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(54) **Title**: CONTROLLED RELEASE COMPOSITIONS WITH REDUCED FOOD EFFECT

(57) **Abstract**: The present invention provides a controlled release pharmaceutical composition which exhibits reduced food ef-

CONTROLLED RELEASE COMPOSITIONS WITH REDUCED FOOD EFFECT

BACKGROUND OF THE INVENTION

[0001] Oral administration of drugs is frequently affected by food-drug interactions, a phenomenon often described by the term "food effect". As generally interpreted, food effect is a very broad term which refers to all aspects of interactions of food on drug dissolution, absorption, distribution, metabolism and elimination. The implications of food effect include changes in bioavailability, rate of on-set, duration of therapeutic effect and incidence and seriousness of side effects.

[0002] The food effect is an important issue during the development of a drug. In some cases where food-drug interactions lead to an increase of drug absorption, the drug formulation is recommended to be taken with food in order to be sufficiently absorbed and exert its expected clinical effect. However, such drug formulations are not preferred because drug absorption can vary with food types and quantity. For example, if a patient forgets to take the drug formulation with food, the drug may be poorly absorbed and therefore not clinically efficient. This problem may be avoided by a formulation without food effect.

[0003] Thus, there is a need for new sustained release compositions with reduced or no significant food effect.

[0004] Metformin is an oral antihyperglycemic drug of the biguanide class used in the management of non-insulin-dependent diabetes mellitus (NIDDM). It has been widely prescribed for lowering blood glucose in patients with NIDDM.

[0005] The benefits of a sustained release dosage form of metformin have been well known: it allows one to simplify the patient's administration scheme by reducing the amount of recommended daily intakes, improves patient compliance, and attenuates adverse events, e.g., related to high plasma peaks. Immediate release compositions of metformin exhibit negative food effect when orally administered to a subject.

[0006] The commercially available sustained-release dosage forms of metformin, such as Glucophage® XR, Glumetza® and Fortamet®, have significant positive food effect. Thus, they are all recommended to be taken with food to increase drug bioavailabiltiy and maximum therapeutic benefits.

[0007] Thus, there is a need for new sustained release compositions of metformin with reduced or no significant food effect.

SUMMARY OF THE INVENTION

[0008] In one embodiment, the present invention provides a controlled release pharmaceutical composition which exhibits reduced food effect as compared to conventional controlled release compositions, wherein said composition comprises an active agent (which may be referred to as a "drug") which has a limited window of absorption and displays a negative food effect when an immediate release dosage form of the drug is orally administered to a subject.

[0009] In one embodiment, the invention provides a controlled release pharmaceutical composition which exhibits reduced food effect as compared to conventional controlled release formulations, said composition comprising:

(a) a sustained release layer comprising:

(i) an active agent, wherein said active agent has a limited window of absorption and displays a negative food effect when an immediate release formulation of said active agent is orally administered to a subject;

(ii) optionally, at least one release modifier; and

(iii) at least one sustained release agent; and

(b) an immediate release layer comprising said active agent and at least one pharmaceutically acceptable excipient.

[00010] In one embodiment, the active agent is metformin.

[00011] In one embodiment, the invented controlled release pharmaceutical composition further comprises a second therapeutic agent.

[00012] In another embodiment, the invention provides a controlled release pharmaceutical composition of metformin, wherein the bioavailability of metformin is not increased more than 50% when said controlled release composition is orally administered to a subject in the fed state.

[00013] In yet another embodiment, the invention provides a method of reducing the food effect of a controlled release composition, said method comprising a step of formulating an active agent into a unit dosage form, wherein the unit dosage form comprises at least one sustained layer and one immediate release layer.

[00014] In yet another embodiment, the invention provides a method of reducing the time necessary to reach steady state for metformin, said method comprising administering a controlled release composition of metformin to a subject in need thereof, wherein the controlled release composition has higher bioavailability than a comparable dose of Fortamet® (metformin hydrochloride) tablets.

[00015] In yet another embodiment, the invention provides a method of improving the bioavailability of a controlled release dosage form of metformin in a fasted mode, said method comprising formulating metformin into a dosage from comprising a sustained release layer and an immediate release layer, wherein metformin is present in both the sustained release layer and the immediate release layer.

[00016] In yet another embodiment, the invention provides a method of manufacturing a matrix controlled release tablet, said method comprising: (a) mixing a portion of an acid salt form of an active ingredient with an alkaline agent to form a mixture; (b) granulating said mixture with a controlled release agent; and (c) compressing the granules from step (b) into tablets.

DEFINITIONS

[00017] The term "food effect", as used herein, refers to a relative difference in AUC (Area under the curve), C_{max} (Maximum plasma concentration), and/or T_{max} (Time to maximum concentration) of an active substance, when said substance or a formulation thereof, such as a tablet or a capsule, is administered orally to a mammal, preferably a human, concomitantly with food or in a fed state as compared to the same values when the same formulation is administered in a fasted state. The food effect F is calculated as

$F=(Y_{fed}-Y_{fasted})/Y_{fasted}$

wherein Y_{fed} and Y_{fasted} are the found values of AUC, C_{max} or T_{max} in the fed and fasted state, respectively.

[00018] The term "reduced food effect", as used herein, refers to the food effect of a composition of an active substance which is less than 50%, preferably less than 40%,

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