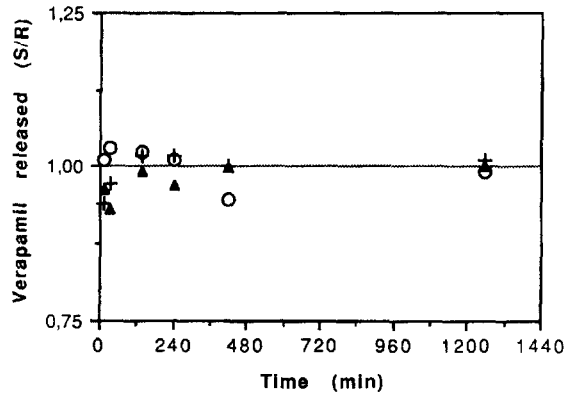


Fig. 3. S/R ratio of verapamil released from the formulations: VI (○), V$\beta$CD (▲) and VHP$\beta$CD (+).

taining HPMC together with cyclodextrin, namely V$\beta$CD and VHP$\beta$CD (Fig. 2): in this case the strong retarding effect of HPMC is only slightly affected by the presence of the two cyclodextrin derivatives. The S/R ratio of released Ver versus time is reported in Fig. 3. No statistically significant difference in the dissolution rates of the two enantiomers can be evidenced ($P > 0.01$). From all these matrix formulations the distribution of the S/R ratio shows a normal population mean around unity.

The formulation VCore, used as active core in the production of the press-coated devices, was designed in order to deliver the drug in about 6 h (Fig. 4). In fact, after the time lag, due to the

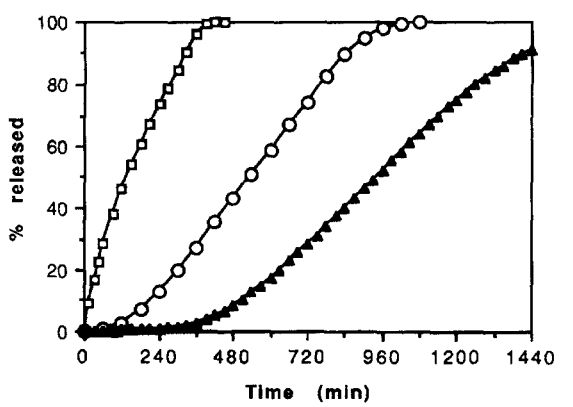


Fig. 4. Dissolution profiles of core formulation VCore (□) and of the devices press-coated with the HPMC shells of two different thicknesses: 1 (○) and 2 mm (▲).

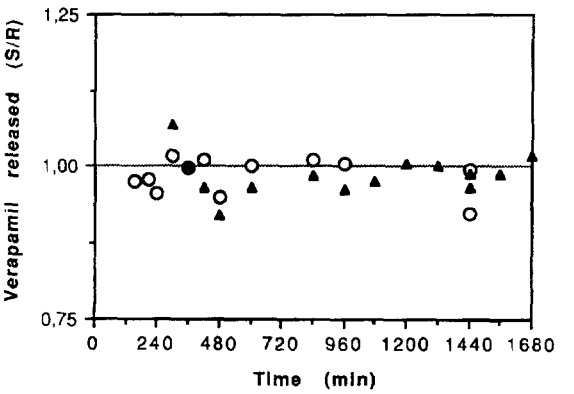


Fig. 5. S/R ratio of verapamil released from the devices press-coated with the HPMC shells of two different thicknesses: 1 (○) and 2 mm (▲).

presence of the polymeric coatings, the drug has to be delivered in a few hours, so that the entire process could take a reasonable time, possibly no more than 20–24 h. The systems press-coated with HPMC show a delay in release-start of 2 h for the 1 mm shell, and of about 6 h for the 2 mm shell (Fig. 4). Even after these time-lags, the presence of the polymeric shell is able to modulate the dissolution rate of the drug from the device. In fact excluding the time lag, the release rate is slower in comparison with the cores without any coating. However, also in this case, no difference in the release rate of the two enantiomers can be detected (Fig. 5).

The shell containing partially cross-linked amylose, CLA, shows the strongest coating efficiency in comparison with the other polymers; in fact, longer time-lags can be achieved from the press-coated systems: 5 h for the 1 mm coating and 9–10 h for the 2 mm shell (Fig. 6) and a very slow release rate is obtained. The S/R dissolution ratio is not altered by the presence of this polymer (Fig. 7).

A comparable delay in the first 5–6 h is observed for the last three polymeric compositions tested, namely PEC, GM and SG. On the other hand, after this time lag, the release rates and kinetics are completely different. The PEC shell shows the fastest delivery rate, followed by the GM and by the SG formulations (Fig. 8). These polymers show a stereoselective dissolution trend.

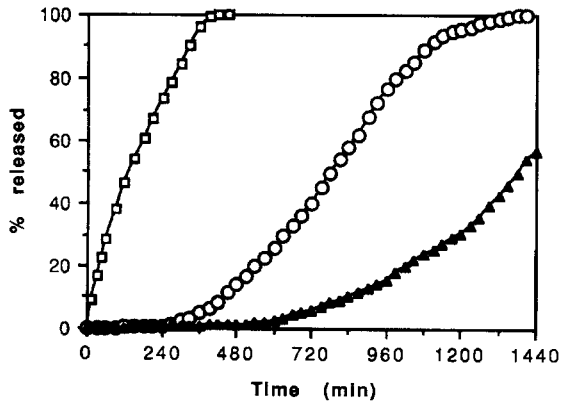


Fig. 6. Dissolution profiles of core formulation VCore (□) and of the devices press-coated with the CLA shells of two different thicknesses: 1 (○) and 2 mm (▲).

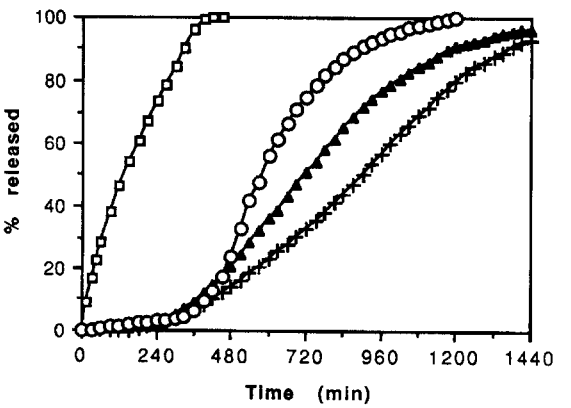


Fig. 8. Dissolution profiles of the devices press-coated with the shell formulations: PEC (○), GM (▲) and SG (+). The formulation VCore (□) is reported for comparison.

In fact in the central phase of the release process a higher amount of the R enantiomer is always detected with an S/R ratio ranging from 0.8 to 0.9 (Fig. 9). By comparing the dissolution profiles of the press-coated devices with the ratio of the two enantiomers released at the same time, it clearly appears that stereoselective interactions happen during the diffusion process (Duddu et al., 1993) when the drug must travel through the gel layer of the swollen polymeric shell. In fact for the PEC shell, the S/R values are smaller than unity between the beginning of release and the 14th hour; after this point the S/R values approach unity and the coating layer itself is no longer efficient. The same behaviour is shown by the GM and SG shell compositions, but as they possess a stronger coating efficiency, the S/R ratio is smaller than unity for a longer time and the drug diffusion process takes about 20–24 h. If a transitory drug-polymer interaction occurs, it is reasonable to expect that, after a certain time, and however at the end of the diffusion process, both enantiomers should be delivered. It is therefore obvious that the S/R ratio approaches unity within the end of the dissolution test.

The dissolution test of the commercial product Calan was carried out in a different dissolution condition as stated above (in a flow-through-cell

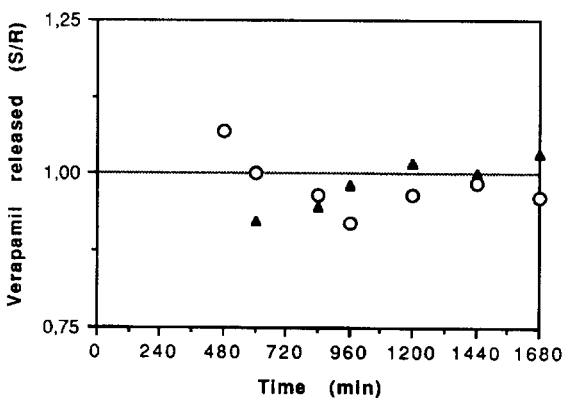


Fig. 7. S/R ratio of verapamil released from the devices press-coated with the CLA shells of two different thicknesses: 1 (○) and 2 mm (▲).

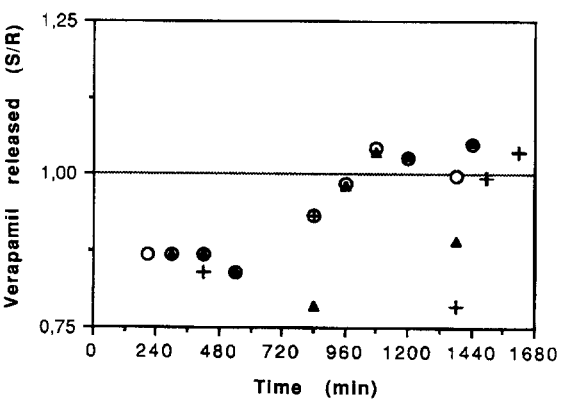


Fig. 9. S/R ratio of verapamil released from the devices press-coated with the shell formulations: PEC (○), GM (▲) and SG (+).

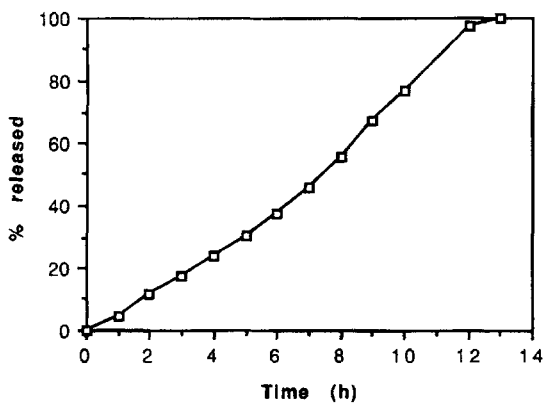


Fig. 10. Dissolution profiles of the product Calan SR carried out in the flow-through-cell apparatus.

apparatus and at a very low flow rate: 8 ml/min) to better approach the test described by Aubry and Wainer; these authors found a statistically significant stereoselective dissolution of Ver from this dosage form, at a very low flow rate (0.13 ml/min), and more of the R enantiomer was released than the S (Aubry and Wainer, 1993). It must be underlined that the dissolution rate (particularly for sustained-release hydrophilic matrices) strongly depends on the stirring conditions and any possible interaction between the retarding polymer and the drug could be enhanced by milder dissolution conditions.

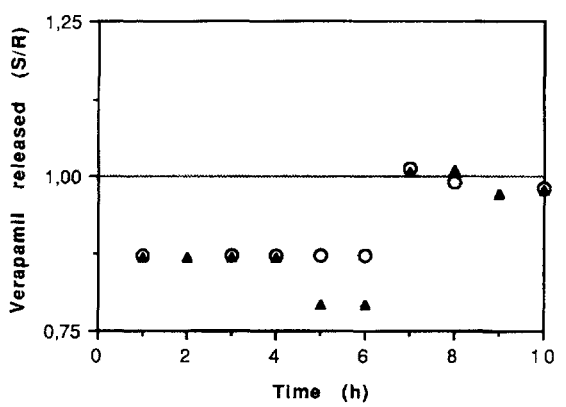


Fig. 11. S/R ratio of verapamil released from Calan SR, two replicates (○, ▲).

As expected, the release of the drug, in our dissolution test, is completed in a shorter time (about 12 h, Fig. 10) compared with the 24 h and more reported by Aubry and Wainer. However a statistically significant difference in the release rate of the two enantiomers can be clearly evidenced in the first phase of the dissolution process (Fig. 11). The S/R ratio is always lower than unity within the sixth hour, then the value approaches unity from the seventh hour to the end of the test.

## 4. Discussion

The results confirm that the polymeric shells of the press-coated devices can delay the release-start and in most cases also modulate the core release profiles (both rate and kinetics). The delay clearly depends on the shell formulation and thickness. The release rate is strongly reduced by the presence of the polymeric shells containing hydroxypropylmethyl-cellulose, cross-linked amylose, galactomannan and scleroglucan, while it is not influenced significantly by the shell containing pectin.

Hydroxypropylmethylcellulose, $\beta$-cyclodextrin, hydroxypropyl-$\beta$-cyclodextrin and cross-linked amylose did not show any stereoselective dissolution properties in the formulations tested, while pectin, galactomannan and scleroglucan seem to produce a slightly higher dissolution rate of the R, compared with the S enantiomer. In the testing conditions used, the S/R ratio is below unity also for the commercial product Calan SR. In all cases the differences in the stereoselective dissolution of the two enantiomers are very little and it is thus fundamental to investigate whether this very small variation may lead to effective differences in pharmacokinetics and/or drug effect.

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## References


Aubry, A.F. and Wainer, I.W., An in vitro study of the stereoselective dissolution of (rac)-verapamil from two sustained release formulations. *Chirality*, 5 (1993) 84–90.

Carr, R.A., Pasutto, F.R., Longstreth, J.A. and Foster, R.T., Stereospecific determination of the in vitro dissolution of modified release formulations of (±)-verapamil. *Chirality*, 5 (1993) 443–447.

Chu, Y.Q. and Wainer, I.W., Determination of the enantiomers of verapamil and norverapamil in serum using coupled achiral-chiral high performance liquid chromatography. *J. Chromatogr.*, 497 (1989) 191–200.

Conte, U., Maggi, L., Torre, M.L., Giunchedi, P. and La Manna A., Press-coated tablets for time-programmed release of drugs. *Biomaterials*, 14 (1993) 1017–1023.

Duddu, S.P., Vakilynejad, M., Jamali, F. and Grant, D.J.W., Stereoselective dissolution of propranolol hydrochloride from hydroxypropyl methylcellulose matrices. *Pharm. Res.*, 10 (1993) 1648–1653.

Hermansson, J., Enantiomeric separation of drugs and related compounds based on their interaction with $\alpha_1$-acid glycoprotein. *Trends Anal. Chem.*, 8 (1989) 251–259.

Jamali, F., Mehvar, R. and Pasutto, F.M., Enantioselective aspects of drug action and disposition: therapeutic pitfalls. *J. Pharm. Sci.*, 78 (1989) 695–715.

Kunz, C.M., Vakily, M. and Jamali F., Stereoselective release of racemic drugs in the presence of chiral excipients. Proceedings of the AAPS Ninth Annual Meeting & Exposition, 6–10 November 1994, San Diego, CA, USA. Pharmaceutical Research 11 (1994) p. S-305. Plenum Press, New York.

Kwon, Y.W. and Triggle, D.J., Chiral aspects of drug action at ion channels: a commentary on the stereoselectivity of drug actions at voltage-gated ion channels with particular reference to verapamil actions at the $Ca^{2+}$ channel. *Chirality*, 3 (1991) 393–404.

Lemmer, B., Circadian rhythms and drug delivery. *J. Controlled Release*, 16 (1991) 63–74.

Lemmer, B., Why are so many biological systems periodic?, Proceedings of the APV course: Pulsatile drug delivery — Current applications and future trends, 20–22 May 1992, Königswinter, Bonn, Germany.