



EP 0106694

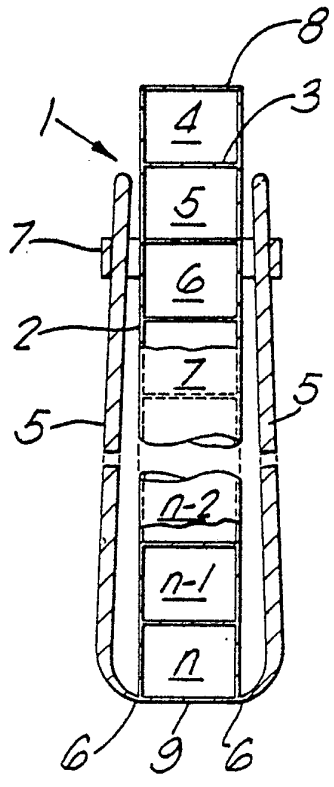
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification<sup>4</sup> :  A61D 7/00</p>	<p>A1</p>	<p>(11) International Publication Number: WO 86/ 00519  (43) International Publication Date: 30 January 1986 (30.01.86)</p>
<p>(21) International Application Number: PCT/GB85/00297 (22) International Filing Date: 3 July 1985 (03.07.85) (31) Priority Application Number: 8417202 (32) Priority Date: 5 July 1984 (05.07.84) (33) Priority Country: GB  (71) Applicant (for all designated States except US): NORBROOK LABORATORIES LIMITED [GB/GB]; Station Works, Newry, County Down BT35 6JP (GB).  (72) Inventors; and (75) Inventors/Applicants (for US only) : HAUGHEY, Edward [GB/GB]; JONES, Robert, Francis, Crawford [GB/GB]; Station Works, Newry, County Down BT35 6JP (GB).</p>	<p>(74) Agents: HUSKISSON, Frank, Mackie et al.; Fitzpatrick's, 4 West Regent Street, Glasgow G2 1RS (GB).  (81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), LU (European patent), NL (European patent), SE (European patent), US.  <b>Published</b> <i>With international search report.</i></p>	

(54) Title: DRUG INTERMITTENT RELEASE DEVICE

(57) Abstract

An intermittent drug release device (1) comprises an orally administrable multi-compartmented container (2), each compartment of which is separated from the next adjacent compartment by a barrier (3) which is degradable under the conditions prevailing within an animal body, means (5) for retaining the device in the animal and, within each compartment means (22) for mechanically rupturing the barrier.



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DRUG INTERMITTENT RELEASE DEVICE

This invention relates to a device for the in vivo intermittent release of medicaments to animals, specifically, but not exclusively, ruminants.

5 Compositions are known for the slow or controlled release of materials into the human or animal body. These known compositions rely on the chemistry of a carrier material, normally of a polymeric nature, to degrade or dissolve over a preselected period of time. The material to be delivered to the animal is encapsulated within a capsule or entangled within a matrix  
10 of the polymeric chains of the degradable or soluble material and is released at a more or less controlled rate determined by the chemistry of the degradable material.

15 Farm animals, particularly ruminants such as cattle and sheep, require seasonal dosages of various materials such as pharmaceuticals, vitamin supplements, trace elements and the like. These have to be delivered at the correct time of the year and in the correct order. These materials will, for the sake of convenience, be  
20 referred to hereinafter simply as "drugs". Drugs are administered to the animals conveniently by oral dosage but this, of course, means that the animals must be herded together to enable the dose of drugs to be given. Each animal has to be individually identified and a  
25 record kept of what has been given. This procedure is lengthy and labour-intensive and consequently, when large herds are involved, extremely expensive to operate.

It has been previously proposed to administer to  
30 the animals a container in which there is held a succession of drugs which are released in the correct sequence by the operation of a spring or a clockwork motor or the like located in the container.

An object of this invention is to provide a drug  
35 release device providing intermittent release of a

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sequence of drugs over a prolonged period of time.

According to this invention there is provided an intermittent drug release device comprising an orally administrable multi-compartmented container, each  
5 compartment of which is separated from the next adjacent compartment by a barrier which is degradable under the conditions prevailing within the animal body, and means for retaining the device in an animal and, within each compartment means for mechanically rupturing the barrier.

10 The container may be formed by a plurality of individual cups having degradable bases and being linkable one with another to form a chain.

Alternatively the container may be an elongate tube having a series of dividing walls transverse to the longitudinal axis of the tube dividing same into a series of  
15 compartments, the dividing walls being composed of a material which is degradable in contact with the stomach contents of an animal.

Preferably the means for mechanically rupturing the  
20 barrier comprises a tongue attached to the container wall, the tongue having a spike directed generally toward the barrier to be ruptured, and a dehydrated compressed sponge disposed relative to said tongue so that an absorption of moisture passing through the barrier as  
25 it degrades the sponge expands urging the tongue and spike through to barrier to rupture same.

It is preferred that the container has means for varying the geometry of the container after administration to the animal so as to prevent regurgitation of  
30 the device or passage of the device onwards through the digestive tract of the animal.

The container may conveniently be an elongate tube having a series of dividing walls transverse to the longitudinal axis of the tube dividing same into a series  
35 of compartments, the dividing walls being composed of a

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material which degrades in contact with the stomach (rumen of a ruminant animal) contents of the animal.

The material may be of any physiologically benign material which has the required ability to degrade.

5 Many suitable materials are available commercially, one such being an ethylene/vinyl acetate based polymer containing starch.

The main intended use of the present invention is in the delivery of a seasonal programme of drugs to ruminants such as cattle and sheep.

10 It is necessary that means be provided to retain the device in the rumen of the animal. This may be achieved by inclusion of a heavy weight, for example a quantity of metal powder or shot may be included in the last compartment to degrade. After the shot or powder has been released it will be relatively easily excreted by the animal. However, it may be inconvenient if some of the shot were to remain in the animal and found after slaughter: iron shot could easily be removed by a magnet but the slaughterhouse may not suspect its presence. However, it is preferred as an alternative or as an addition to the use of a weighted container the container has means for altering its geometry once located in the rumen.

25 Therefore, the present invention includes the provision on the container of one or more laterally extendable wing members held temporarily in a folded condition against the container during administration and releasable to the extended condition in the rumen. In one such configuration a pair of spring plastic wings may be held against the sides of an elongate container by a simple gummed paper or like band which breaks when moistened allowing the wings to extend.

30 In another embodiment of this invention, the device comprises a plurality of containers adapted to be joined

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end to end in snap-fit or nesting fashion to form an elongate chain, the base of each container being formed of degradable material.

5 The container of the device of this invention may be itself composed of degradable material which will disperse after all the drugs have been released, that is, it will degrade over a period of time greater than the time allowed for release of the drugs.

10 Each compartment may include, in addition to the drug to be released, means for assisting rupture of the compartment to assist drug release. For example a tablet of effervescent material may be included to release a quantity of gas on contact with moisture.

15 The present invention will now be described by way of example, with reference to the accompanying drawings, in which:

Fig. 1 shows a longitudinal part-section of a tubular device of this invention.

20 Fig. 2 shows a second embodiment of the present invention, also in section.

Fig. 3 is an enlarged view of a compartment of the device to illustrate the tongue and sponge arrangement.

Referring to Fig. 1, an intermittent drug release device (1) is formed from an elongate tubular container (2) having therein a plurality of internal walls (3) transverse to the longitudinal axis of the container (2) dividing same into a series of compartments indicated in Fig. 1 by 4 to 'n'. Attached to the container (2) are a pair of laterally sprung wing members (5) attached by outwardly biased spring joints (6). As shown in Fig. 1 the wing members (5) are held against the spring-biased joint (6) along the longitudinal sides of the tubular container (2) by means of a securing band (7). The top of the container is closed by a lid (8) and the bottom by closure member (9). In the embodiment shown

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in Fig. 1, the tubular container (2), the wing members (5) and the bottom closure member (9) are made of a material which degrades in contact with the ruminal contents of an animal over a relatively long period of time, characteristically in excess of one year. The dividing internal walls (3) are made of a material which degrades in a much shorter time, typically one month.

A second embodiment of this invention is shown in Fig. 2. An intermittent drug release device is made up of a plurality of cup-shaped members (10) having a tubular wall (11) with a base (12) made of degradable material. The plurality of cups (10) are engageable one with another to form a chain giving in effect the same configuration to the device as in Fig. 1. The engagement of cups (10) may be snap-fit or by the use of a suitable sealing technique to produce a water-tight seal. Top and bottom closures (13) and (14) and wings (15) are equivalent to the parts 8, 9 and 5 in Fig. 1. The wings (15) are shown in the extended position.

Referring to Fig. 3, each compartment of the device, bounded by degradable internal biodegradable partition walls 3, contains a dosage unit of a drug (20). In each compartment there is disposed a dehydrated, highly compressed sponge (21). A tongue member (22) having a terminal spike (23) is attached to the internal wall of container (2). As the biodegradable wall (3) degrades moisture from the animal's stomach leaks through the wall (3) and is absorbed by sponge (21) causing the sponge to expand to several times its original volume. This expansion urges the tongue (22) towards the wall (3) and the spike (23) to rupture the wall. This arrangement assists in the release of the drug (20).

In an example of this invention, a device having the physical structure described above has three main compartments separated by membranes of a polyethylene/

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vinyl acetate copolymer containing starch. The first chamber has a closure membrane which is soluble more or less immediately on contact with moisture. Each compartment contains a dosage of anthelmintics. Each membrane  
5 takes around three weeks to degrade and thus the device provides anthelmintic protection over a period of nine weeks in total. It is convenient to incorporate into the polymers used in construction of the device trace  
10 nutrient elements as a convenient method of delivery of these to the animal.



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CLAIMS

1. An intermittent drug release device comprising an orally administrable multi-compartmented container, each compartment of which is separated from the next adjacent compartment by a barrier which is degradable under the conditions prevailing within an animal body, means for retaining the device in the animal and, within each compartment means for mechanically rupturing the barrier.
2. A device as claimed in claim 1, in which the container is formed by a plurality of individual cups having degradable bases and being linkable one with another to form a chain.
3. A device as claimed in claim 1, in which the container is an elongate tube having a series of dividing walls transverse to the longitudinal axis of the tube dividing same into a series of compartments, the dividing walls being composed of a material which is degradable in contact with the stomach contents of an animal.
4. A device as claimed in any preceding claim in which the means for mechanically rupturing the barrier comprises a tongue attached to the container wall, the tongue having a spike directed generally toward the barrier to be ruptured, and a dehydrated compressed sponge disposed relative to said tongue so that an absorption of moisture passing through the barrier as it degrades the sponge expands urging the tongue and spike through to barrier to rupture same.
5. A device as claimed in claim 4, wherein the sponge is biodegradable.
6. A device as claimed in any preceding claim in which the means for retaining the device within the animal is a weight sufficient to cause the device to sink into the stomach of the animal.

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7. A device as claimed in any preceding claim, in which the means for retaining the device within the animal is one or more laterally extensible wings attached to the device, and means for holding said wings in a temporarily folded position during administration of the device to the animal and being releasable to the extended position in the stomach after administration.

8. A drug delivery device as claimed in any preceding claim, in which each compartment of the device contains a dosage unit of a drug.

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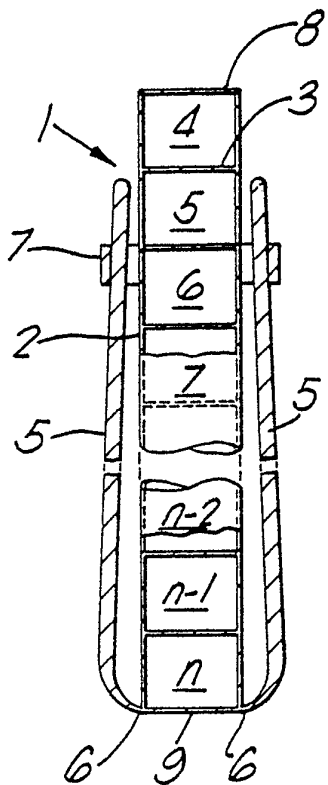


Fig. 1.

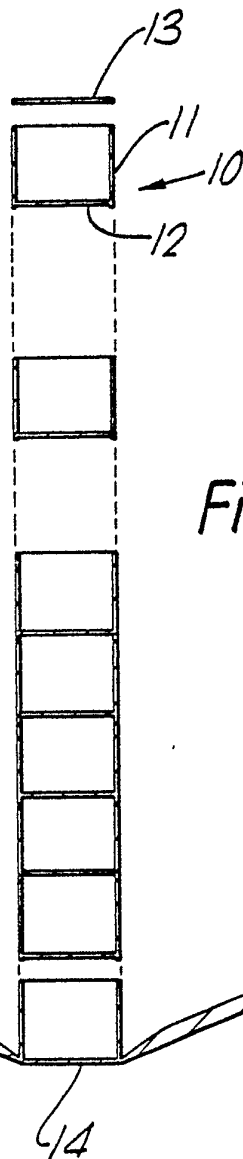


Fig. 2.

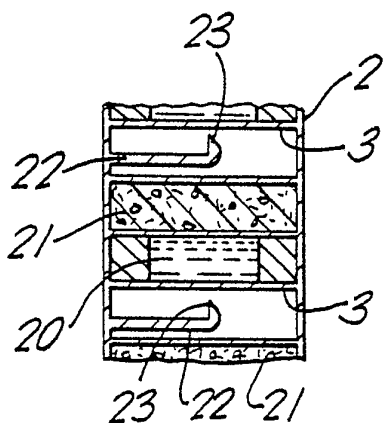


Fig. 3.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 85/00297

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>4</sup> According to International Patent Classification (IPC) or to both National Classification and IPC IPC <sup>4</sup> : A 61 D 7/00														
<b>II. FIELDS SEARCHED</b> <div style="text-align: center; margin-top: 10px;">Minimum Documentation Searched <sup>7</sup></div> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30%; border-bottom: 1px solid black;">Classification System  </td> <td style="border-bottom: 1px solid black;">Classification Symbols</td> </tr> <tr> <td style="border-bottom: 1px solid black;">IPC<sup>4</sup></td> <td style="border-bottom: 1px solid black;">A 61 D A 61 M</td> </tr> </table> <div style="text-align: center; margin-top: 10px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup></div>			Classification System	Classification Symbols	IPC <sup>4</sup>	A 61 D A 61 M								
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IPC <sup>4</sup>	A 61 D A 61 M													
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>9</sup></b> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%;">Category <sup>9</sup></th> <th style="width: 70%;">Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup></th> <th style="width: 20%;">Relevant to Claim No. <sup>13</sup></th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top;">Y</td> <td style="vertical-align: top;">EP, A, 0062391 (RESEARCH CORP.) 13 October 1982, see abstract; figure 1 --</td> <td style="text-align: center; vertical-align: top;">1, 3, 4, 6, 8</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">Y</td> <td style="vertical-align: top;">FR, A, 2137253 (ALEMANY) 28 December 1972, see page 8, lines 10-26; figure 11 --</td> <td style="text-align: center; vertical-align: top;">1, 3, 4, 6, 8</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td style="vertical-align: top;">EP, A, 0079724 (ELI LILLY) 25 May 1983, see page 7, lines 4-7; figure 1  -----</td> <td style="text-align: center; vertical-align: top;">7</td> </tr> </tbody> </table>			Category <sup>9</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>	Y	EP, A, 0062391 (RESEARCH CORP.) 13 October 1982, see abstract; figure 1 --	1, 3, 4, 6, 8	Y	FR, A, 2137253 (ALEMANY) 28 December 1972, see page 8, lines 10-26; figure 11 --	1, 3, 4, 6, 8	A	EP, A, 0079724 (ELI LILLY) 25 May 1983, see page 7, lines 4-7; figure 1  -----	7
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<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; vertical-align: top; padding: 5px;"> <sup>10</sup> Special categories of cited documents:            "A" document defining the general state of the art which is not considered to be of particular relevance            "E" earlier document but published on or after the international filing date            "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)            "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         </td> <td style="width: 50%; vertical-align: top; padding: 5px;">           "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            "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step            "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.            "A" document member of the same patent family         </td> </tr> </table>			<sup>10</sup> Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "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) "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	"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 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "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. "A" document member of the same patent family										
<sup>10</sup> Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "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) "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	"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 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "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. "A" document member of the same patent family													
<b>IV. CERTIFICATION</b> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 5px;">Date of the Actual Completion of the International Search  10th October 1985</td> <td style="width: 50%; padding: 5px;">Date of Mailing of this International Search Report  30 OCT 1985</td> </tr> <tr> <td style="padding: 5px;">International Searching Authority  EUROPEAN PATENT OFFICE</td> <td style="padding: 5px;">Signature of Authorized Officer   G.L.M. Zuysdenberg</td> </tr> </table>			Date of the Actual Completion of the International Search  10th October 1985	Date of Mailing of this International Search Report  30 OCT 1985	International Searching Authority  EUROPEAN PATENT OFFICE	Signature of Authorized Officer   G.L.M. Zuysdenberg								
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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/GB 85/00297 (SA 10076)

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0062391	13/10/82	JP-A- 57163310	07/10/82
		AU-A- 7958282	29/07/82
		US-A- 4381780	03/05/83
		CA-A- 1182352	12/02/85
FR-A- 2137253	29/12/72	None	
EP-A- 0079724	25/05/83	GB-A- 2109232	02/06/83
		JP-A- 58088310	26/05/83
		AU-A- 9010882	19/05/83
		US-A- 4416659	22/11/83

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