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Interactions of and Regulatory Requirements of Microcapsules for New Animal Drugs

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Interactions of and Regulatory Requirements of Microcapsules for New Animal Drugs

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ABSTRACT

Microencapsulation techniques have been developed to produce microcapsules of nanometer size when necessary. The control of the ratio of wall thickness to capsule diameter and the control of microcapsule diameter size have been improved. Animal digestive systems differ; e.g. Ruminants have a more complex digestive system than other animals. A microencapsulated drug orally administered will remain unaltered as it passes through the rumen and abomasum to the feces. For example, control of fecal breeding flies by retention of a microencapsulated pesticide drug into the manure has been achieved. Unsaturates may also be protected from hydrogenation and be absorbed unaltered in the abomasum by this process. Considerable attention has been given to control the rate, extent, and site of action for pharmaceuticals. These mechanisms are discussed and some examples are given. A description of the Food and Drug Administration requirements for approval of these drug delivery systems are presented.

Microencapsulation techniques have been developed and refined for many years [1-23,25,26]. With the passing of time it has become increasingly clear that the unique advantages that can be obtained by utilizing such specialized processes cannot continue to be cast aside merely because of cost pressures from competing products, technological state-of-the art, or reluctance to abandon the normally accepted drug delivery systems.

Table I depicts the number of all new animal drug applications approved from 1968 to the present time. You will notice the in-

Table I New Animal Drug Applications Approved

1968	171	
1969	304	
1970	373	
1971	296	
1972	419	
1973	469	
1974	515	
1975	528	(45 Original Applications)
1976	440	(51 Original Applications)
1977	524	(28 Original Applications)
1978	508	(24 Original Applications)
1979 (to Nov. 15)	554	(9 Original Applications)

crease in the number of applications approved over the years. However, if you will look at the year 1979, you will notice that of the total number approved, only 9 were original drug applications, as defined by a.) use of new drug substance. b.) a novel or new route of administration, c.) use in animal species not previously approved, and/or a new medical claim for the drug, of these categories, the number of approved new drug substances is indeed a small part of these numbers, and shows promise of being even smaller in the future. The decrease in number is because of increasing inflation, and increasing amounts of information required by FDA to be submitted in support of a new animal drug application.

In some cases, because the animal digestive systems differ in their activity, selective approaches must be considered for each animal system. A drug substance may need to be administered in a formulation that will remain unaltered through the rumen into the abomasum for subsequent dissolution and/or excretion. USDA workers found that a microencapsulated pesticide was able to pass into the feces sufficient active ingredient to obtain efficacy

against two types of fly larvae. The products "Rabon" and "Dimilin" have also been studied experimentally using this type of delivery system.

Dosing large groups of animals once with a sustained-release, implant, or "depot" drug give some unique advantages[25-26]. Feedlot dosing is made easier by single administrations rather than repeated dosing of the animals. FDA has recently approved the use of the microencapsulation process as a feed additive for cattle. Tallow is encapsulated with a coating of formaldehyde-treated protein which produces a gel of droplets of 1-5 micron diameter. The capsules are then mixed with the grain, which improves flowability of the ration[19]. By delaying digestion 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].

Similarly the enrichment of unsaturates in the milk fat content of dairy animals has been reported. The 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 as 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 microns[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 include stabilization of the active ingredient to achieve a desired shelf life under expected environmental conditions prior to use. Examples of this would be to protect the drug formulation from heat, light, oxidation, moisture, mechanical stress, 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 temperature restrictions are important[16].

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

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 water-permeable starch particle, slowly releases the active ingredient.

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, the 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 claims should be delineated. Next, the submission of any Investigational New Animal Drug application (INAD)

Table 2

Sequence for Approval of a

New Animal Drug Application

1. Protocol for studies
2. Filing of INAD
3. Submission of NADA

   a. Safety)
   b. Efficacy) 21 CFR §§514.1
   c. Manufacturing controls)

4. Environmental Impact Analyses Report where applicable.
5. Review by the Bureau and by the Administration.
6. Approval of Application.
7. FEDERAL REGISTER Announcement.

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 generated which provides studies that determine an adequate margin of human and animal safety. The submission should also demonstrate 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 thru 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 an NADA. The following BVM suggestions will be limited to the area of manufacturing controls for the proposed drug:

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 polymeric 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 blood stream for intravenous 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 evaluation of appropriate statistical data demonstrating these properties or special effects should be submitted.

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 attraction 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 active ingredient, particle size of the microencapsules, 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 micrencapsulation 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 process produced by one company are supplied for further formulation, or packaging and labeling, or simply marketing by another firm which 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 autorization from the microencapsulator to the sponsor and/or FDA.

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