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# In vitro evaluation of a new controlled release veterinary device

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**Summary**

The aim of this study was to develop a reservoir constituted by a nonwoven hydrophobic polymeric membrane containing the drug. To allow water permeation through this layer, the membrane was treated with a surfactant. This form can be easily produced at low cost and the total amount of inert material can be as low as 10% of the total weight, avoiding the disavantages of currently available dosage forms. Dissolution tests were performed and different parameters were studied (nature of the polymer, nature and amount of surfactant, membrane surface, nature and amount of drug). The amounts of drug and surfactant were found to have no effect while the other parameters significantly affected the release rate. Finally, an optimal reservoir was designed and studied over a 22 day dissolution testing period. The results showed a constant release rate of the drug over this period.

## Introduction

Coccidiosis of ruminants, especially of sheep, is a very common disease and can lead to considerable financial losses for the breeders. Very effective drugs are available (most being of the sulfonamide class) but the results of the treatments are often disappointing because of the possible re-infestation of the animals by ingestion of oocysts present in the grass. Controlled release boluses have been designed in order to avoid such re-infestation (the oocysts present in the pasture do not remain indefinitely infestant). Because of the special anatomy of the stomach of ruminants, these forms can remain in the rumen of the animals for a considerable period of time provided their size or density is appropriate to avoid regurgitation or further transit in the gastrointestinal tract (Dewey et al., 1958; Laby, 1974). Long acting dosage forms present the additional advantage of not requiring daily administration which is always problematic when the animals are grazing. These forms have also been developed for use in other parasitic diseases of ruminants (Prichard et al., 1978), for example, lungworm infections; nevertheless, they present several disadvantages such as their cost, or the significant amount of inert material required for their formulation.

The aim of this study was to develop a reservoir that is readily produced at low cost, constituted of a nonwoven polymeric membrane surrounding the drug. This membrane was partially

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permeable to water in order to allow the controlled release delivery of the drug.

## Materials and Methods

*Description of the reservoir*

The device is described in a French Patent (Ehret et al., 1991) as a small square bag of 50–100 $cm^2$. This bag contains the drug; it is made from two nonwoven membranes assembled by heating on their sides. Each membrane is in fact a composite material comprising two elementary nonwoven webs. The inner one is made from polymer filaments of 3 $\mu$m average diameter (Fig. 1); due to its tortuosity, it plays an important part in the control of the diffusion of the drug; its mechanical resistance is weak. The outer web is made from polymer filaments of 30 $\mu$m average diameter and weighs 70 $g/m^2$ (Fig. 2); its function is to provide sufficient mechanical resistance to the device. Water can circulate almost freely through this external sheet. In addition to the drug, the reservoir contains semi-rigid polyethylene netting. The whole device is rolled up and kept in this position by a gelatine strap. This allows the oral administration of the device. Once in the animal's rumen, the gelatine strap disintegrates and the device unrolls; because of its dimensions, regurgitation or further migration in the gastrointestinal tract are then avoided. The device is expected to remain in the rumen until the slaughtering of the animal.

*Production of the membranes*

The outer web of the membrane was first produced according to a spinning technology (see Casper (1975) for a review of the manufacturing processes). The polymer used was polypropylene. The inner web was then produced by extrusion of the melted polymer through a spinneret. Four kinds of polymers were used: polyethylene (PE), polypropylene (PP), polybutylene terephthalate (PBT) and polyhexamethylene adipamide (PA). The filaments were then assembled by a preheated calender. Some of the membranes were

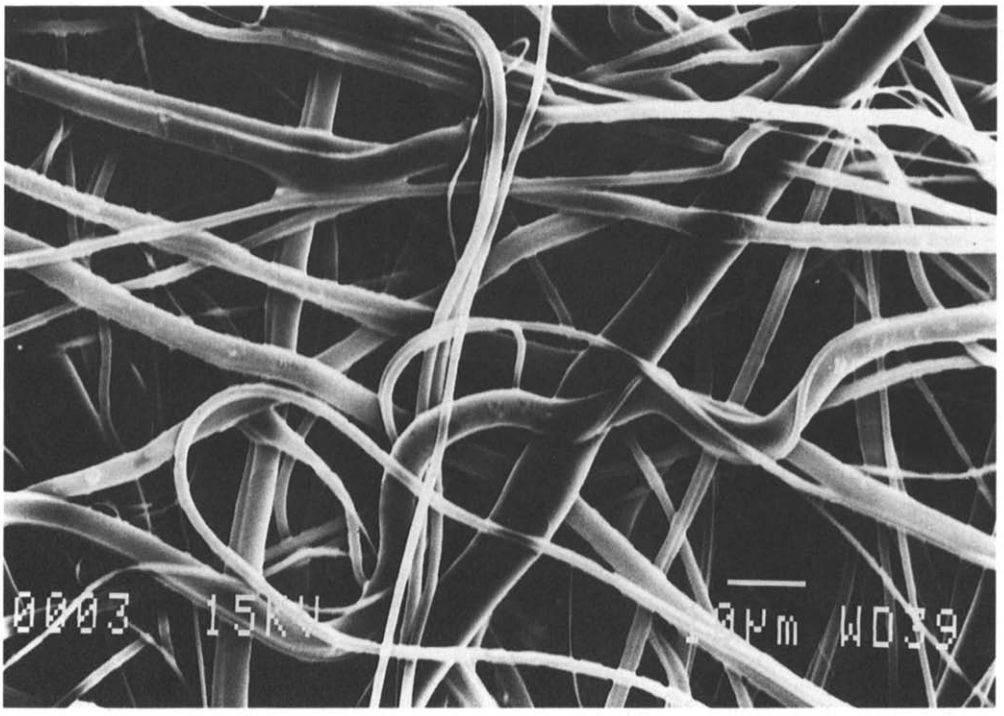

Fig. 1. Scanning electron micrograph of the internal nonwoven web.

sprayed with 0.0025 and 0.01% ethanolic solutions of surfactant in order to modify their water permeability. Three different surfactants were used in this study: octylphenoxy-polyethoxy-ethanol (Ope, Röhm Germany), *N*-alkyl amino-betaine (N-AB, Sandoz, Switzerland) and a polyether-polydimethylsiloxane copolymer (PSc, Hansa Chemie, Germany).

*Production of the reservoirs*

Reservoirs of different sizes were produced (50 or 100 $cm^2$ of diffusion surface). These reservoirs were then loaded with three different doses (300, 1000 or 10000 mg) of three drugs (levamisole hydrochloride, acetaminophen and sulfamethazine). These drugs were chosen because their solubility in water is very different.

*Dissolution studies*

Dissolution tests were performed according to the second edition of the European Pharmacopoeia (paddle method) in a six-station apparatus (Dissolutest Prolabo, France). Because of the low density of the devices, they were fixed on the paddles with elastic straps. The speed of the paddles was set at a low value of 10 rpm in order to avoid turbulent flow of the medium. A deaerated phosphate buffer pH 5.5 was used as dissolution medium; the temperature was adjusted to $37 \pm 0.5$°C. Its volume was fixed at 1000 ml for the reservoirs which contained 300 or 1000 mg of drug. In both cases, the tests lasted 20 h. Preliminary experiments showed that the total amount of drug released at the end of this period never exceeded one-tenth of the saturation concentration of the drug in the chosen medium. The protocol was modified for the reservoirs which contained 10 g of drug. In this case, to avoid saturation, the dissolution medium was completely changed every 24 h and the experiment lasted 22 days. 500 $\mu$l samples were collected for the determination of drug concentration. The sampling interval was fixed at 1 h for the 20 h tests and at 24 h for the 22 day tests. The analysis were performed by measuring the absorbance of the solutions (after dilution if necessary) on a

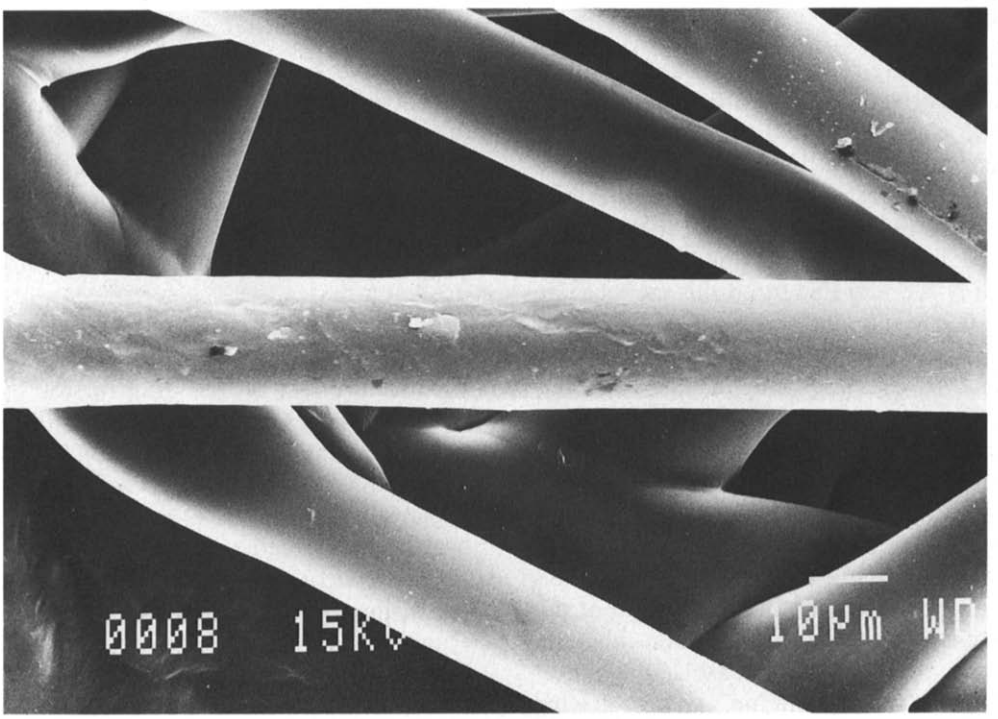


Fig. 2. Scanning electron micrograph of the external nonwoven web.

spectrophotometer (UV 2101 PC, Shimadzu Co., Japan). Each experiment was conducted with at least five identical devices.

## Results and Discussion

*Influence of the surfactant (Figs 3–5)*

No drug release could be observed from reservoirs made with control PP membranes (not treated with surfactant). PP webs with no surfactant were not permeated by water. The membrane then acted as a perfect barrier. This was also the case for membranes treated with OPE. In contrast, drug release could be observed from those treated with N-AB and PSc which led to respective values for acetaminophen liberation after 16 h of $930 \pm 45$ mg ($n = 6$) and $637 \pm 28$ mg ($n = 6$). These values are significantly different ($t$-test, $P < 0.05$). A general model of diffusion is given by Fick's first law which, after integration, can be expressed as:

$$\frac{dQ}{dt} = kSD\Delta C \qquad (1)$$

where $dQ/dt$ is the release rate, $k$ a constant, $S$ the diffusion surface, $D$ the diffusion coefficient and $\Delta C$ the concentration difference across the membrane. One can see that if $S$, $D$ and $\Delta C$ are held constant, the release rate will be constant, i.e., the cumulative curve of drug liberation vs time will be linear. Data obtained over a 16 h period with N-AB and PSc fitted this model quite well ($R^2 = 0.988$ and 0.989, respectively). During the final hours of the test, the release rate decreased due to the emptying of the reservoir. However, autocorrelation analysis of the residuals showed that a linear model was not perfectly adequate to describe the drug liberation even at the beginning of the test. A phenomenon other than pure diffusion probably occurred in the mechanism of drug release. These results could be explained by the progressive desorption of the surfactant itself towards the dissolution medium, resulting in a progressive decrease in the water permeability of the membrane, i.e., a slowing down of the drug release. This loss of surfactant would have been total and rapid in the case of OPE (resulting in the absence of drug release), partial and slow in the case of PSc and N-AB (resulting in a progressive slowing down of the drug release). One can conclude that the choice of an appropriate surfactant seems to be an important parameter in the control of drug release in such a device.

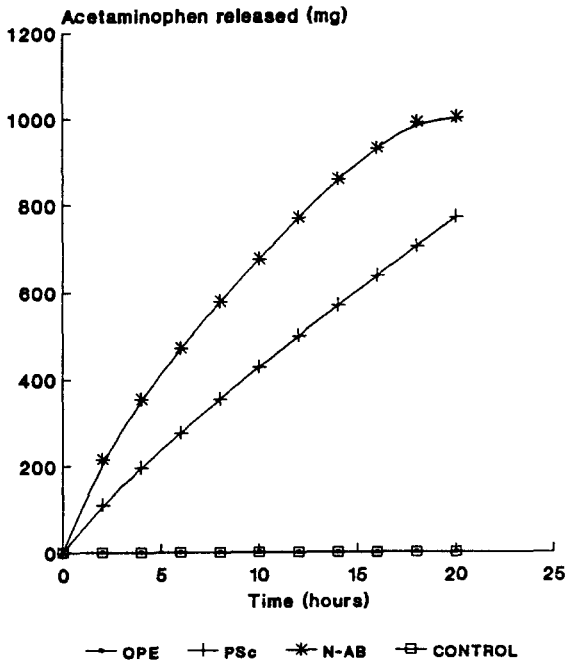


Fig. 3. Time course of acetaminophen release: effect of nature of surfactant.

In contrast to the chemical nature of the surfactant, its concentration was found to have no significant effect on the drug release (see Figs 4 and 5). This result was observed with two different surfactants (N-AB and PSc) used in 0.0025 and 0.0100% solutions. These results could be explained by a possible saturation of the membrane by adsorbed surfactant at both concentrations, in accordance with the general models of adsorption of Langmuir and Freundlich (see Rupprecht and Lee (1988) for review): the amount in excess would have readily diffused in the dissolution medium without influencing the drug liberation.

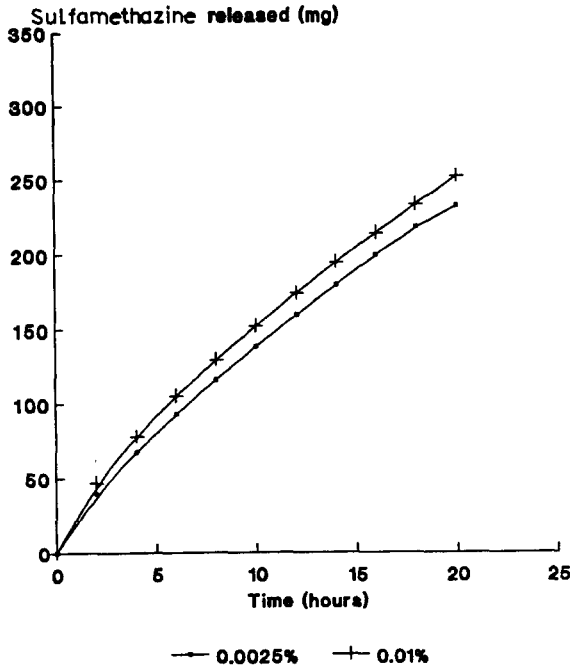


Fig. 4. Time course of sulfamethazine release: effect of surfactant concentration.

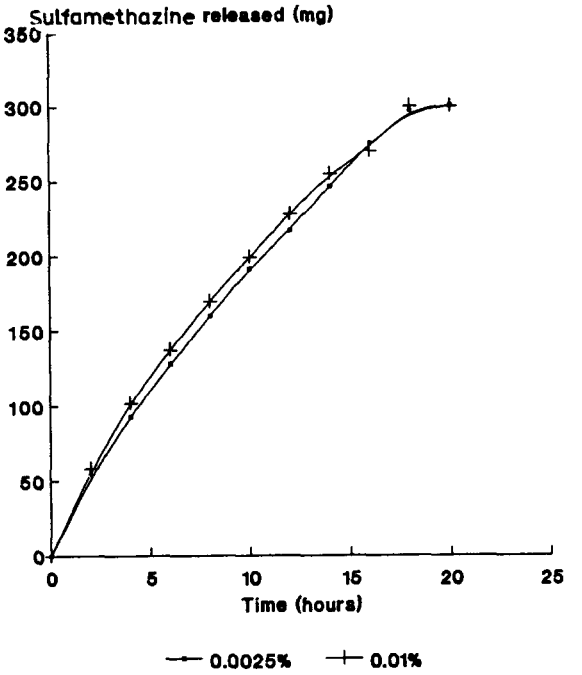


Fig. 5. Time course of sulfamethazine release: effect of surfactant concentration.

*Nature of the polymer (Fig. 6)*

Drug release kinetics achieved with PE, PP and PBT nonwoven membranes were found to be not significantly different: the amounts of drug released after 20 h were $790 \pm 35$ mg ($n = 5$), $770 \pm 24$ mg ($n = 6$) and $859 \pm 40$ mg ($n = 5$), respectively. In contrast, the entire drug content in PA reservoirs was released in less than 2 h. Polyethylene, polypropylene and polybutylene terephthalate are known to be strongly hydrophobic. Membranes prepared with these materials are almost totally impermeable to water except if a surfactant is added. This compound appears to be the real factor that controls the drug release. Conversely, polyhexamethylene adipamide is a hydrophilic polymer. Surfactant treatment is unlikely to modify its wettability. Under these conditions the membrane does not play any role in drug release control. These results can lead to the conclusion that the ideal polymers for such an application would probably be those presenting a moderately hydrophilic character. This would make the presence of surfactant unnecessary.

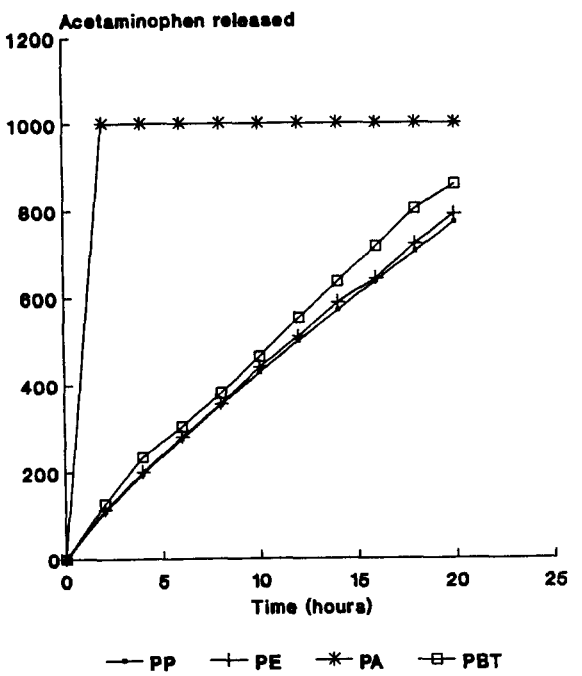


Fig. 6. Time course of acetaminophen release: effect of nature of polymer.

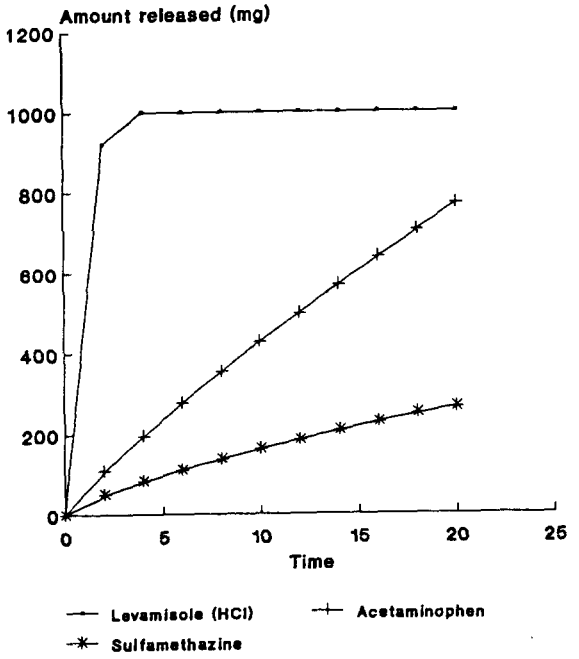


Fig. 7. Time course of drug release: effect of nature of drug.

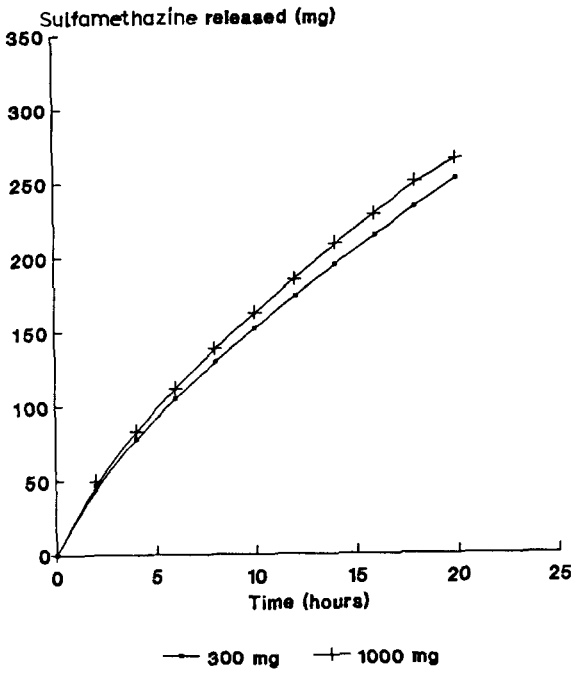


Fig. 8. Time course of sulfamethazine release: effect of amount of drug.

*Nature of the drug (Fig. 7)*

The drug release kinetics were found to be very closely related to the solubility of the drug. Levamisole hydrochloride is very soluble in water (about 500 g/l). In this case, saturation in the donnor compartment did not occur and the release kinetics fitted a first order model. This result is in accordance with the general theory of diffusion in a reservoir and indicates that highly water soluble drugs are poor candidates for such systems. Conversely, less soluble drugs like acetaminophen and sulfamethazine (respective solubility in water at 37°C and pH 7.00: 24 and 1.92 g/l) allow constant saturation in the donor compartment, resulting in much more progressive drug release.

*Amount of drug present in the reservoir (Fig. 8)*

Drug release kinetics of reservoirs loaded with either 300 or 1000 mg sulfamethazine were found to be not significantly different. These results showed that the device really acted as a controlled release system, the kinetics of release being independent of the drug content, as long as

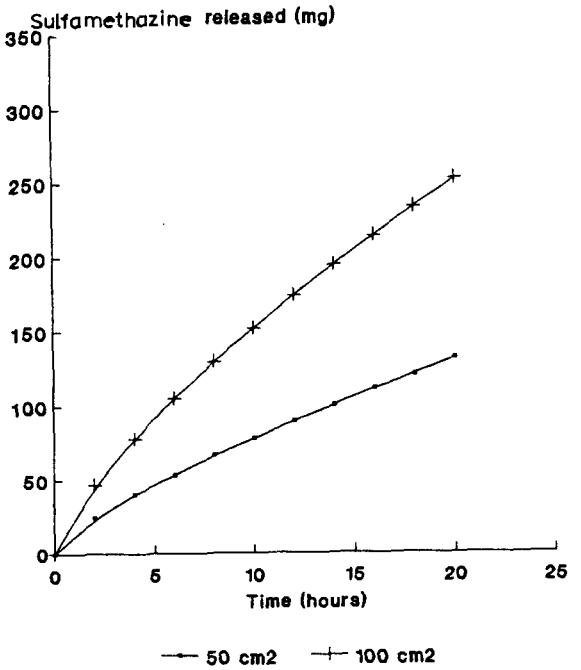


Fig. 9. Time course of sulfamethazine release: effect of membrane surface.

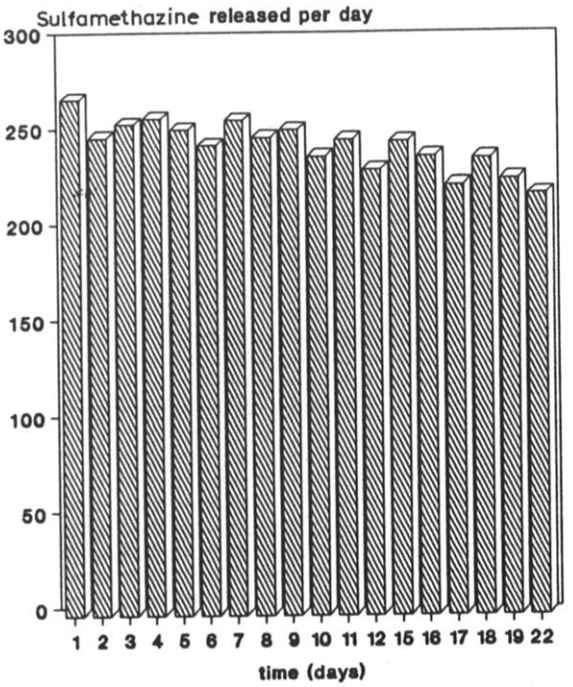


Fig. 10. Long-lasting study of sulfamethazine release.

saturation conditions were maintained in the donor compartment.

*Membrane surface (Fig. 9)*

The amounts of sulfamethazine released in 20 h by devices presenting diffusion surfaces of 50 and 100 $cm^2$ were $131 \pm 9$ ($n = 5$) and $252 \pm 18$ mg ($n = 5$), respectively. One can note that when the diffusion surface increased 2-fold, the amount of drug released increased in the same proportion (1.93). This result is in accordance with Fick's first law of diffusion.

*Long lasting dissolution study (Fig. 10)*

Dissolution studies performed on devices loaded with 10 g sulfamethazine showed a constant rate of drug release of $245 \pm 13$ mg ($n = 5$) per day over a period of 22 days. A linear model of release according to Eqn 1 fitted these data well ($R^2 = 0.9995$). This result seemed to be inconsistent with the former where the drug release over a 20 h period never appeared to be completely linear. A possible explanation can be the existence of a significant lag time before equilibrium conditions are reached: the membrane can probably bind only a fraction of the surfactant, and the fraction present in excess would diffuse in the dissolution medium during the first hours of the study. This would decrease the membrane permeability to water, i.e., the release of drug. After this period, equilibrium would be attained, i.e., the release rate would become constant.

## Conclusion

In this study, the ability of a nonwoven textile polymeric membrane to control the release of a drug has been investigated and this material has shown to be of great interest. A veterinary drug delivery system has been developed and different parameters influencing the release rate have been studied in vitro. A mechanism has been proposed to explain the release profiles. A reservoir has been tested over a 3 week period and has proven to release the drug at a constant rate.

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