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In Vitro Evaluation of Lipid Matrices for the Development of a Sustained-Release Sulfamethazine Bolus for Lambs

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ABSTRACT

The aim of this study is the development of a high-density bolus to be given to lambs in order to release sulfamethazine during 4 days after a single oral administration. The suitability of 12 lipid matrix formulations was assessed in order to maintain the integrity of the tablet even after complete dissolution of the active substance. The influence of both nature and concentration of the lipid excipient on the in vitro release of sulfamethazine was investigated. The influences of the granulation method and of the compression force were assessed on a formulation containing Cutina® HR as a binding and sustained-release agent. Finally, stability tests showed that the in vitro release characteristics remain unchanged during storage.

INTRODUCTION

Sulfamethazine (SMZ) is one of the most commonly used sulfonamides for the treatment of coccidiosis in lambs, but such a treatment requires daily administrations of the drug during 4 days (1-2).

More intensive animal husbandry prescribes the necessity of avoiding repeated administrations of medications to animals with difficult handling and of developing controlled- and sustained-release dosage forms. These forms were also developed in veterinary medicine, but they are generally complicated devices with a high production cost (3). Despite the widespread use of SMZ as a therapeutic agent in cattle and its potential for use in sheep, no long-acting preparation has been marketed for sheep until now. Bulgin et al. (4) already tested a sustained-release preparation registered for use in calves (Calfspan®, Norden), but the preparation ensured effective blood levels of SMZ for only 2 days after an oral administration.

The purpose of this work is the development of a bolus that is easily produced at a low cost, to be given to lambs in order to release SMZ during 4 days after a single oral administration.

The physiological characteristics of the digestive tract of ruminant animals provide a unique opportunity for prolonged-release technology, especially with the reticulorumen retention ability (5). A pharmaceutical form retained in this organ should be able to release its active ingredient for a long period of time. However,

the regurgitation of this type of pharmaceutical devices is a well-known problem. To avoid this problem, the pharmaceutical forms must fulfill special requirements in terms of density, shape, size, and integrity. Reduced iron is often used in order to obtain a minimal density of 1.6 to 2, values that were reported by Rinner et al. (6) to prevent regurgitation from reticulorumen. The problem of the integrity could be solved by producing high-density devices with a slow erosion from which the drug progressively diffuses. The incorporation of drugs into lipid matrices is a popular approach to prolong drug release. In this study, the suitability of several lipophilic excipients was evaluated in order to obtain the integrity of the tablet. The influence of both nature and amount of the lipidic excipient on the in vitro release of SMZ was closely examined as well. Several methods of manufacture of lipid matrices such as direct compression, wet granulation, melt granulation, and spray congealing were described (7–10). We compared a melt granulation process (11–12) using a laboratory high-shear mixer (Pellmix®, Niro) to a manual melt granulation technique and to a conventional method of wet granulation. The impact of the granulation process on the integrity of the tablet and on the release rate of sodium sulfamethazine (NaSMZ) was investigated. The influence of the compression force on the characteristics of the matrix tablet and on the release rate of the drug was also studied.

MATERIALS AND METHODS

Materials

Active Substance

Sodium sulfamethazine (BP 88), Federa, Belgium

Densifying Agent

Reduced iron (DAB 7) ref. 3815, Merck, Germany

Lipid Excipients

Carnauba wax	Carnauba wax	Mosselman, Belgium
Sucrose stearate	Crodesta® F160	Croda Chemicals, UK
Stearyl alcohol	Lorol® C18	Henkel, Germany
Glycerylpalmitostearate	Precirol® ATO 5	Gattefosse, France
Glycerylbehenate	Compritol® 888	Gattefosse, France
Glycerylstearate	Precirol® WL2155	Gattefosse, France
Hydrogenated vegetable oil	Lubritab®	Edward Mendell, USA
Glycerylmonostearate	Myvaplex® 600 P	Eastman Chem., USA
Glycerylmonostearate	Cutina® GMS	Henkel, Germany
Hydrogenated castor oil	Cutina® HR	Henkel, Germany
Hydrogenated soybean oil	Sterotex® C	Karlshamms, Sweden
Hydrogenated soybean oil	Sterotex® HM	Karlshamms, Sweden

Other Excipients

Magnesium stearate (Ph Eur. II), Federa, Belgium
Calcium diphosphate dihydrate, Emcompress®, Mendell, Germany
Polyvinylpyrrolidone (Kollidon® 25), BASF, Germany

Methods

Granulation

Wet Granulation

A 500 g mixture consisting of 32.5% NaSMZ, 52.5% reduced iron, 2.0% Kollidon® 25, and 12.5% Cutina® HR was progressively moistened with 72 ml purified water. The wet mass was passed through a 1.5 mm sieve of an oscillating granulator (Erweka KU 1). The granules were dried for 30 minutes at 37°C in a fluidized-bed dryer (Glatt).

Manual Melt Granulation

Since lipidic excipients are easily melted, the granulation was performed by heating the mixture of active substance and excipients to 90°C on a water bath and by passing this molten mixture through a 1.5 mm sieve of an oscillating granulator (Erweka KU 1). Granules were allowed to cool at room temperature. Before tableting, the granules were mixed with 0.5% magnesium stearate for 1 minute in a Turbula mixer. Tablets of 1 g were made on an excenter press (Courtoy AC 27) with 13 mm flat-faced punches. Typical compositions of the final tablets are given below:

Na sulfamethazine	30–40%
Densifying agent	40–55%
Lipidic excipient	10–20%
Magnesium stearate	0.5 %

Melt Granulation with a High-Shear Mixer

A vertical laboratory scale high-shear mixer (Pellmix®, type PL 1/8, Niro, Denmark) with a bowl capacity of 8 liters was used for the production of batches of

about 1 kg (13). Batches of 1 kg granules having the following composition were prepared:

NaSMZ	32.5%
Reduced iron	55%
Cutina® HR	12.5%

After mixing the materials at 400 rpm during 1 minute, the speed of the impeller was adjusted to 1400 rpm. The heat produced by friction increased the temperature of the mix until the hydrogenated castor oil began to melt and promoted the formation of granules. During the process, there was a water cooling supply to the bowl jacket to prevent the adhesion of material to the walls. After granule formation, the material was discharged, screened to remove lumps, and allowed to cool at room temperature.

Tablet Fabrication

The granules were mixed for 1 minute with 0.5% magnesium stearate and tableted on a Courtoy AC 27 excenter press to produce 13 mm diameter flat-faced tablets weighing 1 g.

Controls

Controls on the Excipients

The hydroxyl number (IOH) and the melting point of each lipidic excipient were determined as prescribed in the European Pharmacopoeia. Furthermore, the viscosity of the molten excipients was measured by using a Wells Brookfield cone-plate viscosimeter LUDV II+ equipped with a 3° cone spindle. The stationary plate, which is the sample cup, was filled with a 2 ml sample of the molten excipient. The system was maintained at 86°C. The results are the average of five determinations.

Controls on Granulations and Tablets

The determination of the geometric mean diameter (d_{gw}) and of the geometric standard deviation (s_{gw}) of the granules was made after sieve analysis.

The tablets are evaluated for uniformity of weight, crushing strength (Erweka TBT), density (volumetric method), and in vitro dissolution rate of SMZ (USP paddle method). Concerning the control of the in vitro dissolution rate of SMZ from the tablets, preliminary experiments showed that the solubility of NaSMZ in 0.1 M phosphate buffer with pH 5.5 was about 600 μg/ml. Therefore, it was impossible to carry out an in vitro release test on boluses containing 5 g or more active drug with respect of sink conditions. For this reason, the in vitro tests were carried out on 13 mm tablets weighing 1 g and containing 300–400 mg of NaSMZ by using the paddle method at 60 rpm with 1 liter of 0.1 M phosphate buffer, pH 5.5, at 37°C. The results are the mean of three determinations. SMZ was assayed by UV spectrophotometry at 320 nm (Diode Array Spectrophotometer HP 8452A). The in vitro release profiles were linearized according to the Higuchi equation (14). The comparison of the different release profiles was made by a statistical analysis (ANOVA) on the slopes of the linear plots.

RESULTS AND DISCUSSION

Influence of the Lipophilic Excipient

Influence of the Nature of the Lipophilic Excipient

A formulation containing 40% NaSMZ, 44.5% reduced iron, 15% lipophilic excipient, and 0.5% magnesium stearate was adopted to compare the influence of the nature of the lipophilic agents. Twelve excipients were tested. They are listed in Table 1 with their physicochemical properties. The in vitro release of SMZ from tablets made at a pressure of 2860 kg/cm^2 are presented in Table 2. Some excipients with a low melting point such as Precirol® ATO 5 and Lubritab® gave sticking problems to punches during the tableting operation. This phenomenon can be due to the heat of compression, which causes the fusion of the material at the surface of the tablet in contact with punches.

The tablets were examined for integrity during the in vitro dissolution tests. Most of them remained intact even after the complete dissolution of the active ingre-

Table 1

Physicochemical Characteristics of the Lipidic Excipients

Commercial Name	I(OH)	Melting Point (°C)	Viscosity at 86°C (mPa.s)
Carnauba wax	45.5	83.3	35.8
Lubritab	53.7	59.8	10.3
Sterotex HM	62.7	66.5	12.7
Sterotex C	62.8	74.3	16.5
Compritol 888	102.6	72.4	15.7
Precirol ATO 5	106.4	56.0	11.1
Precirol WL 2155	123.5	69.7	13.3
Cutina HR	158.3	84.5	42.5
Lorol C 18	208.9	60.3	4.7
Cutina GMS	236.0	60.0	17.7
Myvaplex 600 P	311.0	70.7	23.4
Crodesta F 160	531.9	72.0	—

Table 2

Influence of the Nature of the Lipidic Excipient on the Release Rate of SMZ from the Tablets

Lipid Excipient	% released after 1 hr	% released after 4 hr	% released after 8 hr	% released after 12 hr	% released after 24 hr
Carnauba wax	12.1	34.4	50.0	60.4	77.4
Lubritab	12.4	34.2	51.2	64.0	99.3
Sterotex HM	11.2	36.2	55.3	69.3	100.0
Sterotex C	14.9	24.0	63.0	76.3	99.2
Compritol 888	12.8	37.3	55.2	67.6	85.7
Precirol ATO 5	11.4	27.9	41.2	51.3	71.5
Precirol WL 2255	11.5	32.9	49.8	62.1	81.9
Cutina HR	12.9	35.4	53.3	65.3	81.9
Lorol C 18	17.0	43.0	62.8	70.0	92.1
Cutina GMS	10.4	33.6	50.8	64.5	84.5
Myvaplex 600 P	12.6	44.5	68.0	82.3	99.5
Crodesta F 160	15.1	50.5	71.7	82.6	95.5

dient except the tablets made with Crodesta® F 160 and Myvaplex® 600 P, which disintegrated during the test. This behavior is related to the more hydrophilic character of these excipients as reflected by their high hydroxyl numbers.

In order to explain the great variety of release profiles obtained with the lipidic excipients, a multiple linear regression was performed to try to correlate the dissolution rates and the values of hydroxyl number, melting point, and viscosity, but no significant effect was found.

Influence of the Amount of Lipidic Excipient

The following basic formulation was used to study the influence of the amount of the lipidic excipients:

NaSMZ	40%
Reduced iron	40%
Lipidic excipient	10–12%–15–20%
Magnesium stearate	0.5%
Emcompress®	q.s. to 100%

Four lipidic excipients were compared:

- Precirol® ATO 5, which gave a slow release in the previous study
- Lorol® C 18, which allowed a fast dissolution of NaSMZ without disintegration of the tablet
- Cutina® HR and Compritol® 888, which gave intermediate results

The results showed that the higher the amount of the lipidic agent is, the larger the size of the granules is. A minimal concentration of 12% was required to obtain a reliable granulation process. Futhermore, a good reproducibility of the characteristics of the granules was obtained.

The rates of dissolution of NaSMZ from these formulations are shown in Figure 1. The influence of the amount of excipients depends on the nature of the lipidic agent. There was a minimal effect with Lorol® C

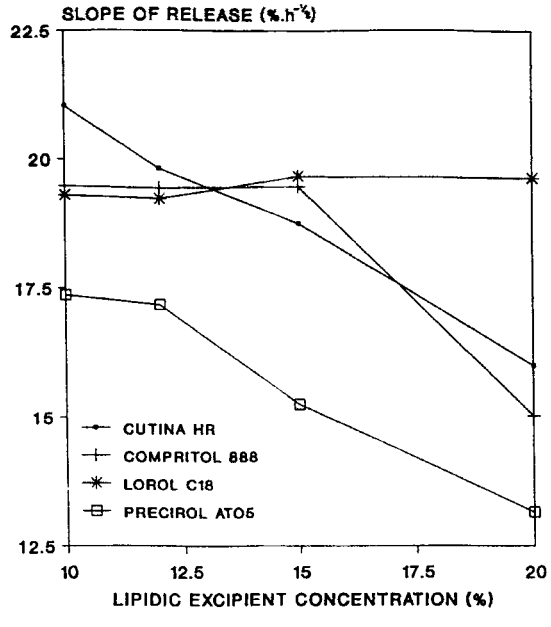

Figure 1. Influence of the amount of lipidic excipient on the slope of release of NaSMZ.

Table 3

Characteristics of Granules and Tablets Containing 12.5% Cutina® HR and 32.5% NaSMZ

Granulation Processs	Wet Granulation	Melt Granulation in a High-Shear Mixer	Manual Melt Granulation
d_{gw} (μm)	594.7	643.4	313.6
s_{gw}	1.7	2.0	2.6
Tablet average weight (g)	1.023	0.986	1.071
Coefficient of variation of weight (%)	1.14	1.19	2.1
Mechanical strength (kg)	12.2	11.2	14.5
Density	2.3	2.4	2.4

18 whereas a significative influence was noticed with Compritol® 888 for a concentration higher than 15%. For Precirol® ATO 5 and for Cutina® HR, the variation of the amount of the lipidic agent allowed an easy modulation of the dissolution rate.

Influence of the Granulation Process

Among the lipophilic agents, hydrogenated castor oil was found to be especially effective for several reasons: its high melting point avoids the occurrence of sticking to punches during the tableting operation; it allows for maintenance of tablet integrity even after the complete dissolution of the drug; and the release rate of NaSMZ can be easily modulated by varying its concentration in the matrix tablet. Therefore, all the experiments of this part of the study were performed with formulations containing Cutina® HR as the binding and sustained-release excipient.

The characteristics of granules and tablets containing 12.5% of Cutina® HR and 32.5% of NaSMZ made by the three techniques are given in Table 3. Both wet granulation and melt granulation with the high-shear mixer gave granules with a larger mean size and a narrower size distribution than granules obtained by the manual melt method. Consequently, tablet weight variations were lower as shown by the values of the coefficient of variation. With the same amount of binding agent (12.5% Cutina® HR), the high-shear mixer promoted a better granule formation than the manual method. The in vitro release profiles of SMZ from the tablets are shown in Figure 2. As previously reported by several authors (7,8,15), these results confirm the importance of the granulation process on the release rate of the drug from lipid matrices. The wet granulation technique gave tablets that disintegrated rapidly and showed a fast release of SMZ. Since the lipidic excipient (Cutina® HR) was not melted during the granulation process, its binding and sustained-release properties were less effective. Moreover, the water-soluble binding agent (PVP) worked toward a higher hydrophilic character of the tablets. Both methods of melt granulation gave similar release profiles. Nevertheless, the manual method gave a faster release of SMZ than the high-shear mixer granulation technique.

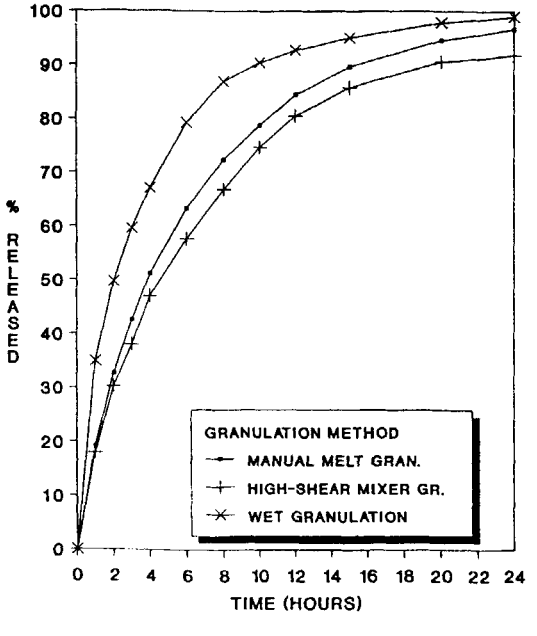

Figure 2. Influence of the granulation process on the release profile of NaSMZ from the matrix formulation.

The melt granulation method with the high-shear mixer was used for the other experiments, namely the study of the influence of the amount of Cutina® HR and of the influence of the granulation time.

Formulations consisting of NaSMZ (30%), Cutina® HR (10–12.5% or 15%), magnesium stearate (0.5%), and reduced iron to 100% were prepared. The characteristics of granules and tablets are given in Table 4.

The geometric mean diameter increased with the amount of Cutina® HR while the size distribution remained similar.

The in vitro release profiles of SMZ from the tablets are shown in Figure 3. As expected, the release rate of SMZ decreased with the increasing concentration of Cutina® HR. It must also be pointed out that even at a 10% level, Cutina® HR showed good binding properties since the integrity of the tablets was maintained during the dissolution test.

When the process was performed with 15% Cutina® HR, the time to obtain granules was very short (about 6 minutes). An additional study was carried out to evaluate the influence of the mixing time on the release rate of SMZ from tablets containing 30% NaSMZ, 15% Cutina® HR, 54.5% reduced iron, and 0.5% magnesium stearate.

For this purpose, after the time of granule formation (about 6 minutes), the speed of rotation was adjusted to 1000 rpm in order to maintain the temperature of the mixture between 85° and 92°C. After a mixing time of 48 minutes, the mixture had the consistency of a paste that is passed through a 1.5 mm sieve of an oscillating granulator. The granules were allowed to cool at room temperature before tableting. The release profiles from these two formulations are shown in Figure 4. No

Table 4

Characteristics of Granules and Tablets Containing 30% NaSMZ, 10–12.5% or 15% Cutina® HR, 0.5% Magnesium Stearate, and Reduced Iron to 100%

Cutina® HR concentration	15%	12.5%	10%
d_{gw} (μm)	634.5	556.0	482.0
s_{gw}	2.2	2.2	2.3
Tablet average weight (g)	1.014	1.040	1.021
Coefficient of variation of weight (%)	2.3	1.6	0.9
Mechanical strength (kg)	9.3	10.7	9.1
Density	2.3	2.4	2.4

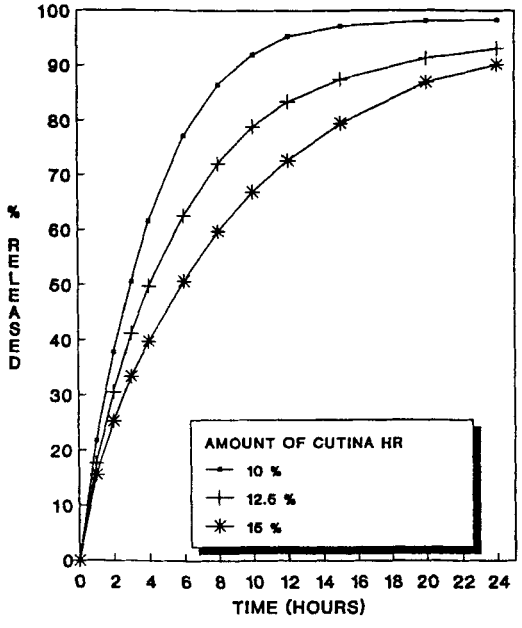

Figure 3. Influence of the amount of Cutina® HR on the release profile of NaSMZ from a matrix formulation produced with the high-shear mixer granulation process.

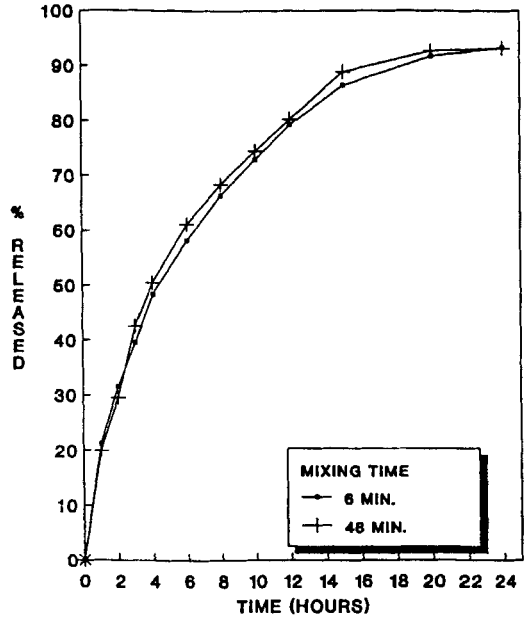

Figure 4. Influence of the mixing time on the release profile of NaSMZ from a Cutina® HR matrix formulation produced with the high-shear mixer granulation process.

significant difference was observed between 6 minutes and 48 minutes of mixing time.

Influence of the Compression Force

The influence of the compression force on the characteristics of the tablets was assessed with the formulation containing 15% Cutina® HR, 30% NaSMZ, 54.5% reduced iron, and 0.5% magnesium stearate. Granules with a geometric mean diameter of 622 μm were tableted at pressures of 1080, 2160, 2700, or 3240 kg/cm^2. The characteristics of the tablets are reported in Table 5.

From Table 5 it can be noticed that the compression force mainly influenced the mechanical strength of the tablet, but only at a low value. The in vitro release profiles of SMZ obtained are presented in Figure 5: there was no influence of the compression force on the release rate of the drug between values of 2160 and 3240 kg/cm^2. Under 2160 kg/cm^2, the release of the drug was a little faster.

Stability Study

The stability of the drug release during storage was evaluated with tablets containing 30% NaSMZ, 12.5% Cutina® HR, 57% reduced iron, and 0.5% magnesium stearate. The tablets produced by using the melt granulation method were stored at 25°C in closed containers. The results of the in vitro release tests presented in Figure 6 indicate a good stability of the tablets during the storage.

CONCLUSION

The results obtained from this study show that it is possible to formulate a high-density matrix tablet that slowly releases sulfamethazine with poor erosion.

Table 5

Characteristics of Tablets Containing 15% Cutina® HR, 30% NaSMZ, 54.5% Reduced Iron, and 0.5% Magnesium Stearate

Pressure (kg/cm^2)	1080	2160	2700	3240
Tablet average weight (g)	1.082	1.105	1.102	1.076
Coefficient of variation of weight (%)	0.9	1.1	1.0	0.9
Mechanical strength (kg)	7.1	12.8	12.7	13.4
Density	2.21	2.26	2.26	2.23

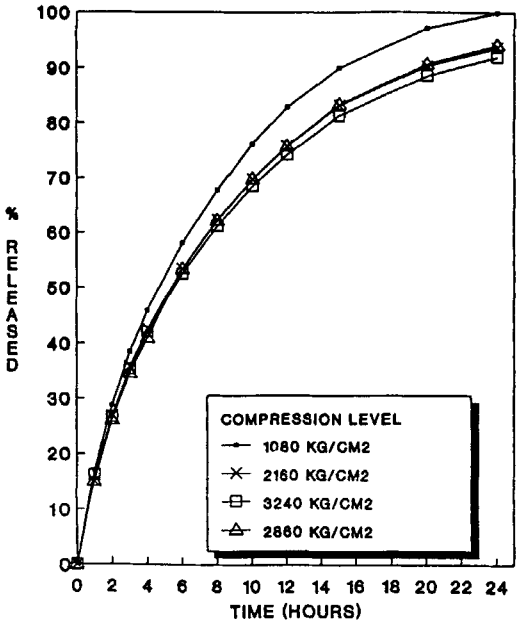

Figure 5. Influence of the compression force on the release rate of NaSMZ from the lipid matrix.

The use of lipidic excipients with hydroxyl numbers lower than 250 allows to preserve the tablet integrity even after the complete release of the active substance. The dissolution rate of NaSMZ from the lipid matrix

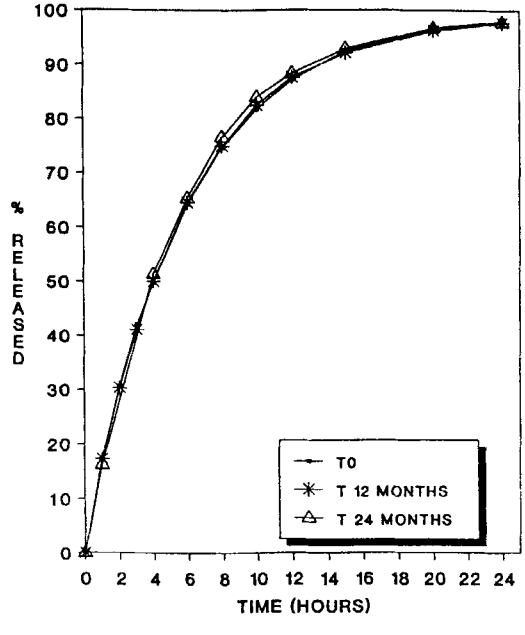

Figure 6. NaSMZ release after storage at 25°C.

can be easily modulated by changing the nature and the concentration of the excipients. This study showed that a melt granulation process in a high-shear mixer could be an adequate method of production of lipid matrices. This process is an appropriate technique for the scale-up to industrial production. It allows the production of tablets with a low amount of binder and with a short time process. A lipid matrix containing Cutina® HR as binder, reduced iron as high-density excipient, and NaSMZ was successfully produced by this method. The influence of technological parameters such as mixing time or compression force on the characteristics of the tablets and the release rate of the drug is negligible. Finally, stability tests performed on tablets stored at 25°C show that the release rate of SMZ remained unchanged after 24 months of storage.

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