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DRUG RELEASE FROM SEMI-SOLID MATRIX SYSTEMS IN HARD CAPSULES

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ABSTRACT

The authors have prepared hard capsules containing semi-solid matrix systems with fatty excipients and acetylsalicylic acid (ASA) in order to decrease the dissolution rate of this active substance. With excipients like Gélucires and Simulsols, they obtained matrix systems easy to prepare and having a good stability, at least until 37°C. These systems release in vitro acetylsalicylic acid in about 8 hours ; but administered p.o. to man they release ASA too rapidly in less then 4 hours.

INTRODUCTION

In order to decrease the dissolution rate of drugs, the authors had examinated their per os administration in hard capsules containing pasty excipients. In previous communications (1,2,3,4), they used pasty excipients with thixotropic properties e.g. mixtures peanut oil-beeswax ; but these mixtures show at least two disadvantages :

- After capsule filling, they need a long time for solidification ; therefore the probility of leakage is very high.
- With these mixtures, it is very difficult to find excipients which decrease notably the dissolution rate of drugs.

It is the reason why the authors have tried to find convenient fatty excipients or mixtures of fatty excipients which answer the following requirements :

- In vitro release of drugs within about 8 hours.
- Regular flow rate above the melting point in the capsule filling machine.
- Solidification during storage, at least until 37°C.

The fatty excipients which fulfil the best the different requirements are those with well definite melting point and solidification point. These excipients are liquefied for capsules filling and, after filling, they return rapidly to the solid state at the room temperature ; they are called "Semi-Solid Matrix" (S.S.M.).

MATERIALS AND PROCEDURES

Active substance

Acetylsalicylic acid (ASA) has been used, because its analytical properties and determination and its bioavailability after p.o. administration are well known ; the quality employed is called "Aspirine moulinée" with a particle size of 20 - 50 µm. Each hard capsule contains 315 mg ASA.

Excipients

Among the excipients tested for matrix systems, Gélucires (Gattefossé), Précirols (Gattefossé) and Simulsols (Montagne Noire) showed to be the most interesting

1. Gélucires : these amphiphilic excipients have a fatty consistency and can be distinguished by their H.L.B. and their melting point ; e.g. Gélucire 50/02 has a H.L.B. - value 2 and a melting point 50°C.

In our experiments, Gélucires 37/02, 50/02, 48/09 and 44/14 were used.

2. Simulsols : they are polyoxyethylated fatty alcohols or acids ; they also show a fatty consistency, but their melting points are often lower than those of Gélucires (about 40°C).

The Simulsols used showed the following characteristics :

- Simulsol 72 : polyethoxylated stearilic alcohol with 2 molecules of ethylene oxide (E.O.) ; H.L.B. = 4.9.
- Simulsol 78 : idem with 20 molecules of E.O. ; H.L.B. = 15,3.
- Simulsol M45 : polyethoxylated stearic acid with 80 molecules of E.O. ; H.L.B. = 11,1.
- Simulsol M49 : idem with 200 molecules of E.O. ; H.L.B. = 15

3. Précirols : these excipients are non waterdispersible glycerol stearates, e.g. Précirol WL 2155 (M.P. : 65°C) and Précirol ATO (M.P. : 55°C).

Formulation of acetylsalicylic acid-excipients mixtures

For swallowing, the capsules must not be too large, but the quantity of excipients has to be sufficient for coating all particles of ASA. Therefore we have used following formulations :

- 315 mg ASA + 315 mg excipients (50 % ASA)
- 315 mg ASA + 315 mg excipients (55 % ASA)
- 315 mg ASA + 210 mg excipients (60 % ASA)

The capsule size n° 0 was employed for the mixtures with 50 and 55 % of ASA, the size n° 1 for the mixtures with 60 % of ASA.

Preparation of ASA - excipients mixtures and filling of capsules

For quantities of capsules lower than 100, the mixture can be prepared with manual stirring and capsules are filled with a syringe ; but the quality of these capsules is not satisfying.

Therefore all mixtures tested for in vitro dissolution have been prepared in an apparatus with a rotating paddle at about 10°C above the melting point of excipients and, before filling, viscosity of the mixtures has been measured. Then the mixture is introduced in a semi-automatic capsule filling machine and capsules are filled at the same temperature.

Controls during and after preparation of capsules

ASA - excipients mixtures were submitted to following controls :

- Before filling, the viscosity of mixtures is measured at filling temperatures.
- Flow regularity of mixtures above their melting temperature.
- Solidification time of the mixtures after filling.
- Stability of mixtures during storage at room temperature and at 37°C.

After filling weight regularity and absence of leakage are also controlled.

Dissolution Test of filled capsules

Mixtures which have shown a good flow regularity and a short solidification time were examined in the dissolution test of the French Pharmacopaea, 10^{th} edition ; for the experiments, the paddle method with a citrate buffer solution pH 1,3 was used.

At regular time intervals, samples of buffer solution are isolated and filtered. On these samples acetylsalicylic acid is determined with a U.V. - spectrophotometric method at 276 nm.

Stability Control of filled capsules

This control is very important, because one leaking capsule can soil a large number of other capsules ; therefore a short solidification time is essential.

Capsules were stored at 20° and 37°C during three months. Then their physical properties were examined and their ASA content was determined.

RESULTATS

Different ASA formulations with one excipient or with excipients mixtures have been examined. Figures 1 to 4 show dissolution rate of ASA from these lipid matrix systems :

- Figure 1 : the comparison of the behaviour of different Gélucires shows that HLB is the most important factor (see Gélucire 44/14) and that the melting point also influence the dissolution rate of ASA (compare Gélucires 50/02 and 37/02).
- Figure 2 : the association of two Gélucires in different proportions allows to choice the release time of ASA in vitro.
- Figure 3 : one can see that 10 % of Précirol are sufficient to delay notably the release time of active substance.
- Figure 4 : the comparison of the influence of different Simulsols shows that Simulsol 72 with a low H.L.B. (4.9) release ASA later than the other Simulsols with higher H.L.B. values.

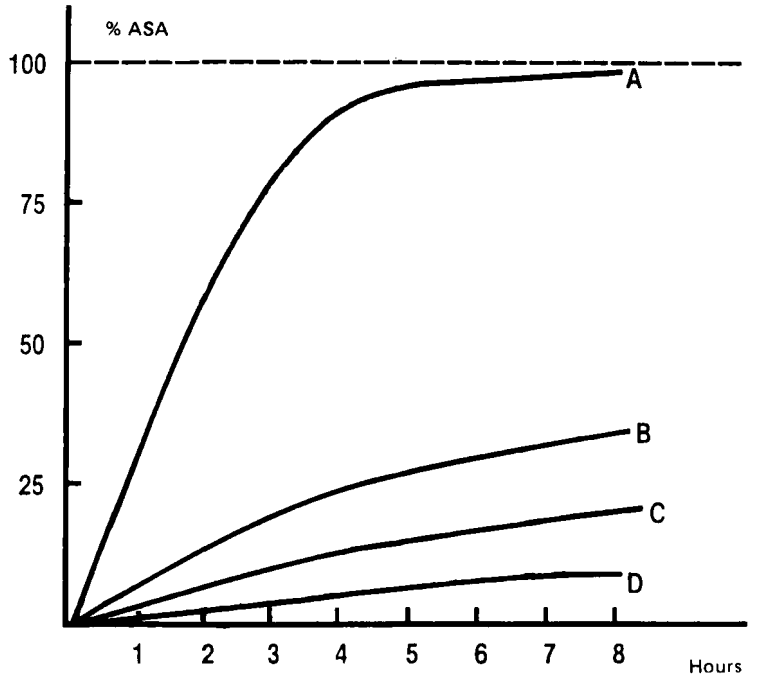

Fig. 1 A Gélucire 44/14 C Gélucire 48/09
B Gélucire 37/02 D Gélucire 50/02

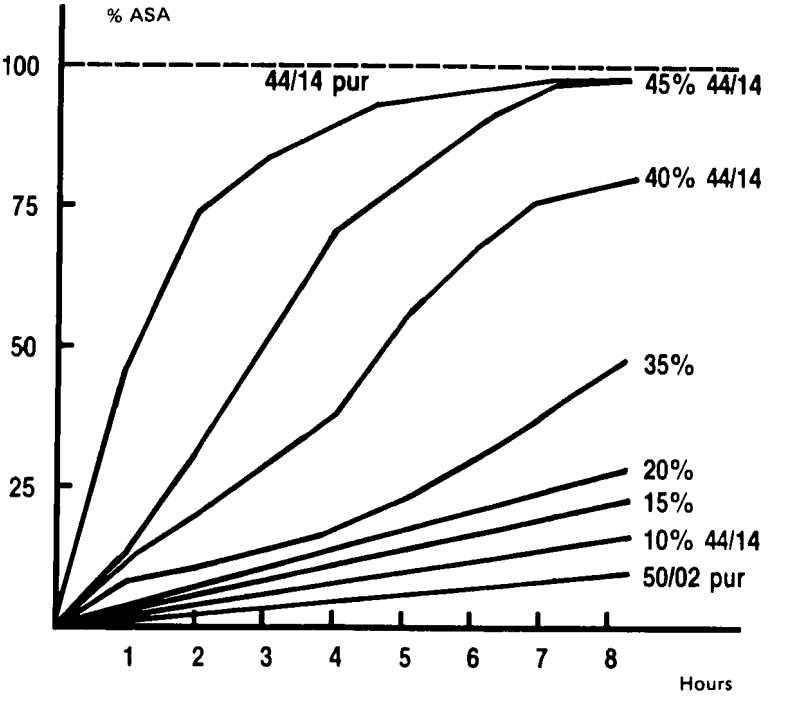

Fig. 2 Mixtures in different proportions of Gélucire 50/02 and Gélucire 44/14

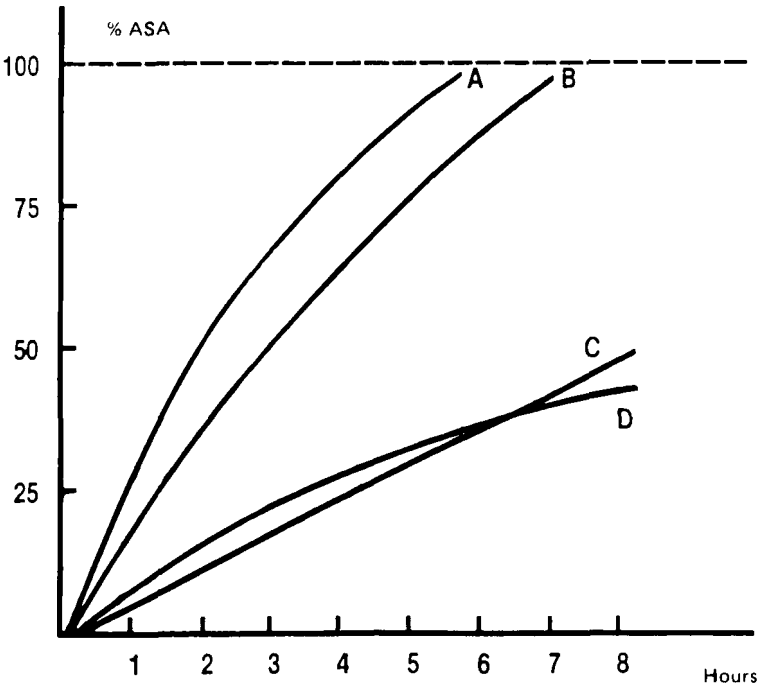

Fig. 3 A Précirol WL - Gélucire 44/14 5-45
B Précirol ATO - Gélucire 44/14 5-45
C Précirol ATO - Gélucire 44/14 10-40
D Précirol WL - Gélucire 44/14 10-40

Following conclusions can be drawn from these experiments :

- The HLB value of the excipient has an essential influence on the in vitro release of the active substance : e.g. Gélucire 44/14 increases notably the dissolution rate of ASA, while Simulsol 72 has the opposite effect.
- The melting point also shows an influence : the higher the melting point, the later the active substance is released. A high melting point (see Gélucire 50/02) enhance stability of capsule content.

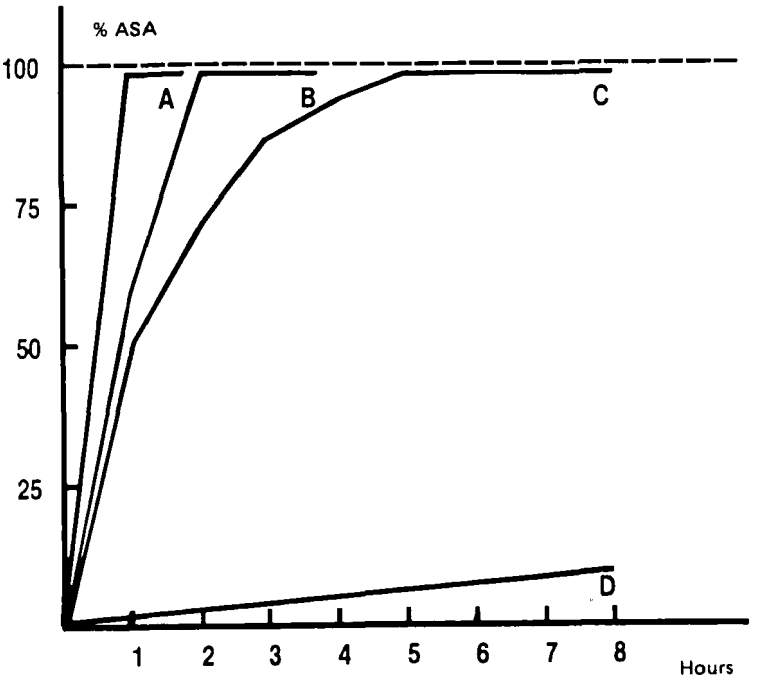

Fig. 4 A Simulsol M49 - C Simulsol M45
B Simulsol 78 D Simulsol 72

These experiments show also that one excipient gives a well defined dissolution rate and release time for 100 % of ASA. But if we have to obtain a well defined release time for an active substance, probably we must use a mixture of two excipients in well defined proportions.

Therefore the in vitro behaviour of these matrix systems will perhaps allow a controlled sustained release of the active substance. This is the reason why we have realized clinical experiments.

CLINICAL EXPERIMENTS

Principle

Our experiments were based on the bioavailability of the active substance in saliva. In the case of acetylsalicylic acid,
- its metabolite, salicylic acid, is eliminated in saliva ;
- a significant correlation exists between plasma concentration and saliva concentration of this metabolit.

Therefore our clinical experiments were the following :
- First one p.o. administration of ASA in form of capsules containing semi-solid matrix systems.
- Then a quantitative determination in saliva during 24 hours, with a spectrofluorimetric method.

Procedure

1. Tested capsule formulations :

- Standard :	ASA "mouliné"	100 % (315 mg)
- S.S.M.1	ASA "mouliné"	55 % (315 mg)
	Gélucire 48/09	23 %
	Gélucire 44/14	22 %
- S.S.M.2	ASA "mouliné"	60 % (315 mg)
	Simulsol M 49	37 %
	Gélucire 50/02	3 %
	Aerosil R 972	0,5 %

2. Oral administration

13 adult persons have been submitted to the clinical experiments. In the morning each person had to swallow three capsules

(945 mg ASA) with 150 ml water. This clinical test was realized with the three formulations.

3. Salicylic acid extraction from saliva

Samples of saliva were collected each hour during 12 hours after p.o. administration.

Salicylic acid was extracted from these samples in the following manner :

- To 3 ml saliva, add 2 ml water and 0,5 ml aqueous 25 % solution of $HKSO_4$; after manual stirring, add 6 ml ether (C_2H_5- O-C_2H_5) and stir mechanically during 20 minutes.
- Take 4 ml of the ether phase, add 5 ml of a phosphate buffer solution pH 7 and stir mechanically during 20 minutes.
- Eliminate the ether phase and use aqueous phase for quantitative determination of salicylic acid.

4. Quantitative determination of salicylic acid

A spectrofluorimetric method at 409 nm is used for the determination of salicylic acid in the aqueous phase.

Results

Compared with the standard, the two semi-solid matrix systems S.S.M.1 and S.S.M.2 give in vivo a sustained release of ASA, but less than the expected release times.

Maximal saliva concentrations	Standard	: 1 h 40 min.
	S.S.M.1	: 4 h 30 min.
	S.S.M.2	: 3 h

The relatively short release times for the lipid matrix systems can probably be explained by the chemical constitution of Gélucires. These excipients are esters, which are submitted to intestinal lipolysis. Therefore new tests must be realized with non-ester excipients to confirm this hypothesis and to obtain longer release times for the semi-solid matrix systems.

REFERENCES

1. A. CUINE, C. MATHIS, A. STAMM and D. FRANCOIS, Labo-Pharma, 26, n° 274, 222 (1978).
2. A. CUINE, C. MATHIS, A. STAMM and D. FRANCOIS, Labo-Pharma, 26, n° 276, 421 (1978).
3. A. CUINE, C. MATHIS, A. STAMM and D. FRANCOIS, Labo-Pharma, 27, n° 292, 863 (1979)
4. A. CUINE, C. MATHIS, A. STAMM and D. FRANCOIS, Labo-Pharma, 27, n° 298, 963 (1979).