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(57) Abstract

Pharmaceutical compositions comprising a calcitonin, an effective amount of an absorption enhancer which is a glycyrrhizinate, an effective amount of benzyl alcohol and a pharmaceutically acceptable carrier are useful in the treatment of conditions such as osteoporosis.

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PHARMACEUTICAL COMPOSITIONS COMPRISING A CALCITONIN, A GLYCYRRHIZINATE AS ABSORPTION ENHANCER AND BENZYL

The present invention relates to novel pharmaceutical compositions containing calcitonins, and to a novel method of enhancing the absorption of a calcitonin across a mucosal membrane.

The calcitonins are a class of pharmacologically active peptides, of both natural and synthetic origin, which contain approximately thirty two amino acids, and which have the ability to regulate serum calcium levels.

Various calcitonins, including e.g. natural human, salmon and eel calcitonins and the synthetic eel calcitonin analogue elcatonin are now commercially available and commonly employed, e.g. in the treatment of Paget's disease, Sudeck's disease and osteoporosis.

A considerable and well known problem with the administration of peptides is that they are susceptible to rapid acid and enzyme-induced degradation when administered orally. For this reason, parenteral administration has been, hitherto, the most widely used means of administration and, in the case of peptides of higher molecular weight, such as the calcitonins, has been the only significant effective means of administration.

It is widely recognised that administration by injection can be both inconvenient and unpleasant for the patient, particularly when the administration has to be repeated at regular intervals for long periods, e.g. in the treatment of post-menopausal osteoporosis with calcitonins. Thus, there has been growing interest in the administration of peptides by more acceptable non-invasive alternative routes, for example in the form of sublingual tablets, suppositories, intrapulmonary powders, intranasal drops, sprays, powders, gels, ointments and inserts.

A significant problem with many peptides, particularly those of higher molecular weights, is that they are only poorly absorbed across biological membranes, e.g. mucosal membranes, and thus the bioavailability of the peptide is often very low. Considerable research has therefore been carried out in order to find methods of improving the trans-epithelial absorption of peptides. One approach is to use an adjuvant or absorption enhancer and there are numerous published reports of compounds which are claimed to have peptide absorption-enhancing properties.

Thus, for example, choline esters (EP 214898), acyl carnitines (EP 215697), aldoses and glucosamines (Japanese Pat. Appl. No. 61 126034), ascorbates and salicylates (EP 37943), alpha-cyclodextrin (EP 0094157), pyroglutamate esters (EP 173990), chelating agents (US 4,476,116) ethanol, benzyl alcohol and polyethylene glycol 400 (EP 371010) have been proposed as absorption enhancers.

There are many published reports that surfactants can enhance the absorption of polypeptides, see for example EP 115627 (Armour), GB 2,127,689 (Sandoz), US 4,548,922 (Carey et al) and Hirai et al., Int. J. Pharm., 9, 165-184, 1981. However, a recognised problem with surfactant absorption promoters is that they can cause irritation and histolesion at the site of administration. These problems become of great importance when the peptide is administered regularly over a prolonged period.

The present applicants have previously found that glycyrrhizinic acid and its salts are excellent absorption promoters for calcitonins and do not give rise to the above-mentioned problems of local toxicity and irritation. Compositions comprising a calcitonin and a glycyrrhizinate are described in our EPA 327756, which includes both liquid and solid formulations. Liquid formulations conventionally contain a preservative and EPA 327756 refers to the use of

alkyl p-hydroxybenzoates (parabens) such as methyl and propyl p-hydroxybenzoate as suitable preservatives.

However, it has subsequently been shown that the antibacterial and preservative actions of the parabens are reduced by the glycyrrhizinate component of the formulation. In addition it would be desirable to increase the absorption of calcitonins still further.

We have now surprisingly found that the inclusion of benzyl alcohol in a composition comprising a calcitonin and a glycyrrhizinate not only gives rise to a preservative action which is not diminished by the glycyrrhizinate, but also enhances the absorption of the calcitonin in a synergistic manner. Thus the use of a glycyrrhizinate in combination with benzyl alcohol increases the transmucosal absorption of a calcitonin by more than the sum of the respective effects of benzyl alcohol and glycyrrhizinate alone.

In a first aspect, therefore, the present invention provides pharmaceutical compositions comprising a calcitonin; an effective amount of an absorption enhancer which is a glycyrrhizinate; an effective amount of benzyl alcohol and a pharmaceutically acceptable carrier.

The present invention also provides a method of enhancing the absorption of a calcitonin across a mucosal membrane, which method comprises co-administering with the calcitonin an effective amount of an absorption enhancer which is a glycyrrhizinate, and an effective amount of benzyl alcohol.

Whilst preservatives are generally only used in liquid formulations, absorption enhancers are required in both liquid and solid formulations of calcitonins, and hence the present invention includes within its scope both solid and liquid compositions.

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