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NATURAL POLYMER HYDROPHILIC MATRIX : INFLUENCING DRUG RELEASE FACTORS

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ABSTRACT

In porous hydrophilic polymeric systems, two phenomena control the release of drugs : the water uptake and polymer swelling.

Directly compressed hydrophilic matrices were prepared with scleroglucan as gelling agent. A principal components analysis enables the authors to study the correlation between the above phenomena and the dissolution behavior in order to interpret the effect of polymer concentration, excipient solubility and compression force on the drug release.

INTRODUCTION

In a recent work (1), we investigated the viscosity of scleroglucan (Actigum CS11) solutions and their stability over a range of temperature, pH and salt concentrations. Subsequently, pharmaceutical compatibility of this polymer with two common diluents, Lactose Fast Flo^{R} and Emcompress^{R} (2) was checked.

Compressed hydrophilic matrices were formulated using the two excipients and various polymer concentrations and compression forces, different dissolution profiles were obtained (3).

When a drug-containing porous polymeric system, made by direct compression, is brought in contact with water, the pores near the surface of the matrix are filled by water and, initially drug release is controlled by the dissolution of the solute in the water-filled pores and by its diffusion in water (4.5).
Matrix porosity and water uptake can influence directly the releasing profile (6), and when the polymer is soluble, the high

viscosity of polymer solution in the pores slows down the drug diffusion (4).

The present work was undertaken to study the physicochemical mechanisms controlling the solute dissolution and diffusion behavior, in order to statistically correlate the formulation and manufacturing variables to the releasing kinetics in hydrophilic polymeric matrices based on scleroglucan.

MATERIALS

Scleroglucan, (Actigum CS11, Sanofi Bio Industries - France) a ß (1-6)-D-Glucan with a single, pendant glucose group attached through a ß (1-3) linkage (7). Scleroglucan is a natural exocellular polysaccharide secreted by a fungus from the genus sclerotium rolfsii (8). This water soluble polymer has been used as a suspending, coating and gelling agent. It exhibits a gel-like structure in aqueous solution at low temperature (9.10).

Lactose Fast Flo : Foremost Foods Co., SEPPIC - France.

Emcompress : E.Mendell intern., SPCI - France.

Theophylline (anhydrous): Boehringer Ingelheim - Germany.

METHODS

Tablet preparation

Four formulas containing two different polymer concentrations and diluents were prepared (TABLE 1).

The powder mixing was performed in a Turbula mixer (W.A Bachafen Switzerland) at a speed of 90 rpm for 10 minutes.

The matrices were made by direct compressing the mixtures in an instrumented alternative press (OA Frogerais Vitry/seine, France). 0.5% magnesium stearate was added to all formulations just before compression.
Two tablet series having hardness of 5 ±1 daN and 10 ±2 daN were prepared for each formulation and coded : 20E5, 30E5, 20L5, 30L5 and 20E10, 30E10, 20L10, 30L10.

Tablet weight, strength and porosity

For each formulation, 20 tablets were weighed on an analytical balance (Mettler AE260 Viroflay France).

The crushing strength was determined on 10 tablets (Erweka TBH 28 Hensentamm Germany).

The matrix was sealed in a chamber of Mercury porosimeter DC 5000 which is then evacuated to vacuum. Mercury is introduced to the chamber, the pressure is applied to force mercury into the interparticle voids and intraparticle pores.

The distribution of the porosity as a function of radius pores, as well as of the mean radius value, was obtained.

Water penetration and swelling force

The water absorbed and the force developed by the matrix were measured using the apparatus described by Catellani and coll. (11.12). This involved the combined use of an electric balance and a force transducer. The sides of the tablet were covered with adhesive tape. The tablet was placed between two sintered glass

TABLE 1.
Formula composition (*)

Formula	20E	30E	20L	30L
Theophylline	20	20	20	20
Actigum CS11	20	30	20	30
Emcompress	60	50	0	0
Lactose	0	0	60	50

(*) 20, 30 : Actigum %, E, L : Emcompress, Lactose.

disks, with upper disk in contact with the force transducer. The swelling force was measured by transducer and, simultaneously, the amount of water absorbed was measured by the balance. Deionized water at 20°C was used.

Dissolution study

The dissolution rate of theopylline from the matrices was measured using an automated procedure in a USP XXII modified dissolution apparatus (13).

The dissolution medium was 500 ml of Hcl 0.1 N at 37 ± 0.5°C. The rotation speed of the paddle was 50 rpm. Six tablets were tested simultaneously (ERWEKA KA DT6R).

Drug concentration was determined by measuring the absorbance at 264 nm by a spectrophotometer (Lambda 15, Perkin Elmer & Co, Vberlinger).

Dissolution efficiency was determined according to the method of Khan (14).

Satistical Analysis

The Principal Components Analysis (PCA) was applied. It is a statistical descriptive method with an own objective : the representation in a graphic of the maximum information of the data given in a table.

The principal step is the transformation of the initial quantitative variables (more or less correlated) to new variables called principal components (or principal axes).

RESULTS AND DISCUSSION

Compaction behavior

The aptitude of formulations to be directly compressed was assessed by evaluating, for each formulation, the compression forces at the upper punch (F) needed to obtain two tablet series having crushing strength of 5 ±1 daN and 10 ±2 daN were measured TABLE 2.

All the formulations tested showed good compressibility and were able to give rise to strong tablets by direct compression.

The Emcompress formulations needed higher compaction forces than Lactose in order to obtain tablets of same hardness.

TABLE 2.
Tabletting behavior.

	Compression Force (KN)	Hardness (daN)
20E5	22	5.2
20E10	30	8.7
30E5	25	5.1
30E10	46	9.8
20L5	20	5.0
20L10	25	9.4
30L5	18	4.8
30L10	29	10.1

TABLE 3.
Porosity characteristics.

	V p (%)	Rp (µm)
20E5	34.10	49
20E10	24.29	46
30E5	34.71	41
30E10	28.80	61
20L5	37.36	313
20L10	19.52	42
30L5	45.09	72
30L10	33.08	87

Porosity

In TABLE 3, the total porosity (Vp) and the mean values of pore radius (Rp) are represented.

The total porosity (Vp) increases when polymer concentration increases and, when Lactose is used as excipient, a slight increase of Vp values is observed.

Vp decreases with tablet hardness increment, due to the high compaction forces applied to obtain the highest crushing strength level. In terms of pore distribution, at low porosities porous regions tend to be disconnected from each others, while at high porosities, most of the pore space is interconnected. At intermediate porosities there exist pore clusters of many sizes ([6]). Moreover, as the total porosity increases, more pores connect to the surface, so more pores can be wetted, essentially with higher values of pore radius (Rp). This will lead to a faster drug liberation.

Water uptake and swelling

The areas under the curves (AUC) of swelling force versus time, the volume of water absorbed to reach the maximum force (Vabs), the maximum force (Fmax) and the time spent to reach the 50% of maximum force (T50f) are represented in table 4.

Considering that the Emcompress and the Lactose contribution to force development are negligible, we can observe that Fmax and the Vabs decrease with polymer percentage increment. Moreover, in Lactose formulations, the high solubility of this excipient, probably affecting the capillary structures, these values are lower. On the contrary Fmax and Vabs increase with tablet hardness increment at the same polysaccharide percentage.
We observed the formation of a more resistant gel-layer that reduced the speed of water penetration and caused a longer time to reach the maximum force (Fmax).

Drug release

The release profiles of theophylline in Emcompress and Lactose formulations are shown in figures 1 and 2.

As shown in TABLE 5, the dissolution efficiency (E%) decreases and the time to reach the 50% of drug dissolved (T50d) increases with polymer concentration increment and tablet hardness increment, especially in Lactose containing formulas.

The presence of Emcompress in the formulas decreases the efficiency of the dissolution, especially at the lowest polymer concentrations.

This decrease in dissolution efficiency, simultaneous to water uptake and swelling behavior, is the consequence of the gel-layer formation that adversely affects the drug diffusion rate by blocking the surface pores of the tablet and slowing down the dissolution medium uptake ([15]).

The solute release kinetics can be estimated using the following empirical relationship suggested by Peppas and coll. (16.17), for M_t/M_∞ lower than 0.6 :

$$M_t/M_\infty = K\, t^n \quad \textbf{(eq. 1)}$$

Where, M_t/M_∞ is the fractional solute release
K is a kinetics constant characteristic of the drug/polymer system.
t is the release time
n is the diffusional exponent.

The exponent n, characteristic of the overall mechanism of solute release, increases with the polymer concentration and in the Lactose formulations (20L5 excepted, due to the high value of pore radius; for 20L5, n was calculated only with six experimental values). The values of n give an indication of the release mechanism. For cylindrical geometry (18.19.20), values of n close to 0.45 ±0.02 have been shown to correspond to fickian release. For n greater than 0.45 a non fickian release can be observed. The values of n less than 0.45 indicate that in the system a strong contribution of the dissolution to the amount of drug released is present.

In effect the shape of the release profiles indicates a biphasic mechanism : dissolution initially prevails (fast drug release) and diffusion controls drug delivery in the successive times (slow drug release). This phenomenon is particullary evident with 20L5 formulas having very high value of pore radius.

TABLE 4.
Water uptake and swelling force development behavior (mean value of three experiments).

	AUC	T50f (s)	Fmax (N)	Vabs (mg)
20E5	34.93	588	21.00	201
20E10	56.64	1098	25.70	255
30E5	108.06	1583	7.80	173
30E10	123.34	2150	14.00	240
20L5	36.60	168	14.00	92
20L10	48.92	1155	14.70	127
30L5	117.14	1353	4.00	64
30L10	134.99	2443	8.50	163

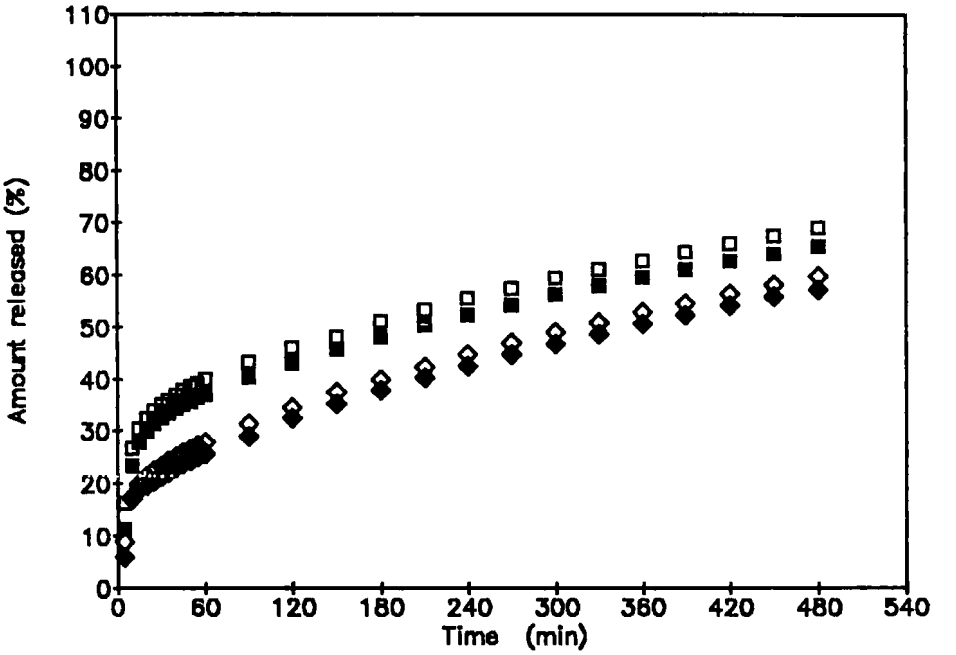

Figure 1.
Release profiles of theophylline from emcompress tablets with different polymer concentration and hardness.

□ 20E5 ◇ 30E5
■ 20E10 ◆ 30E10

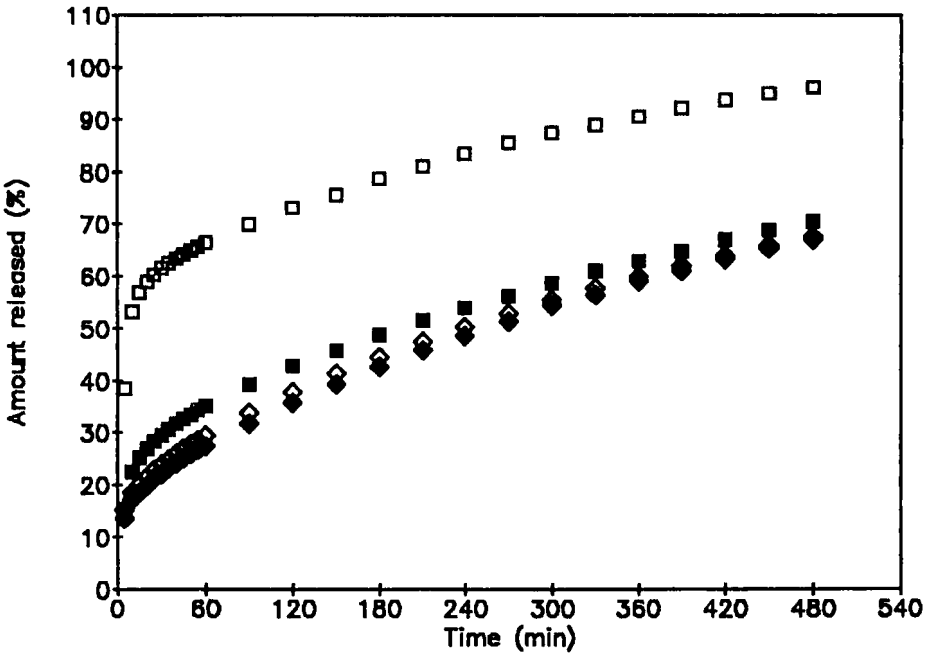

Figure 2.
Release profiles of theophylline from Lactose tablets with different polymer concentration and hardness.

□ 20L5 ◇ 30L5
■ 20L10 ● 30L10

TABLE 5.
Release parameters.

	E(%)	n	T50d (min)
20E5	54.47	0.255	171
20E10	53.59	0.320	209
30E5	41.00	0.413	363
30E10	40.70	0.426	398
20L5	78.73	0.216	10
20L10	55.31	0.382	201
30L5	48.01	0.484	252
30L10	45.85	0.516	278

Statistical study

The twelve factors studied for all tablet formulations, enable us to establish a **correlation matrix** (TABLE 6) and then to assess the relative importance of five factors to represent the four following groups in the Principal Components Analysis PCA :

- Technical group : a high positive correlation exists between compression force (F) and tablet hardness (H). As H is a qualitative factor, we will conserve only F for the PCA.
- Porosity group : Vp is positively correlated with Rp. Only Vp will be selected for the PCA, because this factor is more representative of the water uptake and the drug dissolution mechanisms.
- Water uptake group : there is a strong positive correlation between AUC and T50f and negative with Fmax. These factors are also positively correlated with Vabs. It is evident that AUC will represent this group.
- Dissolution group : a strong negative correlation exists between T50d and E%. A decrease of drug release in the time will lead to a diminution of the efficiency and an increment of the T50d. So T50d can be eliminated in our statistical study.

A strong negative correlation exists between E% and n, that indicates a decrease of the E% when n increases. The two factors n and E% will represent this group. n represents the release kinetics between 20 and 60% and E% represents the integral of the all 8 hours kinetic dissolution.

In conclusion, five factors (F, Vp, AUC, n and E%) will be subjected to the PCA. The matrix of the linear correlation coefficients presented in TABLE 6 allows us to estimate the relations between the five variables taken two by two .

This statistical study will give rise to a global factors classification.

The FIGURE 3 shows the variables and the correlation circle on the first factorial plane.
The axis 2 shows on the left positive side (n, AUC and F) in opposition to E% .
The axis 1 shows an opposition between F and Vp.

In the PCA (FIGURE 4), axes 1 (58.5%) and 2 (28.6%) contribute to 87.1% of the total variation.

In TABLE 7 the co-ordinates of individual formulations and the square cosines were represented. The sums of the square cosines ($\epsilon\cos^2$) are all greater than 0.67 this shows the high quality of the first factorial plane representation of each formulation.

In FIGURE 4, on the principal axis plane 1-2, two groups with different release behavior can be differenciated. In reference to axe 2, in the right side are grouped the formulations containing 20% of Actigum : this group has highest dissolution efficiencies and lowest values of n. The 30% polymer group is located in the left side, with values of n closer to 0.45 The axis 1 enables us to differentiate the two groups with 5 and 10 daN of hardness respectively (30L10 excepted) : this last requires higher compression forces for presenting lower (Vp) values.

CONCLUSIONS

In conclusion, when a porous scleroglucan matrix is brought in contact with dissolution medium, the formation of a gel-layer more or less quickly blocks the surface pores and prevents ingress of the dissolution medium, assuming the control of drug transport.

TABLE 6.
Correlation between the variables and the principal axes.

	F	Vp	AUC	E%	n
F	1.000				
Vp	-0.459	1.000			
AUC	0.474	0.309	1.000		
E%	-0.501	0.062	-0.752	1.000	
n	0.351	0.122	0.916	-0.757	1.000

From table 6 it can be seen that :
F a moderate negative correlation with Vp and E%
a moderate positive correlation with AUC and n.
Vp a moderate positive correlation with AUC and n.
a non correlation with E% .
AUC a strong positive correlation with n
a moderate negative correlation with E%.
E% a moderate negative correlation with n.

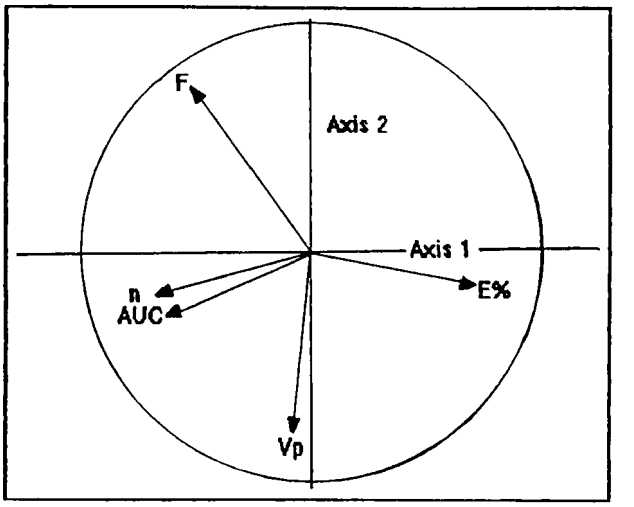

Figure 3.
Representation of the variables on the correlation circle on the first factorial plane.

TABLE 7.
Correlation between the experiments and the principal axis.

	Axe 1		Axe 2		∈cos²
	a	b	a	b	
20 E5	1.812	0.787	-0.276	0.018	0.805
20 E10	0.601	0.176	1.293	0.814	0.990
30 E5	-1.038	0.662	-0.453	0.126	0.780
30 E10	-2.214	0.632	1.315	0.223	0.855
20 L5	2.969	0.853	-0.586	0.033	0.886
20 L10	0.689	0.127	1.428	0.546	0.673
30 L5	-0.908	0.136	-2.271	0.853	0.989
30 L10	-1.912	0.855	-0.450	0.047	0.902

a : co-ordinates of individual formulations or the particle axis ;
b : square cosines (quality of the representation).

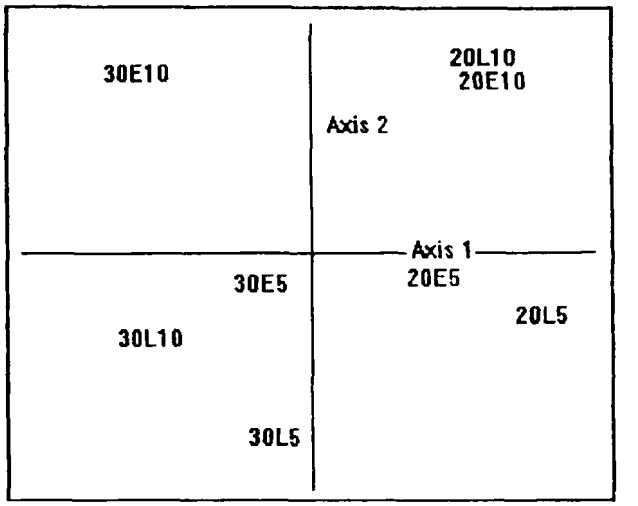

Figure 4.
Representation of the experiments on the first factorial plane.

The release kinetics of drug evidentiates two mechanisms : drug dissolution and, after polymer swelling, drug diffusion.

Strong correlation was established between (n) and (AUC). In our experimental conditions, this correlation shows the importance of measuring in within two hours the kinetics of water uptake and swelling in prediction to mechanism of drug release on eight hours.

The mechanism of drug-release is affected by the scleroglucan concentration and additive nature.

The compression force, despite it is negatively correlated with the total porous volume (Vp), has a slight effect on drug-release, which is essentially controlled by water uptake and swelling.

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