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Hydroxyapatite/Eudragit® Matrix For Continuous And Controlled Release Of Ibuprofen

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SUMMARY

Introduction

We were interested in developing a hydroxyapatite/Eudragit matrix for continuous and controlled release of ibuprofen. The choice of hydroxyapatite and Eudragit (RS 100 and RSPO) as main excipients is justified by the fact that the latter are used to modify the release of active ingredients. In addition, the hydroxyapatite has a mineral whose composition close to that of bone and teeth, gives it the ability to be used as bone restorative material.

Materials and method

We have developed hydroxyapatite/Eudragit matrix with hydroxyapatite annealed at 800°C and not annealed. As plasticizer we used butylphthalate, the active ingredient being ibuprofen which is a nonsteroidal anti-inflammatory used in the treatment of pain and fever. The study of the release of ibuprofen was performed in phosphate buffer medium (pH = 6.8) at room temperature with a UV-visible spectrophotometer (model 1371) at 264 nm and lasted 28 days. For each batch, the study was conducted on three units of known mass.

Results

Quantities released depend on the form of hydroxyapatite used (annealed or unannealed) but also on the initial load of ibuprofen. The release profiles follow first order kinetics, modeled by the following equation : $Qt = Q_{28}\ A_1 + e^{-(t/k)}$. This setting allows not only to predict the precise amounts of ibuprofen to release at the sites of action based on need, but also to control the release of the latter.

Conclusion

These results show that hydroxyapatite powder is suitable for the development of a hydroxyapatite/Eudragit matrix for the controlled and sustained release of ibuprofen. Such a system would allowed not only bone or dental restoration but also as well as an adapted and controlled formulation in terms of dose of active principle provided to the patient.

Keywords: Matrix - hydroxyapatite / Eudragit® - controlled release - ibuprofen

INTRODUCTION

During the last two decades, significant progress has been made in the pharmaceutical industry to improve adherence to treatment through the development of controlled and continuous release systems of active ingredients [**1, 2**]. Thus, these systems with proper release profiles will contribute to reducing the risks of overdose, the number of outlets, oversights and allow permanently delivery of an effective dose of active ingredients in the body. Thus, we have developed and evaluated systems for the controlled and continuous release of ibuprofen which is a nonsteroidal anti-inflammatory widely used in the treatment of pain, fever and inflammation. We choose hydroxyapatite, as main vehicle for the development of systems thanks to its properties [**3**] and Eudragit (RS100 and RSPO). Indeed, hydroxyapatite is a ceramic-based biomaterial having the same mineral composition as bones and teeth, which ensures biocompatibility (osteoconductivity, ostéophily, ability to contain and release active principles) [**3**].

MATERIALS AND METHODS

MATERIAL

- The active ingredient

As active principle, we used ibuprofen as a white crystalline powder. Ibuprofen comes from PHARMACARE LIMITED, THAILAND laboratories.

- Hydroxyapatite

Hydroxyapatite was produced by direct precipitation by adding with stirring a solution of phosphoric acid 0.3M (H_3PO_4) at a rate of 25 ml per minute to a freshly prepared suspension of calcium hydroxide (Ca ($OH)_2$) 0.5 M according to the reaction :

$$6H_3PO_4 + 10Ca(OH)_2 \rightarrow Ca_{10}(PO_4)_6(OH)_2 + 18H_2O$$

Thus, two powder samples were selected for the realization of matrix:

ISSN 2348 – 7968

- The powder precipitated between 80-95 °C, then filtered and dried in an oven at 80 °C for 24 hours. This powder corresponds to the Unannealed Hydroxyapatite (HNR) sample, it has a specific surface of 40 m^2/g and is formed with 10 to 20 nm sized grains;

- The powder precipitated between 80-95 °C, filtered and dried in an oven at 80 °C for 24 hours, then annealed at 800 °C during 3 hours. This powder corresponds to the Annealed Hydroxyapatite (HR) sample, it has a specific surface of 75 m^2/g and is formed with 100 to 200 nm sized grains.

Before use, the samples are passed through sieve equipped with a gate bore 125 µm.

➢ Eudragits

The binders that we have chosen for the development of matrix are Eudragit. They are esterified copolymers of acrylic and methacrylic acid containing a low content of quaternary ammonium groups [**4, 5**] that make them permeable. They are insoluble in water and in biological fluids, which explains their use in controlled release systems. As Eudragit, we have:

- Eudragit® RS PO which are in powder form ready to be used directly in internal phase in the formulation of matrix;

- Eudragit® RS 100 that are used in external phase through the wetting liquid. These form a microporous film.

- Butylphthalate

Butylphthalate, belong to a family of chemical products made of a benzene ring and two carboxylate groups generate a diester structure. It is used as a plasticizer to reduce the stiffness of the material and allow to modify the diffusion properties of the latter [**6**].

METHODS

Matrix preparation

For matrix development, work has been carried out and the proportions for obtaining proper consistency matrix are:

- X% hydroxyapatite;

- Y% active ingredient;

- RS PO Eudragit 20%;

- Eudragit RS 100 5%;

ISSN 2348 – 7968

Y ranges from 5 to 25%; X ranges from 50 to 70%.

Eudragit RS 100 are used as binder in outer phase at 11.6% in a mixture of ethanol (85.5%) and butyl phthalate (2.9%).

Protocol for preparing matrix is described as follows:

- weigh the amounts of hydroxyapatite of Eudragit RS PO and active ingredient (ibuprofen) for a total mixture of 10 grams;
- mix these three products using a glass mortar until obtaining a homogeneous mixture;
- add the wetting liquid containing Eudragit RS 100 (external phase binder);
- grind during 10 minutes, we get a homogeneous mass that does not adhere to fingers and mortar walls;
- Using a spatula, fill to the brim, the alveoli previously coated with absolute ethanol;
- Dry them in an oven at 30 °C during 24 hours. Composition of these different batches is shown in Tables I and II.

Table I : *Composition (%) of matrix based on annealed hydroxyapatite (HR) Composition*

	HAP recuite	**Liants**		**Ibuprofène**
		Eudragit interne	**Eudragit externe**	
HR5	70	20	5	5
HR10	65	20	5	10
HR15	60	20	5	15
HR20	55	20	5	20
HR25	50	20	5	25

- ***Table II*** *: Composition (%) of matrix based on non annealed hydroxyapatite (HNR)..*

	HAP non recuite	**Liants**		**Ibuprofène**
		Eudragit interne	**Eudragit externe**	
HNR5	70	20	5	5
HNR10	65	20	5	10
HNR15	60	20	5	15
HNR20	55	20	5	20
HNR25	50	20	5	25

From this protocol, batches of hydroxyapatite-polymer-active ingredient controlled release matrix were manufactured.

For each batch 20 units were manufactured; the alveoli used have an internal diameter of 12 mm to a depth of 4 mm.

All systems prepared were weighed after drying in an oven; which allowed us to calculate the average mass, standard deviations minimum and maximum allowable weights to meet the standards of the pharmacopoeia.

Study of ibuprofen's liberation

The study of the release of ibuprofen was carried out in phosphate buffer medium at pH = 6.8. For each batch, the study was carried out on three units of known mass. The average cumulative release curve is calculated from a calibration curve (**Figure 1**).

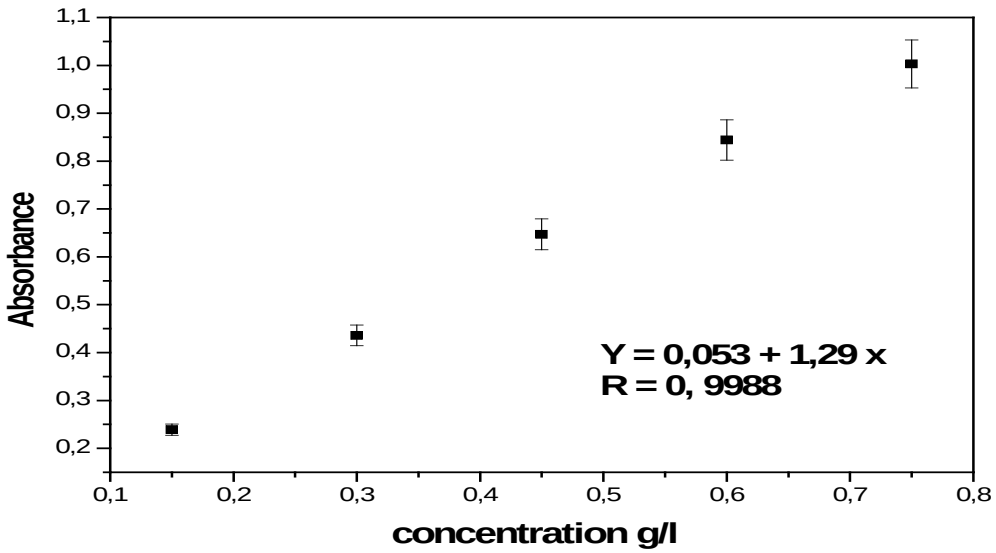

Figure 1 *: Ibuprofen calibration curve.*

The release of ibuprofen was studied according to the following protocol:

- we used plastic pots, cylindrical, with a nominal capacity of 100 ml in which we have introduced an equivalent amount of a solution of phosphate buffer at pH = 6.8. These pots are provided with a screw-on lid to limit evaporation of the dissolution medium;

- samples selected for each batch are introduced without stirring in the dissolution medium, the pots are kept at room temperature, protected from light;

- 1 ml samples are taken every 24 hours and are immediately replaced by a fresh solution of phosphate buffer at pH = 6.8;

- the container is returned three times before each withdrawal;

- aliquots collected parts are properly diluted before dosing amounts of ibuprofen released, with visible UV spectrophotometer (1371 model) at 264 nm.

RESULTS

Mass uniformity test

Average mass of controlled release hydroxyapatite - polymers - ibuprofen matrix, standard deviation, minimum and maximum weights allowable to meet the standards of the pharmacopoeia are calculated and reported in Tables III and IV.

Table III *: Pharmaco-technical parameters of matrix containing ibuprofen in annealed hydroxyapatite (IHR).*

	Masse moyenne	**Ecart-type (g)**	**Max. autorisé (g)**	**Min autorisé (g)**
IHR5%	0,848	0,03952	0,890	0,805
IHR10%	0,803	0,01805	0,843	0,762
IHR15%	0,773	0,01743	0,811	0,734
IHR20%	0,709	0,02821	0,744	0,673
IHR25%	0,721	0,03097	0,757	0,684

Table IV *: Pharmaco-technical parameters of matrix containing ibuprofen in non annealed hydroxyapatite (IHNR).*

	Masse moyenne (g)	***Standard deviation (g)***	***Max. autorised (g)***	***Min autorised (g)***
IHNR5%	0,849	0,02254	0,891	0,806
IHNR10%	0,762	0,03244	0,800	0,723
IHNR15%	0,734	0,02864	0,770	0,697
IHNR20%	0,702	0,02353	0,737	0,667
IHNR25%	0,700	0,02010	0,735	0,665

All lots are considered compliant to Pharmacopoeia [**7**], indeed we have:

$$M_{max} = m_{mean} \pm 0{,}050 m_{mean}$$

ISSN 2348 – 7968

The results obtained in the ibuprofen release studies from matrix based on annealed hydroxyapatite (HR) and unannealed hydroxyapatite (HNR) forms are shown in curves (Figures 2 and 3) and tables (V, VI, VII et VIII).

Thus, the quantities released by unit area Qs (g/cm^2) versus time are shown in Figures 2 and 3, the modeling parameters of release profiles in Tables V and VI and the average dissolution efficiencies of each batch are shown in tables VII and VIII.

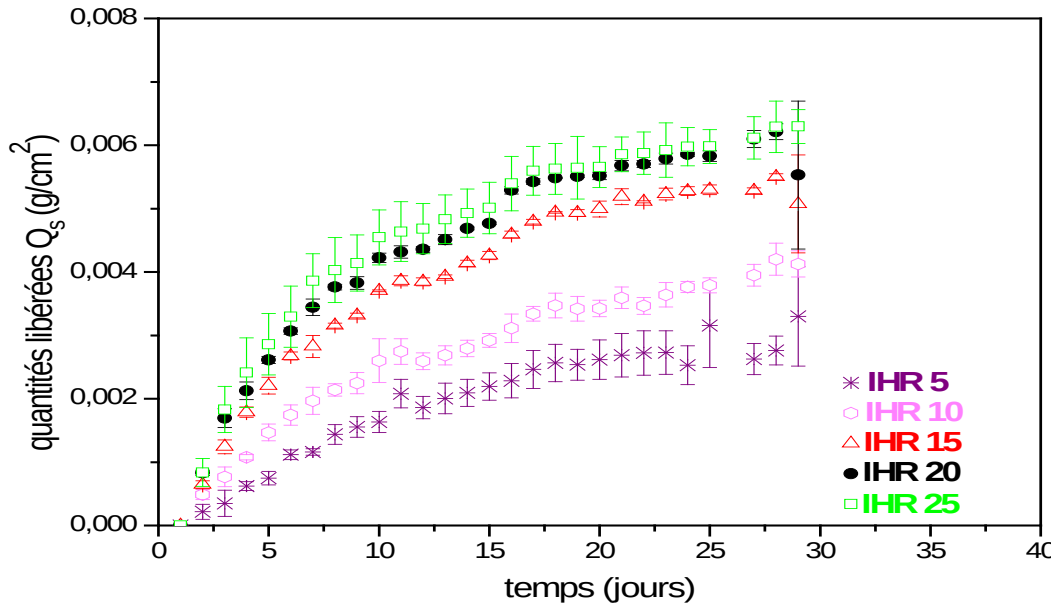

Figure 2 : *Ibuprofen releasing profiles in matrix IHR5, IHR10, IHR15, IHR20 and IHR25*

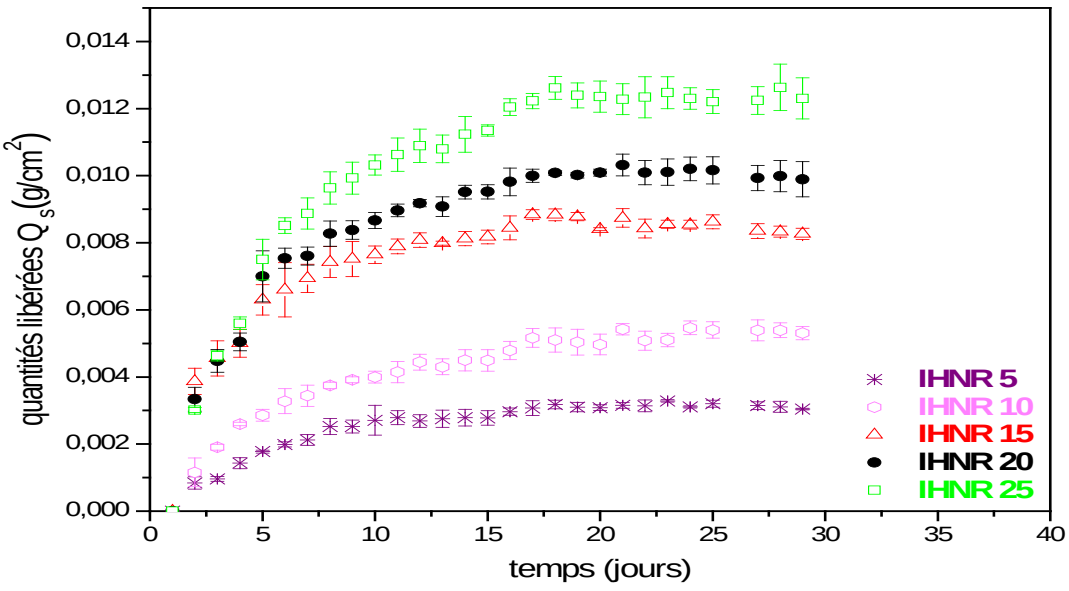

Figure 3 : *Ibuprofen releasing profiles in matrix IHNR5, IHNR10, IHNR15, IHNR20 and IHNR25.*

Table V *: Modeling parameters of release profiles in Figure 2.*

matrix	parameters		
	Q_{28}	A_1	K
IHR 5	0,00334	-0,00370	12,39507
IHR 10	0,00437	-0,00460	11,74577
IHR 15	0,00561	-0,00615	8,86956
IHR 20	0,00614	-0,00668	8,19263
IHR 25	0,00621	-0,00686	7,33139

Table VI *: Modeling parameters of release profiles in figure 3.*

matrix	parameters		
	Q_{28}	A_1	K
IHR 5	0,00317	-0,00372	5,19556
IHR 10	0,00537	-0,00582	6,38410
IHR 15	0,00846	-0,01036	3,34838
IHR 20	0,01004	-0,01200	4,14035
IHR 25	0,01244	-0,01472	4,92443

Table VII *: Average dissolution efficiencies in matrix IHR5, IHR10, IHR15, IHR20 and IHR25*

matrix	7th day	14^{th} day	21^{th} day	28^{th} day
IHR 5%	16,181	35,277	48,864	61,630
IHR 10%	15,400	28,223	36,818	45,635
IHR 15%	16,297	28,816	37,289	45,183
IHR 20%	16,106	27,471	34,875	41,879
IHR 25%	13,848	23,358	29,002	34,444

ISSN 2348 – 7968

Table VIII *: Average dissolution efficiencies in matrix IHNR5, IHNR10, IHNR15, IHNR20 and IHNR25*

matrix	7th day	14th day	21th day	28th day
IHNR 5 %	36,012	59,234	71,008	81,492
IHNR 10%	33,636	52,284	63,469	74,084
IHNR 15%	51,295	72,192	82,502	91,057
IHNR 20%	42,126	62,382	72,776	81,792
IHNR 25%	37,294	58,624	70,344	80,070

DISCUSSION

Ceramic based controlled release matrix doesn't release their entire load of active ingredient in less than 12 hours [**8; 9; 10, 11**] so we chose to perform assays every 24 hours.

The ibuprofen release studies that we performed on batches based on hydroxyapatite annealed and not annealed lasted 28 days.

In general, the release curves obtained from units within the same batch are comparable. This is confirmed by reproducing the standard deviation for each point in the form of vertical bars at the release curves.

The analysis of curves representing the amounts of ibuprofen released per unit area as a function of time shows that the various systems have the same release profiles. Modeling these release profiles can be obtained by the following relationship, which recalls a first-order kinetics release which is identical to that of release of acetaminophen and acetylsalicylic acid [**12, 13, 14, 15**].

$Qt = Q_{28} + A_1\, e^{-(t/k)}$; (Qt is the amount of ibuprofen released per unit area after time t; Q_{28} is the amount of ibuprofen released per unit area after 28 days; A_1 is a dimensionless constant; K is a time constant).

Release profiles show that for both matrix based of annealed hydroxyapatite and those based on unannealed hydroxyapatite, the amount of ibuprofen released (Qe (mg/cm^2) increases when the initial load increases. This confirming that annealed and unannealed hydroxyapatite are suitable to prepare controlled release matrix of active ingredients [**16, 17**].

Ibuprofen release curves for the annealed from the hydroxyapatite-based matrix have substantially the same manners as those matrix based of unannealed hydroxyapatite, ie we have first kinetics order profiles. The release of ibuprofen in such systems is a function of its residual concentration in the pharmaceutical considered form [12**, 13**].

Regarding the efficiencies of dissolution, we note that average dissolution efficiencies vary according to the composition of the matrix. Indeed, the specific area of hydroxyapatite particles plays a key role on the amount of released ibuprofen [**18, 19, 20]**.

For hydroxyapatite annealed based matrix, specific area and particle size explain their high affinity for ibuprofen. Thus, they tend to retain it in the matrix, resulting in relatively low dissolution efficiencies. Moreover, in these systems, batches with low initial load of ibuprofen present the most important dissolution efficiencies. For non-annealed hydroxyapatite based matrix, ibuprofen dissolution rate is significant hence much larger dissolution efficiencies. In these systems, the affinity between the hydroxyapatite powder and the drug ingredient is less important. Therefore these matrix are emptied more rapidly than the systems based on annealed hydroxyapatite [**2, 20**].

CONCLUSION

Given the results, we can say that hydroxyapatite powder is suitable for the development of a hydroxyapatite/Eudragit matrix for controlled and controlled release of ibuprofen. Such a system would not only allowed bone or dental restoration but also an adapted and controlled formulation in terms of dose of active principle to provide the patient.

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