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# POST-RUMINAL DELIVERY SYSTEMS

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**Abstract**

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Livestock industry and organization for animal wellfare underlie the need for drug and nutrient delivery systems for ruminants that protect active ingredients from ruminal fermentation. To deliver drugs or nutrients directly to the small intestine for absorption, therapeutical systems must meet the safety and cost criteria. An effective post-ruminal delivery system is a prerequisite to implement some significant advances in animal nutrition and health in ruminants. Comparing with the products developed for human use, cost constraints have impeded the development of effective post-ruminal delivery systems and rumenstable products. This article outlines physiological and technical considerations encountered in the design of effective post-ruminal delivery systems. The requirements and formulation of a pH-dependent rumen stable coating systems and possible future developments will be discussed.

ruminant, amino acid deficiency, active ingredient delivery, rumenstable product

In the past, the only drugs available for animal treatment were those developed for human use. Recently only several decades ago, animal science research has provided many new drugs with specific applications for animals. Considerable emphasis has been seen in the field of growth promotion, the treatment and prevention of disease in farm animals, potential food sources. Many specialized dosage forms have been developed to meet this need for efficient administration of new drugs. The multiplicity of species differences has led to dosage forms specific to a single species. The value of animals to human society is steadily increasing with the ecological understanding and with the need for improved quality and quantity of food resources.

Pharmaceutical science, its methodology and techniques used in developing human drug dosage forms are equally applicable to the formulation of veterinary dosage forms. The ability to control the administered dose of drug over long time period, and to direct the medicament or therapeutical system to a preferred site of action in the body, has led to a variety of therapies which are more effective, use less drug, have fewer side-effects, increase patient compliance. Controlled release products for human pharmacotherapy have been developed and used already since 1970. The principles used in human medicine had been later used also in veterinary drug delivery systems.

**Need for post-ruminal systems**

Ruminant animals, such as cattle, sheep and goats, are major sources of meat, milk, wool and leather and are important contributors to the agricultural economy. Ruminants play a particulary important role in food production because they utilize cellulose and non-protein nitrogen which are abundant in nature (straws, grasses, etc.) and which are either indigestible or are poorly utilized by other domestic animals and humans. Their ability to digest fiber is a function of their digestive physiology and symbiotic relationship between the host animal and ruminal microbes including bacteria, protozoa and fungi (RATHBONE, GURNY; 2000).

Until recent time, the ruminant nutritionists payed a little attention to the adequacy of the amino acid supply as they assumed, that the microbial proteins would meet the animals requirements. However with high level production (especially the milk production) this adequacy is not often valid. To remedy the amino acid deficiency, farmers offer their animals more high protein feed and are interested in the supplementation of specific amino acids, e.g. lysine and methionine (CLARK, 1975).

Although highly productive ruminants may benefit from amino acid supplementation, direct addition of amino acids to the diet is not practicle because ruminal microbes will utilize these amino acids before they reach absorption sites in the small intestine (SANTOS, THEURER et al., 1998). Therefore, there is a need to somehow protect the protein (active ingredient) from degradation in the rumen in order to make it available to the animal in the small intestine – the site of absorption. This would allow the animal to get increased nutritional benefit of the feed.

**Conditions in the ruminant digestive system**

The ruminant stomach has four compartments: the reticulum, rumen, omasum and abomasum (SLANINA, DVOŘÁK et al., 1993; MATHISON, OKINE, VAAGE et al., 1995). The rumen and the reticulum are often considered as the reticulorumen as they fulfil similar functions. Almost all of the pregastric fermentative activity and absorption of the end products of this fermentation occurs here. The end products of anaerobic fermentation (acetate, propionate and butyrate) are important sources of energy for the animal (40–80%). Ruminant microbes are adapted to live at pH ranging from 5.5 to 7.4. However diet can significantly affect ruminal pH value. The omasum filters large particles back to reticulorumen, thus protecting them from passing to the lower gastrointestinal tract. It allows fine particles and fluid to be passed to abomasum, aids in water resorption and recycling of buffers for the saliva. The functions of abomasum are generally similar to those of the other mammals´ stomach. Secretion of hydrochloric acid maintains abomasal pH at approximately 2 so that there is a rapid decrease in the pH value between upper parts of stomach and abomasum (MATHISON, OKINE, VAAGE et al., 1995). This sharp reduction in pH provides the basis for pH-dependent controlled release systems for abomasal delivery. In ruminants, the small intestine is the primary site of digestion and absorption. The pH of the chyme is returned almost to the neutral value by buffers secreted from the mucosa of the small intestine within a short distance of the pylorus.

Ruminal retention time depends on the feeds and on the animal (SNIFFEN, O´ CONNOR, Van SOEST et al., 1992; HERRERA-SALDANA, GOMEZ, TORABI et al., 1990). Longer rumen residence time increases ruminal nutrient availability, however it is a disadvantage for ruminal protection.

Ruminants rely on pregastric fermentation by enzymes degrading plant material high in cellulose for their energy requirement. Most ruminal microbes are anaerobes, their fermentation yields gas, short chain fatty acids and microbial mass. The ruminal microbes are also used as sources of protein by the host animal. When they pass to the intestine, they are digested by enzymes and the resulting amino acids and short peptides are absorbed HESPELI, AKIN, DEHORITY; 1998).

The rumen microbial system is complex with the ability to degrade starch, xylans, pectin, lipids, protein and sugars (EVANS, PEARCE, BURNETT et al., 1973). This broad range of activities causes the development of the coating, that protects active ingredient from ruminal degradation, very difficult.

Another problem for a rumen-protected particle are chewing and rumination, which can cause the premature release of the active substance from protected particles (KASKE, ENGELHARDT; 1990). It can be averted if the particles are heavy enough to avoid being transfered to the rumination bolus, but they must not be so heavy that they sink to the bottom of the reticulorumen with a low probability of passage to the lower gastrointestinal tract (WELCH, 1990).

**Possibilities of ruminal protection**

Three areas must be considered in the development of an effective postruminal drug delivery system: physiological considerations, feeding practices and environmental concerns.

The delivery system should provide ruminal protection and post-ruminal delivery of the active ingredients. Ideally they should be protected in the rumen environment, then completely released and thus become available for absorption. Three parameters of the postruminal delivery system are: minimal degradation due to rumination, an ability to withstand the chemical and microbiological conditions in the rumen and maximized rate of passage through it.

The understanding of the particle movement dynamic in the ruminant digestive system is essential in the design of an effective post-ruminal therapeutical system, i.e. it is important to optimize particle size, shape and specific gravity to minimize their retention time in reticulorumen. As mentioned above, the coating must in addition protect the particle from ruminal microbial activity and withstand pH conditions in reticulorumen and omasum.

Most of the data on the effects of specific gravity on ruminal passage and digestibility have been obtained by feeding inert pellets (usually plastic or rubber) and recovering them either from the duodenum or the faeces (WELCH, 1990; DESBORDES, WELCH, 1984; TŘINÁCTÝ, ŠIMEK, ZEMAN et al., 1999 a; TŘINÁCTÝ, ŠIMEK, HOMOLKA, 1999 b; TŘINÁCTÝ, SCHMEISEROVÁ, SUCHÝ, 1999 c; TŘINÁCTÝ, HOMOLKA, RICHTER et al., 2002). By varying the types of plastics used (polyethylene, polypropylene, nylon, acetal, polyvinylidene fluoride and teflon) and by mixing them with barium sulfate, the range of specific gravity can be varied from less than 1 to more than 2 $g.cm^{-3}$. Although recovery of the particles from the faeces or digesta is laborious, it is possible to distinquish intouched particles that have not been chewed. It has been reported that particles with a specific gravity of approximately 1.2 $g.cm^{-3}$ or more are less likely to be retained in the rumen and be ruminated than those which are lighter (FIRKINS, 1997). Pellets with a specific gravity of 1.77 $g.cm^{-3}$ or higher sank to the bottom of the reticulum and remained there.

Based on the published data on specific gravity, the movement of the particles through the gastrointestinal tract appears to be relatively simple: protected particles should be small and dense to maximize passage from the rumen and to minimize rumination. Unfortunately, the situation is more complex as the ruminal retention time is dependent on the size and physiological status of an animal and on the feeds (MURPHY, KENNEDY, WELCH, 1989).

Although few large particles are passing the rumen intact (the estimates of the maximum size of the opening of the reticulo – omasal orifice have ranged from 10 x 45 mm to 40 x 60 mm in cattle, while the opening in sheep is from 10 x 20 mm; MATHISON et al., 1995), the effects of dietary particle size on passage are varied. Tested particle size (1; 2; 3; 5; 7 and 10 mm) was shown to be a more determinant of passage in dairy cows than beef cows (KENNEDY, 1995). Consistency of mat (i.e. mass of floating digesta present under some dietary conditions in the dorsal rumen) affects the speed of small particles from the reticulorumen, that means the diet has great influence on the passage of suitable particles there. This fact has practical implications in rumen protection schemes.

The obtained data underline the need to evaluate rumen protection systems in different species of animals and in animals in different physiological states to ensure that the ruminal protection is adequate.

### Experience with the formulation of a postruminal therapeutical system

A variety of postruminal delivery systems have been developed using heat and chemical treatments, methionine analogues (WU, PEPAS; 1997), lipid-based formulations and pH- sensitive polymers. The most sophisticated system, which was developed and commercialized by Rhone – Poulenc (Samartamine®), was based on the use of a ruminally inert, pH-sensitive polymer (Pat. CZ 280981 B6, 1996). The system was used for the delivery of amino acids to abomasum with their absorption in the small intestine. This polymeric coating system can be also used for protection of other active ingredients formulated into particulate forms. The system has been refered to as a reverse – enteric coating system (WU, 1990).

Formulation considerations of an effective postruminal system are coming out of two important features: core formulation and coat properties.

First, it is essential to prepare suitable pellets or small tablets, that will subsequently be coated. The core should have high active ingredient content, optimal size (up to 4 mm), optimal shape (sphere or short cylinder), smooth surface, sufficient hardness, specific gravity 1.2 –1.5 $g.cm^{-3}$ and must dissolve in the abomasal or gastrointestinal fluid.

The coating should posses sufficient mechanical strenght, remained intact in feed, be rumen stable and non absorbable in the gastrointestinal tract and release amino acids in the abomasum. A polymer suitable for formulation of a pH-dependent rumen-stable coating should be physiologically inert, non-mutagenic, thermally stable, soluble in abomasal fluid and safe for the use in food-producing animals. The coating efficiency is highly dependent on the solubility of active ingredients, core size and smoothness of its surface (WU, 1994).

In early formulations, cellulose propionate 3-morpholinobutyrate (WU, DANNELLY, KOMAREK; 1981) and subsequently copolymers of vinylpyridine and styrene (US Pat. 4,837,004 (1989), were used. The coating system was usually composed of a basic polymer, a pigment and a hydrophobic substance (e.g. stearic acid). Some other patented formulations are using coatings of laminar structure with tubular crystals (US Pat. 5,635,198; 1997), particles protected with zein and formaldedyd US Pat. 5,714,185; 1998), fatty acid matrices (US Pat. 5,928,687; 1999), the coatings composed of aliphatic $C_{12-24}$ monocarboxylates and zein (Eur. Pat. 0963 703 A1; 1999) etc.

The components used for system formulation must be safe for the target animal, the environment and for inclusion in the human food supply, without generating any undesirable residues.

Most of the systems can be used also to deliver micronutrients and pharmaceuticals to ruminants. There is also the possibility to combine them with other sophisticated devices to enhance controlled delivery.

## SUMMARY

Future investigations offer significant improvement of ruminant nutrition and health, and thus also the

production efficiency. Post-ruminal systems play an important role in the effort to optimize both rumen and postruminal function, i.e. not only efficient supply of nutrients, but also the control of other important parameters such as pH, microflora, prevention and treatment of disease. There are currently two possibilities of further developments: low cost protection formulations or high value micronutrients and drugs targeted systems. Cost constraints will indicate future efforts consideration.

SOUHRN

Postrumineální transportní systémy

V současné době se objevuje snaha jak ze strany masného průmyslu tak i ze strany veterinárních organizací zabývajících se zdravotním stavem dobytka o získání hlubších znalostí o transportních systémech, které by dokázaly ochránit živiny popř. i léčiva před bachorovou fermentací. Vlastní transportní systémy musí splňovat pro doručení účinných látek-léčiv nebo živin k absorpci do tenkého střeva nejen bezpečnostní, ale i cenová kritéria. Základním požadavkem kladeným na tyto systémy je jejich významný přínos pro výživu a zdravotní stav přežvýkavců. Ve srovnání se situací u podobných přípravků pro humánní použití, je další vývoj efektivních postruminálních systémů a stabilních produktů v bachoru omezován především vysokými finančními náklady. Práce se zabývá fyziologickými i technologickými požadavky souvisejícími s návrhem a formulací efektivních postruminálních transportních systémů, jejich hodnocením a možnostmi dalšího vývoje.

přežvýkavci, nedostatek aminokyselin, aktivní přísady, stabilita bachorového prostředí

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