ADVANCES IN CONTROLLED RELEASE TECHNOLOGY FOR HERBIVORES

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SUMMARY

Modern developments in drug therapy for the treatment of disease or for the manipulation of metabolic processes, together with the increased recognitionof the potential value of nutritional supplements, have led to the development of a range of techniques to ensure long-term dosing of livestock without the need for repeated handling. Such techniques may be referred to collectively as Controlled Release Technology. It is the aim of this review to present some of the underlying concepts of the field as it relates to ruminants and some related herbivores, and to report on a number of products resulting from CSIRO research which are being developed both in Australia and overseas.

INTRODUCTION

The provision of medication for a variety of conditions which include disease control and metabolic manipulation, and in some cases the supply of supplementary nutrients to overcome dietary deficiencies is an ever-increasing part of intensive livestock production in . agriculturally "advanced" countries. Furthermore, the ability to provide such supplements in an inexpensive and relatively unsophisticated manner has a great potential for improving the efficiency and productivity of animal production in virtually all environments.

Apart from the availability of a suitable supplement or medicament, (hereafter referred to as the "active"), one of the major factors limiting their use is the ability to maintain a regular supply to the animal. While in the feed-lot situation one can often mix "actives" with the ration, the free-range grazing animal presents particular difficulties determined by the infrequent periods of yarding, or by the relatively large areas grazed. In some cases for example, stock may only be yarded once or twice per year; this provides an upper limit to the number of times an animal may be individually treated. The provision of an "active" via a reticulated water supply is only reliable if that is the sole source of drinking water; but seasonal conditions often provide watercourse drinking for at least some of the year. Similarly, “self-medication” depots of “active” such as might be found in roller drums or salt-licks may not always be readily encountered by stock moving in a very large paddock.

EARLY DEVELOPMENTS

It was because of factors such as these that slow release forms of supplementation were originally developed, with one of the first and most successful being the cobalt bullet (Dewey et al. 1958) to overcome "coast disease” or “enzootic marasmus", more simply known as cobalt deficiency.

The concept of the heavy density bullet for ruminants has been extended to other trace elements, and to a limited range of other "actives", but it suffers from there generally being little control of the rate of release of “active” from the bolus, and an uncertainty about the reliability of retention.

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With this in mind, a number of groups throughout the world are turning increasingly to developing Controlled Release (CR) systems for administering "actives" to animals. One of the pioneers in this field was Dr Ralph Laby, of the CSIRO Division of Animal Production - beginning with the challenge of bloat control (Laby 1970), he has developed a number or CR systems which are applicable to a wide variety of "actives", and which are now finding their place on the world agricultural and veterinary chemical markets.

THE CONCEPT AND TERMINOLOGY OF CONTROLLED RELEASE TECHNOLOGY

Four important characteristics of any CR system are the description of the timing of the dose, the control of the required dose level, the site to which the dose is delivered, and the payload of the device.

(i) Timing The timing may be either pulsating (e.g., to mimic periodic dosing by conventional means), continuous (constant), or continuous but changing predictably over time.

(ii) Dose level The required dose level is determined in part by the condition being treated and by the efficacy of the "active", but it must be a feature of the CR system which maintains that required level, or changes it at the predetermined rate.

(iii) Site of release Clearly the effectiveness of any dose relies on the "active" reaching its targeted site relatively quickly and without being altered or destroyed by other metabolic processes - an "active" which is subject to degradation by rumen microbes but which is to be carried rapidly through the bloodstream may be best administered directly into the blood rather than orally, while a nutrient for which those same microbes have a specific requirement, may be wasted if not dosed directly into the rumen.

(iv) Payload This refers to the total amount of "active" required to serve the full lifetime of the device. In the simplest case of continuous and constant release this is equal to the daily requirement multiplied by the number of days duration.

DESCRIPTION OF A CR SYSTEM

Having decided on the dose-related factors referred to above, one needs then to consider the form the system or device may take. There are three major areas to be described.

(i) Retention By definition, any CR device must be capable of retaining the large depot of "active", the payload, either on or within the target animal for an extended period of time. The cobalt bullet is an example of the use of gravity to retain a high density object in the rumen, while a dog flea collar is a simple external retention device. Other examples include subcutaneous implants, intravaginal devices, eartags and ocular implants.

A unique feature of Dr Laby's work has been the invention of variable geometry (Laby 1970) systems for ruminants - in its simplest form, such a device is administered to the animal of a shape and size which is readily swallowed, but then the device changes to a shape which cannot be regurgitated. Examples of this include folded half-cylinders, rolled up sheets, compressible doughnuts, and a variety of "winged" devices.

(ii) The release process A variety of physical, chemical, mechanical or biological processes may be employed to achieve the desired release rate and profile. In some cases this may be by simple abrasion or dissolution, but other devices rely on factors such as electrochemical activity, diffusion, or gel formation. In the case of a multiple "active" or complex pulsating system, there may be several release processes working in concert.

(iii) Biological action of the "active" While the general biological action of any "active" may usually be predicted from previous experience, it is often the case that the pharmaco-kinetic properties differ when administered continuously. It is therefore important that the biological activity be carefully evaluated to ensure that optimum dose levels are used, that the most appropriate release profile is chosen, and that there are no unexpected toxicities or side effects.

THE CSIRO "STABLE" OR CR PRODUCTS

Because the bias of this Division's research is towards the sheep and cattle industries, and also because of the original interest in bloat control, Dr Laby's work has concentrated largely on devices suitable for these two species of animal. However, it is important to note that both the retention mechanisms, and the release processes to be described below are generally applicable to other domesticated ruminants such as goats and deer, and with only minor modifications are probably suited to other foregut fermenting herbivores (Hume 1984).

Iodine

Gross iodine deficiency, whether absolute or "conditioned" by the presence of goitrogens, is readily recognized by the occurrence of goitre in livestock. Lesser deficiencies can also be important, since the thyroid hormone system plays an active part in many physiological processes (Underwood 1977), and responses to iodine supplementation might be expected in neonatal survival, wool growth, milk production, fertility and general growth rates. As with many nutritional deficiencies, the iodine "status' of the animal may fluctuate with season or climate (Ellis 1980), and care needs to be exercised not to overdose in times of adequacy.

Since the minimum daily requirement of elemental iodine for a sheep is only of the order of 100 micrograms, a one gram payload is more than sufficient for a lifetime supply. Laby has made ingenious use of one of the fundamental properties of elemental iodine, its tendency to sublime, in his invention (Laby 1974). Coupled with the diffusive properties of gases through a plastic membrane, a release system has been achieved which delivers approximately 500-1000 µg/day, and which is retained in the rumen by a set of flexible wings or fingers (Ellis et al. 1983). Toxicity is of no worry with this system, since the normal homeostatic mechanisms of the sheep are quite capable of ensuring urinary excretion of these amounts if the daily intake from the feed is already adequate.

This device has been tested in a number of environments, showing a reduction in the incidence of enlarged thyroid glands in known risk areas (Mason and Laby 1978), and an increased lamb survival rate where goitrogen intake reduces the thyroid status of the foetal lamb (Ellis and Coverdale 1982). Commercial prototypes have been manufactured, registration documentation has been prepared for this product, and it is hoped that it may be released onto the market within the next year or two.

Magnesium

Magnesium deficiency results in grass tetany, a usually fatal disease in cattle. If frequently strikes the biggest milk producers in a herd, and the suddenness of onset generally precludes any treatment. A continuous supply of supplementary magnesium is required during the risk period of some three to four months if the disease is to be avoided. The Sire Sine Magnesium Capsule (Laby 1973) is the modern way of providing this supplement. Marketed by Cheetham Rural Division under licence from CSIRO, this capsule consists of two half cylinders of a magnesium alloy, joined by a rubber hinge. It is dosed in the folded cylindrical form, but opens to a wide flat object in the rumen (variable geometry). The release of magnesium ions is by an electrochemical process, and is controlled by the prior formulation of the alloy and the properties of the hinging rubber. About 2 g of magnesium is released each day over a three-month period, and is quickly absorbed into the bloodstream, providing a significant reduction in tetany incidence in treated animals. Sales of this product have increased steadily since its introduction about three years ago, and are expected to be about 40,000 units in the coming season. Overseas markets are being pursued, and it is anticipated that the product may be released into New Zealand later this year. CSIRO looks forward to its continuing success.

The LABY General Purpose CRD

As its name implies, this device has, and will continue to find application to a wide range of "actives". It consists of a plastic cylinder with folding wings at one end. A spring-loaded plunger slowly drives a core of "active" out of an orifice at one end of the cylinder (Laby 1978, 1987). By matching the properties and formulation of the "active" and subsidiary "carrier " materials to the spring strength and orifice size, virtually any desired release profile can be achieved, the only major limitation being the volume of the required payload.

Applications

(i) Bloat The Rumensin ABC (Anti-Bloat Capsule) from Elanco Products Company was first test-marketed in NSW during the spring and summer of 1987/88. The "active" is the rumen modifying growth promotant, monensin, and large field trials involving several thousand head of treated and untreated cattle have confirmed a weight gain advantage of some 5-10%, together with a reduction in bloat deaths of about 80% and a concomitant reduction in both the incidence and severity of non-fatal bloat.

Although the price is high, the added weight gain makes the bloat control particularly cost effective. This preventative product now provides the opportunity to use pastures when at their most productive phase of growth, by reducing the "fear" of bloat which has often left paddocks under-utilized in the past. Furthermore, the disruptions to the grazing pattern caused by bloat discomfort are reduced, resulting in a greater feed intake and subsequent added weight gains. Last year, in its first real test, 100,000 units were sold to beef cattle producers in Eastern Australia. Application to the dairying industry and overseas markets is now being actively investigated.

(ii) Anthelmintics Captec Pty Ltd has followed the initiative set by Anderson and Laby (1979) in applying the continuous administration of an "active" to control internal parasites. A product containing

Albendazole (ABZ) has been developed and will be marketed in Europe shortly, and probably released in Australia within the next 6-12 months. The implications of this new form of worm control have been explored extensively, and it is clear that there can be a significant advance in the control of benzimidazole-resistant worms, and that the device will become a powerful tool for modifying parasite epidemiology (Ralph 1988).

(iii) Chromic oxide This material has long been used as a faecal and digesta marker substance (Corbett 1978). It is inert in the digestive tract, and 100% of a given dose should be recoverable in the faeces. Captec Chrome (Ellis and Rodden 1987) is now available for both sheep and cattle, delivering about 200 mg and 1500 mg per day respectively for three to four weeks. Because of the way it is used as a research tool, and unlike many other applications where some fluctuations in rate could in all probability be tolerated, a requirement of this product is for precise dose control throughout its lifetime. It is testimony to the robust character and precision of Laby's system, however, that the same techniques and similar type of formulation are used to manufacture both the ABZ and Chrome devices.

The release rate is constant throughout the lifetime, and the combined between device and between animal coefficient of variation is only of the order of five per cent. Thus for group assessment of faecal output, Captec Chrome provides opportunities for studies which were previously considered to be far too labour intensive or too disruptive on the animal's behaviour to provide meaningful results. Examples of its uses can be found in productivity comparisons of different breeds of cattle using several hundred cattle (Barlow et al. 1988), and the evaluation of differences in feed intake between sheep and fallow deer (Kelly et al. 1987) when grazing together.

(iv) Trace elements Trace elements (TEs), as the name implies, are generally required in low amounts, so that payload constraints are few in developing a device for any particular application. Indeed, applications of experimental formulations have included single element studies (e.g., cobalt (Duncan et al. 1986)) through to eight-element mixtures being used to study multi-element effects in the nutrition of sheep (Panggabean et al. 1984). These devices are currently being used as diagnostic tools in collaborative studies in China.

(v) Other applications The list of potential applications is endless. From within this laboratory, we have provided devices to study a range of other anthelmintics and growth promoting agents, a variety of TEs (Peter and Ellis 1981) and vitamin formulations, fluoride containing devices for studies of fluoride balance and toxicity (Wheeler et al. 1988), drugs to increase the rate of depletion of dieldrin residues from contaminated livestock, thiomolybdate to alleviate copper toxicity, and "act ives" to alter the composition and flavour of meat.

CONCLUSIONS

The Laby devices are clearly valuable tools for animal scientists to exploit in a-range of pursuits. Furthermore, the infrastructure now exists for a company such as Captec to "fast-track" any product which is shown to have potential for wide-scale use on farm, since much of the initial testing, proving, and registration of the device has already been achieved. Providing that Government authorities can be convinced as to the reliability and value

of the devices, one can hope that it may eventually be possible to submit for approval a package of known pharmacology of an "active", together with the details of the appropriate and already approved delivery system.

ACKNOWLEDGEMENTS

We wish to thank Dr Laby and his group for their contributions to our work, and to Ms K Zirkler, Mr S Philp, and Mr P Kliendeinst for valued technical assistance. The collaboration of staff of the companies involved in these developments, and of other research organizations is gratefully acknowledged.

REFERENCES

ANDERSON, N. and LABY, R.H. (1979). Aust. Vet. J. **55:** 244.

BARLOW, R., ELLIS, K.J., WILLIAMSON, P.J., COSTIGAN, P., STEPHENSON, P.D., ROSE, G. and MEARS, P.T. (1988). J. Agric. Sci., Camb. **110:** 217.

CORBETT, J.L. (1978). In "Measurement of Grassland Vegetation and Animal Production", p. 163, editor L. 't Mannetje. (CAB: Farnham Royal, UK.)

DEWEY, D.W., LEE, H.J. and MARSTON, H.R. (1958). Nature (Lond.) 181: 1367.

DUNCAN, I.F., GREENTREE, P.L. and ELLIS, K.J. (1986). Aust. Vet J. 63: 127.

ELLIS, K.J. (1980). Proc. Aust. Soc. Anim. Prod. **13:** 209.

ELLIS, K.J. and COVERDALE, O.R. (1982). Proc. Aust. Soc. Anim. prod. **14:** 660.

ELLIS, K.J., GEORGE, J.M. and LABY, R.H. (1983). Aust. J. Exp. Agric. Anim. Husb. **23:** 369.

ELLIS, K.J. and RODDEN, B. (1987). 4th AAAP Animal Science Congress, Hamilton, NZ, Paper IX-14, Program p. 54.

HUME, I.D. (1984). In "Ruminant Physiology; Concepts and Consequences", p. 15 editors S.K. Baker, J.M. Gawthorne, J.B. Mackintosh and D.B. Purser. (University of Western Australia.)

KELLY, T.J., THOMPSON, J.M., ELLIS, K.J. and ROWE, M.D. (1985). "Proceedings of ANZAAS Deer Farming Seminar", Publication No. 159, p. 34, editor R.P. Couchman. (Victorian Dept of Agriculture and Rural Affairs.)

LABY, R.H. (1970). Australian Patent No. 449,029.

LABY, R.H. (1973). Australian Patent Application No. 55556/73.

LABY, R.H. (1974). Australian Patent Application No. 59779/74.

LABY, R.H. (1978). Australian Patent Application No. 35908/78.

LABY, R.H. (1987). Australian Patent No. 520409.

MASON, R.W. and LABY, R.H. (1978). Aust. J. Exp. Agric. Anim. Husb. 18: 653.

PANGGABEAN, T., MOIR, R.J., PURSER, D.B. and LABY, R.H. (1984). In "Ruminant Physiology; Concept; and Consequences", p. 347, editors, S.K. Baker, J.M. Gawthorne, J.B. Mackintosh and D.B. Purser. (University of Western Australia.)

PETER, D.W. and ELLIS, K.J. (1981). Proc. Nutr. Soc. Aust. **6:** 146.

RALPH, W. (1988/89). Rural Research **141:** 4.

UNDERWOOD, E.J. (1977). "Trace Elements in Human and Animal Nutrition", 4th ed. (Academic Press: New York.)

WHEELER, S.M., TURNER, A.D. and ELLIS, K.J. (1988). J. Trace Elem. Electrolytes Health Dis. 2: 185.