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Microencapsulation of Astiban Acid for the Treatment of *Schistosomiasis mansoni*

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ABSTRACT

Schistosomiasis is among the top five diseases in the world in terms of morbidity, affecting perhaps 200 million people in tropical and subtropical countries. Antischistosomal drugs are toxic and rapidly metabolized. Hence, they must be given in a number of spaced doses. In spite of this there are severe side effects leading to poor patient compliance. This is an ideal situation for the application of sustained drug release to avoid the toxic peak concentration of drug.

This study was carried out using Astiban acid, an antimonial drug that is effective against *S. mansoni*. Unfortunately, the drug is sufficiently soluble that 50 mg will dissolve in 100 mL water in less than a minute. To permit sustained release of intramuscularly injected drug, microcapsules of astiban acid in poly(*d,l*-lactic acid) were formed by coacervation.

Release studies show that an appreciable fraction of the drug is available at the surface for rapid solution. After this surface drug dissolves, the remaining drug is released slowly with half-times of many hours. After the initial burst, the release of drug follows Higuchi's equation up to approximately 80% release, with exponentially decreasing release rates thereafter.

Index Entries: Microencapsulation, of astiban acid; tropical diseases, microencapsulation for; biodegradable microcapsules, for schistosomiasis; poly(*d,l*-lactic acid), in microencapsulation of astiban acid;

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schistosomiasis, microencapsulated astiban acid for; astiban acid, microencapsulation for schistosomiasis.

INTRODUCTION

Tropical parasite diseases affect a high fraction of the world's population. Schistosomiasis is a good example, ranking only behind malaria as a cause of morbidity in the underdeveloped countries according to the World Health Organization (*1*). It is estimated that the three forms of this disease affect perhaps 200 million people.

The form of the disease that is widespread throughout much of Africa is *Schistosomiasis hematobium,* a genitourinary form of the disease. A second form, found in the central part of Africa and parts of the Caribbean area is *Schistosomiasis mansoni,* in which the intestinal tract is affected. The most virulent form of the disease is *Schistosomiasis japonicum,* which causes severe liver disease and is endemic to parts of mainland China, Taiwan, and the Philippines.

We will focus on the treatment of *Schistosomiasis mansoni,* in which the blood flukes move eventually to the inferior mesenteric veins, and can cause death in a few years if untreated (*2*).

Schistosomes are blood flukes that develop from microscopic organisms entering the body from infected water, move to the blood stream and grow there, attaching themselves and remaining for their entire adult lives. The adults are 0.3–0.5 cm in length and continuously produce eggs that are excreted in the urine or feces of the infected person. These eggs are not directly infective to humans, but are infective for particular species of snails. It is in the snail that the transformation to the form infective for humans occurs.

DRUG

The drug of choice for *S. mansoni* is antimony *a,a'*-dimercapto potassium succinate, or "Astiban"®, made by Hoffman-LaRoche. The structure is shown in Fig. 1. It is typically administered by intramuscular injection as a suspension in oil. As is true for nearly all drugs used in the treatment of tropical parasite diseases, the drug is also toxic to the host.

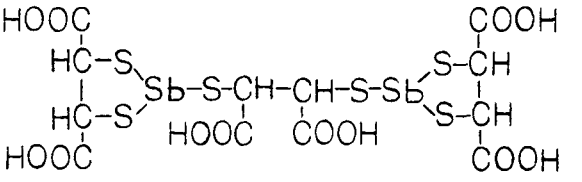

Fig. 1. Structure of Astiban® acid.

Hence, multiple doses must be given, typically 0.5 g/d every 2 d for up to 10 d (*3*). The drug is rapidly metabolized and at the end of the 2-d period the concentration in the blood has fallen to the minimal therapeutic level. However, this means that the drug is present in high concentration during the first few hours. The patients experience muscle cramps, nausea, headaches, and other side effects. Because of the severe side effects, most patients do not return for a sufficient number of injections to be cured. Unfortunately, this is true for many tropical diseases.

It is apparent that the administration of these drugs is an ideal application of sustained drug release. Since the concentration of Astiban in the blood initially can be 50 times higher than the minimal therapeutic level, the amount of drug given in one injection would approach the curative dose if it could be administered such that the concentration was held at, e.g., 2–3 times this level. Microencapsulation will be used to achieve the sustained release. The work reported below was carried out with the acid form of the drug, which has been shown to be even more effective than the potassium salt (*4*).

POLYMER

The long-term goal is the injection of a single dose of Astiban acid, to be released over a period of 10–14 d. Since the particles must be injected through 21- or 23-gage hypodermic needles, the diameter of the particles must be held below 100 μm. The polymer used to retard the release of the drug must be biodegradable to prevent the formation of a sterile abscess or leave debris in the body. Hence, poly (*d,l*-lactic acid) (PLA) was used, since it has been shown to be acceptable in the body and because its degradation time can be controlled between a few weeks and perhaps 2 yr by adjusting the molecular weight and by the formation of copolymers.

The PLA used in this study was synthesized in our laboratory and had a number-average molecular weight, calculated from intrinsic viscosity, of 80,000. Detailed degradation studies have been carried out in a variety of media (*5*), showing that the polymer begins to disappear from pig plasma in a period of approximately 8 wk. Hence, it would perform its job of controlling drug release, then disappear.

Based upon studies of solubility of the polymer, trichloroethylene was chosen as the solvent for the microencapsulation since its high density would permit easier suspension of the particles of the drug (density = 2.1 g/cc) during the process.

MICROENCAPSULATION PROCEDURE

Microencapsulation was carried out by a coacervation procedure developed by Thies (*6*). In this procedure, 3.0 g of astiban acid was sus-

pended in a 2% solution of PLA by stirring for 15 min. Then a prepared solution of 5 mL of polyisobutylene in 10 mL of trichloroethylene was added dropwise. The suspension of the liquid microcapsules was then cooled to low temperature and 600 mL of cold heptane (a nonsolvent) was added to harden the microcapsules.

MICROCAPSULE CHARACTERISTICS

Since the microcapsules are liquid after formation, the drop size distribution can be easily controlled by varying the agitation. The variation which can be obtained is illustrated by the smoothed size distributions shown in Fig. 2. Some variation was observed in the actual payload of the microcapsules from the design payload, as shown in Table 1. The smaller microcapsules also show a somewhat lower payload than the larger ones.

DRUG RELEASE

Drug release studies were carried out by gentle agitation of 10–50 mg of microcapsules in 50–200 mL of deionized water at 37°C in a shaker bath. The concentration of drug in the extraction medium was maintained at much less than 10% of saturation to approximate perfect-sink conditions. In order to set this limit the solubility of the drug was deter-

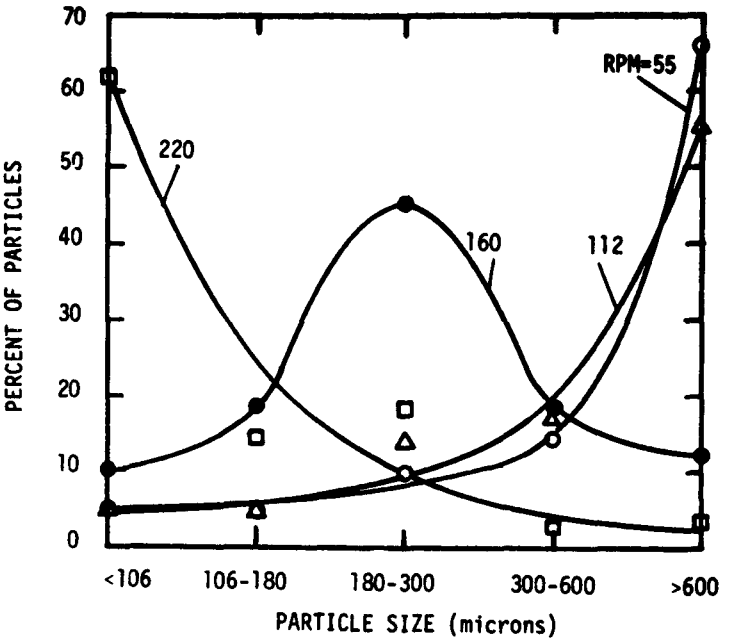

Fig. 2. Effect of stirring rate on size distribution.

TABLE 1
Actual Percent Payload vs Size Fraction

	Run No.				
Size	1	2	3	4	5
63–106μ	55.9	41.0	55.8	60.8	56.7
106–180μ	68.7	51.5	61.3	65.3	58.1
180–300μ	68.1	52.3	64.2	65.9	62.8
300–600μ	69.2	62.3	—	—	—
Design payload	75.0	66.7	66.7	66.7	66.7

mined to be 4.02 ± 0.11 mg/mL compared to the solubility of the potassium salt of 428.5 mg/mL.

The maximum amount of drug that could possibly be released from the microcapsules depends upon the partition coefficient of the drug between the polymer and the solution. This was measured with blank microcapsules containing no drug (but formed using the complete microencapsulation procedure) by permitting equilibration of the drug for 48 h at 37°C. The measured partition coefficient was 6.75 ± 1.45.

Typical release data are shown in Fig. 3, which indicates that the release is much different than release from simple monolithic spheres. It is apparent that there is appreciable release initially, the so-called "burst effect," possibly caused by drug particles that are on the surface or near the

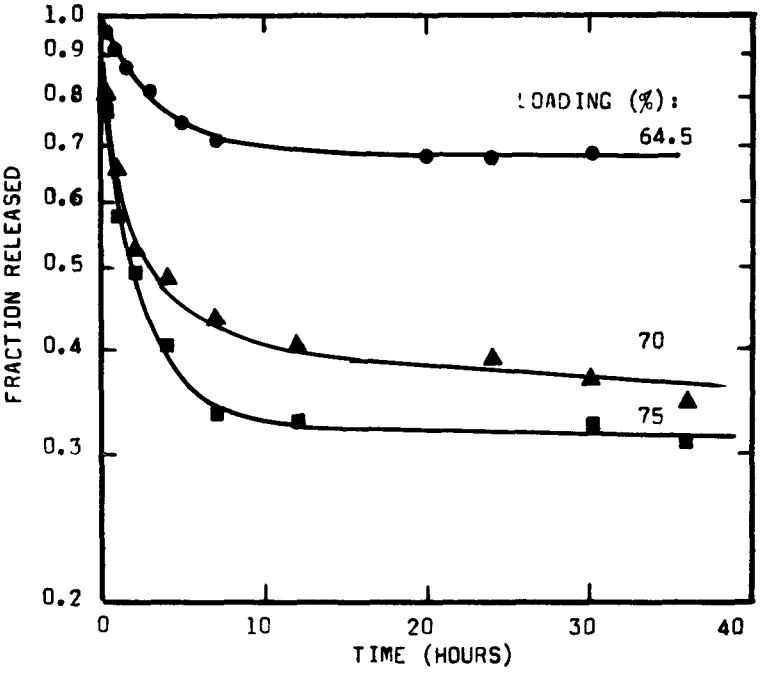

Fig. 3. Release of Astiban acid from 150 to 180 μm microcapsules.

surface and are easily extracted. If the remainder of the release curve could be described, perhaps the extent of the burst effect could be estimated.

Since it was known that there was a large number of small drug particles trapped in each microcapsule, a portion of the release curve should be described by the Higuchi equation (*7*).

$$1 + 2(1 - M^*) - 3(1 - M^*)^{2/3} = BT$$

where B is a constant and M^* is the fraction of the drug that has been released.

Since the factor multiplying the time on the right side of the equation should remain constant during the release, the left side of the equation should be linear with time. The data are plotted in this form in Fig. 4. Although the extent of the linear portion of the curve is open to considerable judgment, it is approximately as indicated by the dashed line. The intersection of this line was taken as the amount of the drug releasesd in the initial "burst" portion. In practice, if no burst was desired, this readily available drug could be removed by an initial rapid washing step.

It is also apparent from the raw data that the latter part of the drug

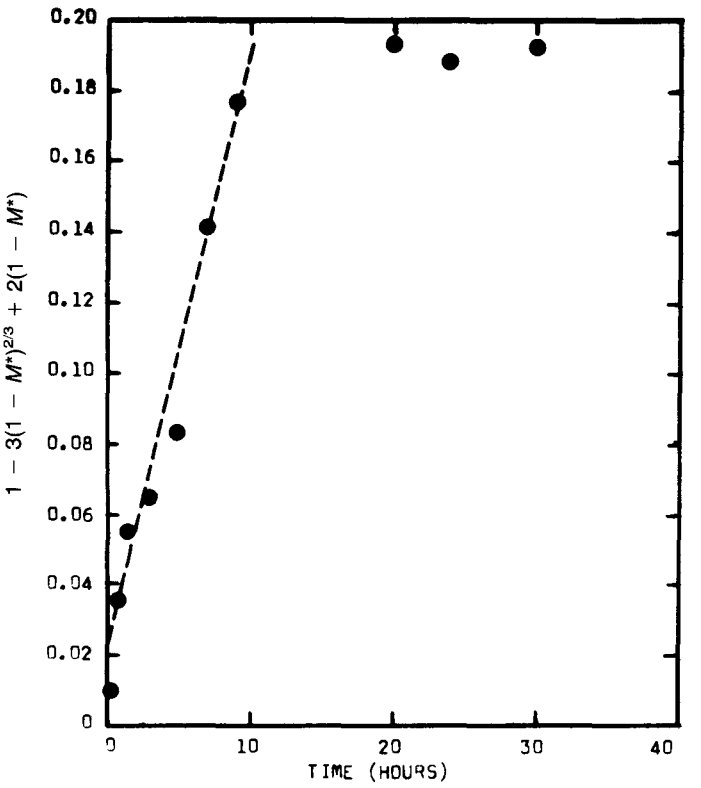

Fig. 4. Region of fit to Higuchi equation.

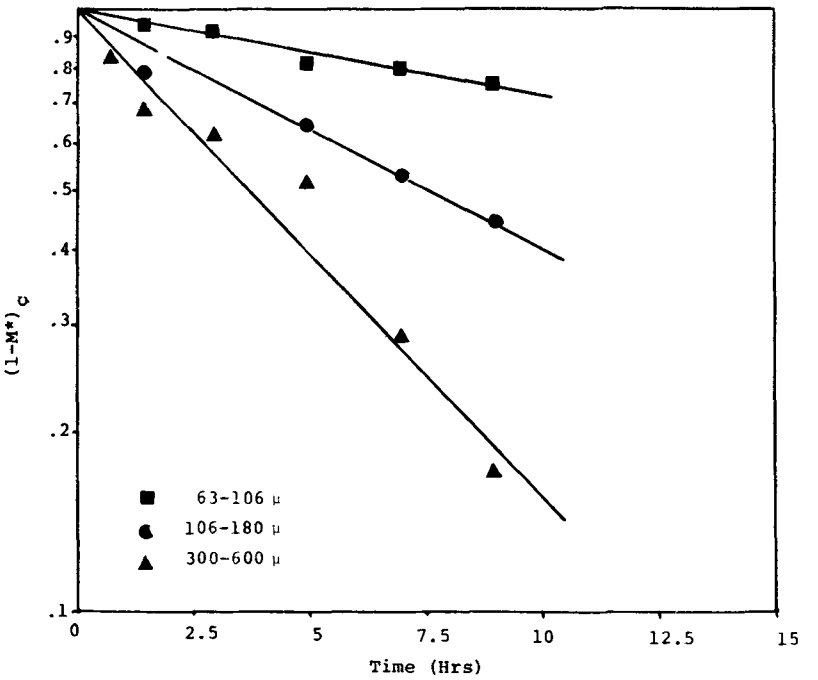

Fig. 5. Effect of particle diameter on release segment fitted by Higuchi equation: 300–600 μm, payload = 77%; 106–180 μm, payload = 43%; 63–106 μm, payload = 35%.

release is much slower than that represented by the Higuchi equation. As shown in Fig. 5, the release at times longer than 9 h is exponential. The amount of drug represented by the extrapolation of these data to the beginning of release was also subtracted from the initial amount to obtain the drug released according to Higuchi's equation.

Preliminary studies in hamsters showed a wide scatter in blood levels of astiban acid for injections of the pure drug as well as the microencapsulated drug. The microcapsules did not give a significant extension of drug release. Hence, the in-vitro half-time of the microcapsules must be raised significantly above 20–30 h to give the desired in vivo release.

CONCLUSIONS

Treatment of tropical parasite diseases is a field where controlled drug release may have important benefits in decreasing the number of doses and also the total amount of drug that must be given. In the case of astiban acid, used for the treatment of *Schistosomiasis mansoni,* the half-time of release can be increased several hundredfold by microencapsulation in poly(*d,l*-lactic acid) by coacervation. The rate of drug release from these microcapsules shows a strong initial burst effect, followed by a period during which the release is well-described by the Higuchi equation.

After release times longer than about 9 h there is slow exponential release.

Achieving a significant extension of in-vivo drug release will require microcapsules having in vitro half-lives well above 20–30 h.

ACKNOWLEDGMENT

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