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(54) Title: FENTANYL CONTAINING AEROSOL COMPOSITIONS

(57) Abstract

Fentanyl and physiologically acceptable derivatives thereof dissolved or dispersed in an aerosol propellant to form an aerosol formulation for administration by inhalation.

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Fentanyl containing aerosol compositions.

This invention relates to analgesic formulations and in particular to analgesic formulations comprising fentanyl suitable for administration by inhalation.

Narcotic analgesics are used to relieve moderate to severe pain, particularly of a visceral origin. The narcotic analgesics are generally administered by sub-cutaneous, intra-muscular or intravenous injection, or orally in the form of elixirs, tablets (optionally sublingual) and capsules, or by rectal administration in the form of suppositories. In the case of patients who are hospitalised narcotic analgesics are often administered in the form of saline drips.

Since the metered dose pressurised inhaler was introduced in the mid 1950's, inhalation has become the most widely used route for delivering bronchodilator drugs and steroids to the airways of asthmatic patients. Compared with oral administration of bronchodilators, inhalation offers a rapid onset of action and a low instance of systemic side effects. More recently, inhalation from a pressurised inhaler has been a route selected for the administration of other drugs, e.g., ergotamine, which are not primarily concerned with treatment of a bronchial malady.

Various publications, e.g., British Patents Nos. 830426, 837465, 994734 and 2125426; European Patent Nos. 0162239 and WO86/04233 which relate to self-propelling pharmaceutical compositions for administration from pressurised inhalers disclose the possibility of employing an analgesic such as morphine, diamorphine and buprenorphine hydrochloride in such formulations although there is no disclosure of any specific formulations containing such analgesics nor any indication of their efficiency when administered by inhalation.

It has now been found that morphine and diamorphine hydrochloride are considerably less potent when administered by inhalation using self-propelling aerosol compositions than might have been expected from the known intravenous dosing data. It has also been found that fentanyl and in particular fentanyl citrate exhibits a potent, quick acting effect when administered by inhalation from a self-propelling aerosol formulation.

Therefore according to the present invention there is provided an aerosol formulation comprising fentanyl or a physiologically acceptable derivative thereof dispersed or dissolved in an aerosol propellant.

The invention also provides a pressurised aerosol inhaler comprising a container, containing an aerosol formulation as defined above, and a valve capable of dispensing metered doses of the formulation. The pressurised aerosol preferably incorporates the means to control the dosing frequency from the valve such that not more than a predetermined maximum number of doses may be dispensed within a set period of time. Such a pressurised inhaler allows the maximum dosage frequency available to the patient to be pre-set, whilst insuring the patient cannot receive an overdose. The inhaler provides the benefits of on-demand dosing for the patient with dosage control, and may be used both in hospitals and homes without requiring medical personnel to administer each dose.

The formulations used in the invention contain fentanyl or a derivative thereof either in solution or suspension in the aerosol propellant system, optionally in the presence of a cosolvent. The solvent for fentanyl will generally be present in an amount in the range 5 to 25% by weight of the composition. The compositions may additionally comprise one or more surface active agents, for example oleic acids, complex esters and ester-ethers, e.g., sorbitan trioleate, Span 85, lecithins such as Epikuron 200, and fluorinated surfactants. The weight ratio of surface active agent to fentanyl is generally in

the range 1 : 100 to 10 : 1. The concentration of fentanyl will generally be within the range 0.05 to 5.00%, preferably 0.1 to 1.0%, by weight based on the total composition.

A wide range of propellants may be used in the aerosol formulations of the invention including:

Propellant 11	trichloromonofluoromethane
Propellant 12	dichlorodifluoromethane
Propellant 13	monochlorotrifluoromethane
Propellant 21	dichloromonofluoromethane
Propellant 22	monochlorodifluoromethane
Propellant 113	trichlorotrifluoroethane
Propellant 114	dichlorotetrafluoroethane
Propellant 115	monochloropentafluoroethane
Propellant 134a	1,1,1,2-tetrafluoroethane
Propellant 500	azeotrope of dichlorodifluoromethane and 1,1-difluoroethane

In addition to chlorofluorocarbon aerosol propellants the formulations may contain other propellants, for example, DME (dimethylether), hydrocarbons and perfluorocarbons.

One preferred propellant system is disclosed in our co-pending British Patent Application No. 8828477.3 and comprises 1,1,1,2-tetrafluoroethane, a surface active agent and at least one compound having a higher polarity than 1,1,1,2-tetrafluoroethane. Suitable compounds having a higher polarity than 1,1,1,2-tetrafluoroethane include alcohols, such as ethyl alcohol, isopropyl alcohol, propylene glycol, hydrocarbons such as propane, butane, isobutane, pentane, isopentane, neopentane, and mixtures thereof. The 1,1,1,2-tetrafluoroethane preferably comprises at least 50% by weight of the formulation, preferably from 60 to 95% by weight of the formulation. The weight ratio of 1,1,1,2-tetrafluoroethane to the compound of higher polarity is generally in the range 50 : 50 to 90: 1, preferably 70 : 30 to 98 : 2, more preferably 85 : 15 to 95 : 5.

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