

- 1 -

**A PHARMACEUTICAL PACK AND A PACKAGED
PHARMACEUTICAL PRODUCT**

DESCRIPTION

5

The present invention relates to pharmaceutical packs and to packaged pharmaceutical products. In particular, the present invention relates to enema (rectal) packs, delivery nozzles therefor and to packaged pharmaceutical products which include at least one readily oxidizable component. The invention also relates to a method of packaging a pharmaceutical composition, which includes a readily oxidizable component.

15

Collapsible tubes have been in use for many years for storing and dispensing creams, jellies or pastes, such as dental, shaving and hair dressing creams, pharmaceutical preparations, food mixtures and similar flowable products. Common types of collapsible tubes include those having flexible sheet metal walls, formed from aluminium, zinc or lead, and those formed from

20

This Sheet Has Been Replaced



REPLACED SHEETS	SG
☒ Description : paged 1 to paged 20	
☒ Claim(s) : paged 23 to paged 27	
☒ Drawing(s) : paged 4 to paged 7	
☒ Abstract : paged 13 to paged 15	
DATE OF RECEIPT	

- 2 -

moulded, or extruded thermoplastic resin materials, such as polyethylene and polypropylene.

Some metal tubes are integrally formed and comprise a rigid head member, defining a discharge nozzle, and a flexible tubular body, which extends from the head member and which is sealed by crimping, at the other end from the head. Other, generally larger, metal tubes have a similar rigid head member, crimped to a flexible tubular body. The tubular body can be formed by extrusion or from a generally rectangular sheet of metal rolled into a tube. In the latter case the tubular body is held together by a lengthwise extending crimped seam. As with integrally formed tubes, the end of the tubular body remote from the head member is sealed by crimping.

Since all metal tubes include at least one crimped seam, atmospheric oxygen can gain access, via the seam, to a product stored within the tube and cause any easily oxidizable component of the product to become degraded. Also, many flowable products can react with, or corrode the metals generally used in the manufacture

This Sheet Has Been Replaced



- 3 -

of collapsible tubes. However, an advantage of metal tubes in some applications is that because they are non-resilient and do not spring back into shape after squeezing, they can be more convenient in use than
5 tubes formed from plastic resin materials, which will regain their shape after squeezing.

Metal tubes which are internally lined with a phenolic resin and which have a latex rubber sealant in their
10 crimped seams are commercially available. However, during filling, the phenolic resin is vulnerable to being scratched and penetrated and the latex is susceptible to chemical attack.

15 It is particularly important that a pharmaceutical product should not be degraded in any way by oxidation, or by reacting with a packaging material. Accordingly, tubes formed from bare metals are only used to package substantially stable pharmaceutical products, which are
20 not easily oxidized and which do not react on contact with metallic surfaces.

This Sheet Has Been Replaced



- 4 -

If a reactive pharmaceutical product is to be packed in a collapsible tube, the type of tube employed is generally one formed from a moulded, or extruded thermoplastic resin material. Such tubes do not have crimped seams, or other potentially leaky seals, are substantially inert and, therefore, are substantially immune to chemical attack. The form of such tubes is similar to those manufactured from metal, in that they generally comprise a tubular body extending from a head member which defines a discharge nozzle. The opposite end of the tubular body from the discharge nozzle is usually sealed, after the tube has been filled with product, by crimping and the application of heat.

A conventional enema pack comprises a reservoir for an enema material, with a tubular delivery nozzle dimensioned for delivering the enema material from the reservoir into the rectum. One known form of enema pack comprises a thermoplastic resin tube, manufactured with a thin walled body and head member so as to be sufficiently soft and flexible for dispensing the enema material, with an elongated discharge nozzle providing a suitably dimensioned tubular delivery nozzle. Another

This Sheet Has Been Replaced

- 5 -

type of enema pack comprises a bag, which is integrally formed with an elongate tubular delivery nozzle from a soft flexible plastic resin material.

5 However, the walls of both types of enema pack and those of thermoplastic resin tubes are not completely leak proof. For example, water can permeate through the walls of a bag type enema pack sufficiently to cause the concentration of an aqueous enema stored in
10 the pack to change, thereby limiting the shelf life of such a product. Moreover, the amount of oxygen which can permeate through the material forming the walls of a plastic resin tube, or of either type of enema pack, is sufficient to oxidize and degrade certain readily
15 oxidizable pharmaceutical products.

An example of such a readily oxidizable pharmaceutical product is 5 amino salicylic acid (5 ASA), which is useful in the topical treatment of ulcerative colitis,
20 Chrones disease and other inflammatory bowel diseases. Indeed, 5 ASA is so readily oxidizable that it is extremely difficult to formulate.

This Sheet Has Been Replaced



- 6 -

A most effective and convenient method of administering this drug is as a rectal enema. However, suitable formulations of 5 ASA cannot be stored under normal conditions in conventional enema packs, because oxygen will penetrate the walls of such a pack and, within a short period, cause the 5 ASA to become sufficiently oxidized to be unusable. Up until the advent of the present invention, this problem has been overcome by individually sealing conventional bag type enema packs, each filled with a 5 ASA composition, within nitrogen filled aluminium foil containers. An example of such a product is that available from Ferring Pharmaceuticals Ltd, of Feltham, England, under the name PENTASA. Needless to say, this form of packaging is both inconvenient and expensive.

Modified metal tubes could not be considered for use as enema packs since their walls are rigid and cannot be sufficiently easily squeezed, for their contents to be completely expelled into the rectum without difficulty, or causing discomfort to the patient.

This Sheet Has Been Replaced

- 7 -

Collapsible tubes comprising a head portion, formed from a plastic resin material, moulded directly onto a laminated plastics-metal foiled tubular body, have been brought into widespread use for storing and dispensing dentifrices (tooth paste), other cosmetics and like flowable products. The laminated body of such a tube generally comprises at least one thin metal (preferably aluminium) layer sandwiched between two layers of plastic resin material, which is preferably polypropylene, polyethylene, or polyvinylchloride. The end of the tubular body remote from the head is sealed, after the tube has been filled, by crimping and heat welding the contacting plastic layers. Examples of such laminated tubes are described in U.S. Patents Nos. 3260410, 3260411 and 3227319.

Tubes of this latter type were developed in order to enjoy the virtues of metal tubes and in order to carry complex and often multi-coloured designs on their exterior surfaces, which could not be successfully formed or retained on metal tubes. This latter feature is of a particular advantage in the packaging of

This Sheet Has Been Replaced



- 8 -

cosmetic products and dentifrices where the appearance of the packed product is important.

5 According to a first aspect of the present invention, there is provided an enema pack comprising a collapsible reservoir and delivery nozzle means arranged for conveying matter from the reservoir into a body cavity, characterised in that the reservoir comprises a tube having a thermoplastic head portion,
10 defining an opening into the delivery nozzle means, and a collapsible tubular body comprising a layer of metal foil sandwiched between external and internal layers of plastic resin material.

15 An advantage of an enema pack in accordance with this aspect of the present invention is that, when filled with a readily oxidizable pharmaceutical product, such as a 5 ASA composition, or with a composition including a leachable component, it can be stored for long
20 periods, without the need for any additional packaging, or other special precautions. Accordingly, by employing enema packs of the present invention, the expensive and inconvenient double layer packages, which

This Sheet Has Been Replaced



- 9 -

have been employed up to date in conjunction with readily oxidizable pharmaceutical products, can be dispensed with.

5 Moreover, it was surprising that the collapsible reservoir could take the form of a collapsible tube as defined, since known collapsible tubes of similar constructions were developed to replace metal tubes and, accordingly, had been considered insufficiently
10 flexible for use in an enema pack.

In an embodiment, the delivery nozzle means comprises self-supporting tube means arranged for detachable engagement with a discharge nozzle means defined about
15 the opening in the head portion of the collapsible tube. Alternatively, the delivery nozzle means can comprise self-supporting tube means integrally formed with the head portion of the tube. The term
"self-supporting" is used herein to define a tube
20 which, in use, does not collapse to any significant extent.

This Sheet Has Been Replaced



- 10 -

According to a second aspect of the present invention there is provided a packaged pharmaceutical product, comprising a flowable pharmaceutical composition, including a readily oxidizable component, retained
5 within a collapsible tube, wherein the tube has a thermoplastic head portion, defining discharge nozzle means, and a collapsible tubular body comprising a layer of metal foil sandwiched between external and internal layers of plastic resin material. Preferably,
10 the packaged pharmaceutical product further comprises delivery nozzle means arranged for conveying the pharmaceutical composition from the collapsible tube into a body cavity.

15 In an embodiment the delivery nozzle means comprises self-supporting tube means arranged for detachable engagement with the discharge nozzle means.
Alternatively, the delivery nozzle means can be formed as an integral extension of the discharge nozzle means.

20 In embodiments of either the first or the second aspect of the invention, the discharge nozzle means and/or the delivery nozzle means is formed with a sealed opening

This Sheet Has Been Replaced



- 11 -

and is arranged so that the seal can be removed by cutting or piercing. Preferably, the discharge nozzle means is provided with means for engaging the delivery nozzle means, or a cap or other sealing means for the
5 nozzle opening.

The packaged pharmaceutical product can be supplied with such a cap and the discharge nozzle opening can be provided with a removable, or pierceable foil,
10 preferably metal foil seal. The delivery nozzle means can be supplied detached from the collapsible reservoir, to be installed on the reservoir prior to use.

15 Optionally, a metal layer can be included in the thermoplastic head, however this has been found to be unnecessary in most cases and, therefore, is not preferred.

20 An advantage of all embodiments of the second aspect of the present invention is that the collapsible tube provides an effective barrier to the ingress of oxygen, preventing oxidizing damage to the pharmaceutical

This Sheet Has Been Replaced



- 12 -

composition, while being sufficiently flexible for use as a dispensing means for a rectal enema.

5 According to a third aspect of the present invention, there is provided an enema delivery nozzle, for conveying matter from a reservoir into a body cavity, characterised by comprising means for releasably engaging a reservoir, so that matter expelled from the reservoir is passed along the enema delivery nozzle for
10 delivery into a body cavity. Preferably, the enema delivery nozzle is arranged for engaging a discharge nozzle means of a collapsible reservoir in the form of a collapsible tube having a thermoplastic head portion, defining the discharge nozzle means, and a collapsible
15 tubular body comprising a layer of metal foil sandwiched between external and internal layers of plastic resin material.

20 In an embodiment, the enema delivery nozzle is arranged for screw threaded engagement with a threaded discharge nozzle means. Preferably, the enema delivery nozzle is formed from a plastic resin material and includes an elongate self-supporting tubular portion.

This Sheet Has Been Replaced



- 13 -

In a fourth aspect of this invention, a pharmaceutical pack comprises a packaged pharmaceutical product, in accordance with the second aspect of the invention, in combination with an enema delivery nozzle, in
5 accordance with the third aspect of the invention.

In a further aspect, the invention provides the use of a collapsible tube having a thermoplastic head portion, defining discharge nozzle means, and a collapsible
10 tubular body comprising a layer of metal foil sandwiched between external and internal layers of plastic resin material, as a collapsible reservoir for an enema pack.

15 In a most preferred embodiment of the invention, a composition including 5 ASA is stored in the enema pack or collapsible tube of the present invention.

In a still further aspect, the present invention
20 relates to a method of packaging a flowable pharmaceutical composition, including a readily oxidizable component, comprising filling a collapsible tube with said composition, wherein the tube has a

This Sheet Has Been Replaced



- 14 -

thermoplastic head portion, defining discharge nozzle means, and a collapsible tubular body comprising a layer of metal foil sandwiched between an external layer and the internal layer of plastic resin material. The collapsible tube can form a part of an enema pack in accordance with the first aspect of the invention.

In preferred embodiments of all aspects of the invention, the enema delivery nozzle is arranged for conveying matter from a reservoir into the rectum or the colon. Also, the internal layer, the head portion and, preferably, other plastic resin layers of the tube, together with the enema delivery nozzle are formed from a plastic resin material selected so as to be substantially inert, in the sense that it will not undergo any significant chemical interaction with a pharmaceutical composition stored within the tube, or passed along the enema nozzle, under normal conditions of use.

This Sheet Has Been Replaced



- 15 -

Collapsible tubes suitable for use in certain
embodiments of the present invention include those
described in U.S. Patent Nos. 3260410, 3260411, 2440339
and British Patent Application Nos. 2151984, 2151985,
5 2151986 and 2168926. Tubes of this type are available
from Betts Tubes of Colchester, Essex; Hydroaluminium
(Tubefabrikken a.s.) of Norway and; Cobal of France.

Specific embodiments of the present invention will now
10 be described with reference to the accompanying
drawings, wherein:-

Figure 1 is a section through a collapsible tube, for
use in the practice of the present invention;

Figure 2 is a section through an enema delivery tube
15 and;

Figure 3 is a section through an enema pack.

Referring, firstly, to Figure 1; a tube 1 has a
flexible walled tubular body 2 extending from a head
20 portion 3. The head portion 3 is moulded from a
thermoplastics material and the body 2 is sealed
thereto by the application of heat and pressure. The
head portion 3 defines a reduced diameter discharge

This Sheet Has Been Replaced


- 16 -

nozzle 4 which is provided with external threads 5. An internally threaded cap 6 is dimensioned to be screw threadably engaged upon said external threads 5 and to thereby come into sealing engagement with the discharge nozzle 4. The wall of the body 2 comprises an internal layer 8, an intermediate layer 9 and an external layer 10. The intermediate layer 9 is formed from aluminium and the internal and external layers 8 and 10 are formed from a thermoplastic material. The tube body 2 is closed permanently by crimping and heat sealing along the end 7, opposite the head portion 3, after a product has been introduced into the body through the other end 7. The preferred thermoplastic material used in forming the tube 1, is polyethylene. The internal and external layers 8 and 10 of the tubular body 2 are each about 0.15 mm thick and the intermediate layer is about 0.05 mm thick, giving an overall wall thickness of about 0.35 mm.

20 An enema delivery nozzle 11, see Figure 2, comprises a marginally tapered tubular portion 12 defining an outlet 13 and extending between the outlet 13 and a collar 14. The collar 14 has greater internal and

This Sheet Has Been Replaced



- 17 -

external diameters than the tubular portion 12 and is joined to the tubular portion 12 by an annular step 15. An annular ridge 16 is formed on the internal surface of the step 15, around the opening of the tubular
5 portion 12, and the internal surface of the collar 14 is provided with a screw thread 17, dimensioned and arranged for screw threaded engagement upon the external threads 5 on the discharge nozzle 4 of the tube 1.

10

In use the collar 14 should be screwed tightly onto the discharge nozzle 4 of the tube 1, until the annular ridge 16 comes into abutment with the nozzle 4, sealing the tube 1 to the enema delivery nozzle 11. The
15 contents of the tube 1 can then be expelled into the enema delivery nozzle 11 and out through the outlet 13.

Figure 3 shows an alternative enema pack 20, in which the enema delivery nozzle 11 is in the form of an
20 integral extension to the discharge nozzle (shown at 4 in Figure 1) of the tube 1. The same reference numerals, which were employed to identify components in Figures 1 and 2, are used to identify the corresponding

This Sheet Has Been Replaced



- 18 -

components in the enema pack 20. As a result of being integrally formed, the enema pack 20 does not have any screw threads 5, annular ridge 16 or internal threads in the collar 14. The collar 14 takes the place of the discharge nozzle 4.

In a preferred embodiment, the product supplied in the tube 1 is a gel comprising 5 ASA in admixture with suitable pharmaceutical excipients. A suitable gel composition comprises the following ingredients:

	INGREDIENT	PERCENTAGE	FUNCTION
	MESALAZINE (5ASA)	6.67% w/w	Active Agent
15	Disodium edetate	0.1% w/w	Sequesting agent
	Sodium acetate	0.82% w/w	Buffering agent
	Sodium metabisulphate	0.50% w/w	Antioxidant/ preservative
	Hydroxy ethyl cellulose	1.20% w/w	Thickening agent
20	Glacial acetic acid	q.s.	Buffering agent
	Purified water	to 100%	

This Sheet Has Been Replaced



- 19 -

5 ASA is available from Schering AG, of Mullerstrasse
170-171 D-1000 Berlin 65, Federal Republic of Germany,
under the Trade Mark MESALASINE.

5 Example 1

Preparation of a 5 ASA gel composition.

A batch of 300 litres is produced from the following
ingredients:

10

Manufacturing Formula

	MESALAZINE	20kg
	Disodium edetate	0.3kg
15	Sodium acetate	2.46kg
	Sodium metabisulphite	1.50kg
	Hydroxy ethyl cellulose	3.60kg
	Acetic acid (glacial)	q.s.
	Purified water	to 300l

20

To provide 5000 dose units.

This Sheet Has Been Replaced



- 20 -

The process is carried out in a vessel which has been pre-prepared with nitrogen and under a nitrogen blanket throughout. The disodium edetate and the sodium acetate are dissolved in the purified water, at a
5 temperature of 35-40°C, and the pH of the resulting solution is adjusted to 4.8 with the addition of glacial acetic acid. The solution is then warmed to 40-45°C, the hydroxy ethyl cellulose is added and the resulting mixture is allowed to gel. The
10 MESALAZINE is then added and the gel is blended until uniform. The gel is then filled into 5000 tubes of either of the types previously described, in 60 ml aliquots.

This Sheet Has Been Replaced



- 21 -

CLAIMS

1. An enema pack comprising a collapsible reservoir and delivery nozzle means arranged for conveying matter
5 from the reservoir into a body cavity, characterised in that the reservoir comprises a tube having a thermoplastic head portion, defining an opening into the delivery nozzle means, and a collapsible tubular body comprising a layer of metal foil sandwiched
10 between external and internal layers of plastic resin material.
2. An enema pack, as claimed in claim 1, wherein the delivery nozzle means comprises self-supporting tube
15 means arranged for detachable engagement with a discharge nozzle means defined about the opening in the head portion of the tube.
3. An enema pack, as claimed in claim 1, wherein the
20 delivery nozzle means comprises self-supporting tube means integrally formed with the head portion of the tube.

This Sheet Has Been Replaced





- 22 -

4. An enema pack, as claimed in any of claims 1-3,
wherein the discharge nozzle means and/or the delivery
nozzle means is formed with a sealed opening and is
arranged so that the seal can be removed by cutting or
piercing.

5

5. An enema pack, as claimed in claims 2 and 4,
wherein the discharge nozzle means is provided with
means for engaging the delivery nozzle means, or a cap
or other removable sealing means.

10

6. An enema pack as claimed in any of claims 1-5,
wherein the delivery nozzle means is arranged for
conveying matter from the reservoir into the rectum or
colon.

15

7. A packaged pharmaceutical product, comprising a
flowable pharmaceutical composition, including a
readily oxidizable component, retained within a
collapsible tube, wherein the tube has a thermoplastic
head portion, defining discharge nozzle means, and a
collapsible tubular body comprising a layer of metal

20

This Sheet Has Been Replaced





- 23 -

foil sandwiched between external and internal layers of plastic resin material.

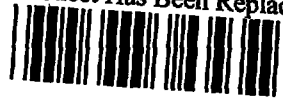
5 8. A packaged pharmaceutical product, as claimed in claim 7, further comprising delivery nozzle means arranged for conveying the pharmaceutical composition from the collapsible tube into a body cavity.

10 9. A packaged pharmaceutical product, as claimed in claim 8, wherein the delivery nozzle means comprises self-supporting tube means arranged for detachable engagement with the discharge nozzle means.

15 10. A packaged pharmaceutical product, as claimed in claim 8, wherein the delivery nozzle means comprises self-supporting tube means and is formed as an integral extension of the discharge nozzle means.

20 11. A packaged pharmaceutical product, as claimed in any of claims 7-10, wherein the discharge nozzle means and/or the delivery nozzle means is formed with a sealed opening and is arranged so that the seal can be removed by cutting or piercing.

This Sheet Has Been Replaced





- 24 -

12. A packaged pharmaceutical product, as claimed in any of claims 7-11, wherein the discharge nozzle means is provided with means for engaging a delivery nozzle means, or a cap or other removable sealing means.

5

13. A packaged pharmaceutical product, as claimed in any of claims 7-12, wherein the discharge nozzle means is provided with a removable, or piercable foil seal.

10

14. A packaged pharmaceutical product, as claimed in any of claims 8-13, wherein the delivery nozzle means is arranged for conveying the pharmaceutical composition into the rectum or colon.

15

15. An enema delivery nozzle for conveying matter from a reservoir into a body cavity, characterised by comprising means for releasably engaging a reservoir, so that matter expelled from the reservoir is passed along the enema delivery nozzle for delivery into a body cavity.

20

This Sheet Has Been Replaced

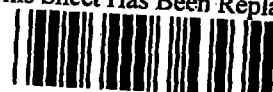




- 25 -

16. An enema delivery nozzle, as claimed in claim 15,
characterised by being arranged for engaging a
discharge nozzle means of a collapsible reservoir in
the form of a collapsible tube having a thermoplastic
head portion, defining the discharge nozzle means, and
a collapsible tubular body comprising a layer of metal
foil sandwiched between external and internal layers of
plastic resin material.
17. An enema delivery nozzle, as claimed in claim 15 or
16, arranged for screw threaded engagement with a
threaded discharge nozzle means.
18. An enema delivery nozzle, as claimed in any of
claims 15-17, formed from a plastic resin material and
including an elongate self-supporting tubular portion.
19. An enema delivery nozzle, as claimed in any of
claims 15-18, arranged for conveying matter from a
reservoir into the rectum or colon.

This Sheet Has Been Replaced





- 26 -

20. A pharmaceutical pack comprising a packaged pharmaceutical product, as claimed in any of claims 7-9 and 11-14, in combination with an enema delivery nozzle, as claimed in any of claims 15-19.

5

21. Use of a collapsible tube having a thermoplastic head portion, defining discharge nozzle means, and a collapsible tubular body comprising a layer of metal foil sandwiched between external and internal layers of plastic resin material, as a collapsible reservoir for an enema pack.

10

22. A packaged pharmaceutical product, or a pharmaceutical pack, as claimed in any of claims 7-14 or 20, wherein a composition including 5 ASA is stored within the collapsible tube.

15

23. A method of packaging a flowable pharmaceutical composition, including a readily oxidizable component, comprising filling a collapsible tube with said composition, wherein the tube has a thermoplastic head portion, defining discharge nozzle means, and a collapsible tubular body comprising a layer of metal

20

This Sheet Has Been Replaced





- 27 -

foil sandwiched between internal and external layers of
plastic resin material.

This Sheet Has Been Replaced

