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Microcapsules for New Animal Drugs

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ABSTRACT

Microencapsulation techniques have been developed and refined for many years. However, in recent years, great strides have been made in controlling the microcapsule size down to the nanometer range when necessary. Progress has also been made in controlling the ratio of wall/capsule and the distribution of microcapsule diameter size in the batching of the capsules.

One area of application for microencapsulation is the convenience of dosing large groups of animals once with a sustained-release dosage form rather than with repeated administration since this involves greater effort at animal management.

For example, targeted dosages can be achieved by a specialized drug delivery system. Since animal systems are varied and ruminant animals have a digestive system that is different from and more complex than that of other animals, oral administration of a drug substance to be retained through the rumen to the abomasum for subsequent dissolution and/or excretion may be affected by a microencapsulation process. Miller and Gordon of USDA achieved this for control of fecal breeding flies by systemic retention of a microencapsulated pesticide drug into the manure.

Perhaps one of the most challenging areas is that of pharmaceuticals. There is now considerable interest in the area of microparticulate drug delivery systems. Examples of how desirable nutritional properties and taste preference are achieved and how these provide improved animal products will be discussed. Additional areas of interest and some possible future systems that have advantages over conventional systems will be discussed.

A brief description of some general requirements by the Food and Drug Administration (FDA) for approval of these drug delivery systems will be presented.

Index Entries: Microcapsules, for animal drugs; animal drugs, microcapsules for; drugs, microcapsules for animal.

INTRODUCTION

Microencapsulation techniques have been developed and used for many years (*1–23, 25–33*). Great strides have been made in achieving desired sizes and capsule diameter range for their intended uses.

There have been achievements such as magnet particle drug microcapsules for target delivery to a specific site (*29*) and prodrug microcapsules (*30*). Since it is possible to achieve nanoparticles (*31*) and liposomes (*32*) that are small enough to be passed through the cell wall to the target sites, as much as 100 times less drug may be needed to achieve the desired pharmacological effect with reduced toxicity in certain cases. Microspheres as parenteral delivery systems (*33*) may be considered for use subcutaneously when localized or longer term use is desired for drugs such as contraceptive steroids, anticancer agents, or flukicides. Intravenous administration of microcapsules may be used to achieve targeting to certain organs or blood cells if the distribution, toxicity, and fate of the capsules can be adequately determined.

With the unique advantages that can be obtained by the use of such specialized processes, increasing consideration must be given to the use of microcapsules for medical purposes. These systems will be developed for use when their unconventional formulation costs are compared to the total expenditure needed from discovery to FDA approval, and when the historic reluctance to abandon currently used drug dosage forms in favor of unconventional drug delivery systems is overcome by the benefits that can be obtained by their use.

DISCUSSION

Table 1 provides the number of new animal drug applications approved for several of the years from 1968 to the present time. You will notice the increase in the number of applications approved over the years. However, if you will look at the year 1982, you will notice that of the total number approved, only 67 were original drug applications as defined by (a) use of new drug substance, (b) a novel dosage form or new route of administration, (c) use in animal species not previously approved, (d) a new medical claim for the drug, (e) a combination drug, and (f) "me too" of a pioneer drug. Of these categories, the number of approved new drug substances is a very small part of these numbers. This is a result of the increasing approval costs caused by continuing inflation, and increasing amounts of information required by the FDA when submitting a new animal drug application.

TABLE 1
New Animal Drug Applications Approved

Year	No. approved
1968	171
1970	373
1972	419
1974	515
1976	440 (51 original applications)
1977	524 (28 original applications)
1978	508 (24 original applications)
1979	735 (17 original applications)
1980	883 (26 original applications)
1981	793 (35 original applications)
1982	680 (67 original applications)

Because animal digestive systems differ substantially in their anatomy, activity, and subsequent metabolism, it may be necessary to administer a drug in a formulation that will remain unaltered during passage through the rumen, reticulum, and omasum, and into the abomasum for subsequent dissolution and absorption or passage into the intestine. USDA workers (*10*) found that a microencapsulated pesticide was able to pass into the feces with sufficient active ingredient to obtain efficacy against two types of fly larvae.

Dosing large groups of animals one with a sustained-release implant, or "depot," drug gives some unique advantages (*25–28, 31–33*). Feedlot dosing is made easier by single administrations rather than repeated dosing of the animals. The FDA has approved the use of the microencapsulation process on cattle feed additives. Tallow is encapsulated with a coating of formaldehyde-treated protein that produces a gel of droplets of 1–5 μm diameter. The capsules are then mixed until the drug reaches the abomasum, deadly soap formation in the rumen is avoided and the cattle can achieve weight gains appreciably below the current average cost to the feedlot producer (*22*).

USDA and other scientists (*11–12*) have found that safflower oil prepared by encapsulation in casein or other proteins treated with formaldehyde and subsequently placed in the grain ration increased the linoleic acid content in cows milk to an average 13.5% of total fat compared with the preexisting 2.7% of unsaturates. The casein wall protected the oil from being hydrogenated by microorganisms in the rumen of the cattle, thereby creating the higher level of unsaturated fat in the milk.

Newborn fish may be fed microencapsulated food of particle sizes of less than 100 μm (*14*). In this manner the fish may be nurtured economically in fish farms or tanks without eutrophication of surrounding water by the breakdown of soluble components, including organic and

nitrogen-containing compounds from currently used fish chow. Microencapsulated vitamins and drugs similarly ingested would be released directly in the gut, controlling the quantities used.

Another area of application would be the stabilization of the active ingredient to achieve a desired shelf life under expected environmental conditions prior to use. The drug formulation can be protected from heat, light, oxidation, moisture, mechanical stress, reactive ingredients in the formulation, or a combination of these factors. Such techniques are particularly applicable to the preparation of the medicated feed premixes.

Additionally, temperature-sensing nonreversible systems could be used for the labeling of containers to indicate whether high or low temperatures have been exceeded in cases where controlled ranges of temperature are necessary for maintenance of drug quality and integrity (*16*).

Still another area for the application of microencapsulation is taste-masking or odor avoidance. Several animal species, including dogs, cats, horses, can be sensitive to unpleasant tastes or odors associated with drug ingredients and/or related impurities, degradation products, or formulation excipients. Combination drug products may need protection from interactions between ingredients.

In 1981, FDA approved Equipalazone, a microencapsulated phenylbutazone powder to be used in the grain ration for horses. The product as a taste-masked form provided palatability for fresh or aged powder added to the horse ration.

Recent work by a USDA chemist (*20*) indicates that starch xanthate polymer may become a popular encapsulation material for pesticides and drugs. The inexpensively derived polymer, as an insoluble but waterpermeable starch particle, slowly releases the active ingredient. Other compounds are also showing promise for use as inexpensive capsule wall materials.

TABLE 2
Sequence for Approval of a New Animal Drug Application

1.	Protocol for studies	
2.	Filing of INAD with the FDA Bureau of Veterinary Medicine	
3.	Submission of NADA to the Bureau	
	a. Safety (including human safety considerations for food producing animals)	21 CFR §514.1
	b. Efficacy	
	c. Manufacturing controls	
4.	Environmental Impact Analyses Report, where applicable, to the Bureau	
5.	Review by the Bureau	
6.	Approval of the application by the Bureau	
7.	*Federal Register* announcement	

NEW ANIMAL DRUG APPROVAL PROCEDURES

I would now like to direct your attention to the procedures to be used for those desiring approval for marketing of a microencapsulated new animal drug. Table 2 provides the normal sequence of events that lead to the approval of a drug for animal use.

In the table, a protocol for studies should be submitted to demonstrate the claim that a microencapsulated product has a special use differing from some other dosage form. Its therapeutic or other medical claim should be delineated. Next, the submission of any Investigational New Animal Drug application (INAD) is a request for studies to be conducted and the number of animals to be used. After the investigational trials are completed, a New Animal Drug Application (NADA) is to be submitted which provides studies that determine an adequate margin of human and animal safety. The submission should also demonstrate the efficacy of the intended microencapsulated drug as administered to the animal. The manufacturing controls should also be included in this submission describing the steps and procedures used for control at each stage through to the finished dosage form.

Safety and efficacy are of principal importance in the development of a microencapsulated new animal drug and should be considered prior to the submission of a NADA. Table 3 provides BVM suggestions limited to the area of manufacturing controls for a proposed drug.

TABLE 3
Bureau of Veterinary Medicine Suggestions for New Animal Drug Applications Using a Microencapsulation Process

1. Limits of solvents remaining in the formulation, including reaction intermediates of the polymetric or other wall-coating materials, must be described.
2. Particle size, range, and distribution should be specified for the capsules, including ratios of core diameter wall thickness with the percent w/w of each. If a multiwall, colony, or aggregate coating system is to be used, then these should be characterized.
3. Permeability of wall(s) material with its expected environment during administration (e.g., the bloodstream for intravenous fluids or the tissue with intramuscular injection, gastric, or other digestive fluids following oral administration, etc.) should be demonstrated and permeation rates measured.
4. If controlled-release, taste-masking, or other special property or effect is claimed, adequate test methods and specifications following the evaluation of appropriate statistical data demonstrating these properties or special effects shoud be submitted.

Table 3 (*continued*)

5. Good Manufacturing Practices § CFR 21, Part 200.
   a. In addition to the normal processes necessary for production of premixes and dosage form, microencapsulation requires many precautions, quality control, and specialized techniques. What precautions are taken to prevent electrostatic attractions of dust to the particles after formulation?
   b. What precautions are used to prevent cross contamination of the drugs in the manufacturing facility?
   c. What steps are taken to prevent sticking together of the capsules, or their rupture or collapse due to improper conditions of storage and handling prior to formulation?
   d. A portion of the Environmental Impact Analyses Report must indicate the nature and levels of materials leaving the manufacturing facilities as air or water effluents and how these effluents are controlled to meet current local, state, and federal pollution control requirements.
6. Stability testing to determine an expiration date for the product stored under expected environmental conditions prior to use should include assays for the active ingredient, the particle size of the microcapsules, and measurements to demonstrate that the advantage claimed for the microencapsulated product in the finished dosage form have not been destroyed or diminished during storage (24).
7. Safety of wall materials and solvents used in the microencapsulation process should be demonstrated. If the wall material persists, environmental impact considerations must be evaluated. An Environmental Impact Statement may be required in these instances.
8. If specific claims regarding the process to differentiate the formulation from competing products, such as "controlled-release" or "stabilized" or "odor-free" are made, then data must be presented to substantiate such claims.
9. The drug content must be expressed in percent such as w/w or w/v. Limits of acceptance of drug content in the formulation should be included as a laboratory control for the finished dosage form. Where controlled release limits are proposed, ranges should be defined utilizing appropriate statistical methods.
10. When microencapsulation processes produced by one company are supplied for further formulation, or packaging and labeling, or simply marketing by another firm that will be the sponsor of a New Animal Drug Application, the microencapsulator may submit manufacturing data, controls, etc., in the form of a Master File to the FDA. This Master File may be referenced to support a New Animal Drug Application by a letter of authorization from the microencapsulator to the sponsor and/or FDA.

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