

Material Surfaces”, *Environ. Sci. Technol.*, 56 (2022), 12045; I.W. Ashworth et al, “Potential for the Formation of N-Nitrosamines during the Manufacture of Active Pharmaceutical Ingredients: An Assessment of the Risk Posed by Trace Nitrite in Water”, *Org. Process Res. Dev.*, 24 (2020), 1629.

Pharmaceutical compositions comprising combinations of sitagliptin dihydrogen phosphate and metformin hydrochloride are disclosed in WO 2007/078726, WO 2009/099734, and WO 2009/111200.

SUMMARY

Provided are sitagliptin – antioxidant compositions for use in pharmaceutical compositions of sitagliptin.

Additionally provided are processes to prepare the sitagliptin-antioxidant compositions.

Processes to prepare the sitagliptin-antioxidant composition for use in pharmaceutical compositions and formulations of sitagliptin, or a salt and/or hydrate thereof, are also provided.

The present disclosure provides for sitagliptin – antioxidant compositions that reduce the amount of NTTP formed in formulations and pharmaceutical compositions comprising sitagliptin, or a salt and/or hydrate thereof.

In one aspect, there is provided a composition comprising: (a) about 90 % to 99.99 % by weight of a sitagliptin, or a pharmaceutically acceptable salt and/or hydrate thereof; and (b) about 0.01 % to 10 % by weight of an antioxidant.

Also provided are pharmaceutical compositions and formulations comprising sitagliptin – antioxidant composition, alone or in combination with ertugliflozin, or a salt or co-crystal thereof. These pharmaceutical compositions and formulations may comprise additional excipients.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a graph showing NTTP reduction in JANUVIA® core tablets containing either sitagliptin dihydrogen phosphate monohydrate – propyl gallate complex powder (PG) or sitagliptin dihydrogen phosphate monohydrate – butylated hydroxyanisole complex powder (BHA) relative to JANUVIA® core tablets containing sitagliptin dihydrogen phosphate monohydrate powder without an antioxidant (control).

DETAILED DESCRIPTION

N-Nitrosamines can also sometimes form in drug formulations via chemical reactions between nitrites and amines in the formulation during manufacturing, formulation and storage.

It was unexpectedly found that there is a potential to form nitrosamines, in particular N-7-nitroso-3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4] triazolo-[4,3-a]pyrazine (NTTP), in sitagliptin formulations. NTTP may be formed due to nitrosation of 3-(trifluoromethyl)-

WHAT IS CLAIMED IS:

1. A composition comprising:

- (a) about 90 % to 99.99 % by weight of a sitagliptin, or a pharmaceutically acceptable salt
5 and/or hydrate thereof; and
(b) about 0.01 % to 10 % by weight of an antioxidant.

2. The composition of Claim 1 comprising:

- (a) about 95 % to 99.95 % by weight of a sitagliptin, or a pharmaceutically acceptable salt
10 and/or hydrate thereof; and
(b) about 0.05 % to 5 % by weight of an antioxidant.

3. The composition of Claim 1 comprising:

- (a) about 99 % to 99.9 % by weight of a sitagliptin, or a pharmaceutically acceptable salt
15 and/or hydrate thereof; and
(b) about 0.1 % to 1 % by weight of an antioxidant.

4. The composition of Claim 1 comprising:

- (a) about 99.3 % to 99.8 % by weight of a sitagliptin, or a pharmaceutically acceptable salt
20 and/or hydrate thereof; and
(b) about 0.2 % to 0.7 % by weight of an antioxidant.

5. The composition of Claim 1 wherein the salt of sitagliptin is sitagliptin
dihydrogen phosphate.

25

6. The composition of Claim 1 wherein the salt and hydrate of sitagliptin is
sitagliptin dihydrogen phosphate monohydrate.

7. The composition of Claim 1 wherein the antioxidant is selected from: ascorbic

30 acid, methyl gallate, ethyl gallate, propyl gallate, butyl gallate, pentyl gallate, octyl gallate,
dodecyl gallate, lauryl gallate, butylated hydroxyanisole, butylated hydroxytoluene, thymol,
tocopherol, and vitamin E.

8. The composition of Claim 1 wherein the antioxidant is selected from: ascorbic acid, propyl gallate, butylated hydroxyanisole, butylated hydroxytoluene, thymol, tocopherol, and vitamin E.

5 9. The composition of Claim 1 wherein the antioxidant is propyl gallate.

10. The composition of Claim 1 wherein the antioxidant is butylated hydroxyanisole.