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Research paper

Subcoating with Kollidon VA 64 as water barrier in a new combined native dextran/HPMC–cetyl alcohol controlled release tablet

Eddy Castellanos Gil [a,b,c,*], Antonio Iraizoz Colarte [b], José Lizardo Lara Sampedro [b], Bernard Bataille [c]

[a] Center of Pharmaceutical Chemistry (CQF), Havana, Cuba
[b] Institute of Pharmacy and Food Sciences, University of Havana, Cuba
[c] Faculty of Pharmacy, University of Montpellier 1 (UMR CIRAD016), France

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Abstract

A novel oral controlled delivery system for propranolol hydrochloride (PPL) was developed and optimized using wet granulation process. We are studying the ability of subcoating with Kollidon VA 64 as a barrier to water penetration in matrix cores combined hydrophilic (native dextran–HPMC)/hydrophobic (cetyl alcohol) prior to film coating with Opradry II-YS-30-18056. The copovidone (i.e., Kollidon VA 64) not only increases the mechanical properties of tablets (less friability) but also reduces the amount of absorbed water from the air in tropical stability condition (25 °C and 75% relative humidity). The in vitro dissolution profiles of coated sustained-release matrix tablets of racemic PPL were determined and compared with uncoated tablet cores according to the United States Pharmacopeia (USP) Tolerance Specifications for Propranolol Hydrochloride Extended-Release Capsules. A comparative kinetic study of the present matrix tablets (coated and uncoated cores) and commercial SUMIAL RETARD capsules (reference formulation (*R*) (Spain) was established). The values for the similarity factor ($f_2 = 61.756$, $f_2 = 72.326$ and $f_2 = 88.509$ for initial time, one year and two years, respectively (uncoated cores vs. capsule) and $f_2 = 63.904$, $f_2 = 69.502$ and $f_2 = 76.348$ (coated tablets vs. capsule) for initial time, one year and 2 two years, respectively) suggested that the dissolution profiles of the present three sustained-release oral dosage forms are similar and stable during two years under stability condition.

Keywords: Coating tablets; Dissolution profiles; Kollidon VA 64; Native dextran; Sustained release

1. Introduction

Dextrans are composed of D-glucan chains (1 to 20×10^6) with α-1,6 as the main chain linkage and variable numbers of α-1,2, α-1,3, or α-1,4 branched chain linkages. Dextran is synthesized from sucrose by dextransucrases, glucansucrases, and glucosyltransferases, produced by Leuconostoc or Streptococcii. These bacteria growing in sugar juices produce dextran [1,2].

As tablets are nowadays coated mostly with aqueous solutions or dispersions, it has become increasingly necessary to provide the tablet cores with a barrier layer prior to sugar or film coating. This is mainly to protect water-sensitive drugs against hydrolysis and chemical interactions, e.g. between different vitamins, etc. and to prevent the swelling of high performance tablet desintegrants that are very sensitive even to small quantities of water. It could be useful especially when controlled release systems with hydrophilic polymer are studied and contained water can change the dissolution profile. Kollidon VA 64 (copovidone) can also be used for improvement in adhesion of subsequent coatings by hydrophilization of the surface [3].

* Corresponding author. Centro de Química Farmacéutica, Calle 200 esquina 21, Atabey, Playa, Habana, Cuba. Tel.: +53 7 271 3994; fax: +53 7 273 6471.
E-mail address: eddy02cu@yahoo.es (E. Castellanos Gil).

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Routinely in the pharmaceutical industry, tablet coating is controlled by employing calculations on tablet weight gain during the coating processes with respect to the amount of coating solution applied. However, weight gain determination does not give information on coating uniformity [4]. Other techniques such as scanning electron microscopy, conventional optical microscopy, and laser induced breakdown spectroscopy may be used but are destructive techniques and consequently difficult to apply in on-line analysis [5]

Sugar-coated tablets have an elegant appearance and also provide protection against the hydrolysis and oxidative degradation of drugs since the outer layer consists of sugar crystals having low gas permeability and low water vapor permeability. In addition, the coating can mask the unpleasant taste and odor of drugs. However, conventional sugar coating has several problems such as a complicated manufacturing process, difficulties in controlling coating conditions, the long time needed to manufacture the tablet, and the high moisture content of the coating layer. In general, sugar-coated tablets are manufactured using a sugar solution or sugar suspension, therefore, the formation of a water-proofing and sealing layer is required to prevent water from entering the core. Additionally, a subcoating layer, a smoothing layer, and a syrup coating layer are applied in turn, making the manufacturing process long and complicated [6,7].

Recently we demonstrated the ability of a new series of native dextran (B110-1-2) in the use of solid controlled release dosage forms [8–10]. We developed an oral controlled delivery system using this natural derivative of sugarcane as a main adjuvant of the matrix for water soluble drugs.

The aim of this work is to develop uncoated and coated controlled release tablets and to evaluate the ability of the copovidone as subcoating for water barrier in this new combined hydrophilic (native dextran–HPMC)/hydrophobic (cetyl alcohol) matrix cores prior to film coating. Properties of tablets and stability of dissolution profile after two years are also analyzed and compared with a reference formulation.

2. Materials and methods

2.1. Materials

Reference substance racemic propranolol hydrochloride (PPL) was obtained from Sigma (Saint Louis, USA). High molecular weight native dextran (DT) (series B110-1-2, $M_w > 2{,}000{,}000$) was obtained from the Center of Studies of Sugarcane (Havana, Cuba). Hydroxypropyl methylcellulose (HPMC) with a viscosity grade of 4000 cps (Methocel K4M) was obtained from Colorcon (Kent, England), Kollidon VA 64 from BASF (Germany) and Opradry II-YS-30-18056 from Blanver (Brazil). Spanish commercial SUMIAL RETARD, Zeneca capsules were used as a reference product (*R*). Other chemicals and reagents were of analytical grade. The rest of excipients were of USP 25/NFXX quality [11].

2.2. Preparation and properties of tablets

The drug and the excipients were sieved (80 mesh). The amount of lubricants (talc and magnesium stearate 9:1 wt/wt) was constant in all cases to prevent their effect on release of PPL from matrix. Compression was performed after granulation process with an Italian Ronchi AM13/8, 63 machine (8 punch press) equipped with 12.7 mm convex punches applying a compression force of 30 kN. Batches of 10 kg tablets were prepared (drug content in the tablet was 160 mg). PPL and polymers (DT and HPMC (4:1 w/w)) were mixed for 10 min, granulated with an ethanol solution of cetyl alcohol (15% wt/wt, i.e. 1500 g per batch) and passed through a 0.8 mm sieve. Granules were dried at 45 °C. The dried granules (moisture content below 3%) were passed through a 0.8 mm sieve. Then, the granules were lubricated for 7 min and pressed to tablet with indicated compression force. The same granules with mean particle size 369 ± 21 μm, tapped density 0.53 ± 0.01 g/cm^3 and true density 1.17 ± 0.04 g/cm^3 were used for uncoated and coated tablets. A microscopic photograph (optical microscopy Olympus BH-2, equipment (Japan) coupled with a digital Olympus camera, model μ600, 6.0 mega pixel (China)) of granules is shown in Fig. 1.

The hardness of each formulation ($n = 20$) was measured using an Erweka hardness tester TBH200 (Germany) in a diametric direction. The results were given as mean values and are expressed in Newton (N). Their friability was measured according to the USP 25 [11] using 20 tablets and 100 rotations during 4 min. A total of 20 tablets of each formulation were evaluated for weight uniformity (analytica l balance PRECISA XT 220A; Switzerland).

The thickness was determined using a micrometer (Roche, Switzerland). Ten individual tablets of each formulation were used per experiment. The results are expressed as mean values ± standard deviation [11,12].

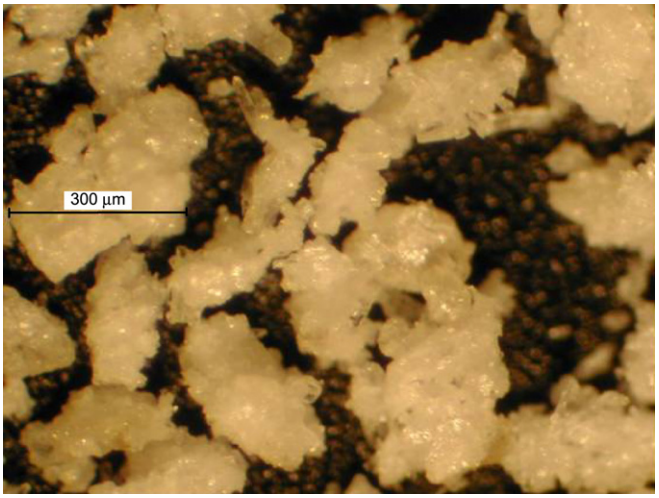

Fig. 1. Photo of granules of uncoated cores and coated tablets.

2.3. Subcoating of cores and film coating

Subcoating of cores was performed with Kollidon VA 64 in a GS multisystem HT/M Italian Pan under previously established condition as shown in Table 1. Barrier to water with copovidone was performed using a 10% solution in ethanol up to an increment of 3% in weight. Coating conditions were performed based on previously optimized methods [13]. Film coating was performed in the same equipment as subcoating process and under similar condition using Opradry II-YS-30-18056 as described in Tables 1 and 2.

2.4. In vitro drug release studies

The in vitro dissolution tests were performed on the USP dissolution apparatus 1 (basket) (SotaxAT7 Smart, Teknokroma, Spain), using 900 ml of each dissolution medium (pH 1.2 or pH 6.8, prepared according to USP 25 Propranolol Extended-Release Capsules Monograph, 2002) [11] with a rotation speed of 100 rpm. Amount of drug dissolved (as racemate) was measured by using an UV–vis spectrophotometer (PC controlled Pharmacia LKB BioChrom 4060 Spectrophotometer, Sweden) at 290 nm [9].

The tablets and capsules (12 replicates for each batch of tablets (coated and uncoated cores) and commercial SUMIAL RETARD capsules, reference formulation (*R*)) were kept for the first hour and a half in a simulated gastric fluid at 37 °C, and subsequently in a simulated intestinal fluid at 37 °C (according to the Drug Release Test 1 of USP 25 specification for Propranolol Hydrochloride Extended-Release Capsules) for up to 24 h. Samples were collected at suitable time intervals. Two milliliters of aliquot was removed from each dissolution vessel and filtered through a 45 μm filter (Millipore Corp., Bedford, MA, USA). The same amount of fresh dissolution fluid was added to replace the amount withdrawn. The total amount of drug present in the tablets and capsules was calculated as the sum of the cumulative mass of drug released at the last sample and the mass of drug remaining (residue).

Table 1
Process parameters for coating system

Coating pan	GS multisystem HT/M
Size of batch	10 kg
Inlet air temperature	37 ± 1 °C
Outlet air temperature	35 °C
Product temperature	35 ± 1 °C
Spraying pressure	2.8 bar
Rate of spraying	30 ± 0.2 ml/min
Pan depression pressure	−2 mm
Pre-heating	3 min
Final drying	7 min

Table 2
Basic formulation for subcoating and film coated tablets

Subcoating with kollidon VA 64	
Ethanolic solution of Kollidon VA 64 (10%)	
Subcoating quantity (increment in tablet weight)	3%
Formulation with Opradry	
Opradry II-YS-30-18056	10.0%
Talc	3.0%
Pigments incl, TiO_2	1.0%
Water	86.0%
Solid content	14.0%
Coating quantity (increment in tablet weight)	0.5%

2.4.1. Studies of mechanism of PPL release from uncoated, coated tablets and SUMIAL RETARD capsules

The mechanism of drug release was analyzed according to Higuchi (Eq. (1)) [14], Hixson–Crowell (Eq. (2)) [15], Korsmeyer (Eq. (3)) [16] and Peppas–Sahlin (Eq. (4)) [17] equations:

$$\frac{Q_t}{Q_\infty} = k_h \cdot t^{1/2} \tag{1}$$

$$\frac{Q_t}{Q_\infty} = (1 - k_w \cdot t)^{1/3} \tag{2}$$

$$\frac{Q_t}{Q_\infty} = K \cdot t^n \tag{3}$$

where Q_t/Q_∞ is the fraction of drug released; k_h, k_w and K are kinetic constants; n is a diffusional exponent that depends on the release mechanism and on the shape of the swelling device tested. Values of $n = 0.45$ indicate Fickian release, values of $0.45 < n < 0.89$ indicate an anomalous (non-Fickian or coupled diffusion/relaxation) drug release, whereas values of $n > 1.0$ show a case II (purely relaxation controlled) drug release.

$$\frac{Q_t}{Q_\infty} = K_d \cdot t^m + K_r \cdot t^{2m} \tag{4}$$

where Q_t/Q_∞ is the fraction of drug released; K_d is the diffusional constant; K_r is the relaxational constant and m is the diffusional exponent that depends on geometric shape of the releasing device through its aspect ratio [18]. For the geometry of our tablets m of 0.43 was appropriate.

A comparative study of dissolution profile for PPL was established as the analysis of a similarity factor. It can be defined as:

$$f_2 = 50.\log\{[1 + (1/n)\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5}.100\} \tag{5}$$

In the equation above f_2 is the similarity factor, n is the number of time points, R_t is the mean percent drug dissolved of capsules SUMIAL RETARD (reference formulation), e.g. the current formulation, and T_t is the mean percent drug dissolved of tablets, e.g. the changed composition.

The evaluation of similarity is based on the conditions of:

- a minimum of three time points
- 12 individual values for every time point

- no more than one mean value of >85% dissolved
- that the standard deviation of the mean should be less than 10% from the second to last time point

An f_2 value between 50 and 100 suggests that two dissolution profiles are similar [19]. In this study, experimental data for up to ⩽85% of cumulative drug dissolved were considered (corresponding to dissolution time from 0 up to 14 h).

2.5. Stability studies

Selected core and coating tablet batch were blistered packaged and kept at 25 °C with 75% RH. Samples were withdrawn at initial time, 7, 14, 21, 28, 30, 60, 90, 120, 150, 180, 270, 365, 510, and 730 days for evaluation of appearance, drug content, friability, water content and in vitro drug release.

3. Results and discussion

3.1. Dextran tablets

The physical attributes of the coated tablets and cores at initial time were found to be satisfactory. Typical tablet defects, such as capping, chipping, and picking, were not observed. Results for other physical evaluations were also found to be within an acceptable range, as for instance, weight variation which was calculated as 1.88% for cores and 2.98% for coated tablets (see Table 3) ($n = 20$). Hardness was found to be 109 and 101 N ($n = 20$) for both formulations, respectively.

Thickness, diameter, and total surface were found to be fixed during the compression and coating cycle; mean values were 5.21 mm, 12.70 mm, and 461.20 mm^2 for cores and 5.56 mm, 12.74 mm and 476.77 mm^2 for coated tablets, respectively. Friability was calculated as 0.001% for coated and 0.138% for uncoated cores ($n = 20$), which was well within the acceptable range of 1% and indicates that tablet surfaces are strong enough to withstand mechanical shock or attrition during storage and transportation and until they are consumed [12]. Properties of cores and tablets through period of 730 days are also shown in Table 3.

The inlet air flow rates influence the coating process and the subsequent quality of the coated tablets. Increasing the inlet air flow rate accelerated the drying of the tablet surface. At high inlet air flow rate, obvious film-coating defects, i.e. unacceptable surface roughness of the coated tablets, are observed and the loss of coating material increased.

Fig. 2 shows a comparative study between uncoated tablets and film coated tablets (3% weight gain with Kollidon VA 64 plus 0.5% weight gain with film coating) of the warm tablet cores, using a 10% solution in ethanol. During two years the coated tablets (with initial humidity 2.5%) are stable (drug content $98.87 \pm 0.91\%$ (initial time), $97.17 \pm 1.01\%$ (365 days) and $98.14 \pm 1.32\%$ (730 days))

Table 3
Core and coated tablets properties up to 730 days under stability studies conditions

Parameter	Days										
	0	7	14	30	90	120	180	270	365	510	730
Core hardness (N)	101 (3%)	100 (2%)	100 (4%)	97 (2%)	98 (5%)	98 (4%)	100 (3%)	99 (1%)	98 (6%)	99 (3%)	97 (4%)
Coated tablet hardness	109 (3%)	108 (2%)	105 (3%)	105 (4%)	106 (3%)	110 (6%)	109 (3%)	108 (4%)	107 (2%)	104 (3%)	105 (5%)
Core weight (mg)	550.2 (2%)	559.5 (2%)	561.5 (1%)	566.7 (2%)	571.6 (2%)	572.8 (2%)	574.4 (2%)	576.1 (3%)	577.2 (4%)	578.3 (3%)	579.9 (3%)
Coated tablet weight	569.1 (3%)	570.2 (3%)	570.8 (3%)	572.5 (3%)	573.9 (5%)	574.4 (3%)	574.8 (4%)	576.3 (5%)	577.6 (4%)	578.8 (4%)	581.4 (3%)
Core thickness (mm)	5.21 ± 0.03	5.21 ± 0.02	5.21 ± 0.04	5.21 ± 0.03	5.22 ± 0.01	5.22 ± 0.05	5.23 ± 0.04	5.23 ± 0.06	5.23 ± 0.05	5.24 ± 0.02	5.24 ± 0.03
Coated tablet thickness	5.56 ± 0.04	5.57 ± 0.07	5.56 ± 0.06	5.56 ± 0.06	5.56 ± 0.08	5.57 ± 0.08	5.56 ± 0.07	5.57 ± 0.06	5.57 ± 0.06	5.57 ± 0.05	5.58 ± 0.06
Core friability (%)	0.138 (1%)	0.136 (2%)	0.142 (4%)	0.152 (2%)	0.177 (3%)	0.174 (5%)	0.184 (3%)	0.192 (4%)	0.211 (1%)	0.236 (2%)	0.243 (4%)
Coated tablet friability	0.001 (3%)	0.001 (2%)	0.001 (3%)	0.001 (4%)	0.002 (6%)	0.002 (4%)	0.002 (5%)	0.003 (3%)	0.003 (6%)	0.002 (3%)	0.003 (4%)

Values in parenthesis corresponding to relative standard deviations.

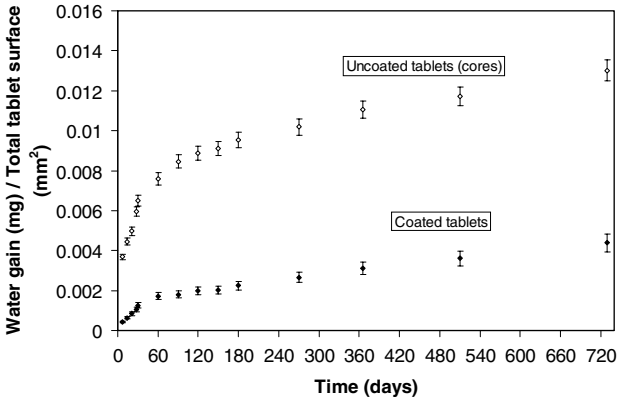

Fig. 2. Moisture content of coated and uncoated cores of combined dextran:HPMC/cetyl alcohol matrix tablets.

and dissolution profiles are similar to initial time with similarity $f_2 \geqslant 80.65$). Good aspect for tablet was observed and friability decreased from 0.138% (uncoated cores) to 0.001% (coated tablets) for initial time. After two years, friability of uncoated cores increased from 0.138% to 0.243% with the increment of water content. A not significant change in this parameter was achieved for coated tablet ($p < 0.05$). All physico-chemical properties above analyzed were within the ranges established by pharmacopoeias [11,12] indicating that tablets and cores are stable during this period.

The water uptake data were fitted to the Vergnaud model to determine the rate of water uptake during stability conditions. The generalized form of this model was proposed by Ebube et al. in 1997 [20–22].

$$W = K_s \cdot t^n \tag{6}$$

being W in our studies the weight gain of the matrix/total surface of tablets; K_s, the kinetic constant of water penetration; t, the penetration time; n, the exponent which depends on the water penetration mechanism. Values obtained for $n = 0.469$ (for coated tablets) and $n = 0.265$ (for cores) from Eq. (6) indicated that mechanisms for water absorption are different. During stability studies a small pre-swelling process occurs in core surface due to the absorption of water and high molecular weight polymers (dextran and HPMC K4M). This phenomenon reduces the lag time, dissolution kinetic constant at initial time (0–4 h) and increases the relaxation (from 4 h). For coated tablets this process does not occur because of the presence of less susceptible to swelling polymers such as Kollidon VA 64 and low molecular weight HPMC contained in Opradry system (see Fig. 3).

The water uptake data were also fitted to logarithmic (for all period) and lineal equations to calculate the rate of water penetration. For coated tablets a plateau state (from 60 days) was observed $y = 0.000004t + 0.0015$ ($r^2 = 0.9927$), while linear slope for uncoated tablets was slightly higher $y = 0.000007t + 0.0081$ ($r^2 = 0.9799$), indicating that in coated tablets water absorption is more stable than in uncoated.

3.2. Studies of dissolution profile and mechanism of PPL release from uncoated, coated tablets and SUMIAL RETARD capsules

PPL is a β-adrenergic blocking agent, i.e. a competitive inhibitor of the effects of catecholamines at β-adrenergic receptor sites. It is widely used in therapeutics for its antihypertensive, antiangorous and antiarrhythmic properties. This drug is a suitable candidate for the design of controlled release delivery systems [23]. According to its solubility in water PPL can be considered as soluble drug [11].

Soluble drugs are considered to be released by diffusion through the matrix and poorly soluble drugs released by erosion of the matrix [24]. Moreover, it is considered that factors affecting swelling and erosion of these polymers may account for differences between in vitro dissolution results and subsequent in vivo performance, when hydrophilic matrix tablets are compared [25].

The Higuchi's (diffusion) and Hixson–Crowell (erosion) model as well as the non-linear regression of Korsmeyer and Peppas–Sahlin were employed to study the release data. The results obtained are shown in Table 4 and Fig. 3A–C. Comparing the influence of the initial moisture content on the release mechanism, the release of less hydrated uncoated and coated tablet surface is seen to be more diffusion controlled than the release from more hydrated tablets, especially for initial dissolution time (first 1.5 h). In the small pre-swelling tablet surface (because of increased moisture content) PPL molecules diffuse with more difficulty from these matrices since the beginning of the dissolution studies and "lag time" necessary for forming gel barrier is shorter, and values for kinetic constants from Korsmeyer equations decreased (values for K from 21.81 to 16.82% hours$^{-0.5}$ and from 20.62 to 18.13% hours$^{-0.5}$ for cores and coated tablets, respectively). On the other hand, it also decreases time for the polymer to relax and mechanism for relaxation becomes more pronounced (values of n become more dissimilar to $n = 0.45$) and k_r/k_d ratios increased (see values of Korsmeyer and Peppas–Sahlin equation in Table 4) and kinetic constants for all dissolution period (0–24 h) increased, according to Higuchi's and Hixson–Crowell's constants.

The mechanisms of drug release from dextran matrix occur in the early stage by polymer swelling, and the tablet thickness increases. Soon, thereafter, the polymer (and drug) dissolution starts occurring. As the polymer chains become more hydrated and the gel becomes more diluted, the 'disentanglement concentration' may be reached faster (in pre-swelling cases), that is, the critical polymer concentration below which the polymer chains disentangle and detach from a gelled matrix. The polymer will then undergo simultaneous swelling, dissolution and diffuse into the bulk medium resulting in erosion of the polymer that

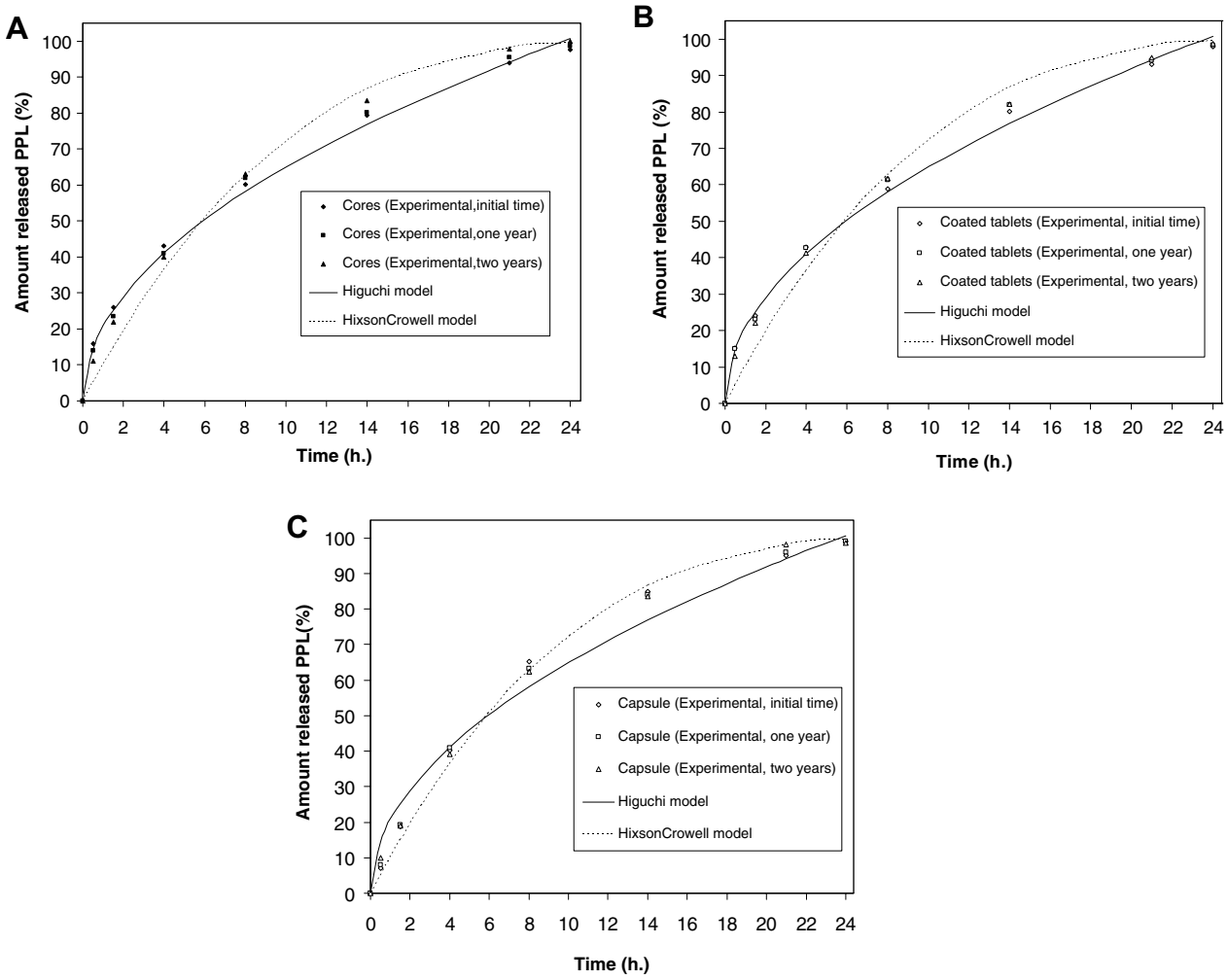

Fig. 3. Plot of experimental, Higuchi and Hixson–Crowell models for release of PPL from uncoated cores (A), coated tablets (B), and reference formulation (capsules) (C).

agree well with other authors [26]. Since at this point a drop in the water holding capacity of the polymer occurred, despite the constant rate of erosion of polymer from the start.

In the anomalous processes of drug release, Fickian diffusion through the hydrated outer layers of the matrix and polymer chain relaxation/erosion are both involved as reported by many authors [27,28]. The contributions of these two mechanisms to the overall release are considered to be additive.

To calculate the percentage of drug release due to the Fickian mechanism the following equation was introduced [17]:

$$F = \frac{1}{1 + (\frac{k_r}{k_d}) \cdot t^m} \tag{7}$$

F is the Fickian release fraction which is the fraction of the drug released due to the Fickian mechanism. The ratio of relaxation to the Fickian contributions can then be expressed as

$$\frac{R}{F} = \frac{k_r}{k_d} \cdot t^m \tag{8}$$

From the parameters obtained in Eq. (4) the contribution of the Fickian diffusion to the overall release (Eq. (7)) and the ratio between relaxation (R) and diffusion (F) were calculated (Eq. (8)). The results of fitting are presented in Figs. 4 and 5. The Fickian contribution to the overall release process (up to 60% and 60–100% of drug released) is observed to decrease with increasing amount of released drug for each one of the investigated formulations (Fig. 4). The relaxation of the polymer chains becomes more pronounced when initial water content increased (after one and two years) (see also Fig. 3).

This observation was expected, since water is taken up simultaneously with drug release, and this water enables polymer chain relaxation. However, the process of Fickian diffusion is the most important from uncoated cores and tablet matrices, since the diffusional rate constant k_d is much larger than the relaxational constant k_r (Table 4). As initial water adsorption (moisture content before dissolution studies) increased, the k_r constants increased indicat-

Table 4
Parameters and correlation coefficient obtained from kinetic equations for the matrix core, coated tablets and reference formulation SUMIAL RETARD capsule (initial time (t_0), 365 and 730 days)

Batch	Higuchi			Hixson–Crowell		
	k_h(% hours$^{-1/2}$)	r^2	(SQR)[a]	k_w (% hours$^{-1/3}$)	r^2	(SQR)[a]
Core						
Initial time	20.616	0.999	27.338	0.034	0.988	375.902
One year	20.766	0.997	31.472	0.034	0.991	269.134
Two years	21.144	0.993	78.468	0.035	0.994	192.614
Coated tablets						
Initial time	20.519	0.997	24.737	0.033	0.990	304.736
One year	20.772	0.995	44.997	0.034	0.990	305.541
Two years	20.805	0.995	51.807	0.034	0.992	249.105
Capsule						
Initial time	20.978	0.982	200.807	0.035	0.999	46.546
One year	20.936	0.987	148.582	0.036	0.998	57.400
Two years	20.960	0.988	132.878	0.036	0.998	58.788
	Korsmeyer			Peppas and Sahlin		
	K (% hours^{-n})	n	r^2	K_d (% hours^{-m})	K_r (% hours^{-2m})	r^2
Core						
Initial time	21.811	0.488	1.000	19.992	1.906	1.000
One year	19.085	0.563	1.000	15.025	4.207	1.000
Two years	16.826	0.633	1.000	10.983	6.060	1.000
Coated tablets						
Initial time	20.617	0.508	0.999	18.312	2.451	0.999
One year	18.833	0.542	0.999	16.390	3.587	0.999
Two years	18.135	0.589	1.000	13.476	4.854	1.000
Capsule						
Initial time	13.925	0.746	1.000			
One year	14.804	0.703	0.999			
Two years	15.024	0.684	1.000			

[a] SQR – sum of squares residual; k_h; k_w; K; K_d and K_r – kinetic constants of each model; n – diffusional exponent; m – diffusional exponent that depends on geometric shape of the releasing device through its aspect ratio; r^2 – coefficients of correlation for each model.

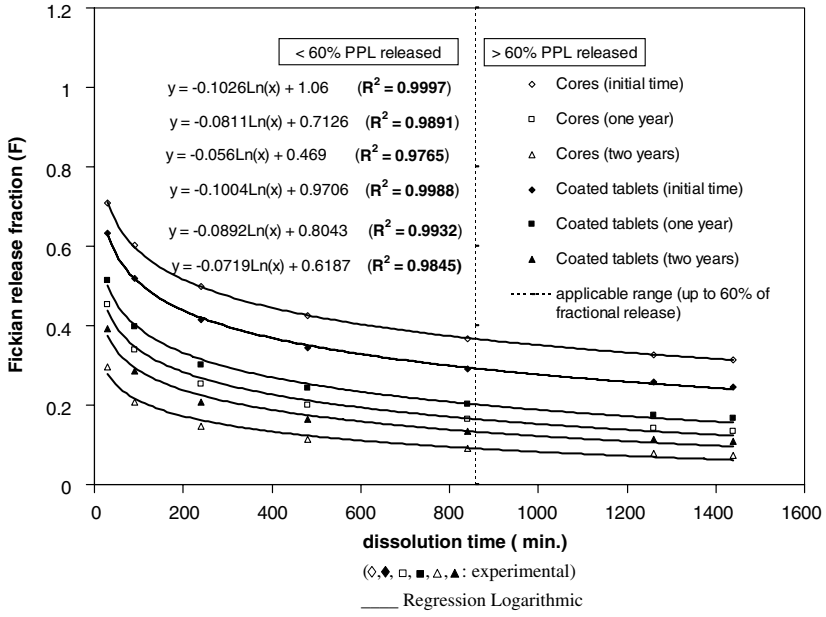

Fig. 4. Fickian release fraction (F) (Eq. (7)) as a function of dissolution time of PPL from uncoated cores and coated dextran:HPMC/cetyl alcohol tablets (initial time, one year and two years under stability conditions). Standard deviation < 4%.

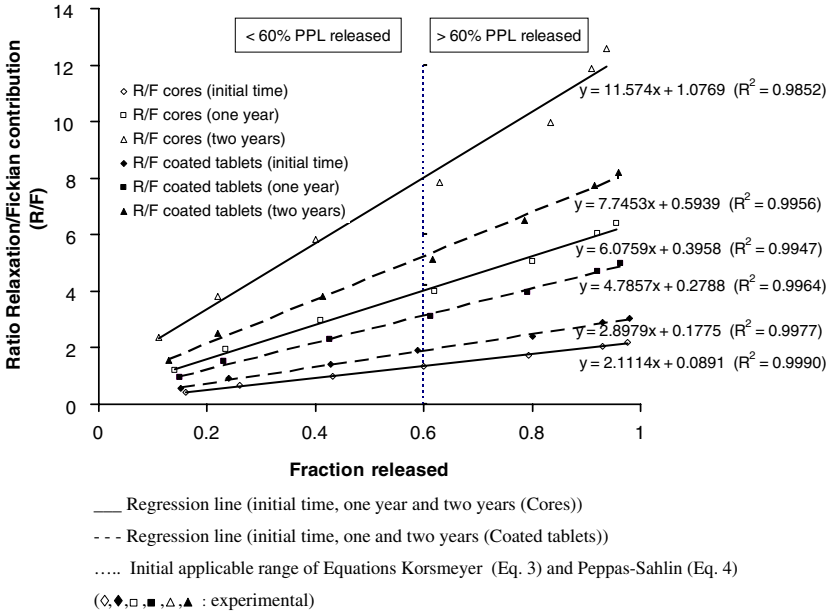

Fig. 5. Ratio of relaxation/Fickian release fraction (R/F) (Eq. (8)) as a function of fraction released PPL from uncoated cores and coated dextran:HPMC/cetyl alcohol tablets (initial time, one year and two years under stability conditions). Standard deviation < 4%.

ing that relaxation between polymer becomes more pronounced ($k_r = 1.91\%$ hours$^{-0.86}$, for 2.5% initial water content up to $k_r = 6.06\%$ hours$^{-0.86}$, for 7.90% initial water content after two years for cores and for coated tablets $k_r = 2.45\%$ hours$^{-0.86}$, for 2.7% initial water content and $k_r = 4.85\%$ hours$^{-0.86}$, for 4.87% initial water content after two years).

The influence of relaxation is seen in Fig. 5, where the curves for more hydrated cores are above those for coated tablets (after two years). Logarithmic correlation was obtained and variations for cores were more pronounced than coated tablets. At the same time similarity factor f_2 were higher than 50 when compared uncoated and coated tablets with reference formulation (SUMIAL RETARD capsule). Results are given in Table 5. In this table we compared f_2 values for the same formulation at initial, one year and two years. The results indicated that dissolution profiles are similar for all formulations even when initial moisture content increased for uncoated cores after 730 days.

Dextran polymer relaxation has a larger influence on the release of pre hydrated tablet surface. This can be the consequence of favourable interactions of the dextran chains with water and therefore relatively easy polymer relaxation and erosion. This relaxation facilitates the release of drugs (see in Fig. 3A and B) changes in dissolution kinetic constant (k initial time $<k$ one year $<k$ two years up to 4 h while in the period 4–24 h: k initial time $>k$ one year $>k$ two years).

Table 5
Similarity factor f_2 obtained for the analysis of uncoated cores, coated tablets and commercial capsule dissolution profile during two years

	Similarity factor f_2		
	Uncoated cores vs. capsules	Coated tablets vs. capsules	Uncoated cores vs. coated tablets
Initial time	61.756	63.904	91.567
One year	72.326	69.502	92.748
Two years	88.509	76.348	80.650
	Uncoated cores	Coated tablets	Capsules
Initial time vs. one year	84.544	91.349	91.781
Initial time vs. two years	71.631	83.819	83.872
One year vs. two years	82.475	91.259	90.896

4. Conclusions

Uncoated and coated tablets such as commercial SUMIAL RETARD capsules are suitable for controlled release propranolol hydrochloride and they comply with the Drug Release Test 1 of USP25 specification for Propranolol Hydrochloride Extended-Release Capsules for 24 h. Their dissolution profiles are similar according to values obtained for similarity factor ($f_2 > 61.7$). Combined tablets dextran:HPMC:cetyl alcohol are highly susceptible to increased water content. Subcoating with Kollidon VA 64 and coating with Opradry II-YS-30-18056 increased properties of tablets (less friability) and offer better protection to cores (minimizing water absorption). The mechanism of drug release from uncoated, coated tablets and commercial capsule was diffusion-dominated coupled with erosion (anomalous) and could be affected by initial moisture content. All formulations are stable up to 24 months under tropical condition (25 °C and 75% HR).

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References

[1] B.A. Newman, E. Kabat, An immunochemical study of the combining site specifies of C57BL/6J monoclonal antibodies to α(1–6)-linked dextran B512, J. Immunol. 135 (2) (1985) 1220–1231.
[2] J.F. Robyt, Dextran, in: H.F. Mark, N.M. Bikales, C.G. Overberger, G. Menges (Eds.), Encyclopedia of Polymer Science and Engineering, John Wiley & Sons, New York, 1986, pp. 752–767.
[3] V. Bühler, Kollidon, Polyvinylpyrrolidone for the pharmaceutical industry, seventh ed., BASF Pharma Ingredients, Germany, 2003.
[4] J.D. Perez-Ramos, W.P. Findlay, G. Peck, K.R. Morris, Quantitative analysis of film coating in a pan coater based on in-line sensor measurements, AAPS PharmSciTech 6 (1) (2005).
[5] M.D. Mowery, R. Sing, J. Kirsch, A. Razaghi, S. Bechard, R.A. Reed, Rapid at-line analysis of coating thickness and uniformity on tablets using laser induced breakdown spectroscopy, J. Pharm. Biomed. Anal. 28 (5) (2002) 935–943.
[6] M. Ando, R. Ito, Y. Ozeki, Y. Nakayama, T. Nabeshima, Evaluation of a novel sugar coating method for moisture protective tablets, Int. J. Pharm. 336 (2) (2007) 319–328.
[7] S. Ohmori, Y. Ohno, T. Makino, T. Kashihara, Development and evaluation of the tablets coated with the novel formulation termed thin-layer sugarless coated tablets, Int. J. Pharm. 278 (2004) 459–469.
[8] E. Castellanos Gil, A. Iraizoz, M. Héctor, A. Alemán, L. Lara Sampedro, E. Urribarri, G. Jordán, Matrix system for controlled release of drugs, using dextran, HPMC and cetyl alcohol. Cuban Patent CU22998, No. 2348/2004, 2004.
[9] E. Castellanos Gil, A. Iraizoz Colarte, B. Bataille, J.L. Pedráz, J. Heinämäki, Development and optimization of a novel sustained-release dextran tablet formulation for propranolol hydrochloride, Int. J. Pharm. 317 (2006) 32–39.
[10] E. Castellanos Gil, A. Iraizoz Colarte, A. El Ghzaoui, D. Durand, J.L. Delarbre, B. Bataille, A sugar cane native dextran as an innovative functional excipient for the development of pharmaceutical tablets, Eur. J. Pharm. Biopharm, 68 (2008) 319–329.
[11] United States Pharmacopoeia 25 (USP 25), National Formulary 20, The United States Pharmacopeial Convention, Rockville MD, 2002.
[12] British Pharmacopoeia (B.P.). London, UK: Stationary Office London, 2004.
[13] E. Castellanos Gil, Controlled released propranolol hydrochloride, Tablets design and quality control [master's thesis], Institute of Pharmacy and Food Sciences, University of Havana, Cuba, 1997.
[14] T. Higuchi, Mechanism of sustained-action medication: theoretical analysis of rate of release of solid drugs dispersed in solid matrices, J. Pharm. Sci. 52 (1963) 1145–1149.
[15] A.W. Hixson, J.H. Crowell, Dependence of reaction velocity upon surface and agitation. I. Theoretical consideration, Ind. Eng. Chem. 23 (1931) 923–931.
[16] R.W. Korsemeyer, J.R. Doelker, P. Buri, N.A. Peppas, Mechanism of solute release from porous hydrophilic polymers, Int. J. Pharm. 15 (1983) 25–35.
[17] N.A. Peppas, J.J. Sahlin, A simple equation for the description of solute release. III. Coupling of diffusion and relaxation, Int. J. Pharm. 57 (1989) 169–172.
[18] P.L. Ritger, N.A. Peppas, A simple equation for description of solute release I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs, J. Control. Release 5 (1987) 23–36.
[19] Annon, Note for guidance on quality of modified release products, Oral dosage forms and transdermal dosage forms, section 1 (quality), The European Agency for the Evaluation of Medicinal Products Human Medicines Evaluation (EMEA), London, UK, 1999.
[20] N.K. Ebube, A.H. Hikal, C.M. Wyandt, D.C. Beer, L.G. Miller, A.B. Jones, Sustained release of acetaminophen from heterogeneous matrix tablets: influence of polymer ratio, polymer loading, and co-active on drug release, Pharm. Dev. Technol. 2 (2) (1997) 161–170.
[21] J.M. Vergnaud, Liquid transport controlled release processes in polymeric materials: applications to oral dosage forms, Int. J. Pharm. 90 (1993) 89–94.
[22] G.W.R. Davidson III, N.A. Peppas, Relaxation-controlled transport in P(HEMA-co-MMA) copolymers, J. Control. Release 3 (1986) 243–258.
[23] E. Kwong, V. Robillo, F. Chen, L. Young, in: Proceedings of the 7th International Conference of Racing Analysts and Veterinarians, KY, 1988, pp. 311–321.
[24] K. Tahara, K. Yamamoto, T. Nishihata, Overall mechanism behind matrix sustained release (SR) tablets prepared with hydroxypropyl methylcellulose 2910, J. Control. Release 35 (1995) 59–66.
[25] B. Abrahamsson, K. Roos, J. Sjögren, Investigation of prandial effects on hydrophilic matrix tablets, Drug Dev. Ind. Pharm. 25 (1999) 765–771.
[26] R.T.C. Ju, P.R. Nixon, M.V. Patel, Drug release from hydrophilic matrices 1. New scaling laws for predicting polymer and drug release based on the polymer disentanglement concentration and the diffusion layer, J. Pharm. Sci. 84 (1995) 1455–1463.
[27] P. Colombo, P. Santi, R. Bettini, S.B. Brazel, N.A. Peppas, Drug release from swelling controlled systems, in: D.L. Wise (Ed.), Handbook of Pharmaceutical Controlled Release Technology, Marcel Dekker, NY, 2000, pp. 183–209.
[28] T. Dürig, R. Fassihi, Guar-based monolithic matrix systems: effect of ionizable and non-ionizable substances and excipients on gel dynamics and release kinetics, J. Control. Release 80 (2002) 45–56.