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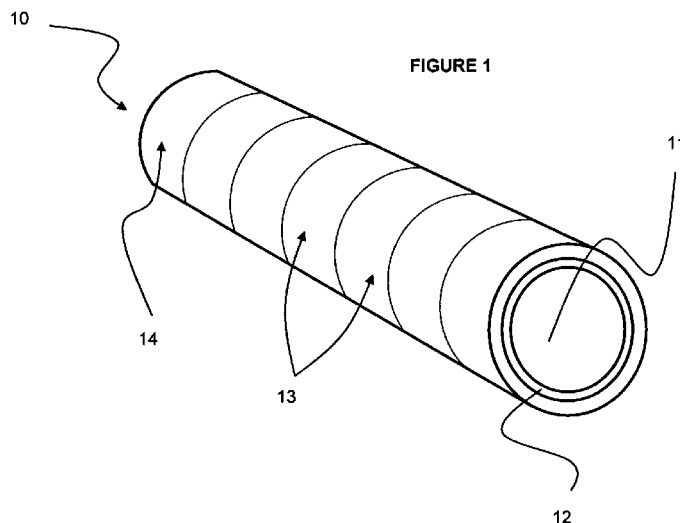
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(54) Title: IMPROVED BOLUS



(57) Abstract: The present invention relates to a bolus for administration to a ruminant by deposition into its rumen, wherein the bolus has a construction including: a) a casing; b) a core inside the casing wherein the core is formed from at least two tablets; and, is characterised in that a permanently amorphous substance at least partially coats one or more of the tablet or tablets. A method of forming such a bolus is also claimed.

IMPROVED BOLUS

TECHNICAL FIELD

The present invention relates to an improved bolus.

More specifically, the invention relates to an improved bolus and method of manufacture using coatings to prevent variation in bolus erosion rates.

BACKGROUND ART

A wide variety of boli have been used for treatment of livestock such as cows and sheep over many years. The basic premise of the bolus is that an active agent is delivered to the animal over an extended period of time.

An advantage of this method of delivery is that the farmer or livestock manager need only administer the bolus once for delivery over an extended period of time rather than having to administer a medication on a more frequent e.g. daily basis. Existing boli may have a useful time period of over one month and therefore this may reduce labour and material costs.

However, there are problems with existing boli. By way of example, the bolus described in US 4,649,042 (equivalent to NZ212181) comprises a biodegradable polymeric core impregnated with medicament that is encased in a stainless steel tube with end caps and an arrangement of holes to allow the passage of rumen fluid to the biodegradable core.

A layer of settable and/or elastic sealant holds the core in place and prevents seepage of rumen fluid between the walls of the bolus (the tube) and the core which would result in unpredictable delivery of medicament.

The required physical properties of the sealant are described as 'the ability to form a moisture-tight adhesive bond to the polymeric core and to the tube, and a high degree of water impermeability to prevent permeation of water through the layer of sealant to the sides of the core.

It is also necessary that the sealant be sufficiently cohesive and elastic to absorb relative movement of the core and tube during thermal expansion and contraction over the temperature range encountered in storage and use, from about -20°C to about 50°C.

However, the degree of elasticity offered by settable sealants can be limited. Cracks or other flaws may develop over time, permitting the ingress of undesired rumen fluid into the core of the bolus.

Another problem with settable sealants is that they do not necessarily break down at the same rate as the tablet core. It can be that the settable coatings protects portions of the tablet core better than other portions, leading to inconsistent rates of erosion of the tablet, depending on how the tablet core is physically eroded.

A further issue is that the settable sealant can break away in large sections from the bolus, thus becoming a non-contiguous coating along portions of the tablet core. This exposes a much greater portion of the tablet core to the rumen fluid than is ideal, and again, can lead to inconsistent rates of erosion of the tablet.

As may be appreciated by those skilled in the art, the spent metal shell of the bolus remains in the rumen after all the biologically active material has been released or paid out. This can cause a problem during slaughter of the animal particularly since the bolus is made of metal which can be hazardous or damage cutting equipment used in slaughter and processing.

Another type of bolus described in NZ220024 (equivalent to US 4,863,455) attempts to resolve the problem of residues left in the animal.

NZ220024 describes a bolus for administration to a ruminant. It comprises a magnesium-alloy tube filed with a core of a mixture of biologically active material and electronically conductive material lower in the electrochemical series than magnesium. The corrosion is galvanic in nature with a potential difference existing between the tube and core.

The tube may be provided with a resin or plastic sheath on its exterior surface to protect the walls of the tube from corrosion by rumen juices. A tube ending is left unprotected to allow gradual corrosion down the length of the tube ideally at the unprotected face. The core may be a single tablet or a series of tablets which are formed in a pelleting die and introduced into the tube or alternatively the ingredients can be forced into the tube using a hydraulic or mechanical press to form a single tablet. The tablet or tablets are said to form a "close fit" with the tube. The use of a series of tablets allows for sequential dosing of different active ingredients or pulse dosing of the same ingredient by having alternate tablets with and without an active ingredient.

As may be appreciated, the above type of bolus has the advantage that all or a substantial amount of the bolus dissolves in the rumen with any remaining parts being excreted.

One problem with this bolus (and many other boli) is that the bolus described can lose integrity by breakdown of the core elsewhere than at the outward face resulting in premature release of tablets or inconsistent pay out of tablets while in situ in the rumen.

In addition, even without significant breakdown described above, the rate of erosion can vary considerably even in "normal" operation.

As may be appreciated by those skilled in the art, it may be important that the rate of erosion from a bolus be maintained at an approximately constant rate. If the animal receives a dose greater than that desired, for example by a fast erosion rate or breakdown, release of the active agent may also be at a faster level and therefore may be harmful to the animals.

At the very least, a fast erosion rate may give a false sense of security to the farmer in that the animal may have a shorter duration of agent delivery than that expected. A fast release rate may also be toxic to the animal. At the other extreme, if the erosion rate is too slow, the animal may receive insufficient active agent for the application required. For some agents such as anthelmintics, low dosage can result in the development of drug resistance.

One issue in arriving at smooth erosion rate is that of egress of rumen fluids into the bolus causing erosion at more than just the interface of the bolus with the fluid. For example, one potential mode of egress is by capillary action with rumen fluid travelling down the inside of the alloy casing and thereby eroding the outside surface of a tablet or tablets contained in the core.

The effect of this is that the animal may receive considerably higher doses than that intended or may even receive unplanned pulsed doses rather than a regular smooth dose. In the pulse dose example, capillary action may dissolve a tablet that is not at the designed interface causing both the interface tablet and tablet behind the initial interface to dissolve simultaneously and be released into the animal's bloodstream concurrently, thereby increasing the dose momentarily before a potential 'no dose' time period after the tablets erode and a new tablet begins delivery.

In the case of anthelmintics, this variation can have significant negative effects. For example, an increased dose could be harmful to the animal. Also the 'no dose' time period allows parasites to grow and multiply resulting in loss of livestock condition.

It should be appreciated from the above discussion that there are at least two problems with existing boli. The first relates to disposability of the bolus from the animal rumen and the second of controlling erosion rate and avoiding egress of rumen fluids into the bolus too early thereby influencing agent dosing and bolus duration of action.

It is an object of the present invention to address the foregoing problems or at least to provide the public with a useful choice.

All references, including any patents or patent applications cited in this specification are hereby incorporated by reference. No admission is made that any reference constitutes prior art. The discussion of the references states what their authors assert, and the applicants reserve the right to challenge the accuracy and pertinency of the cited documents. It will be clearly understood that, although a number of prior art publications are referred to herein, this reference does not constitute an admission that any of these documents form part of the common general knowledge in the art, in New Zealand or in any other country.

It is acknowledged that the term 'comprise' may, under varying jurisdictions, be attributed with either an exclusive or an inclusive meaning. For the purpose of this specification, and unless otherwise noted, the term 'comprise' shall have an inclusive meaning - i.e. that it will be taken to mean an inclusion of not only the listed components it directly references, but also other non-specified components or elements. This rationale will also be used when the term 'comprised' or 'comprising' is used in relation to one or more steps in a method or process.

Further aspects and advantages of the present invention will become apparent from the ensuing description which is given by way of example only.

DISCLOSURE OF THE INVENTION

According to one aspect of the present invention there is provided a bolus for administration to a ruminant by deposition into its rumen, the bolus having a construction including:

- a) a casing;
 - b) a core inside the casing wherein the core is formed from at least two tablets;
- and,

characterised in that a permanently amorphous substance at least partially coats one or more of the tablet or tablets.

For the purposes of this specification, the term 'permanently amorphous' refers to the coating layer being a non-settable substance that slows the rate of erosion of the core by rumen fluids.

The term 'erosion' refers to the breakdown into particulate form that occurs when the bolus casing and tablet(s) are exposed to rumen fluids or other aqueous solutions.

The invention broadly relates to a bolus for use in ruminants which delivers an active agent or agents to the animal.

Preferably, the bolus includes a casing which contains a core of one or more tablets that may include biologically active agents.

In preferred embodiments, the casing is made of an alloy of some type, but this should not be seen as limiting. Other casing materials may be used, for example

biodegradable plastic or cellulose.

In one preferred embodiment, the casing defines a tube shape with an approximately circular cross-section. It should be appreciated that other shapes may also be used such as ellipses or cuboid shapes but a tube is preferable for easy tooling and manufacture since most tabulating machines produce tablets in a circular shape.

In a preferred embodiment, the casing may be coated with a water impermeable material such as plastic or rubber on its outer surface to prevent the casing from being corroded on selected surfaces by rumen fluid.

In one embodiment, each distal end of the bolus tube may be left uncovered. Rumen fluids then erode the uncovered ends of the bolus eroding back the facing tablet and casing cross-section. In an alternative embodiment, one end of the bolus is also covered in water impermeable plastic so that erosion occurs only at the opposing distal end of the bolus.

In one embodiment, the water impermeable coating is a series of plastic rings on the outer surface that are intermeshed together to form a liquid impermeable surface. In one preferred embodiment, the rings are intermeshed using a tongue and groove joint between rings. As the casing and core tablets erode, the rings become loose and eventually fall away from the bolus and are excreted from the rumen.

This bolus has the advantage of the bolus structure either eroding away as particles or as small rings which are excreted by the animal with few if any residues. Any metal used such as an alloy casing are dissolved and therefore remove any slaughter and processing issues. As noted in the background section above, a disadvantage of many existing devices, particularly those including metals, is that they remain present in the rumen and, when the animal is sent to slaughter, can damage freezing works machinery.

The core includes one or more tablets which is eroded by rumen fluid to release active agents which may be beneficial to the animal being treated.

In one preferred embodiment, the active agents may include anthelmintic compounds such as abamectin and ivermectin and the bolus administered to control to parasite infestation. When introduced to the rumen, the bolus slowly erodes due to mixing with rumen fluids, releasing active agent from the tablet or tablets.

However, persons skilled in the art will appreciate that a wide variety of agents may be used in the present invention, according to the requirements of the user. For example, the active agents may be nutritional supplements such as vitamins or the like.

In one preferred embodiment, the core material may contain electronically conductive material lower in the electrochemical series than the alloy used for the bolus casing. As should be appreciated in this embodiment, the corrosion is galvanic in nature with a potential difference existing between the alloy casing and core. The permanently amorphous coating alters the corrosion pattern.

Preferably, each tablet included in the core contains at least one active agent mixed with electronically conductive material lower in the electrochemical series.

Preferably, the electronically conductive material lower in the electrochemical series is graphite.

In this embodiment of the invention, the alloy is magnesium based with magnesium comprising approximately 70 to 98% of the alloy. Such alloys are known in the art and erode in the presence of rumen fluids, particularly where the core includes electronically conductive material lower in the electrochemical series, yet maintain their structural integrity when stored in the absence of aqueous solutions.

In the above embodiment, the aim is to control or further manipulate the rate of galvanic corrosion using at least one permanently amorphous substance.

In a further embodiment of the present invention, each active containing tablet may be interspaced with a blank or non-active containing tablet. In this embodiment, blank tablets are preferably formed from graphite and active containing tablets in this embodiment may be formed from a starch base. In a further variation to this embodiment, active agent may be carried in the graphite and the remaining tablets may be starch based blanks.

It should be appreciated that in the embodiments described above, the way the core is loaded and placement of blanks (if used) will result in active agent(s) being released on a continuous basis or on a pulse basis as may be required depending on the application.

In preferred embodiments, the permanently amorphous substance is an oily or oil based substance. However, this should not be seen as limiting. A number of substances have properties which lend themselves to being permanently amorphous. For example, the permanently amorphous substance may be a silicone based grease.

Preferably, the permanently amorphous substance has a similar viscosity to Vaseline™ or is a petroleum jelly like Vaseline™, although other permanently amorphous substances with lower viscosities may also be used without departing from the scope of the invention. Examples of such substances include oils such as linseed oil and mineral oils such as liquid paraffin.

It is understood by the inventors that the extra viscosity provided by substances such as Vaseline is important where a slower rate of erosion is desired. The higher viscosity of these substances makes it harder for rumen fluids to erode the tablet(s) and therefore achieve longer delivery time periods.

It should be appreciated that where a faster rate of erosion is desired (and a steady rate) other permanently amorphous substances may be preferable. Irrespective of rate though, coatings have been found to reduce erosion rate variation.

As may be appreciated from the above description, the permanently amorphous substance may be applied in various ways to the core of the bolus.

It should be appreciated that the location of where the tablet(s) have the substance applied will influence the rate and/or smoothness of release. For example, in applications where there is some tolerance for variation in the speed of release, only the tablet face(s) need have the substance coated.

In other applications where a tighter erosion control may be desired, the whole of each tablet may be coated. In a yet further embodiment, the tablet(s) may only be coated on the outer ring area and the face(s) remain uncovered. It should therefore be appreciated that by varying the location of the coating, the erosion rate may be controlled.

Another advantage of using a permanently amorphous coating such as Vaseline™, is the ability of the coating to remain in place despite any flexing or movement that may occur in the bolus, both in storage and use. For example, it is known that the bolus may contract or expand depending on the temperature. In boluses which have a settable coating, such as that discussed in the prior art, the settable coating can crack or otherwise fail, permitting undesired ingress of rumen fluid to the core.

A further advantage is the amorphous nature of the coating of the present invention allows it to better fill in any gaps, cracks or other flaws that may be present or develop in the bolus casing or tablet core. Settable coatings are relatively inflexible once set, so any flaws in the bolus casing or tablet core which may develop after the coating has set may not be adequately protected.

According to a further aspect of the present invention there is provided a method of forming a bolus including a casing and a core containing tablets for delivery of an active agent or agents to the rumen of an animal wherein the method includes the steps of:

- (a) producing a tablet or tablets containing active agent or agents;
- (b) at least partially coating one or more of the tablets from step (a) with at least one permanently amorphous substance;
- (c) packing at least two tablets into a casing to form a bolus wherein at least one of the tablets packed into the casing is produced from step (b).

Preferably, the tablet or tablets used in the core are formed in a pelleting die sized such that the tablet or tablets form a snug fit within the casing.

In one embodiment, the casing is packed with both active agent tablets and blank or non-active agent tablets.

Preferably, where blank tablets are used, these are also at least partially coated in a permanently amorphous substance.

In one embodiment, the casing is coated with a water impermeable material after step (c) with either one or both ends of the bolus not covered in water impermeable material. In an alternative embodiment, the casing is coated with a water permeable material before step (c) with either one or both ends of the bolus left open and uncovered.

It should be appreciated from the above description that there is provided a bolus and method of manufacture that attempts to solve the problem of variation in rates of erosion of a bolus.

The method utilises permanently amorphous substances such as oils to in effect slow the egress of rumen fluids and therefore smooth out the rate of erosion compared to that which would be observed if no permanently amorphous substances were used.

The use of oils as the permanently amorphous substance reduce the capillary action that may take place in the alloy casing, which contributes to a consistent erosion rate.

The use of permanently amorphous substances such as VaselineTM offers a number of advantages over the prior art:

- The use of permanently amorphous substances as a coating for the tablet core of a bolus provides a consistent and smooth erosion rate for the tablets.
- Permanently amorphous substances may also provide superior protection for bolus tablets when the bolus is subject to fluctuations in the shape of the bolus due to temperature changes.
- Permanently amorphous substances may provide better coverage of the bolus tablet core than settable coatings, filling in any flaws that may develop in the tablet core over time.
- Permanently amorphous substances are more contiguous with the tablet core, providing superior and consistent protection of the core in the long term.

BRIEF DESCRIPTION OF THE DRAWINGS

Further aspects of the present invention will become apparent from the following description which is given by way of example only and with reference to the accompanying drawings in which:

Figure 1: illustrates a perspective view of a bolus used in trials;

Figure 2: shows a graph of Bolus 1 - MT30 – Vaseline™ erosion as measured by the mean length of alloy (mm) measured by week;

Figure 3: shows a graph of Bolus 1 - MT30 – Vaseline™ erosion rate as measured by mean alloy erosion rate (mm) by week;

Figure 4: shows a graph of Bolus 2 - MT31 - Linseed Oil erosion as measured by the mean length of alloy (mm) measured by week;

Figure 5: shows a graph of Bolus 2 - MT31 – Linseed Oil erosion rate as measured by mean alloy erosion rate (mm) by week;

Figure 6: shows a graph of Bolus 3 - MT32 – Liquid Paraffin erosion as measured by the mean length of alloy (mm) measured by week;

Figure 7: shows a graph of Bolus 3 - MT32 – Liquid Paraffin erosion rate as measured by mean alloy erosion rate (mm) by week;

Figure 8: shows a graph of Bolus 4 - MT33 – Control erosion as measured by the mean length of alloy (mm) measured by week;

Figure 9: shows a graph of Bolus 4 - MT33 – Control erosion rate as measured by mean alloy erosion rate (mm) by week;

Figure 10: shows a graph comparing the mean weekly alloy erosion (mm) for each bolus used over time. This was calculated by comparing the actual alloy length at the time of reading to the initial length at the start of the trial.

BEST MODES FOR CARRYING OUT THE INVENTION

The invention is now described with reference to two experiments completed by the inventors to determine the benefits of using a coating in vitro and to determine in vivo the rate of erosion of the bolus of the present invention in the rumen of an animal.

EXAMPLE 1

Premature failure of the bolus and tablets was noted from a bolus similar to that described in NZ220024. Other manufacturing steps such as increasing the amount of compaction (making the tablets harder) were tested and the same problems occurred.

In this trial simple immersion tests were completed using various coatings on tablets to determine what if any improvements could be made in slowing the rate of egress of aqueous liquid into tablets.

Method

A control tablet was produced by weighing on a chemical balance a tablet, then immersing the tablet on edge into the bottom of a 250ml beaker full of water for 12 hours overnight at room temperature. The tablet was then rinsed gently in warm tap water and the surface padded dry with a paper towel. The tablet was subsequently re-weighed and the 12 hour water absorption determined by subtracting the original weight from the weight post immersion.

Various substances were then coated onto further tablets to determine what effect if any these would have on preventing water absorption.

The coatings tested were silicon spray, vacuum impregnation with resins, vacuum impregnation with light mineral oils (liquid paraffin), application of light mineral oil to the tablet surface by immersion and then drip dry, application of boiled linseed oil by

immersion and drip dry and finally application of Vaseline™ petroleum jelly onto the surface of the tablets tested.

The linseed oil used had a density of 0.942g/cm^2 at 15.5°C and a viscosity of approximately 1 Poise at 25°C .

The mineral oil used had a density of approximately 0.81 to 0.89g/cm^2 at 20°C and a viscosity of 100-140 Poise at 40°C .

The Vaseline™ used was standard Vaseline™ with a viscosity of approximately 640 Poise at 20°C .

Results

Vacuum impregnation did not work as the tablets were destroyed in the process.

Silicon spray was found to not be very effective at blocking absorption.

Immersion in mineral oil, boiled linseed oil and Vaseline™ petroleum jelly gave results that were about 1/2 to 2/3rds less absorption when compared with control (no coating) tablet.

Further in vivo tests were completed in Example 2 using tablets coated in liquid paraffin, linseed oil and Vaseline™ to further determine erosion characteristics.

EXAMPLE 2

In Vivo Trial Background

The trial involved use of boli in fistulated sheep to evaluate erosion dynamics as a predictor of potential use of the bolus as a successful method for delivery of agents such as anthelmintic compounds.

The boli 10 used in the trial (Figure 1) were made up of a series of cylindrical tablets 11 tightly encased within a magnesium alloy tube 12 which itself was encased in a plastic sheath 13 made up of multiple rings meshed together using a tongue and groove joint to seal the tube. One end of the tube 14 was also sealed by the plastic sheath whilst the opposing end was free of any plastic. The aim was to have erosion occur at the open face end (11,12) and, as the face of each tablet 11 and metal alloy 12 eroded, the plastic rings 13 would drop away.

As noted in the background of this specification, a problem with such boli is that rumen fluids can erode tablets inside the tube rather than purely eroding at the open face. Erosion of tablets and/or alloy deeper in the tube may result in uneven dispersion of active agent, breakdown in the structure of the bolus, lowered duration of time that the bolus remains in the rumen and so on.

In the trial completed, four types of bolus were used. Three of the boli contained a series of tablets with the face of each tablet being coated as a smear prior to assembly into a tube. The fourth bolus type used was negative control that did not have any coating applied to the tablets inside the tube. Coatings were applied to investigate whether or not the additional coating had an effect on erosion dynamics and leakage.

In summary, the boli used were as follows:

1. Bolus 1 - MT30 – Vaseline™ coated
2. Bolus 2 - MT31 – Linseed Oil coated
3. Bolus 3 - MT32 – Liquid Paraffin coated
4. Bolus 4 - MT33 – Plain (Control); no additional treatment coating.

For the purposes of the trial, the tablets used were "blank" starch tablets (same dimensions as envisaged for active containing tablets) interspersed with graphite spacer tablets.

The overall dimensions and weight were the same for all boli variations, with all resulting boli having a weight of roughly 182g, a volume of 67.7cc and a density of 2.69g/cc.

For a preferred embodiment of the invention, the ideal weekly erosion rate of the current alloy was considered to be 0.5mm/day. Measurements and subsequent analysis were based around this erosion rate although it should be appreciated by those skilled in the art that other rates could be used or designed for without departing from the overall concept of trying to regulate the rate of erosion and avoid uneven erosion rates.

Method

Boli from each treatment group were administered (one per animal) to rumen-fistulated sheep n=9 for all four variations of the boli, thus n=36 in total. The sheep were maintained on standard ryegrass/clover pasture with some additional hay (due to poorer winter grazing) for the duration of the trial. They were brought into a shed on a weekly basis to allow for measurements to be taken.

The bolus length (mm) from the base to the top of the exposed tablet and the magnesium alloy length (mm) were measured and recorded once weekly using digital vernier callipers.

The trial ran for a total of 20 weeks although measurements for Bolus 2 - MT31 - Linseed Oil and Bolus 3 - MT32 - Liquid Paraffin ceased part way.

Results

The results are now discussed with reference to Figures 2 to 10.

Mean Length of Alloy

As shown in Figures 2, 4, 6 and 8, initially, all the alloys within the boli were around 98mm in length. By week 20, the mean readings were 28.8mm and 33.8mm respectively for the Vaseline™ coated and Control boli (MT30 and MT33). The R^2 value for all four boli was always within a range of 0.05.

Bolus 2 and 3 (MT31 and MT32) eroded at a faster rate and were completely eroded by the end of the trial duration (20 weeks).

Alloy Erosion Rate

As shown in Figures 3, 5, 7, 9 and 10, the overall alloy erosion dynamics varied between the different boli from week to week and also from comparison with the initial reading. The greatest differences were seen in the comparisons on a weekly basis. The R^2 values for all boli had a range of up to 0.6. There are obvious differences in the erosion dynamics of the alloy depending on what the weekly readings were compared with (either by comparison on a week to week basis or by comparison of the initial reading to the actual reading).

The results indicate that the Vaseline™ coated boli were closest to having the desired erosion rate of 0.5mm/day for both the week to week comparison and the actual to the initial comparison (mean = 0.49mm and 0.52mm respectively).

In general all boli, to differing extents, appeared to follow a trend that prior to and when a tablet paid out the erosion rate increased.

The mean erosion rate for Vaseline™ compared on a week by week basis was 0.49mm/day, this compared to 0.43mm/day for the Control boli.

It was noted that during the time period that the Liquid Paraffin and Linseed Oil were eroding, they exhibited faster erosion rates compared to the other two with mean erosion rates (compared on a week by week basis) of 0.54mm/day and 0.57mm/day respectively but with a smoother rate of release than the Control bolus.

Conclusions

Coatings appear to help in smoothing the rate of erosion of tablets and alloy from the bolus. For the preferred embodiment of an erosion rate of 0.5mm/day, the best results were found when the bolus was coated with a more viscous and water immiscible substance such as Vaseline™ (Bolus 1 - MT30).

Despite other coatings eroding faster than 0.5mm/day, these coatings also gave more consistent erosion rates than the control which did not utilize a coating.

Results indicate that the different coatings had an effect on erosion dynamics of the boli and that the previous problem of leakage to the underlying tablets appears to have improved greatly with the use of water immiscible coatings.

As should be appreciated from the above trial example, coating tablets used in the bolus appears to solve the problem in the art of uneven erosion rates which, when active agents are used, could result in uneven dosing of agent(s).

A preferred form of coating was found to be Vaseline™ but it should be appreciated that other similar viscous and water immiscible substances may be used without departing from the scope of the invention. In addition, whilst an aim of the present invention was to achieve an erosion rate of 0.5mm/day, those skilled in the art should appreciate from the above results, that although faster erosion rates may result, other

water immiscible substances may be used such as the oils to smooth the rate of erosion.

Aspects of the present invention have been described by way of example only and it should be appreciated that modifications and additions may be made thereto without departing from the scope thereof as defined in the appended claims.

WHAT I/WE CLAIM IS:

1. A bolus for administration to a ruminant by deposition into its rumen, the bolus having a construction including:
 - a) a casing;
 - b) a core inside the casing wherein the core is formed from at least two tablets; and,characterised in that a permanently amorphous substance at least partially coats one or more of the tablet or tablets.
2. A bolus as claimed in claim 1 wherein the permanently amorphous substance is an oil based substance.
3. A bolus as claimed in either claim 1 or claim 2 wherein the permanently amorphous substance is petroleum jelly.
4. A bolus as claimed in either claim 1 or claim 2 wherein the permanently amorphous substance is liquid paraffin.
5. A bolus as claimed in any one of claims 1 to 4 wherein the casing is coated with a water impermeable material.
6. A bolus as claimed in claim 5 wherein the water impermeable material is plastics material.
7. A bolus as claimed in claim 6 wherein the plastics material is in the form of a series of intermeshed plastic rings.
8. A bolus as claimed in claim 7 wherein the rings are intermeshed using a

tongue and groove joint between rings.

9. A bolus as claimed in any one of claims 1 to 8 wherein the casing is a tubular shape with an approximately circular cross-section.
10. A bolus as claimed in any one of claims 1 to 9 wherein the casing is an alloy casing.
11. A bolus as claimed in claim 10 wherein the tablets of the core contain electrically conductive material lower in the electrochemical series than the constituents of the alloy casing.
12. A bolus as claimed in claim 11 wherein the electrically conductive material of the core is graphite.
13. A bolus as claimed in any one of claims 10 to 12 wherein the alloy casing is magnesium based.
14. A bolus as claimed in claim 13 wherein the magnesium forms approximately 70 to 98% of the alloy casing.
15. A method of forming a bolus including a casing and a core containing tablets for delivery of an active agent or agents to the rumen of an animal wherein the method includes the steps of:
 - (a) producing a tablet or tablets containing active agent or agents;
 - (b) at least partially coating one or more of the tablets from step (a) with at least permanently amorphous substance;
 - (c) packing at least two tablets into a casing to form a bolus wherein at least one of the tablets packed into the casing is produced from step

(b).

16. A method of forming a bolus as claimed in claim 15 wherein the method includes an additional step of:
 - (d) coating the casing with an water impermeable material with either one or both ends of the bolus not covered in water impermeable material.
17. A bolus as substantially described herein and with reference to the accompanying drawings.
18. A method of forming a bolus as substantially described herein and with reference to the accompanying drawings.

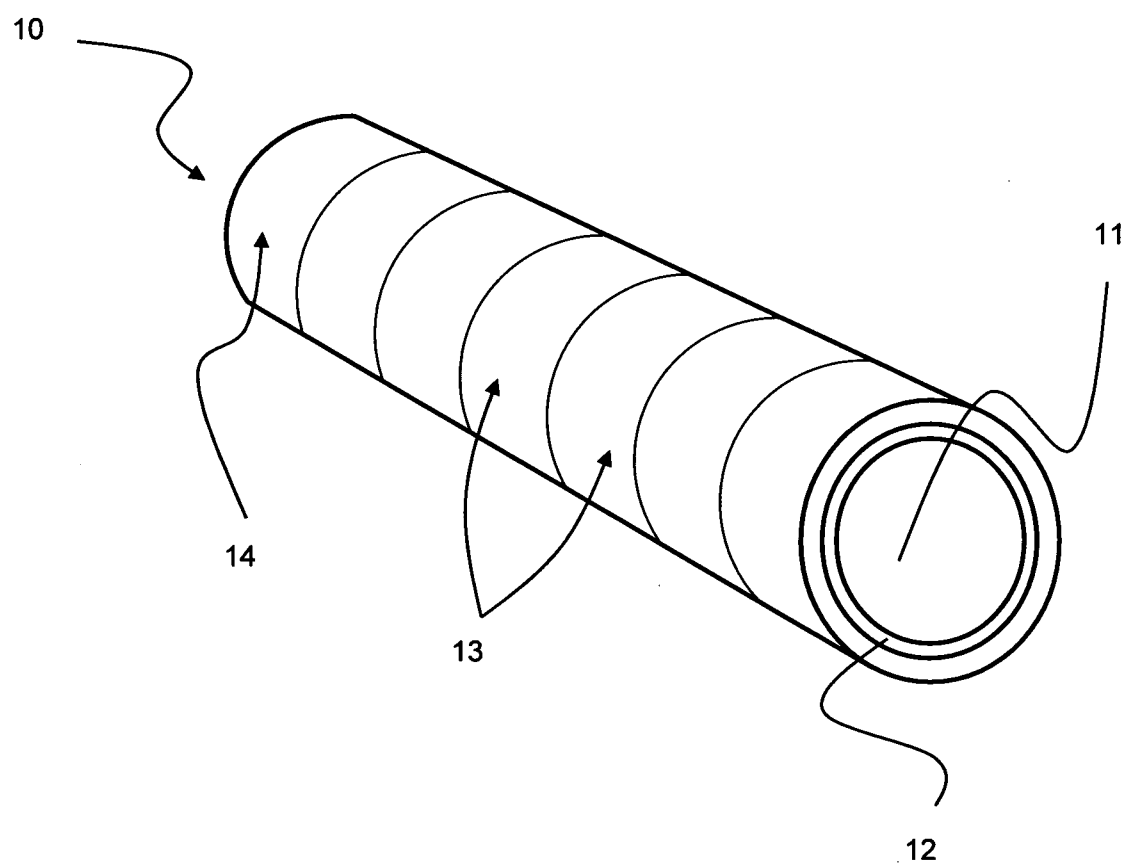


FIGURE 1

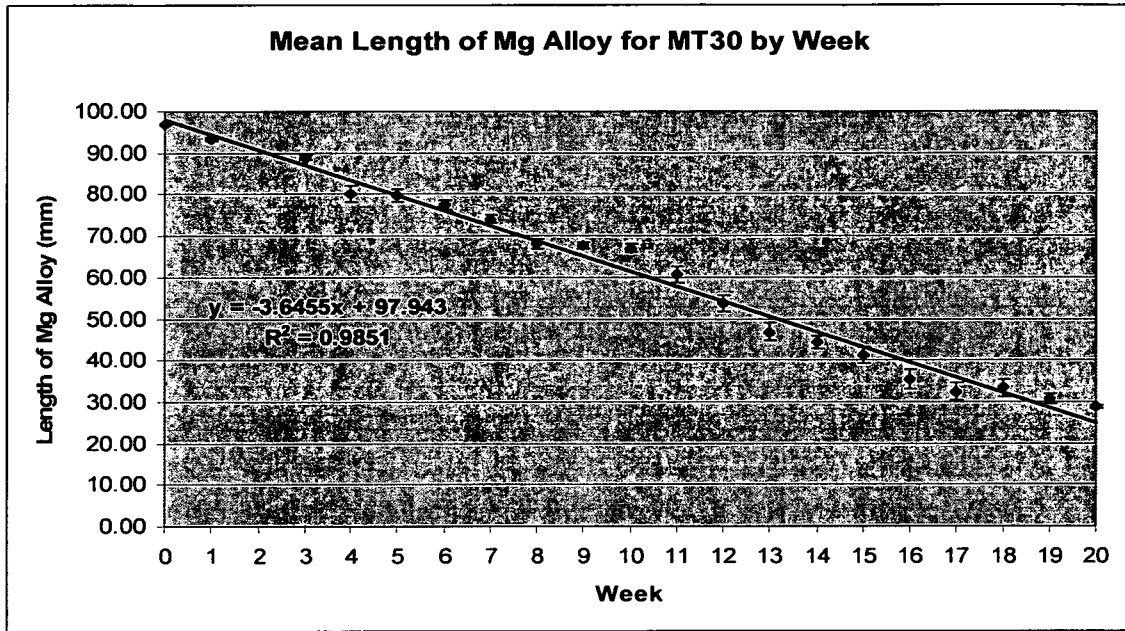


FIGURE 2

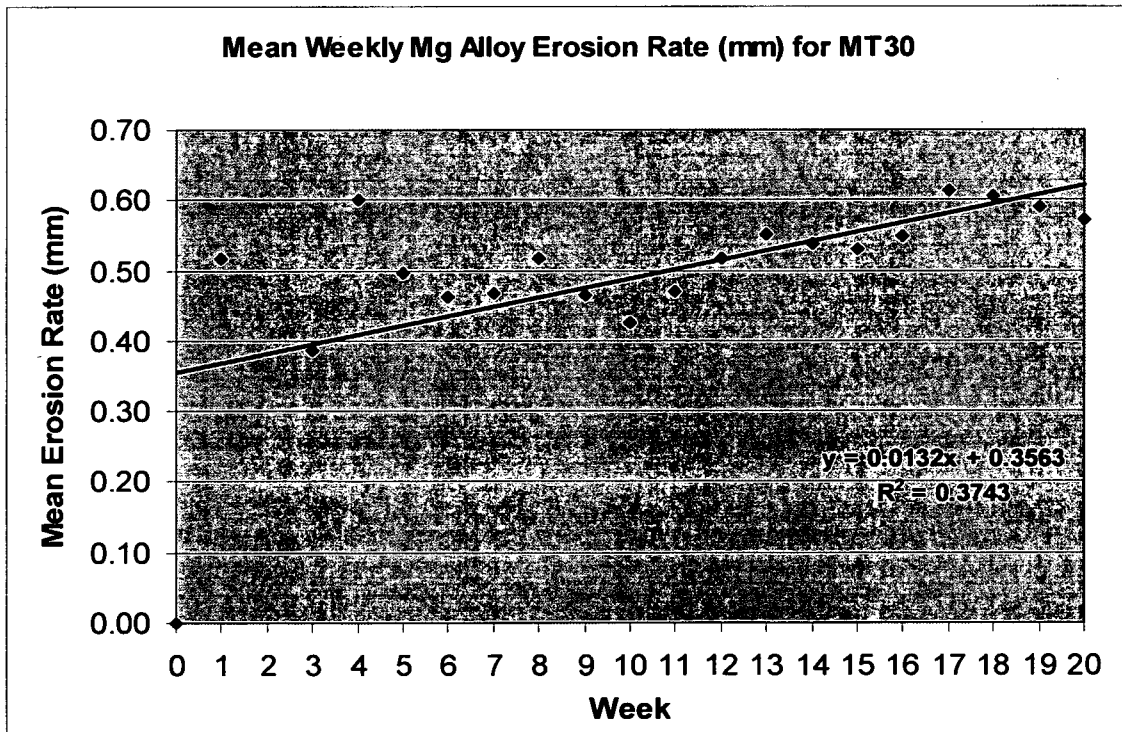


FIGURE 3

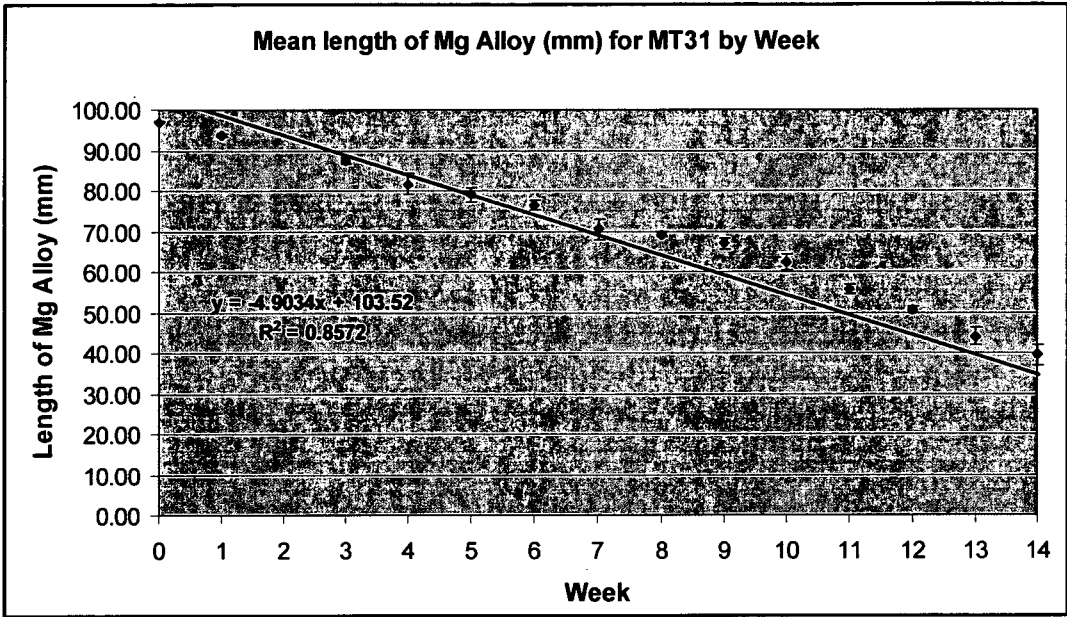


FIGURE 4

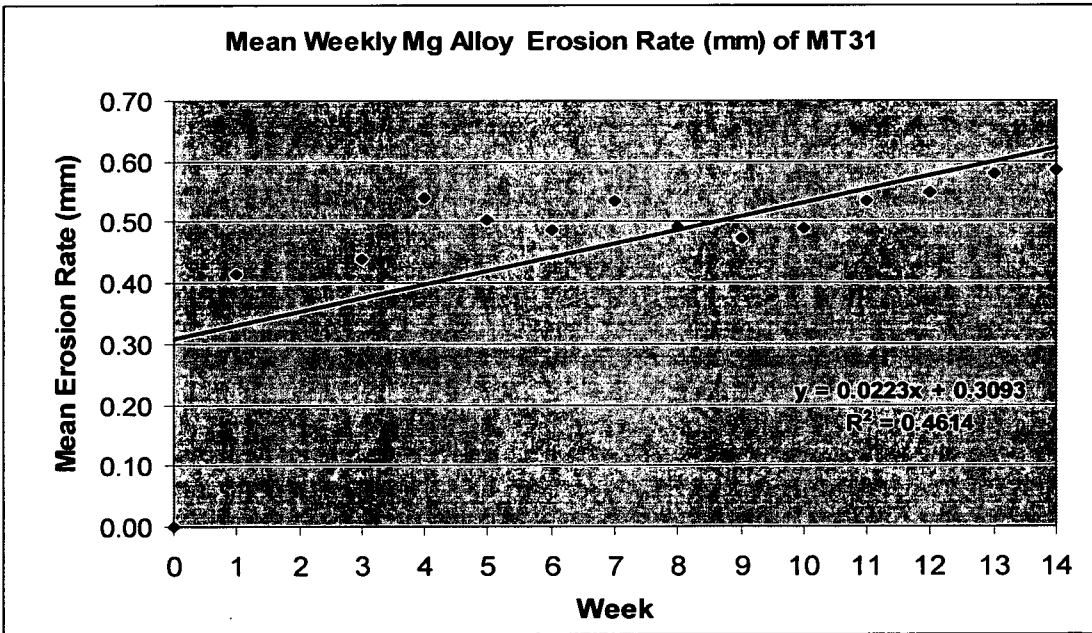


FIGURE 5

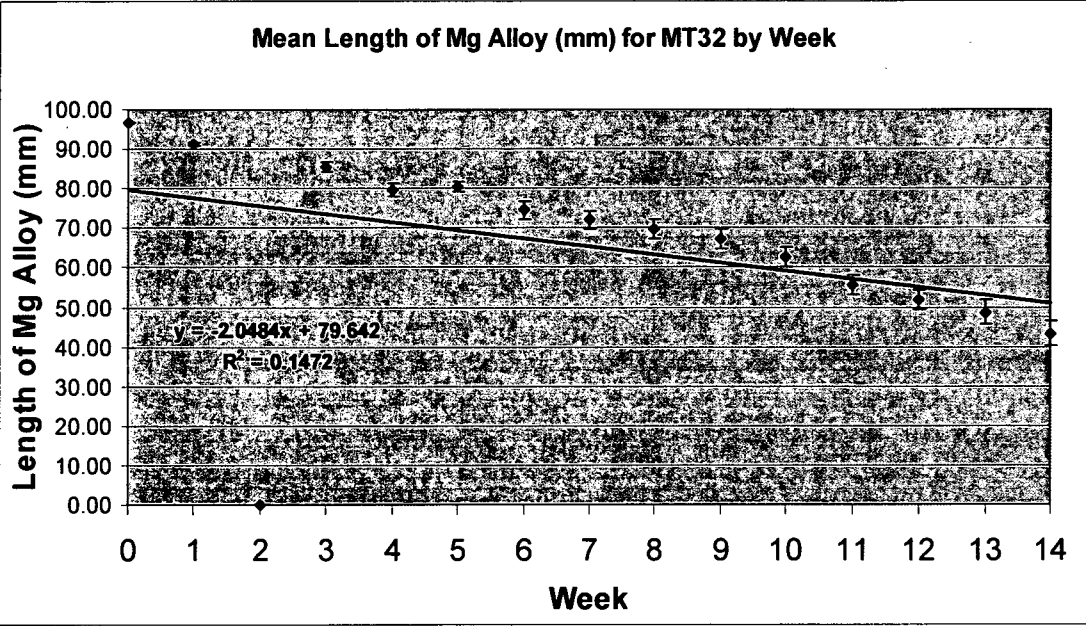


FIGURE 6

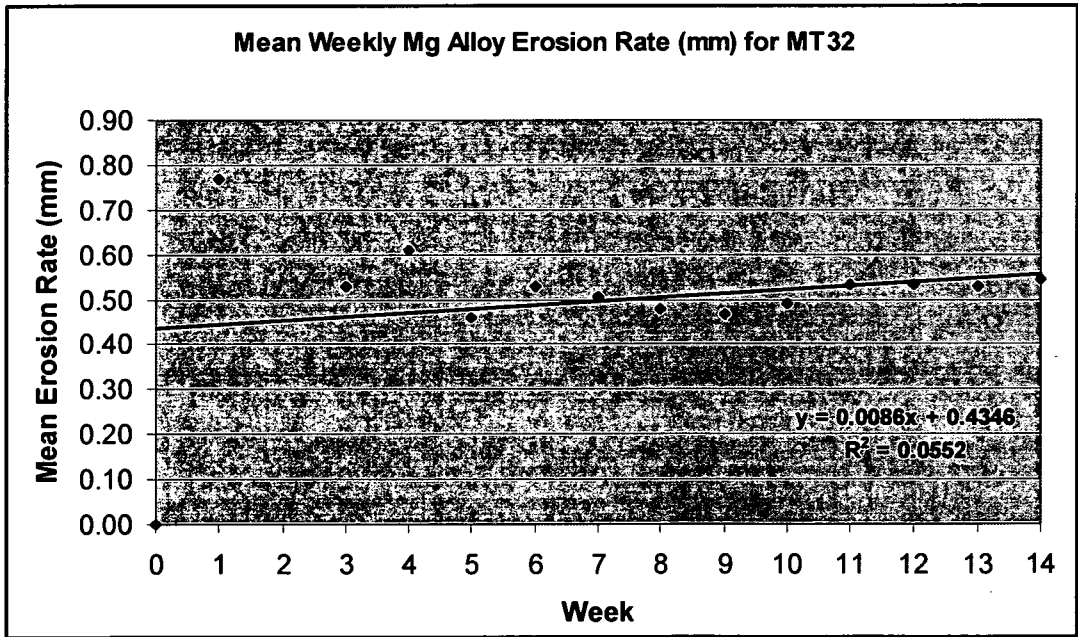


FIGURE 7

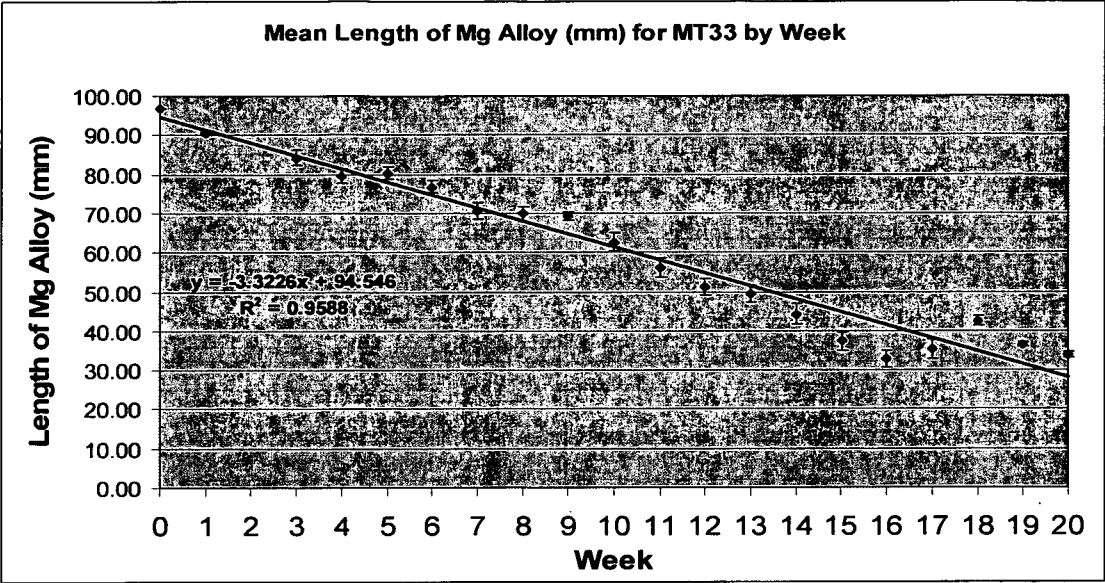


FIGURE 8

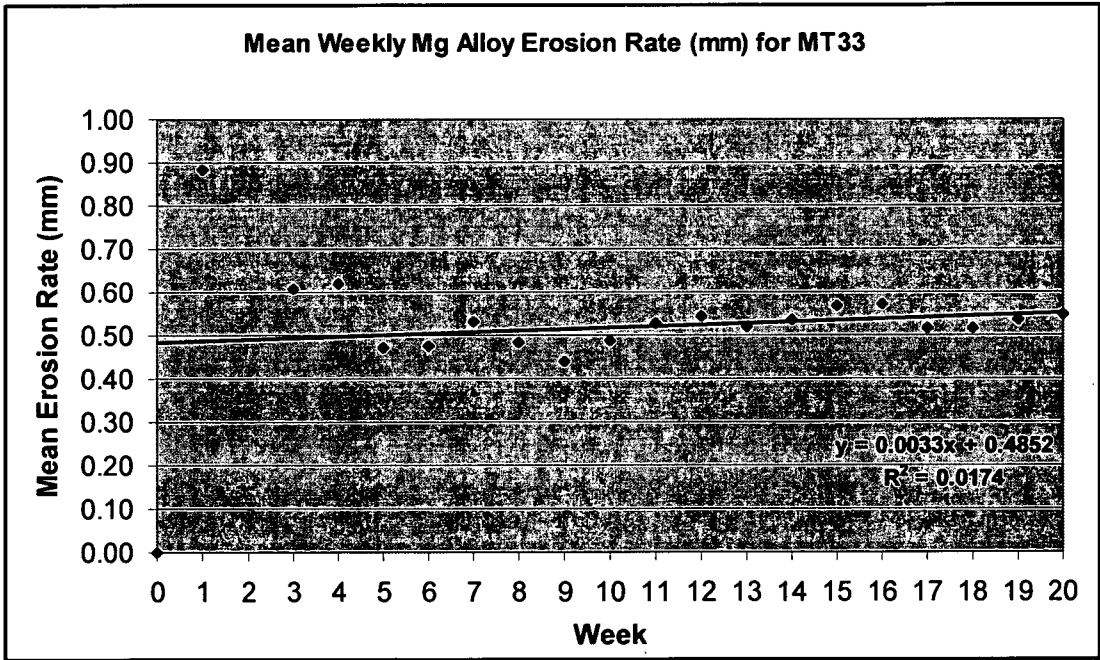


FIGURE 9

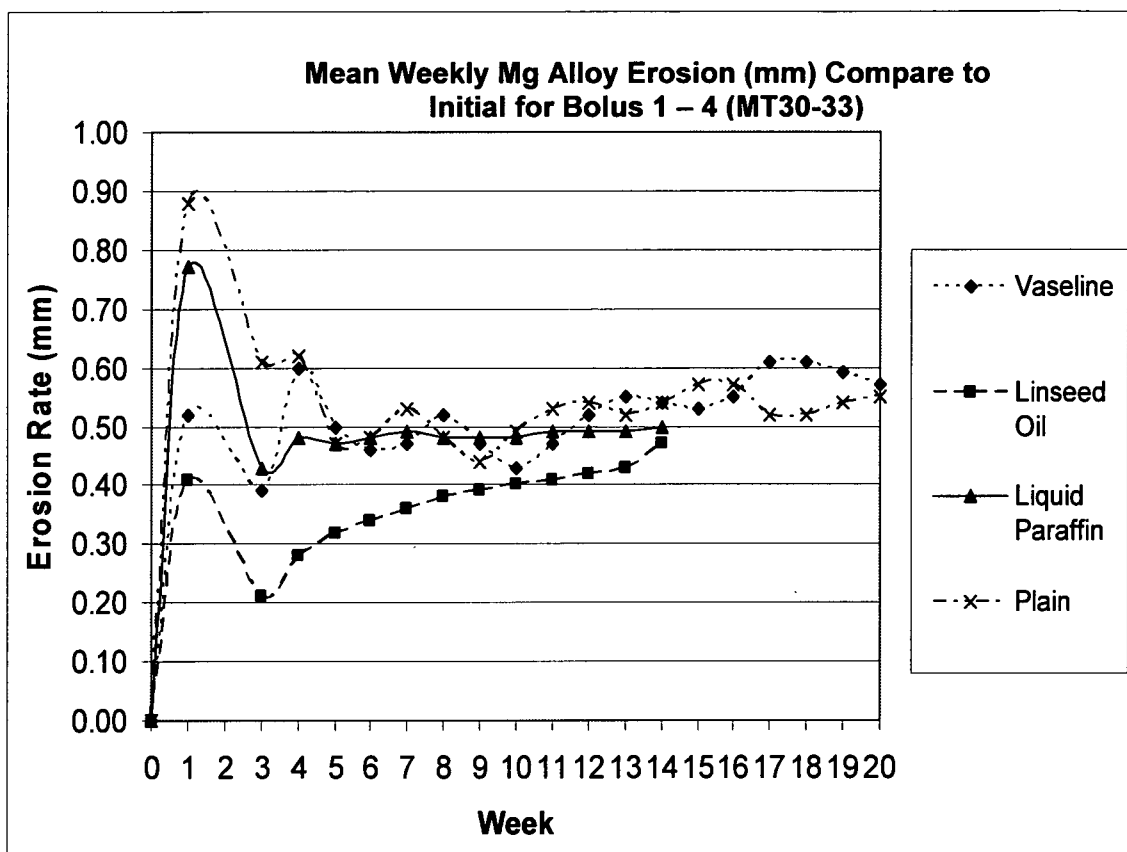


FIGURE 10

INTERNATIONAL SEARCH REPORT

International application No.

PCT/NZ2009/000173

A. CLASSIFICATION OF SUBJECT MATTER

A61F 2/00 (2006.01)

A61J 3/00 (2006.01)

A61J 3/08 (2006.01)

A61M 31/00 (2006.01)

A61K 9/02 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPIDS, EPODOC, MEDLINE, AGRICOLA, VETU: rumen, ruminant, intra ruminal, bolus, alloy, amorphous, petroleum jelly, paraffin, core, tablet, pellet, casing, tubular and related terms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 243 111 A2 (CASTEX PRODUCTS LIMITED, GB) 28 October 1987 (see entire document, in particular abstract, page 1 line 9-page 2 line 8, page 3 lines 2-4)	1 - 6, 9, 10, 13 - 16
A	US 4 418 686 A (CHILD) 6 December 1983 (see entire document, in particular abstract, column 3 lines 5-44, figures 3-5)	1 - 16
A	US 2005/244459 A1 (DEWITT et al.) 3 November 2005 (see abstract, [0002], [0008]-[0009])	1 - 16

☒ Further documents are listed in the continuation of Box C☒ See patent family annex

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
16 October 2009Date of mailing of the international search report
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Telephone No : +61 2 6225 6112

INTERNATIONAL SEARCH REPORT

International application No.

PCT/NZ2009/000173

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 333 452 A (WILLIAM LESLIE PORTER) 28 July 1999 (see entire document, in particular abstract, page 1 para 4, page 2 paras 2-3 and 7)	1 - 16
Y	WO 1995/019763 A1 (NEW ZEALAND PASTORIAL AGRICULTURE RESEARCH INSTITUTE LIMITED) 27 July 1995 (see entire document, in particular abstract, page 1 lines 5-6, page 1 line 29-page 2 line 7)	1 - 6, 9 - 16
Y	EP 0 482 947 B1 (CASTEX PRODUCTS LIMITED) 6 March 1996 (see entire document, in particular column 1 lines 3-7 and 26-31, column 3 lines 14-53, figure 1)	1 - 6, 9 - 16
A	US 6 030 367 A (WHITEHEAD) 29 February 2000 (see entire document, in particular abstract, column 2 lines 18-21 and 51-54, column 3 lines 36-50, figures 1-5)	1 - 16

INTERNATIONAL SEARCH REPORT

International application No.

PCT/NZ2009/000173

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 17 - 18
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 17 - 18 do not comply with Rule 6.2(a) because they rely on reference to the description and/or drawings.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

International application No.

PCT/NZ2009/000173

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report				Patent Family Member			
EP	0243111	AU	71718/87	GB	2190291	NZ	220024
		US	4863455				
US	4418686	US	4308859	US	4359044	US	4453930
US	2005244459	CA	2563069	CA	2563150	CA	2563253
		CN	1964748	CN	1964749	CN	1964750
		EP	1740235	EP	1740236	EP	1868666
		US	7541048	US	7544673	US	2005220839
		US	2005220840	US	2005220841	US	2005220842
		US	2005220843	US	2006083772	WO	2005097228
		WO	2005099786	WO	2005099787	WO	2006107336
GB	2333452	NONE					
WO	1995019763	AU	15470/95	AU	26578/95	BR	9506533
		CA	2181693	EP	0739198	NZ	278977
		US	5472470	US	5720972	WO	1995032924
EP	0482947	AU	86769/91	NZ	240343	US	5342576
US	6030367	US	6176846	US	6190362		
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.							
END OF ANNEX							