

NOVEL DRUG DELIVERY SYSTEMS

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During the past decade a new era of science and technology has emerged in pharmaceutical research aimed at the development of novel or advanced drug delivery systems. The development of novel delivery systems for veterinary medicine is generally more complex than for human dosage forms due to the variety of animal species treated with differing gastrointestinal and anatomical features. As a result, a close working relationship between veterinarians and pharmaceutical scientists is essential for the development of a successful product. The emphasis in this manuscript will be on systems for human use; however, similar technology and scientific principles are employed in drug delivery systems for animals.

For human and animal health novel delivery systems, common concerns exist in areas of cost-efficient treatment, "patient compliance" and optimum drug delivery and bioavailability (1). Ideally, controlled drug release entails carefully programming the output of a chemical from a physicochemical system such that drug release can be activated on demand.

Background

All drugs are formulated into a dosage form or a drug delivery system, such as a capsule, tablet, paste or ointment. In addition to the active drug substance, these formulations contain ingredients known as adjuvants or excipients. These excipients are essential to the physical properties of the drug product and may influence the physical and chemical stability of the drug and its clinical effectiveness. Tablet dosage forms, for example, contain lubricants such as stearic acid or magnesium stearate. These ingredients prevent powders and granulations from sticking to the punch and die sets in the tablet press. Other excipient materials include disintegrating agents, binding agents, and filler or diluent materials such as lactose. With the introduction of high speed tablet presses that produce up to 10,000 tablets per minute, constraints on tablet formulations are necessary to insure product uniformity and overall quality of conventional dosage forms.

Advanced drug delivery systems possess several advantages over conventional dosage forms. Ideally, they may improve drug potency, control drug release to give a sustained therapeutic effect, provide greater safety, and decrease toxic side effects. Finally, they may target a drug specifically to a desired tissue, organ or location in the body.

Microencapsulation

Microencapsulation technology, discovered by scientists nearly forty-five years ago, is a process whereby small discrete solid particles or small liquid droplets are completely surrounded and enclosed by an intact shell. The structure resembles that of a living cell with a thin membrane or wall surrounding a discrete amount of core material. The method selected to prepare microcapsules depends to a great extent on the core and wall materials used and the ultimate application of the product. Pharmaceutically, the most commonly

used membrane materials include cellulose acetate phthalate, gelatin, ethyl cellulose, polyamides, polymethyl methacrylate, polystyrene, rubber and waxes. Core materials are generally liquids or solids including polymers, waxes and resins (3).

The first commercial use of microencapsulation was carbonless copy paper. Since the mid-1940's, tremendous advances have been made in this field by chemical engineers, physical chemists and pharmaceutical scientists. Table 1 lists the pharmaceutical applications of microencapsulation, and it also summarizes some of the problems that drugs present to the pharmaceutical scientist which must be solved during formulation into the finished dosage form. A major advantage of microencapsulated drug products is with drugs which irritate linings in the stomach and intestines. The drug concentration is controlled by slow release characteristics of the microcapsules. Thus, the safety of potential ulcer-producing drugs is increased.

Table 1. Pharmaceutical Applications of Microencapsulation

- (a) Sustained or prolonged-release of drugs
- (b) Masking taste and odor of drugs
- (c) Stabilizing drugs sensitive to atmospheric conditions
- (d) Prevent vaporization of volatile substances
- (e) Elimination of incompatibilities via physical separation
- (f) Overcome flow problems by formation of free-flowing particles
- (g) Increase density of light fluffy powders
- (h) Overcome static charge
- (i) Turn liquids into solids

New processes for the preparation of biodegradable microspheres containing dl-poly-lactic acid have been developed. Depending on the physicochemical properties of the drug encapsulated and the drug-polymer ratio, the microspheres will release drug in the body from an intramuscular injection over a period of days to several months. The spherical nature of these particles containing dl-poly-lactic acid is shown in Figure 1. The drug is released by slow diffusion from the particle and by the slow biodegradation of the polymer. By reducing the particle size, it may be possible to target the drug containing microspheres to specific body organs such as the lung, liver or spleen following intravenous administration. This has been successfully accomplished by other research using liposomes as the targeted drug delivery system.

One of the important phases of research associated with microparticulate drug delivery systems is to be sure that the physicochemical properties of each system are well understood when various stress conditions of temperature, light and humidity are applied. For conventional dosage forms such as tablets and topical pharmaceuticals, stability studies on the active ingredient are routine. With microparticles, stress conditions can alter the porosity of the membrane, degrade the drug and polymer, or cause polymorphic or crystalline changes in the encapsulated drug. Scanning electron microscopy, powder X-ray diffraction, and differential scanning calorimetry have proven to be invaluable techniques to help explain stability data.

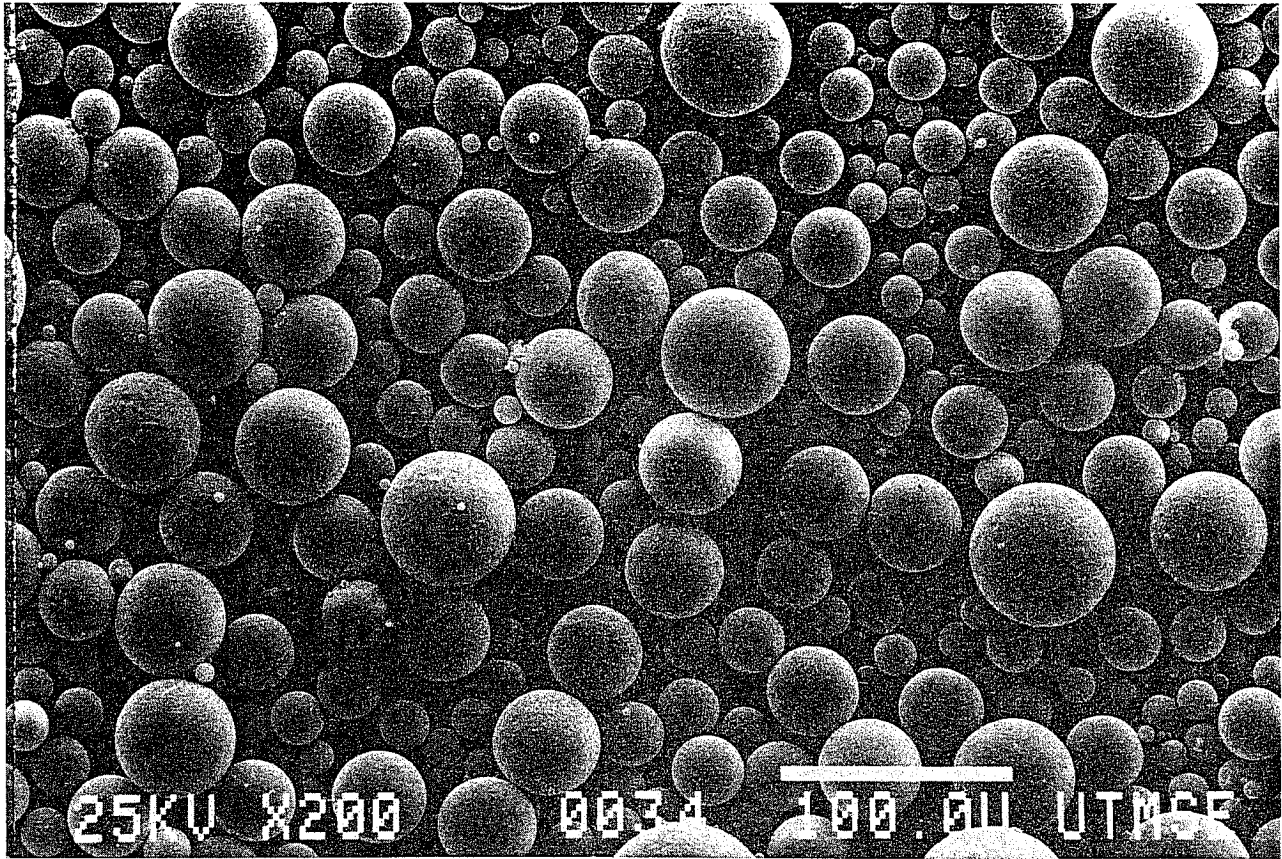


Figure 1 - Scanning electron micrograph of dl-poly(lactic acid) microspheres.

Oral Controlled-Release Tablets

A second specialized delivery system is oral controlled-release tablets made by one of three processes: wet granulation, direct compression and recompression. Prior to compression in a tablet machine, the drug and other ingredients of the dosage form must be in a granular state.

In the wet granulation process, the drug-excipient blends are mixed with a binder solution containing agents such as gelatin or sucrose. The damp mass is passed through a screen and then dried to form the granules. For drugs that are unstable to heat or moisture, the recompression method is used. Large, soft tablets are prepared from the powder mixture of drug and excipients and

then ground to the desired particle size. The resulting granules are used to prepare the final tablet dosage form. In the direct compression method, the powdered drug is simply mixed with commercially available excipients that are in the granular state prior to compression in the tablet machine. Many commercially available oral controlled-release tablets are made with the wet granulation process. The retardant substance in the tablet is generally wax or polymer. These materials are dissolved in a solvent, and the solution is used as a vehicle to prepare granules from the drug-excipient powder mix. Complete elimination of the solvents from the compressed tablets poses challenging problems in the production of these dosage forms. At The University of Texas we have studied the use of aqueous colloidal dispersions of acrylic resins to develop new formulations of oral controlled-release tablets. Drug is released from these tablets at a slow and controlled rate, thus eliminating the necessity of multiple administration to the patient of conventional tablets. In addition to being more economical, the aqueous granulation process eliminates contamination of the final dosage form with potentially harmful solvents.

Using various polymeric and clay materials, oral controlled-release tablets also have been developed by using direct compression methodology on high speed tablet machinery. This process eliminates the necessity of adding solvents to form granules prior to the tableting step since approximately 80 percent of the tablet components (drug, polymer, diluents, and so forth) is in the granular state.

The new direct compression technology is advantageous compared to traditional wet granulation methods but the path from academic curiosity to finished drug product contains pitfalls and challenging problems. One of the most important parameters to investigate is the compressibility of the drug in combination with other components of the dosage form. We now conduct these studies on a Manesty B3B 16-stage instrumented rotary tablet press. This press can produce up to 500 tablets per minute. The compressional force on each tablet is transmitted to a strain gauge on the lower punch of each punch and die assembly. This force is then relayed and recorded on an oscilloscope. The force or pressure employed to compress the tablet or compact is then related to the hardness of the tablet. The resulting pressure-hardness profiles are extremely useful in the optimization of tablet dosage forms.

Intravenous Fat Emulsions

Research has been initiated on two additional advanced drug delivery systems: intravenous fat emulsions and transdermal patch devices. The preparation and physicochemical properties of intravenous fat emulsions are being studied. The applications of microemulsions as drug delivery systems for poorly water soluble drugs show great promise. The oils in these emulsions include safflower or soybean oil. Commercially available emulsions are used as a source of calories for patients who cannot or will not eat solid food.

The intravenous (I.V.) route of administration is valuable when the rapid administration of drugs is required. It is also employed for the long-term infusion of drugs and nutrients (vitamins, proteins, carbohydrates) via indwelling catheters. However, numerous drugs present problems when administered by the intravenous route. Physical problems may arise with drugs possessing limited aqueous solubility, or drugs present in a salt form which

can revert to a less soluble form upon I.V. administration. Drugs with solubility limitations may precipitate at the site of injection leading to severe complications, including thrombophlebitis. Precipitation is a potential problem with poorly soluble drugs because solutions of the drug in mixtures of solvents, such as propylene glycol and ethanol, with water must be employed. Upon injection into the bloodstream the solvents are rapidly diluted, and this may result in precipitation of the drug at the site of injection. The potential for this to occur with drugs like diazepam and phenytoin has been reported in the literature.

The drugs we have under investigation include diazepam, prednisolone and phenytoin. The emulsions containing drugs in the oil phase comprise submicron size oil droplets emulsified and stabilized with egg yolk phospholipids. We have successfully prepared the microemulsions, and preliminary data from the drug solubility studies are encouraging. Future studies with these systems will include anticancer drugs, such as methotrexate, and drugs that possess stability problems in aqueous media.

Transdermal Patch Devices

Transdermal patch devices are applied topically to the skin and contain a reservoir of the drug which slowly diffuses through a rate controlling membrane prior to absorption through the skin (Figure 2).

The advantages of these systems are twofold: controlled-release of medication is achieved for long periods of time, and rapid metabolism of the drug by the liver is avoided (4). Only two drugs are commercially available for human therapy in transdermal systems -- scopolamine for the prevention of travel sickness and nitroglycerin for the treatment of angina. Research efforts with these systems are aimed not only to identify candidate drugs for patch devices but to optimize the membrane component of the system that controls the rate of drug release. Some drugs cannot be formulated into these systems because they are not absorbed through the skin. When a steroid such as hydrocortisone is applied to the skin it stays on the surface. Only small quantities of the steroid are absorbed systemically into the blood stream. On the other hand, when drugs such as nitroglycerin or methyl salicylate (oil of wintergreen) are applied, a systemic effect is obtained since these drugs rapidly diffuse across the skin barrier. Many factors related to drug potency, therapeutic index and site of action must be considered in selection of a drug candidate. The advantages to the patient of these advanced drug delivery systems over conventional cream and ointment formulations and in some cases oral dosage forms are numerous. However, many scientific and technical problems related to the physicochemical properties of the drug and the membrane must be solved before an optimized product is achieved. The potential application of transdermal patch systems as animal health products is being evaluated by several companies.

Many additional sophisticated and innovative methods for prolonged-drug delivery have been reported. Such animal health delivery systems include animal licks, ear tampons, implants, bio-erodible ocular devices, intramammary preparations and vaginal sponges (1).

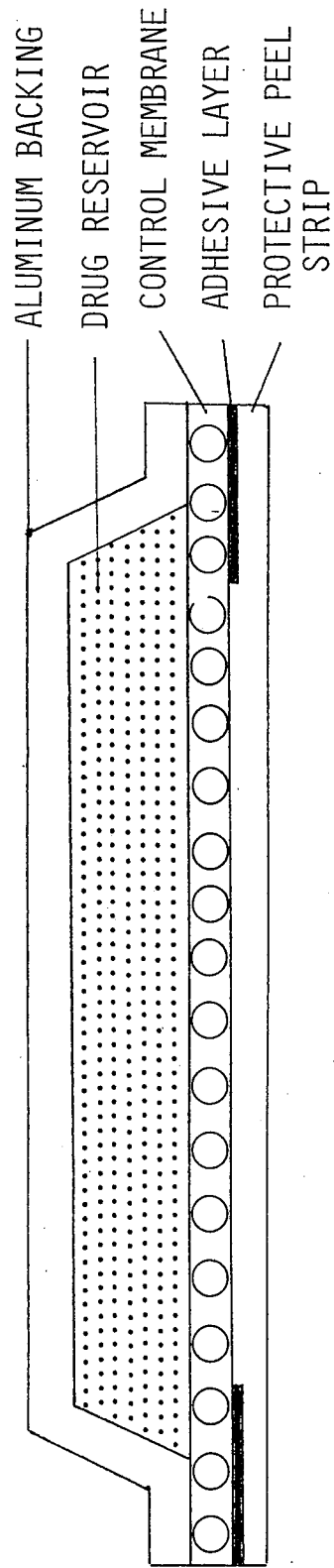


Figure 2 - Schematic diagram of a transdermal drug delivery system (cross-section).

Pope also describes in his article several miscellaneous animal health specialized formulations including medicinal dog foods and rumen-stable coatings for a number of irritant drugs that require such coatings (1). In addition, several pour-on preparations having systemic activity, and orally administered pastes and gels are listed along with guns, syringes and applicators to deliver these medications to the animal.

Conclusions

The complexities involved in the development of advanced drug delivery systems for human applications appear minuscule when compared with those used in animal health care. Aspects such as geographical locations, feeding techniques, dietary habits and the physiology of the gastrointestinal tract are all very important. In addition, other parameters such as drug distribution, metabolism, excretion, endocrinology and skin type must be considered. There are other factors that complicate the development of drug delivery systems for animals including animal behavior, age of the animal, disease state, methods of dosing, product stability and tissue residues. All of these factors have been discussed in detail by Pope and Baggot (5) in an excellent review article concerned with special considerations in veterinary formulation design. This author is in complete agreement with Pope and Baggot who concluded that veterinary drug delivery design has an extremely bright and challenging future.

Suggested Readings

1. D.G. Pope, "Animal Health Specialized Delivery Systems," in Animal Health Products, Design and Evaluation, Ed. D.C. Monkhouse, A.Ph.A., Washington, D.C., p. 78-114 (1978).
2. G.L. Flynn, "Considerations in Controlled-Release Drug-Delivery Systems," in Pharmaceutical Technology, 6, No. 2, 33-39 (1982).
3. J.W. McGinity, G.W. Cuff and A.B. Combs, "Microencapsulation of Pharmaceuticals," in Australian Journal of Pharmaceutical Sciences, 10, No. 1, 17-19 (1981).
4. J.F. Dasta and D.R. Geraets, "Topical Nitroglycerin," in American Pharmacy, NS22, No. 2, 29-35 (1982).
5. D.G. Pope and J.D. Baggot, "Special Considerations in Veterinary Formulation Design," in International Journal of Pharmaceutics, 14, 123-132 (1983).

Points raised during discussion

Question: The fact that we now have these new tools to work with not only in terms of what they can do in the marketplace but also what they can tell us about these compounds in the development process has a direct impact in the regulatory area. I wonder whether there are any comments that either of you could make, based on your experiences, about what could be the case for a sponsor of a new chemical compound, a new drug entity or a new product in terms of what will be needed to demonstrate what an appropriate dosage is.

Dr. McGinity: The first step that a drug company will take is generally to develop a conventional dosage form unless they are going to something like a transdermal or a liposome, nanoparticle microsphere-type system. I think very few companies would advocate an advanced form of drug delivery system as their first option. They would usually go with their conventional dosage form and then from there acquire a lot of the basic scientific clinical data before going on to the next step.

Dr. Deluisio: In the FDA regulations in the United States, there is no question that we are now, on any new drug, wanting to know if we have maximized the absorption of a product. Therefore, anytime a new drug is developed there are several steps. One is to give the drug parenterally without an absorption step so you have a baseline of tissue levels against which you can measure a non-intravenous administration form. You then will have a measure whether absorption is 50%, or 10%, or 20%. In humans, this sometimes can present a risk, so therefore we have to really develop a conventional dosage form whether you want to or not, and very often a company will produce what is called a readily available dosage form or a conventional dosage form - a solution, suspension, capsule or whatever. So there is a parallel development that has to take place. There is also a school of thought that says one should titrate a patient - establish the blood levels on a conventional dosage form and then switch to the novel drug delivery system (NDDS). The advantage of this is the speed at which you establish the steady state.

Dr. McGinity: Many companies are also finding as their patents are coming to an end on some very successful compounds, that as they want to extend their product lines with sophisticated pelletized forms or controlled-release or enteric coated-controlled-release matrix all combined, they are learning a lot about the drug they should have known 10-15 years ago. Tagamet, the biggest drug on the world market right now, could be site-specific as far as its absorption is concerned and that may prevent it from being put into a controlled-release dosage form. This is just one of many examples. Drug companies often want to include their drugs in

these various formulations and have found that they are only absorbed in the first third of the g.i. tract. So a lot of basic work has to be done that is complicated from a technology standpoint.

Question: Which drugs are being considered for inclusion in novel delivery systems?

Dr. McGinity: Getting information from companies about what drugs they are working on is very difficult. That is a closely kept secret. But there certainly are opportunities and something that should be investigated further.