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(54) Benævnelse: **Ikke-mucoadhæsive filmdoseringsformer**

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DESCRIPTION

Field of the invention

[0001] The present invention relates to orally disintegrating film dosage forms for delivering active pharmaceutical agents, methods of formulating the dosage forms to promote gastrointestinal absorption comparable to immediate release solid oral dosage forms, and to methods of using the dosage forms for the treatment of various medical conditions.

Background of the Invention

[0002] Orally administered film strip dosage forms have been recently developed for the pharmaceutical industry, and are currently used for the sale of several popular over-the-counter drug products, including Listerine® breath strips, Triaminic® thin strips (active agent = diphenhydramine HCl), and Sudafed PE™ quick dissolve strips (active ingredient = phenylephrine HCl). The absolute bioavailability of diphenhydramine when ingested orally is approximately 61%, and the time to maximum serum concentration is about 3-4 hours. Phenylephrine is subject to extensive presystemic metabolism in the gut wall, such that the absolute bioavailability of phenylephrine when ingested orally is approximately 40% relative to intravenous dosing, and peak plasma concentrations are achieved in about 1-2 hours.

[0003] In addition, several manufacturers have proposed formulations that could be used to deliver prescription drugs. The vast majority of these formulations are "mucoadhesive" formulations designed for adhesion of the dosage form to mucosal tissue in the mouth, and transmission of the drug from the dosage form through the mucosal tissue into the systemic circulation. As described in U.S. Patent No. 6,750,921 to Kim et al., film-forming agents have been used to manufacture drug delivery formulations for percutaneous or transdermal application, but these necessarily involve an adhesive composition to retain the agent in situ long enough to cause sustained release of the active ingredient. Bioerodible films are described in Tapolsky et al., U.S. Patent No. 5,800,832. The films have an adhesive layer and a non-adhesive backing layer and are intended to adhere to the mucosal surface. Biegajski et al., U.S. Patent No. 5,700,478, describes a water-soluble pressure-sensitive mucoadhesive suitable for use in a mucosal-lined body cavity.

[0004] The purported advantage of these mucoadhesive films resides in their ability to bypass the gastrointestinal tract, and barriers in the gastrointestinal tract to drug absorption such as first pass metabolism and decomposition of the active ingredient in the stomach. An additional advantage for these dosage forms, when compared to tablets, capsules and other dosage forms that must be swallowed, is that some patient populations have difficulty swallowing, such as children and the elderly.

[0005] From WO2005/039543 A1 self-supporting films for pharmaceutical and food use are known. The teaching of that disclosure aims at providing a film which rapidly disintegrates and has a clean mouth sensation. This is achieved by using maltodextin as the filmogenic substance. The

film can contain ondansetron as the active ingredient.

[0006] Until now the prior art has been focused principally on improving the delivery profile of a given pharmaceutical agent with this dosage form, by increasing its rate of dissolution or absorption, or bypassing metabolic processes that reduce the bioavailability of the drug. The prior art has not appreciated that an innovator's drug product, be it a tablet, capsule, or other oral dosage form, has already proven itself effective through rigorous clinical testing, and that the innovator's product may already provide the optimum bioavailability of pharmaceutical agent. What is needed is a film product that mimics the pharmacokinetics of an innovator's product, and that follows the same metabolic and bioabsorption pathways as the innovator's product, to ensure that the dosage form achieves the proven clinical efficacy of the innovator product.

Objects of the invention

[0007] Accordingly, it is an object of the present invention to provide non-mucoadhesive orally disintegrating film dosage forms containing ondansetron that mimic the pharmacokinetic profile of orally administered drug products such as tablets, capsules, liquid suspensions, and orally dissolving/dispersing tablet (ODT).

[0008] The object of the invention is to provide non-mucoadhesive orally disintegrating film dosage forms containing ondansetron that follow the same metabolic and bioabsorption pathways through the gastrointestinal tract as existing orally administered drugs, such as tablets, capsules, liquid suspensions, and orally dissolving/dispersing tablet (ODT).

[0009] It is thus the object of the present invention to provide non-mucoadhesive orally disintegrating film dosage forms containing ondansetron so that they follow the same metabolic and bioabsorption pathways, and obtain the same pharmacokinetic profiles, as existing orally administered drugs such as tablets, capsules, liquid suspensions, and orally dissolving/dispersing tablet (ODT).

[0010] Another object of the present invention is to provide methods of treatment using the film dosage forms of the present invention, and methods that promote bioequivalence to orally administered drug products such as tablets, capsules, liquid suspensions, and orally dissolving/dispersing tablet (ODT).

Summary of the invention

[0011] The present invention provides film dosage forms that are formulated or administered for gastrointestinal absorption of the active pharmaceutical agent, and that are bioequivalent to and interchangeable with existing orally administered drug products. These film dosage forms are non-mucoadhesive; they quickly disintegrate in the mouth when exposed to saliva; and they are absorbed predominantly through the gastrointestinal tract. Most importantly, these dosage forms are specially formulated to meet exacting bioavailability requirements, or to be bioequivalent to

existing orally administered dosage forms.

[0012] Therefore, in a first principal embodiment, the invention provides a non-mucoadhesive orally disintegrating film, able to disintegrate upon contact with saliva in the buccal cavity within about sixty seconds, wherein said film comprises 15.84 % ondansetron as base, 43.56 % polyvinylalcohol, 11.88 % polyethylene glycol, 3.96 % glycerol anhydrous, 19.80 % rice starch, 0.40 % acesulfam K, 0.59 % titanium dioxide, 1.98 % menthol and 1.98 % polysorbate per film, all percentages being by weight. The film strip of the present invention can be defined by its pharmacokinetics, and the film strip has an absolute bioavailability of greater than 65%, 75%, 85% or even 95% when administered orally. The film strip has an absolute bioavailability that is greater than about 45%, 50%, or 55%, and peak plasma concentrations (C_{max}) in less than 3.0, 2.5 or 2.0 hours. Finally, because the film dosage form is specially formulated or administered for gastrointestinal absorption, the film dosage form has a comparable absolute bioavailability or T_{max} as an immediate release tablet or capsule or orally dissolving/dispersing tablet (ODT) that comprises the same amount of active pharmaceutical agent.

[0013] The films themselves, and the methods of using the films, are characterized by a number of features that ensure their bioequivalence to a comparable immediate release tablet or capsule or orally dissolving/dispersing tablet (ODT), including:

- the films are engineered or used so that the active pharmaceutical agent is swallowed and absorbed predominantly or entirely through the gastrointestinal tract, instead of being absorbed through the oral mucosa;

- the films or active pharmaceutical agent are formulated so that absorption of active pharmaceutical agent through the oral mucosa is retarded;

- the films are designed for rapid disintegration when taken orally, and are most often swallowed in less than thirty or sixty seconds after administration;

- the films are usually applied directly onto the tongue to promote mixing with the saliva and subsequent swallowing of the active ingredient, and thereby discourage mucosal absorption; and

- water could be aditionally swallowed within about thirty or sixty seconds after administration of the film, to further promote swallowing of the active agent and gastrointestinal absorption.

[0014] The drug is an ondansetron film strip, which is characterized by an absolute bioavailability of ondansetron of from about 45% to about 75%, and which is formulated as a base to retard absorption through the oral mucosa.

[0015] Additional advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and

explanatory only and are not restrictive of the invention, as claimed.

Description of the figures

[0016]

Figure 1 is a comparison of dissolution profiles over time comparing three commercially available formulations of ondansetron with two ondansetron RapidFilm formulations, as described in Table 4. The upper line at 1 minute is Zofran® 4 mg Zydis® Lingual; the second line at 1 minute is Zofran® 8 mg Zydis® Lingual; the third line is ondansetron 8 mg RapidFilm; the fourth line is ondansetron 4 mg RapidFilm; the bottom line is Zofran® 8 mg Filmtablet.

Figure 2 depicts mean (FIG 2A) and log mean (FIG 2B) drug plasma concentration profiles versus time for 8 mg ondansetron RapidFilm investigational product versus Zofran® 8 mg Lingual orally disintegrating tablets, as described in Table 6.

Figure 3 is a stacking x-ray diffraction pattern for three samples - (1) ondansetron base Form B polymorph, (2) RapidFilm comprising 4 mg of ondansetron having the formulation of Table 4 and stored at 40 °C, and (3) RapidFilm comprising 4 mg of ondansetron having the formulation of Table 4 (OND 013 OD), and stored at 60 °C (84201506).

Figure 4 is an X-ray diffraction pattern for ondansetron base Form B.

Detailed description of the invention

[0017] The present invention may be understood more readily by reference to the following detailed description of preferred embodiments of the invention and the Examples included therein.

Definitions and Use of Terms

[0018] As used in this specification and in the claims which follow, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an ingredient" includes mixtures of ingredients, reference to "an active pharmaceutical agent" includes more than one active pharmaceutical agent, and the like.

[0019] The term "disintegrate" has its usual and customary meaning in the pharmaceutical arts, as described in <701> of the U.S. Pharmacopoeia (2005 USP/NF) for uncoated tablets, using a basket rack assembly operating at 30 cycles per minute through a distance of 5.5 cm, in a disintegration medium at 37 °C. When disintegration requirements are discussed herein, they are preferably met under the foregoing testing conditions, at a pH of 4.0 or 6.8. A film or other dosage form is said to be "disintegrated" if it is completely disintegrated, a state in which any residue of the

unit remaining on the screen of the test apparatus, or in the mouth, is a soft mass having no palpably film core, or fragments of a tablet coating or capsule shell. Disintegration thus does not imply complete dissolution of the dosage unit or even the active constituent, although a dissolved dosage unit would typically be completely disintegrated. When reference to Ph. Eur. 2.9.1 (disintegration) is made herein, it will be understood that the disintegration conditions described above under <701> USP can also be employed.

[0020] The term "dissolution" also has its usual and customary meaning in the pharmaceutical arts, as described in <711> and <724> of the U.S. Pharmacopoeia (2005 USP/NF). Therefore, a film is said to be "dissolved" if, upon testing by the method of U.S. Pharmacopoeia (2005 USP/NF), the amount of active agent dissolved in the dissolution medium exceeds a predetermined percentage. When dissolution conditions are given, it will be understood that stirring preferably occurs in 0.1N hydrochloric acid buffer (pH=2), or at pH 1.2, pH 4.0 or 6.8, at 37° C, using the paddle method at 50 rpm in a type II dissolution apparatus.

[0021] The term "immediate release," when used in this document, refers to a dosage form that allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug. The term includes tablets, capsules, liquid suspensions, orally disintegrating/dispersing tablet (ODT), and other dosage forms intended for immediate release of active ingredient upon administration (preferably oral administration). In contrast, a "modified release" dosage form is a dosage form whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or immediate release dosage form. Modified release solid oral dosage forms include both delayed and extended release drug products.

[0022] An "immediate release" dosage form as used herein preferably refers to a dosage form adapted to release at least 80% or 90% of an active pharmaceutical ingredient in 60 minutes or less when measured in a type II dissolution apparatus (as described in <711> and <724> of the U.S. Pharmacopoeia (2005 USP/NF)), in 0.1N hydrochloric acid buffer (pH=2), or at pH 1.2, pH 4.0 or 6.8, at 37° C. In a preferred embodiment, at least 80%, 90% or 100% is dissolved in no more than 45 or 30 minutes. Stirring preferably occurs using the paddle method at 50 rpm. Finally, it will be understood that when reference to Ph. Eur. 2.9.3 (paddle over disc) is made herein, the foregoing dissolution conditions under <711> and <724> of the U.S. Pharmacopoeia (2005 USP/NF) can be applied.

[0023] An immediate release solid oral dosage form is considered "rapidly dissolving" when not less than 80% of the label amount of the drug substance dissolves (i.e. releases) within 15 minutes in each of the following media: (1) pH 1.2, (2) pH 4.0, and (3) pH 6.8, in accordance with Q6 ICH-guideline.

[0024] A "orally dissolving or orally dispersible tablet" ("ODT") refers to an uncoated tablet intended to be placed in the mouth where it can disperse rapidly before being swallowed, as described in Eur. Ph. 5.0. An ODT disintegrates within three minutes when tested according to the disintegration testing described herein.

[0025] The term "non-mucoadhesive" means that the dosage form is not designed for administration of the active pharmaceutical agent through the oral mucosa. I.e. the dosage form is not designed to adhere to the mucosal surfaces of the buccal cavity as an intact film or disintegrated film residue.

[0026] Unless specified otherwise, the term "wt. %" as used herein with reference to the final product (i.e., the film, as opposed to the formulation used to create it), denotes the percentage of the total dry weight contributed by the subject ingredient. This theoretical value can differ from the experimental value, because in practice, the film typically retains some of the water and/or ethanol used in preparation.

[0027] When doses are given for a drug and its salt, it will be understood that the calculated dose is based on the molecular weight of the active pharmaceutical ingredient, which includes the cationic and anionic species in the case of a salt, and just the base when the active principle is not present as a salt. In addition, when reference is made to the salt of a drug and pharmaceutically acceptable salts thereof, it will be understood that salts of the base form of the base drug are intended.

[0028] When ranges are given by specifying the lower end of a range separately from the upper end of the range, it will be understood that the range can be defined by selectively combining any one of the lower end variables with any one of the upper end variables that is mathematically possible.

[0029] When used herein the term "about" or "ca." will compensate for variability allowed for in the pharmaceutical industry and inherent in pharmaceutical products, such as differences in product strength due to manufacturing variation and time-induced product degradation. The term allows for any variation which in the practice of pharmaceuticals would allow the product being evaluated to be considered bioequivalent to the recited strength of a claimed product.

[0030] The term "absolute bioavailability" refers to the availability of the active drug in systemic circulation after non-intravenous administration (i.e., after oral, rectal, transdermal, subcutaneous administration). In order to determine absolute bioavailability of a drug, a pharmacokinetic study must be done to obtain a plasma drug concentration versus time plot for the drug after both intravenous (IV) and non-intravenous administration. The absolute bioavailability is the dose-corrected area under curve (AUC) non-intravenous divided by AUC intravenous.

[0031] When pharmacokinetic parameters are given herein (i.e. T_{max}, absolute bioavailability, etc.), it will be understood that they can refer to the mean, median, or individual observed pharmacokinetics, and that mean pharmacokinetics are intended when claimed unless stated to the contrary.

[0032] As discussed above, the invention provides a physiologically acceptable film that is particularly well adapted to disintegrate rapidly when placed on the tongue of a patient, and to facilitate gastrointestinal absorption of the pharmaceutically active agent. The film and active agent need not dissolve entirely in the mouth, and preferably the film is not entirely dissolved. When tested according to Ph. Eur. 2.9.3, paddle over disc, the film preferably dissolves (at least 80% or

100% active agent release) within about 15, 10 or 5 minutes, when tested at pH 1.2, 4.0 or 6.8.

[0033] The film may also be characterized by the time it takes to disintegrate completely, and it preferably disintegrates to a soft residue within about 10, 20, 30 or 60 seconds of administration, after which it is swallowed. These disintegration times are preferably observed in the oral cavity when the film is administered, as well as when tested for disintegration using the method described in Ph. Eur. 2.9.1. The prompt disintegration and swallowing of the film helps to assure gastrointestinal absorption of the dosage form. The film is not of the conventional mucoadhesive type, designed to deliver active agent transmucosally.

[0034] The film can be defined by the absolute bioavailability (i.e. total extent of absorption) of the active ingredient and the film has an absolute bioavailability that is greater than about 45%, 55%, 65%, 75%, 85% or even 95%. The film is defined by the rate or extent of absorption of active agent into the bloodstream, in addition or alternatively to the absolute bioavailability of the active agent. For example, the film can be defined by T_{max} (i.e. time to maximum concentration of the active agent in plasma) and the film has a T_{max} less than about 3.0, 2.5 or 2.0 hours. Alternatively or in addition, the film can be defined by an absolute bioavailability greater than about 45%, 50%, or 55%.

[0035] The invention is defined by its bioequivalence to an immediate release dosage tablet or capsule or orally dissolving/dispersing tablet (ODT) that contains the same amount of active pharmaceutical agent (i.e. a "reference product").

[0036] The reference product can be defined by various pharmacokinetic or physical properties. For example, the reference product could be characterized by its absolute bioavailability, and preferably the absolute bioavailability is greater than about 65%, 75%, 85% or even 95% when administered orally, and/or a T_{max} greater than about or 4.5 hours. The reference product could also be characterized by its T_{max} and/or absolute bioavailability, i.e. a T_{max} less than about 3.0, 2.5, 2.0 or even 1.5 or 1.0 hours, and/or an absolute bioavailability greater than about 45%, 50%, or 55%.

[0037] Alternatively, the reference product could be characterized by its disintegration time which, in various embodiments could exceed 5, 10, 20, 30, 40 or 45 minutes, when tested according to Ph. Eur. 2.9.1, and preferably would be less than 60, 75 or 90 minutes. The reference product could also be defined by its dissolution time. Dissolution times for the comparative reference products of the present invention, when tested according to Ph. Eur. 2.9.3, based on the time it takes to dissolve 75, 80, 85, 90 or 95 wt.% of the drug substance, when tested at pH 1.2, 4.0 and/or 6.8, are preferably greater than about 5, 10, 20, 30, 40 or 45 minutes, and less than about 90, 75 or 60 minutes. In a preferred embodiment, the dissolution profile for the reference product is in accordance with the following specification: not less than 70, 80, 90 or 95% dissolved after 60 minutes when tested according to Ph. Eur. 2.9.3 (paddle over disc). In one embodiment, the reference product is a capsule, optionally characterized by a gelatin shell. In another embodiment, the reference product is a tablet, optionally characterized by a film or enteric coating. In another embodiment, the reference product is a orally dissolving/dispersing tablet (ODT).

[0038] The film can also be characterized by various physical characteristics, including its structure, size and shape. For example, in one embodiment, the film is a single layer homogeneous film. In another embodiment, the film has a weight of from about 30 to about 150 milligrams, preferably from about 40 to about 120 milligrams. The film may vary in thickness anywhere from about 10 to about 200 microns, and preferably does not exceed 8 or 7 cm^2 in surface area.

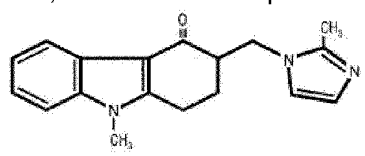
Bioequivalence Testing

[0039] Bioequivalence testing typically requires an in vivo test in humans in which the concentration of the active ingredient or active moiety, and, when appropriate, its active metabolite(s), in whole blood, plasma, serum, or other appropriate biological fluid is measured as a function of time. Defined as relative bioavailability ("BA"), bioequivalence ("BE") involves a comparison between a test and reference drug product. Although BA and BE are closely related, BE comparisons normally rely on (1) a criterion, (2) a confidence interval for the criterion, and (3) a predetermined BE limit.

[0040] A standard in vivo BE study design is based on the administration of either single or multiple doses of the test and reference products to healthy subjects on separate occasions, with random assignment to the two possible sequences of drug product administration. Statistical analysis for pharmacokinetic measures, such as area under the curve (AUC) and peak concentration (C_{max}), is preferably based on the so-called "two one-sided tests procedure" to determine whether the average values for the pharmacokinetic measures determined after administration of the test and reference products are comparable. This approach is termed average bioequivalence and involves the calculation of a 90% confidence interval for the ratio of the averages (population geometric means) of the measures for the test and reference products. To establish BE, the calculated confidence interval should fall within a BE limit, i.e. 80-125% for the ratio of the product averages. Further detail regarding BE procedures can be found in FDA's July 1992 Guidance Document entitled "Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design," the contents of which are incorporated herein by reference.

The active Agent

[0041] The pharmaceutically active agent is ondansetron as its base. Ondansetron is chemically known as (±) 1,2,3,9 tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, and its base is represented by the following chemical structure:



[0042] The invention provides an ondansetron film strip, wherein the ondansetron is provided in base form to promote GI absorption of the ondansetron.

[0043] The invention also provides a non-mucoadhesive orally disintegrating film, able to disintegrate upon contact with saliva in the buccal cavity within about sixty seconds, consisting of 8.0 mg ondansetron as base, 22.0 mg polyvinylalcohol, 6.0 mg polyethylene glycol, 2.0 mg glycerol anhydrous, 10.0 mg rice starch, 0.2 mg acesulfam K, 0.3 mg titanium dioxide, 1.0 mg menthol and 1.0 mg polysorbate.

[0044] In a further embodiment the invention relates to a non-mucoadhesive orally disintegrating film, able to disintegrate upon contact with saliva in the buccal cavity within about sixty seconds, consisting of 4.0 mg ondansetron as base, 11.0 mg polyvinylalcohol, 3.0 mg polyethylene glycol, 1.0 mg glycerol anhydrous, 5.0 mg rice starch, 0.1 mg acesulfam K, 0.15 mg titanium dioxide, 0.5 mg menthol and 0.5 mg polysorbate.

[0045] It is known that ondansetron can exist in several polymorphic forms, including Forms A, B, C, D and E (see WO 03/093260 and WO 2005/080381). It has been unexpectedly found that the crystalline purity of the ondansetron in the final product influences the physical properties of the final film, and that highly pure form B is particularly preferred. In particular, for films stored at higher temperatures 60 °C, physical changes in the RapidFilm have been detected, including added rigidity, warps and folding, and these changes are associated with a decrease in peak intensity and decreased purity of Form B. See Fig. 4 (where OND 013 OD refers to a RapidFilm product stored at 40 °C, and 84201506 refers to the same formulation stored at 60 °C).

[0046] Therefore, in yet another embodiment, the film comprises form B polymorph that is essentially free of other polymorphic forms, i.e. greater than 70, 80, 90, 95, 98 or even 99% pure. Form B can be evaluated by X-ray diffraction as described more particularly in Example 8. Alternatively or in addition, the product is characterized by a melting endotherm at 244±2 °C when subjected to differential scanning calorimetry.

[0047] In another embodiment, the invention provides methods of using the ondansetron film strips of the present invention, for the treatment or prevention of emesis, including emesis resulting from postoperative nausea and vomiting, chemotherapy induced nausea and vomiting, and radiation induced nausea and vomiting. Therefore, the invention also provides a method of treating or preventing emesis in a human patient comprising administering to the tongue of said patient, preferably from one to three times daily, an ondansetron film strip of the present invention that contains from about 4 to about 24 mg of ondansetron base, preferably 4 or 8 mg of ondansetron base. The method is preferably practiced with an additional step that promotes gastrointestinal absorption of said ondansetron, such as swallowing said film within about sixty seconds of said administration, with or without water.

[0048] Particular pharmacokinetic profiles of drug of interest are set forth below in Table A.
TABLE A

Pharmaceutical Agent	Preferred Dose	Preferred Dosing Schedule	Preferred Pharmacokinetic Parameters
Ondansetron Base (Zofran®)	4 mg 8 mg 24 mg	1-3 Times Daily, Not To Exceed 24 mg Per Day	Bioavailability in Healthy Subjects = ca. 45-75% (56% for 8 mg tablet)
			T_{max} = 1.5 - 2.5 Hours
			Plasma concentrations are not dose proportionate
			Bioavailability slightly enhanced by food

Dispensing/Packaging Format

[0049] The films of the present invention can be provided in various dispensing and/or packaging configurations. For example, in one embodiment, the films would be packaged in a dose card that contains a plurality of individually wrapped films protected by moisture impermeable removable laminar covers. Examples of suitable dose cards are reported, for example, in U.S. Patent No. 6,520,329, WO 2006/056161, WO 02/059012, EP 1 353 857, and WO 01/62621.

[0050] In another embodiment, the films would be packaged in a hermetically sealed, moisture impermeable flat pouch comprising two walls adhered around the edges. In a preferred embodiment, the packaging prevents the dosage form from absorbing more than 4.0, 3.0, 2.0 or even 1.0 wt.% moisture in three months when stored at 40 °C and 75% relative humidity.

[0051] The invention relates to a non-mucoadhesive orally disintegrating film, able to disintegrate upon contact with saliva in the buccal cavity within about sixty seconds, comprising ondansetron or as a base, wherein said film comprises 15.84 % ondansetron as base, 43.56 % polyvinylalcohol, 11.88 % polyethylene glycol, 3.96 % glycerol anhydrous, 19.80 % rice starch, 0.40 % acesulfam K, 0.59 % titanium dioxide, 1.98 % menthol and 1.98 % polysorbate per film, all percentages being by weight. Said film is characterized predominantly by gastrointestinal absorption when placed on the tongue, allowed to disintegrate, and subsequently swallowed;
said film can comprise from about 4 to about 24 mg of ondansetron or pharmaceutically acceptable salt thereof and can have a T_{max} of from about 1.5 to about 2.5 hours. Said ondansetron has an absolute bioavailability in said dosage form of from about 45% to about 75%.

[0052] In one embodiment said ondansetron containing film comprises Form B ondansetron base.

[0053] The invention relates further to the use of said non-mucoadhesive orally disintegrating film containing odansetron in the manufacture of a medicament for the treatment or prevention of emesis in a human patient, for the administration of said film to the tongue of said patient, for swallowing said film within about sixty seconds of administration, and predominantly for the

gastrointestinal absorption of said ondansetron or pharmaceutically acceptable salt thereof.

[0054] The invention relates further to the use of said non-mucoadhesive orally disintegrating film containing ondansetron in the manufacture of a medicament for the treatment or prevention of emesis in a human patient, wherein said emesis is from postoperative nausea and vomiting, chemotherapy induced nausea and vomiting, or radiation induced nausea and vomiting.

[0055] The invention relates further to the use of said non-mucoadhesive orally disintegrating film containing ondansetron in the manufacture of a medicament for the treatment or prevention of emesis in a human patient wherein said film comprises Form B ondansetron base.

[0056] The invention relates further to the use of said non-mucoadhesive orally disintegrating film containing ondansetron in the manufacture of a medicament for the treatment or prevention of emesis in a human patient wherein greater than 95 wt.% of said ondansetron is absorbed gastrointestinally.

[0057] In one embodiment said film is in the form of a single layer.

[0058] In a further embodiment said film used in the manufacture of a medicament is provided on a dose card that contains a plurality of individually wrapped films protected by moisture impermeable removable laminar covers.

[0059] In one embodiment of the invention said film used in the manufacture of a medicament is wrapped individually in a moisture impermeable flat pouch comprising two walls adhered around the edges.

[0060] In a preferred embodiment said method further comprises packaging said film from said second batch in a dose card that contains a plurality of individually wrapped films protected by moisture impermeable removable laminar covers.

[0061] In one embodiment said method further comprises packaging said film from said second batch in a moisture impermeable flat pouch comprising two walls adhered around the edges.

Examples

[0062] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.) but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C or is at room temperature, and pressure is at or near atmospheric.

Example 1 -- Representative Ondansetron Formulation

[0063] Table 1 depicts a representative film formulation that contains 8.0 mg of ondansetron as its base, in order to promote gastrointestinal absorption.

Table 1: Representative Formulation of Ondansetron Base Film Dosage Form

Pos.	Ingredient	Amount per Film [mg]	Amount per Film [%]
1	Ondansetron (as base)	8.0	15.84
2	Mowiol (Polyvinylalcohol)	22.0	43.56
3	PEG (polyethylene glycol)	6.0	11.88
4	Glycerol anhydrous	2.0	3.96
5	Rice Starch	10.0	19.80
6	Acesulfam K	0.2	0.40
7	Titanium dioxide	0.3	0.59
8	Menthol	1.0	1.98
9	Polysorbate	1.0	1.98
	TOTAL	50.5	100.0

Example 1A -- Comparative Bioavailability of Zofran® Brand Tablets

[0064] Tables 2 and 3 present clinical pharmacokinetic data for Zofran® brand immediate release 8 mg and 24 mg tablets, as reported in the Food and Drug Administration (FDA) approved prescribing information for this product:

Table 2: Pharmacokinetics in Normal Volunteers Single 8 mg Zofran® Tablet Dose

Age-group (years)	Mean Weight (kg)	n	Peak Plasma Concentration (ng/mL)	Time of Peak Plasma Concentration (h)	Mean Elimination Half-life (h)	Systemic Plasma Clearance L/h/kg	Absolute Bioavailability
18-40 M	69.0	6	26.2	2.0	3.1	0.403	0.483
F	62.7	5	42.7	1.7	3.5	0.354	0.663
61-74 M	77.5	6	24.1	2.1	4.1	0.384	0.585
F	60.2	6	52.4	1.9	4.9	0.255	0.643
≥75 M	78.0	5	37.0	2.2	4.5	0.277	0.619
F	67.6	6	46.1	2.1	6.2	0.249	0.747

Table 3: Pharmacokinetics in Normal Volunteers Single 24 mg Zofran® Tablet Dose

Age-group (years)	Mean Weight (kg)	n	Peak Plasma Concentration (ng/mL)	Time of Peak Plasma Concentration (h)	Mean Elimination Half-life (h)
18-43 M	84.1	8	125.8	1.9	4.7

Age-group (years)	Mean Weight (kg)	n	Peak Plasma Concentration (ng/mL)	Time of Peak Plasma Concentration (h)	Mean Elimination Half-life (h)
F	71.8	8	194.4	1.6	5.8

Example 2 - Comparative Ondansetron Dissolution Study

[0065] Dissolution studies were conducted on five different orally administered ondansetron products: Zofran®4 mg Zydis® Lingual; Zofran® 8 mg Zydis® Lingual; ondansetron 4 mg RapidFilm having the formulation of Table 4; ondansetron 8 mg RapidFilm having the formulation of Table 4 (punched in 6 cm^2 rectangles); and Zofran® 8 mg Filmtablet.

Table 4: Ondansetron RapidFilm Formulation

Ingredients		**Master Batch Formula [g/100g]**	**Formula dosage form [mg/unit] [3.00 cm^3final film]**
Ondansetron Base		**6,8116**	4,000
Polyvinylalcohol 4-88		**18,7321**	11,000
PEG 1000		**5,1088**	3,000
Glycerol anhydr.		**1,7032**	1,000
Rice starch		**8,5149**	5,000
Acesulfam K		**0,1707**	0,100
Titanium dioxide		**0,2559**	0,150
Levomenthol		**0,8514**	0,500
Polysorbate 80		**0,8514**	0,500
Ethanol 96%		**23,7519**	Removed
Purified Water		**33,2481**	Removed

[0066] Dissolution studies were performed according to Ph. Eur. 2.9.4, paddle, sinker, 900 ml, using 0.1N HCl buffered water at pH 1.0. Stirring occurred at 100 rpm and 37 °C. Relative pharmacokinetics are reported in Table 5 below and Figure 1.

Table 5:

Lot.	5G033	R208046	OND008OD_mg	5H010	OND008OD_4mg
Time	Zofran 8mg Film tablet	Zofran 8 mg Zydis Lingual	Ondanaetron 8 mg Rapid Film	Zofran 4 mg Zydia Lingual	Ondanaetron 4 mg Rapid Film
[min]	[%]	[%]	[%]	[%]	[%]
0	0	0	0	0	0
1	0.8	100.3	97.1	102.3	71.8
3	9	104.6	102	101.7	98.4
5	22.7	103.4	102.4	101.4	103.3
7	63.4	102.1	101.7	101.3	105
10	103.3	100.8	100.8	101.8	105.2

Example 3 - Comparative Ondansetron Bioavailability Study

[0067] A clinical study was conducted to compare the bioavailability profile and the pharmacokinetic parameters of two medicinal products containing 8 mg ondansetron: (1) ondansetron RapidFilm formulated having the formulation reported in Table 4, and (2) Zofran®8 mg. Zydis Lingual-Orally Disintegrating Tablets.

[0068] The study was a randomized, single dose, two way, two sequence crossover, open label with seven days washout period study under fasting conditions. Orally disintegrating tablet and RapidFilm was allowed to dissolve in the subject's mouth for about 10 seconds before the patient was asked to swallow. The study included 7 healthy adult Caucasian males.

[0069] Table 6 reports pharmacokinetic and bioequivalence parameters observed during the study. Figure 1 is a comparison of dissolution profiles over time comparing three commercially available formulations of ondansetron with two ondansetron RapidFilm formulations, as described in Table 4. Figure 2 depicts mean (FIG 2A) and log mean (FIG 2B) drug plasma concentration profiles versus time for 8 mg ondansetron RapidFilm investigational product (Table 4) versus Zofran®8 mg. Lingual orally disintegrating tablets.

Table 6:

Pharmacokinetic Parameter	Investigational Product (Algebraic Mean ± SD)	Reference Product (Algebraic Mean ± SD)
C_{max}(ng/ml)	18.75 ± 6.262	20.37 ± 6.470
AUC_{0-t}(ng*hr/ml)	94.11 ± 38.078	100.05 ± 48.826
$AUC_{0-\infty}$(ng*hr/ml)	98.18 ± 39.345	103.66 ± 49.691
T_{max}(hr)	1.58 ± 0.408	1.71 ± 0.749
T_{lag}(hr)	0.08 ± 0.204	0.08 ± 0.204

Pharmacokinetic Parameter	Investigational Product (Algebraic Mean ± SD)		Reference Product (Algebraic Mean ± SD)
$T_{1/2}$(hr)	3.45 ± 0.817		3.62 ± 0.624
$K_{elimination}$(hr^{-1})	0.2111 ± 0.05284		0.1965 ± 0.03480
(AUC_{0-t}/$AUC_{0-\infty}$)%	95.67 ± 1.467		96.24 ± 1.362
BE Assessment Parameter	C_{max} (80.00-125.00)	AUC_{0-t} (80.00-125.00)	$AUC_{0-\infty}$ (80.00-125.00)
Point Estimate (%)	91.84	96.32	96.79
Lower Limit (%)	72.64	82.87	83.81
Upper Limit (%)	116.13	111.96	111.78
Prob<80.00	0.1389	0.0291	0.0239
Prob>125.00	0.0244	0.0105	0.0096

Example 4 -- Methods of Characterizing Crystalline forms

[0070] *Instrumentation* - X-ray diffraction patterns can be obtained on a Miniflex X-ray diffractometer (Rigayu), by laying the sample on a static sample holder. The goniometer radius is 150 mm.

[0071] The X-ray tube has a copper target, with a current intensity of 15 mA and a voltage of 30 kV: the radiation generated by the Cockcroft-Walton method, is constituted by $K_{\alpha 1}$(1.540562 Å) and $K_{\alpha 2}$(1.544398 Å); nickel filter is used for the suppression of K_{β} radiation (1.392218 Å).

[0072] The detector is a NaI scintillator with a beryllium window. Continuous scanning occurred using a sampling width of 0.01 deg and a scanning rate of 2 deg/minute; 2 θ range of 2 ÷ 50 deg. The sample holder was amorphous glass , and the sample was pressed with a glass plate.

[0073] Differential Scanning Calorimetry (DSC) thermograms is carried out with a DSC 821^e instrument (Mettler Toledo). Temperature is set at 10 °C/minute, and the nitrogen flow at 30 ml/min.

[0074] An X-ray diffraction pattern for ondansetron base Form B is depicted in Figure 4; X-ray diffraction peaks are reported in Table 7.

Table 7:

Peak no.	2theta	Flex Width	d-value	Intensity	I/Io
1	5.560	*****	15.8817	477	8

Peak no.	2theta	Flex Width	d-value	Intensity	I/Io
2	7.160	0.188	12.3359	6800	100
3	10.360	0212	8.1400	5031	74
4	11.120	0235	7.9502	3949	59
5	13.140	0259	6.7322	1855	28
6	14.640	0.188	6.0456	2315	35
7	16.320	0.306	5.4269	2690	40
8	17.180	0212	5.1571	968	15
9	20.600	0.188	4.3080	2995	45
10	21.220	0.212	4.1835	2184	33
11	22.020	0.141	4.0333	1150	17
12	23.980	0235	3.7079	3420	51
13	24.660	0259	3.6072	3563	53
14	25.260	0306	3.5228	5176	77
15	26.500	0.282	3.3607	2324	36
16	27.700	0.165	3.2178	1443	22

[0075] It is intended that the specification and examples be considered as exemplary only, with a true scope of the invention being indicated by the following claims.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- US6750921B [0003]
- US5800832A [0003]
- US5700478A [0003]
- WO2005039543A1 [0005]
- WO03093260A [0045]
- WO2005080381A [0045]
- US6520329B [0049]
- WO2006056161A [0049]

- WO02059012A **[0049]**
- EP1353857A **[0049]**
- WO0162621A **[0049]**

PATENTKRAV

1. Oralt opløselig, ikke-mucoadhæsiv film, der kan opløses efter kontakt med spyt i mundhulen inden for ca. tres sekunder, hvor filmen omfatter 15,84 % ondansetron som base, 43,56 % polyvinylalkohol, 11,88 % polyethylenglycol, 3,96 % vandfri glycerin, 19,80 % risstivelse, 0,40 % acesulfam K, 0,59 % titandioxid, 1,98 % menthol og 1,98 % polysorbat pr. film, hvor samtlige procentsatser er efter vægt.

2. Oralt opløselig, ikke-mucoadhæsiv film ifølge krav 1, hvor filmen består af 8,0 mg ondansetron som base, 22,0 mg polyvinylalkohol, 6,0 mg polyethylenglycol, 2,0 mg vandfri glycerin, 10,0 mg risstivelse, 0,2 mg acesulfam K, 0,3 mg titandioxid, 1,0 mg menthol og 1,0 mg polysorbat.

3. Oralt opløselig, ikke-mucoadhæsiv film ifølge krav 1, hvor filmen består af 4,0 mg ondansetron som base, 11,0 mg polyvinylalkohol, 3,0 mg polyethylenglycol, 1,0 mg vandfri glycerin, 5,0 mg risstivelse, 0,1 mg acesulfam K, 0,15 mg titandioxid, 0,5 mg menthol og 0,5 mg polysorbat.

4. Oralt opløselig, ikke-mucoadhæsiv film ifølge et hvilket som helst af de ovenstående krav, der omfatter Form B ondansetron.

5. Oralt opløselig, ikke-mucoadhæsiv film ifølge et hvilket som helst af de ovenstående krav til anvendelse i behandling eller forebyggelse af opkastning.

DRAWINGS

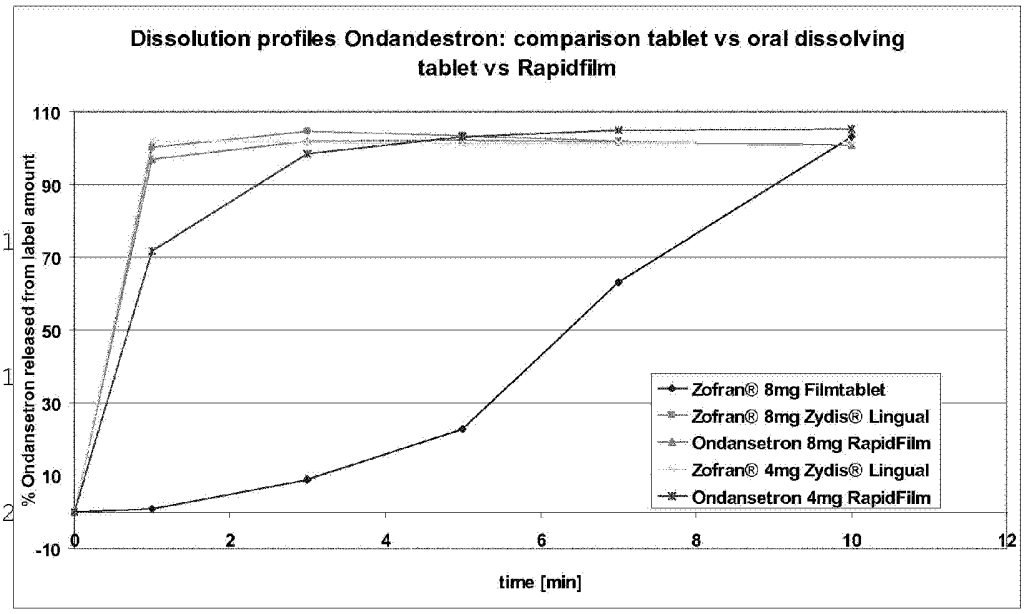


FIG 1

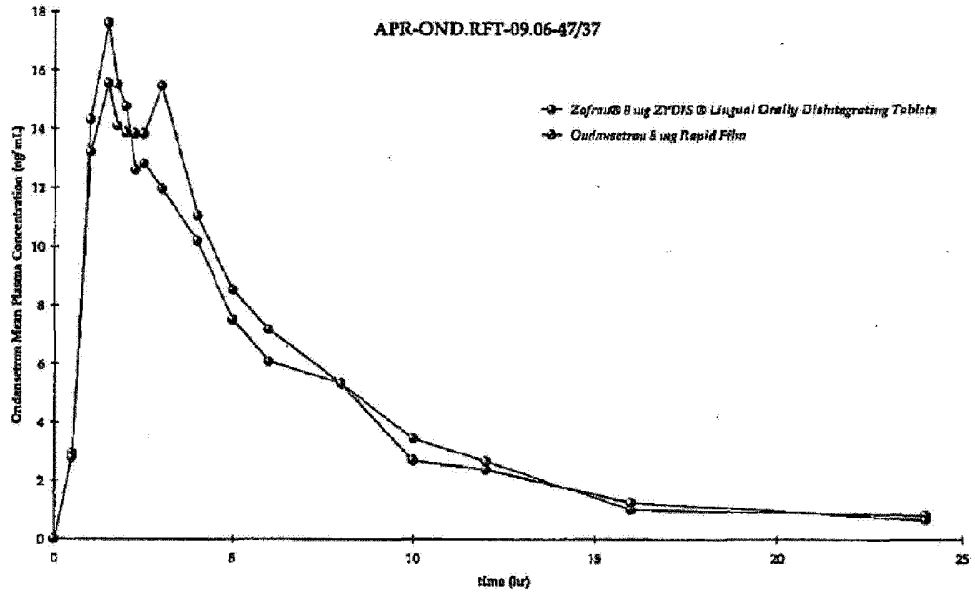

APR-OND.RFT-09.06-47/37
Zofran® 8 mg ZYDIS ® Lingual Orally Disintegrating Tablets
Ondansetron 8 mg Rapid Film
Ondansetron Mean Plasma Concentration (ng/mL)
time (hr)

FIG 2A

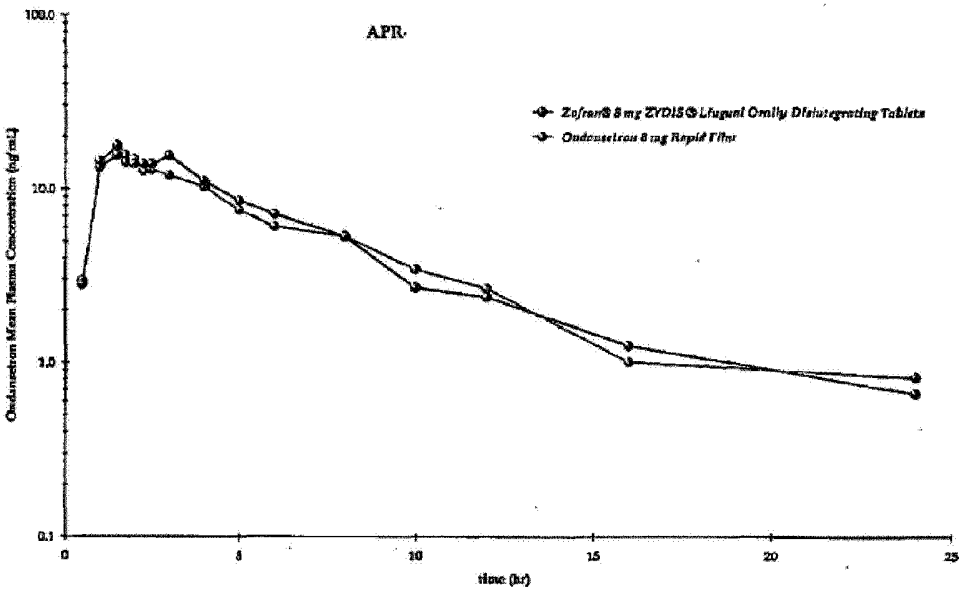

APR-
Zofran® 8 mg ZYDIS® Lingual Orally Disintegrating Tablets
Ondansetron 8 mg Rapid Film
Ondansetron Mean Plasma Concentration (ng/mL)
time (hr)

FIG 2B

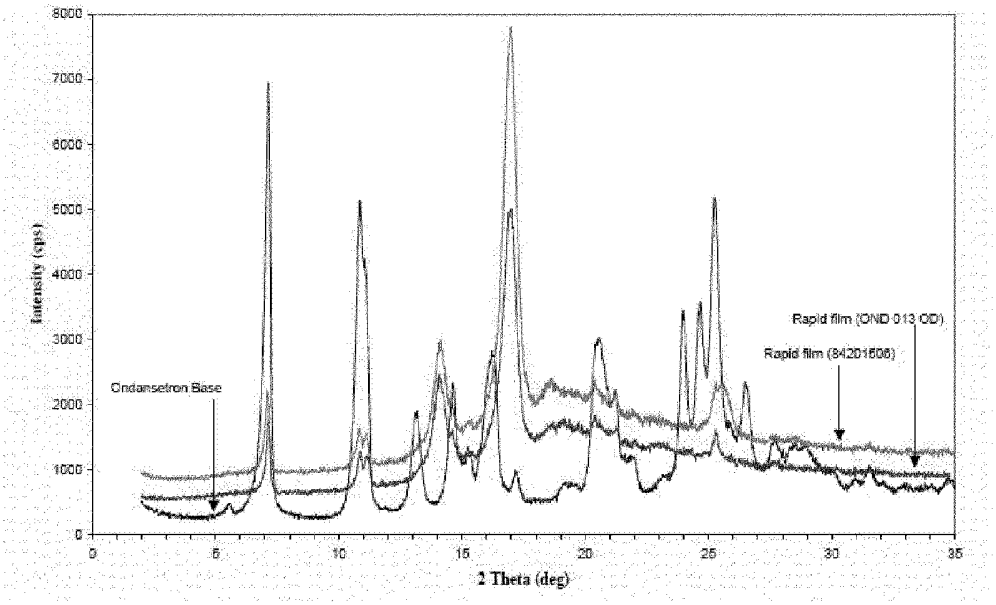
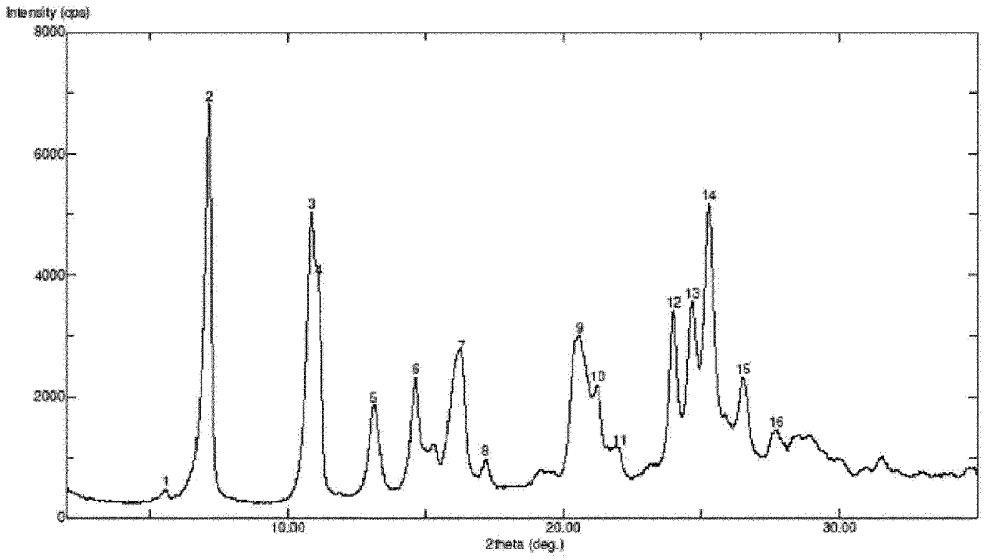

8000
7000
6000
5000
4000
3000
2000
1000
0
Intensity (cps)
0
5
10
15
20
25
30
35
2 Theta (deg)
Ondansetron Base
Rapid film (OND 013 OD)
Rapid film (84201606)

FIG 3



X-ray diffraction pattern for ondansetron base Form B

FIG 4