CONTAINERS FOR COMPOSITIONS COMPRISING MELOXICAM

TECHNICAL FIELD

This invention relates to containers for storage, dispensing and preservation of compositions containing meloxicam.

BACKGROUND OF THE INVENTION

Some pharmaceutical compositions as for example injectable compositions require to be sterilised prior to administration. These pharmaceutical compositions have to be manufactured and stored under sterile conditions. A multi-layered plastic polymeric container for the storage of a chemical composition that may or may not be sterilised is disclosed in WO2008/152122. The herein disclosed bottles have a volume of 50 ml to 500ml. A plastic container made of polyethylene naphthylate with a closure device for storing and preserving a composition of sodium benzoate and cefdinir is disclosed in WO2007/087214.

It is crucial that the material of the container is pharmaceutically acceptable meaning that it should not interfere with the pharmaceutical composition or alter the quality of the compositions. The reverse must also be valid, that the pharmaceutical compositions should not interfere or alter the nature and/ or composition of the container. Any alterations that may occur can result in the migration of chemicals from and to the container material and/ or the pharmaceutical composition. Any chemicals from the container material that may mix with the solution will be impurities within the solution that may affect the solution by degrading the composition or may not be tolerated in any other way. Degradation may also occur over time under the action of oxygen, light and/ or temperature. If the container and/ or solution has been sterilised by for example irradiation, then this may also result in degradation of any of the material. The chemical properties of the pharmaceutical composition, such as the stability of the active ingredient may alter over time because of any interactions and thus reduce the lifetime of the formulation. Another interaction that has to be avoided is adsorption of any of the components, especially sodium benzoate, within the solution to the material of the bottle.

The pharmaceutical composition comprising meloxicam is a very frequently used drug for veterinary medicine for the treatment of for example pain, post-operative pain, inflammation, fever, diarrhoea, lameness, problems with the locomotor apparatus, respiratory complaints, osteoarthritis. It is available not only in different formulations but also in dosage forms which are optimised for the use of a pharmaceutical composition for several animal species.

Oral suspensions of meloxicam with a concentration of 1.5 mg/ ml are established for the treatment of dogs for more than 10 years. This formulation is revealed in the patent application WO99/49845.

In addition it was found that the drug is suitable for the treatment of cats as well. The palatability of the formulation in both dogs and cats is exceptional, thus ensuring an excellent compliance of drug treatment. For cats an oral suspension with 0.5 mg/ ml of meloxicam has been developed, which allows accurate dosing according to the body weight of the animal.

Oral suspension of 0.5 mg/ ml meloxicam for chronic treatment has been approved. This suspension is available in 25 ml high-density polyethylene (HDPE) bottles filled with 15 ml of the suspension. For both the 1.5 mg/ ml and the 0.5 mg/ ml suspension a decrease of the sodium benzoate content over time can be observed. It could be proven that this loss of the preservative is explained not by chemical degradation, but by adsorption of sodium benzoate to the bottle wall. Sodium benzoate is used as the preservative and is the only substance of the solution, which can be active as a preservative and because of its adsorption it needed to be assessed whether the formulation is still adequately preserved over the shelf-life of the product. It could be demonstrated that at a sodium benzoate content of 70 % of the label claim of 0.15 mg/ ml the formulation is still fulfilling all requirements of the European Pharmacopoeia for preservative efficacy. This approach of increasing the preservative in order to prolong the potential shelf-life of the formulation is undesirable as it cannot be completely excluded that preservatives may cause irritation or allergic reactions. It would be an unnecessary amount of preservatives that would be given to the animals.

For the acute treatment in cats a smaller bottle is required which contains enough of the pharmaceutical solution for the treatment of up to five (5) days. A container with approximately three (3) ml of an oral suspension comprising 0.5 mg/ ml meloxicam would fulfil these requirements. In addition such a composition would allow the treatment of several other species like small dogs (with a body weight of 0.5 kg up to 5 kg), rabbits and guinea pigs. Thus the problem underlying the present invention was to provide a plastic container containing a pharmaceutical composition comprising benzoic acid or a derivative thereof or a pharmaceutical acceptable salt thereof and a COX-inhibitor of the oxicam-type or a pharmaceutical acceptable salt thereof avoiding a significant loss of benzoic acid or a derivative thereof during storage. Furthermore, the problem underlying the present invention was to provide a plastic container containing a pharmaceutical composition comprising sodium benzoate and meloxicam avoiding a significant loss of sodium benzoate during storage.

BRIEF SUMMARY OF THE INVENTION

The present disclosure relates to a plastic container containing a pharmaceutical composition comprising benzoic acid or a derivative thereof or a pharmaceutical acceptable salt thereof and a COX-inhibitor of the oxicam-type or a pharmaceutical acceptable salt thereof, wherein the container material is selected from one or more members of the group consisting of a homopolymer of polypropylene (PP), a copolymer of polypropylene (PP), a homopolymer of polyethylene terephthalate (PET) and a copolymer of polyethylene terephthalate (PET), and optionally non-polymeric components. In one aspect, there is provided a plastic container containing a pharmaceutical composition comprising sodium benzoate and meloxicam or a pharmaceutical acceptable salt thereof, characterised in that the container material is selected form one or more members of the group consisting of a homopolymer of polypropylene (PP), a copolymer of polypropylene (PP), a homopolymer of polyethylene terephthalate (PET) and a copolymer of polyethylene terephthalate (PET), and optionally one or more non-polymeric components. This container stores and/ or preserves a pharmaceutical composition comprising sodium benzoate and meloxicam or a pharmaceutical acceptable salt thereof, wherein the container material is constituted of polypropylene (PP) or polyethylene terephthalate (PET), i.e. the container material is selected from the group consisting of homopolymer of polypropylene (PP), copolymer of polypropylene (PP), homopolymer of polyethylene terephthalate (PET) and copolymer of polyethylene terephthalate (PET), and optionally non-polymeric components. The container also includes a closure device for storing and preserving a pharmaceutical composition, which can also be connected to a dispensing device.

The plastic container for storing, preserving and/ or dispensing a pharmaceutical composition comprising sodium benzoate and meloxicam or a pharmaceutical acceptable salt thereof has a volume of 3 to 11 ml with a total volume of the liquid composition of 2 ml to 10 ml.

The pharmaceutical composition that is stored and preserved within the bottle is a meloxicam-containing composition with meloxicam in a concentration of 0.2 mg/ ml to 20 mg/ ml. The pharmaceutical composition also comprises sodium benzoate in the concentration range of 0.8 mg/ ml to 2.0 mg/ ml.

Surprisingly the combination of the container according to the current disclosure and the pharmaceutical composition comprising meloxicam and sodium benzoate enables the composition to remain substantially stable over 18 months or at least 18 months.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: PET Bottles – Sodium Benzoate Content over Storage Time
Figure 2: Glass Bottles – Sodium Benzoate Content over Storage Time
Figure 3: PC Bottles – Sodium Benzoate Content over Storage Time
Figure 4: PP Bottles – Sodium Benzoate Content over Storage Time
Figure 5: HDPE Bottle – Sodium Benzoate Content over Storage Time
Figure 6: LDPE Bottle – Sodium Benzoate Content over Storage Time
Figure 7: Storage at 25 °C / 60 % r.h. – Meloxicam Content for PP, HDPE and Glass Bottles (TW = Thin-walled HDPE bottles)
Figure 8: Dropper provided an integrated adaptor
Figure 9: Bottle - Plug-in device – Oral/ Dosing Syringe
Figure 10: Oral/ Dosing syringe

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a plastic container containing a pharmaceutical composition comprising benzoic acid, a derivative or pharmaceutically acceptable salt thereof and

an oxicam or a pharmaceutical acceptable salt thereof, characterised in that the container material is polypropylene (PP) or polyethylene terephthalate (PET). The plastic container is made of container material containing plastic/ polymers such as PP or PET and optionally one or more, preferably one or two, most preferably one, non-polymeric components. Furthermore, the present invention relates to a plastic container containing a pharmaceutical composition comprising benzoic acid, a derivative or pharmaceutically acceptable salt thereof and a COX-inhibitor of the oxicam-type or a pharmaceutical acceptable salt thereof, wherein the container material is selected from one or more members, preferably one member, of the group consisting of a homopolymer of polypropylene (PP), a copolymer of polypropylene (PP), a homopolymer of polyethylene terephthalate (PET) and a copolymer of polyethylene terephthalate (PET), and optionally one or more non-polymeric components. The present invention also relates to a plastic container containing a pharmaceutical composition comprising sodium benzoate and meloxicam or a pharmaceutical acceptable salt thereof, wherein the container material is selected from one or more members, preferably one member, of the group consisting of a homopolymer of polypropylene (PP), a copolymer of polypropylene (PP), a homopolymer of polyethylene terephthalate (PET) and a copolymer of polyethylene terephthalate (PET), and optionally one or more non-polymeric components. The container is equipped with a closure device for storage and preservation of a pharmaceutical composition. The container allows a stable preservation of said composition for 18 months or at least 18 months. Throughout the whole specification, by the terms polypropylene (PP) is meant a homopolymer, one or more copolymers or a combination thereof, especially random coplolymers. Throughout the whole specification, by the terms polyethylene terephthalate (PET) is meant a homopolymer, one or more copolymers or a combination thereof, especially random copolymers.

A vast variety of polymeric materials are commonly used for containers or packaging, which contain pharmaceutical compositions such as for example polyvinyl chloride (PVC), poly(ethylene-vinyl acetate) or any other polyolefin. Different types of containers made from different polymers are not suitable for the use in the current invention such as high-density polyethylene (HDPE), low-density polyethylene (LDPE), polycarbonate (PC) or glass. Only the material according to the current invention, polypropylene (PP) and polyethylene terephthalate (PET), is usable and fulfils for purpose of the invention. Different types of PP are suitable for the intended purpose such as but not limited to Purell

RP270G white (Basell), RB845MO (Borealis), PPM R021 (Total Atofina). It has been surprisingly found that polypropylene and polyethylene terephthalate but particularly polypropylene does not result in any adsorption of the preservative from the solution onto the wall of the bottle and thus leads to an increased stability of the solution. Thus the invention relates to a plastic container containing a pharmaceutical composition comprising sodium benzoate and meloxicam or a pharmaceutical acceptable salt thereof, wherein the container material is polypropylene (PP) or polyethylene terephthalate (PET) with the purpose of storing and/ or preserving a pharmaceutical composition. The container further comprises a closure device for storing and preserving a pharmaceutical composition. A suitable closure is e.g. a two-piece tamper-proof and child-resistant closure. A suitable type is e.g. a cap type LT.9171 supplied by Gerresheimer Boleslawiec S.A., Boleslawiec, Poland.

The inventions also relates to an oral dispenser of the pharmaceutical composition that can be connected to the container, which allows a precise administration of the pharmaceutical composition. Thus the bottle according to the invention is suitable for connecting a dispenser to the bottle opening. Due to the necessity of accurate but flexible dosing according to the body weight of the animal to be treated, oral dispensers are the first choice for administration of a specific volume of the formulation from the bottle. For this purpose plastic materials are more suitable due to the fact that the containers are slightly collapsible so that the pressure differences by pulling of a certain volume of liquid from the bottle can be neglected. The material of this dispensing equipment may comprise for example either polyethylene (PE), low-density polyethylene (LDPE) or high-density polyethylene (HDPE). The dispenser can be connected for administration of the pharmaceutical composition and disconnected after usage. Thus the plastic container can be connected to a dispensing device.

The dosing system as described above consists of a plastic adapter and a dosing syringe. The plastic adapter is pressed into the bottle with the bottom part. The adapter has a cylindrical and slightly conical shape. An example is given in figure 8. The adapter may also have a dropper function which is obtained by either a plate with a bore on the inside of the plastic part or a funnel-shaped design with a bore at the bottom of the funnel towards the bottle. When the bottle with the adapter with a dropper function is held in a horizontal to vertical position the suspension inside the bottle will flow towards the bore due to gravity and a drop will be formed and fall off. In other cases and if not required due to the dosing

scheme the dropper can be designed without a bore thus allowing constant flow of liquid through the cylindrical adapter. Suitable materials for such kind of dropper adapters or tips are e.g. LDPE. Suitable adapters are commercially available as supplied by e.g. Gerresheimer.

In case no dropper function is required, a plug-in device can be used instead. An example is given in figure 9. A plug-in device is a plastic piece which is also pressed into the bottle by its bottom part. The upside is flat and has a bore in its center into which the tip of a dosing syringe fits so that a tight connection is obtained allowing to turn the bottle with the syringe docked into the plug-in upside down and pull the suspension to the required mark of the imprint of the dosing syringe. Such plug-ins may consist of e.g. LDPE. A suitable supplier can be Hubert De Backer, Sint-Niklaas, Belgium. An example of a suitable dosing syringe is given in figure 10. A suitable supplier can be Baxa or Hubert De Backer.

A plastic container for storing, preserving and/ or dispensing a pharmaceutical composition comprising sodium benzoate and meloxicam or a pharmaceutical acceptable salt thereof wherein the liquid composition has a volume of 2 ml to 10 ml, 2.5 ml to 8 ml, 2.5 ml to 5 ml, preferably 3.5 ml to 4.5 ml, even more preferred 3 ml to 4.5 ml.

A plastic container for storing, preserving and/ or dispensing a pharmaceutical composition, wherein said container has a volume of 3 ml to 11 ml, 3 ml to 10 ml, 3 ml to 8 ml, 3 ml to 5 ml, preferably 3.5 to 4.5, even more preferred containing a volume of 3 ml to 4 ml.

The container can for example have a volume of 8 ml and can contain a volume of liquid of 5 ml but is actually filled with a liquid volume of 3.5 to 4 ml in order to secure a dispensing volume of 3 ml.

A dispensing volume may be the volume that has to be guaranteed for availability and thus dosing.

Containers of the present invention may contain a solution or suspension comprising meloxicam and sodium benzoate. The preferred concentration of meloxicam in the pharmaceutical composition is 0.2 mg/ ml to 20 mg/ ml, preferably 0.5 mg/ ml to 15 mg/ ml, more preferably 0.5 mg/ ml, 1.5 mg/ ml or 15.0 mg/ ml. The preferred concentration of so-

dium benzoate in the pharmaceutical composition is 0.8 mg/ ml to 2.0 mg/ ml, preferably 1.5 mg/ ml.

The active ingredient can be any nonsteroidal anti-inflammatory drug, which is a cyclooxygenase (COX) inhibitor of the oxicam-type such as meloxicam, piroxicam, lornoxicam, tenoxicam, droxicam, isoxicam, preferably meloxicam.

The formulation used according to the invention may contain the oxicam compound as a base or a pharmaceutically acceptable salt thereof. Preferably the salt of meloxicam is selected from the group consisting of meglumine, sodium, potassium or ammonium salt, most preferably the meloxicam meglumine salt.

Other ingredients of the solution or suspension comprise commonly known agents for suspensions or solutions such as suspending agents, preservatives, flavouring agents, ph adjusters and solvents such as for example water that are used for said formulations. Specific examples for a typical suspension are displayed in table 1.

Suspending agents used may be for example organic hydrocolloid forming agents such as cellulose ether and/ or silicon dioxide, preferably hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose and/ or silicon dioxide or colloidal anhydrous silica, preferably colloidal anhydrous silica and/ or hydroxyethyl cellulose.

Preservatives used may be for example benzoic acid or any derivatives or salts thereof, preferably sodium benzoate.

Flavouring agents used may be for example sugar alcohols such as glycerol, sorbitol, mannitol, xylitol or artificial sweeteners such as saccharin or any of its salt, cyclamate, aspartame, sucralose, taumatin, or any of their salts, acesulfam-potassium, aqueous solutions thereof, or mixtures thereof, preferably sorbitol, glycerol saccharin or sodium saccharin and glycerol. Other flavouring agents may be artificial aromas such as an artificial fruit or meat aroma as for example honey, strawberry, raspberry, or beef or fish flavour, preferably honey.

The pH adjusters used may be for example sodium dihydrogen phosphate dihydrate/ citric acid monohydrate buffer, glycine/ HCl, K-hydrogen phthalate/ HCl, citric acid/ phosphate, citrate-phophate-borate/ HCl or Britton-Robinson buffer, mixtures thereof or mixtures with other physiologically acceptable liquids such as glycerol or optionally aqueous solutions of sugar alcohols, preferably sodium dihydrogen phosphate dihydrate and citric acid monohydrate.

In a further embodiment the plastic container is made of PP or PET with a volume of 8 ml comprising meloxicam with a concentration of 0.5 mg/ ml and sodium benzoate in a concentration of 1.5 mg/ ml. More specifically said plastic container has a volume of 8 ml containing a pharmaceutical composition with a volume of 3.5 ml to 4 ml comprising meloxicam in a concentration of 0.5 mg/ ml and sodium benzoate in a concentration of 1.5 mg/ ml.

In a further embodiment the plastic container is made of PP or PET with a volume of 8 ml containing a pharmaceutical composition with a volume of 3.5 ml to 4 ml comprising meloxicam in a concentration of 1.5 mg/ ml and sodium benzoate in a concentration of 0.8 mg/ ml to 2.0 mg/ ml, preferably 1.5 mg/ ml.

In a further embodiment the plastic container is made of PP or PET with a volume of 8 ml containing a pharmaceutical composition with a volume of 3.5 ml to 4 ml comprising meloxicam in a concentration of 15.0 mg/ ml and sodium benzoate in a concentration of 0.8 mg/ ml to 2.0 mg/ml, preferably 1.5 mg/ ml.

The preferred pharmaceutical composition filled into containers made of the different types of packaging has been subject to a long-term stability programme according to the conditions as described in the VICH guideline 3. The conditions used for storage were 25 °C / 60 % r.h. (r.h. = relative humidity), 30 °C / 70 % r.h., and 40 °C / 75 % r.h..

The stability studies of a 0.5 mg/ ml suspension were carried out with 3 ml and 4 ml of the suspension being filled into 5 ml HDPE bottles. It was found that the decrease of sodium benzoate over time was surprisingly high, even directly after filling the container a significant loss of the preservative due to adsorption was observed (see Figure 5). This has not been observed before for any of the suspensions (1.5 mg/ ml or 0.5 mg/ ml) or the differ-

ent fill volumes. The shelf-life of the 1.5 mg/ ml suspension with a 10 ml fill (in a 25 ml bottle) is for example at least 18 months. An acceptable shelf-life for commercial use of the product with a volume size for the treatment of cats for a few days (up to five days) cannot be established by using HDPE as the container material. Storage of the 0.5 mg/ ml in the positive reference, namely glass bottles, shows no decrease in the sodium benzoate over time (see Figure 2).

Table 1:

		0.5 mg/ ml		1.5 mg/ ml	
Ingredient	Function	g/ 100 ml	mg/ ml	g/ 100 ml	mg/ ml
Meloxicam, jet milled, BP	Active ingredient	0.050	0,50	0,150	1,50
Sodium Benzoate, USP, Ph. Eur.	Preservative	0.150	1.50	0.150	1.50
Silica, colloidal anhydrous, USP, Ph. Eur.	Suspending agent	1.000	10.00	1.000	10.00
Hydroxyethyl cellulose, USP, Ph. Eur.	Suspending agent	0.100	1.00	0.100	1.00
Sorbitol Solution 70%, USP, Ph. Eur.	Flavouring agent	35.000	350.00	35.000	350.00
Glycerol	Flavouring agent	12.750	127.50	12.750	127.50
Saccharin Sodium Dihydrate, USP, Ph. EUR.	Flavouring agent	0.010	0.10	0.010	0.10
Xylitol, USP, Ph. Eur	Flavouring agent	15.000	150.00	15.000	150.00
Sodium Dihydrogen Phosphate Dihydrate, USP, Ph. Eur.	pH adjuster	2.000	20.00	2.000	20.00
Citric Acid Monohydrate, USP, PH. EUR.	pH adjuster	0.120	1.20	0.120	1.20
Honey Aroma (203180)	Flavouring agent	0.150	1.50	0.150	1.50
Water for Injection, USP, PH. EUR.	q.s. to 100ml	q.s. to 1 ml	q.s. to 100 ml	q.s. to 100 ml	q.s. to 1 ml

Surprisingly, it was found that the decrease of sodium benzoate content over a time period of 18 months or at least 18 months is significantly lower in PP bottles than in bottles made of either HDPE or LDPE (see Figure 6). Thus, polypropylene is a suitable material for holding small volumes of oral suspensions comprising meloxicam and sodium benzoate as preservative. The suitability of PP is further shown by comparison with the unsuitable negative reference containers made of PET and PC, see figures 1, 3, and 4.

The meloxicam assay is very stable over time and it is demonstrated that the type of packaging material has no impact on meloxicam, see figure 7.

The bottle may be opaque or transparent, preferably opaque.

CLAIMS

1. A plastic container containing a pharmaceutical composition comprising sodium benzoate and meloxicam or a pharmaceutical acceptable salt thereof, characterised in that the container material is selected from one or more members of the group consisting of a homopolymer of polypropylene (PP), a copolymer of polypropylene (PP), a homopolymer of polyethylene terephthalate (PET) and a copolymer of polyethylene terephthalate (PET), and optionally one or more non-polymeric components.

2. A plastic container according to claim 1 having a closure device for storing and preserving a pharmaceutical composition.

3. A plastic container according to any one of claims 1 to 2, which is connected to a dispensing device.

4. A plastic container according to any one of claims 1 to 3 containing a pharmaceutical composition with a volume of 2 ml to 10 ml.

5. A plastic container according to any one of claims 1 to 3 having a volume of 3 ml to 11 ml.

6. A plastic container according to any one of claims 1 to 5 wherein the pharmaceutical composition is a suspension.

7. A plastic container containing a pharmaceutical composition comprising sodium benzoate and meloxicam or a pharmaceutical acceptable salt thereof according to

any one of claims 1 to 6 comprising meloxicam in a concentration of 0.2 mg/ ml to 20 mg/ ml.

8. A plastic container according to claim 7 comprising meloxicam in a concentration of 0.5 mg/ ml to 15 mg/ ml.

9. A plastic container according to claim 7 comprising meloxicam in a concentration of 1.5 mg/ ml.

10. A plastic container according to claim 7 comprising meloxicam in a concentration of 15 mg/ ml.

11. A plastic container containing a pharmaceutical composition comprising sodium benzoate and meloxicam or a pharmaceutical acceptable salt thereof according to any one of claims 1 to 10 comprising sodium benzoate in the concentration range of 0.8 mg/ ml to 2.0 mg/ ml.

12. A plastic container according to claim 11 comprising sodium benzoate in a concentration of 1.5 mg/ ml.

13. A plastic container according to claim 1 to 12 in which its pharmaceutical composition remains substantially stable over a period of 18 months.

14. A plastic container according to any one of claims 1 to 6 and 11 with a volume of 8 ml containing a pharmaceutical composition with a volume of 3.5 ml to 4 ml comprising meloxicam in a concentration of 0.5 mg/ ml and sodium benzoate in a concentration of 1.5 mg/ ml.