PHARMACEUTICAL FORMULATIONS

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims priority to International Application No. PCT/CN2020/119816, filed 5 October 2020, which is incorporated in its entirety by reference for all purposes.

TECHNICAL FIELD

[0002] The invention provides pharmaceutical formulations of SGLT2 inhibitors useful for treating diabetes mellitus and other conditions, and in particular oral formulations of bexagliflozin with improved pharmacokinetic properties.

BACKGROUND OF THE INVENTION

[0003] Bexagliflozin (EGT0001442, EGT1442, THR1442, THR0001442) is an inhibitor of SGLT2 (renal Na^+/glucose transporter) that is useful for the treatment and management of various conditions, including diabetes (see: Zhang *et al.* (2011) *Pharmacol Res* 63(4):284-93; Allegretti *et al.* (2019) *Am J Kidney Dis.* 74:328 doi: 10.1053/j.ajkd.2019.03.417; Zhang *et al.* (2019) *Xenobiotica* doi: 10.1080/00498254.2019.1654634). It has been tested in humans in the form of oral solid dosage forms (*e.g.* see NCT01377844 or NCT01029704) as well as oral solutions, and has been shown to be well-tolerated and to provide a durable, clinically meaningful improvement in glycemic control, as well as a reduction in body mass and blood pressure in diabetic adults (Halvorsen *et al.* (2019) *Diabetes Obes Metab* doi: 10.1111/dom.13833, Halvorsen *et al.* (2019) *Diabetes Obes Metab* 21:2248 doi: 10.1111/dom.13801).

SUMMARY ~~OF THE INVENTION~~

[0004] Studies of human subjects who have been administered bexagliflozin in the form of oral capsules or oral solutions have shown that the plasma concentration of bexagliflozin displays a high peak/trough ratio (both C_{max} to C_{min} and C_{max} to C_{24h}), with a steep decline during the alpha phase. The inventors have found that a better pharmacokinetic profile can be achieved by formulating bexagliflozin as an extended release tablet. Compared with standard immediate-release dosage forms, these tablets can permit lower doses to be administered while still providing the same pharmacological effect (a lower peak plasma concentration, C_{max}, while maintaining plasma concentrations at therapeutic levels), and can reduce the likelihood of side effects for any given dose. It is well known in the art that adverse drug reactions, especially poorly predictable idiosyncratic reactions (which frequently are not detected during the pre-approval testing of new drugs but, once discovered, can lead to restriction or withdrawal of the approved medication) are more likely to occur in drugs that must be administered in large doses, and that the likelihood of adverse reactions often increases as the C_{max} increases. Thus, in a first ~~aspect~~example, the ~~invention~~disclosure provides an extended release tablet of bexagliflozin.

[0004a] In an aspect, there is provided an extended-release tablet that contains bexagliflozin and a mucoadhesive.

[0004b] In another aspect, there is provided the use of the tablet of any one of the preceding claims in the manufacture of a medicament for the treatment of diabetes or its symptoms.

[0005] A particularly preferred tablet of the first ~~aspect~~ example releases bexagliflozin *in vivo* to provide a plasma C_{max} in fasted subjects which is at least 125,000× lower per milliliter than the tablet's total bexagliflozin content. Thus, for example, a tablet containing 20 mg bexagliflozin would provide a fasted C_{max} of ≤160 ng/mL. Ideally the plasma C_{max} is at least 135,000× lower than the bexagliflozin

content (*i.e.* ≤148 ng/mL for a tablet containing 20 mg bexagliflozin), or even at least 145,000× lower (*i.e.* ≤138 ng/mL for a 20 mg tablet).

[0006] According to a second ~~aspect~~example, the ~~invention~~disclosure provides an extended release tablet that contains between 10 mg and 20 mg of bexagliflozin and that provides an *in vivo* plasma C_{max} of ≤160 ng/mL in fasted subjects. Ideally the C_{max} is ≤133 ng/mL. In one ~~embodiment~~example, the tablet contains 10 mg bexagliflozin and the C_{max} is ≤80 ng/mL; in another ~~embodiment~~example, the tablet contains 20 mg bexagliflozin and the C_{max} is ≤160 ng/mL.

[0007] According to a third ~~aspect~~example, the ~~invention~~ disclosure provides an extended release tablet that contains between 30 mg and 60 mg of bexagliflozin and that provides an *in vivo* plasma C_{max} of <400 ng/mL in fasted subjects. In one ~~embodiment~~example, the tablet contains 40 mg bexagliflozin and the plasma C_{max} is <320 ng/mL; in another ~~embodiment~~example, the tablet contains 50 mg bexagliflozin and the plasma C_{max} is <400 ng/mL.

[0008] For both the first and second example~~aspect~~s, a preferred tablet contains 20 mg bexagliflozin and provides an $AUC_{0\text{-}t}$ between 600 and 1200 ng h mL^{-1} in fasted subjects. Similarly, a preferred tablet contains 20 mg bexagliflozin and provides an $AUC_{0\text{-}\infty}$ between 675 and 1275 ng h mL^{-1} in fasted subjects.

[0009] For both the first and second ~~aspect~~examples, a preferred tablet contains 20 mg bexagliflozin and provides a plasma C_{max} between 80 and 150 ng/mL in fasted subjects.

[0010] For the first, second and third ~~aspect~~examples, a preferred tablet provides a bexagliflozin plasma concentration 24 hours after administration (*i.e.* C_{24h}) of ≥5 ng/mL, and ideally ≥10 ng/mL.

[0011] For the first, second and third ~~aspect~~examples, a preferred tablet provides a time to maximum bexagliflozin plasma concentration (*i.e.* T_{max}) that is between 2 and 6 hours in fasted subjects, and ideally between 2 and 4.5 hours.

[0012] As explained in more detail below, the properties defined for a tablet will typically be measured after administration of representative specimens of a batch of which that tablet is an exemplar, and an appropriate average (*e.g.* geometric mean) of the results will be calculated. With this in mind, a batch of tablets according to the first ~~aspect~~example may release bexagliflozin *in vivo* to provide a geometric mean plasma C_{max} in fasted subjects which is at least 125,000× lower per milliliter than each tablet's total bexagliflozin content. Similarly, a batch of tablets according to the second ~~aspect~~example may provide, an *in vivo* geometric mean plasma C_{max} of ≤160 ng/mL (*e.g.* a geometric mean C_{max} ≤133 ng/mL) in fasted subjects; for instance, tablets may contain 10 mg bexagliflozin and provide a geometric mean C_{max} ≤80 ng/mL, or they may contain 20 mg bexagliflozin and provide a geometric mean C_{max} ≤160 ng/mL. Similarly, a batch of tablets according to the third ~~aspect~~example may provide an *in vivo* geometric mean plasma C_{max} of <400 ng/mL in fasted subjects; for instance, tablets may contain 40 mg bexagliflozin and provide a geometric mean plasma C_{max} <320 ng/mL, or may contain 50 mg bexagliflozin and provide a geometric mean plasma C_{max} <400 ng/mL. Furthermore, a batch of tablets of the first and second ~~aspect~~examples containing 20 mg bexagliflozin may provide in fasted subjects (i) a

geometric mean AUC_{0-t} between 600 and 1200 ng h mL^{-1} and/or (ii) a geometric mean $AUC_{0-\infty}$ between 675 and 1275 ng h mL^{-1} and/or (iii) a geometric mean plasma C_{max} between 80 and 150 ng/mL. Similarly, for the first, second and third ~~aspect~~example**s**, a batch of tablets may provide a geometric mean C_{24h} of ≥5 ng/mL, and ideally ≥10 ng/mL.

[0013] For a batch of tablets according to the first, second and third ~~aspect~~example**s**, the ratio of the median bexagliflozin plasma C_{max} and C_{min} values may be less than 10 *e.g.* between 5-10, between 6-8, or between 7-8. The high peak/trough ratio seen in the prior art can thus be avoided. A median C_{min} of at least 10 ng/mL is preferred. As shown below, these pharmacokinetic parameters represent robust statistical estimates based on measurements from over 800 subjects from various regions in the world, using various different extended release bexagliflozin tablets.

[0014] The inventors have also observed that bexagliflozin is a P-gp substrate, and that absorption of bexagliflozin from the large intestine is minimal. Because P-gp expression increases with distance along the small intestine, absorption is likely greater in the duodenum than the ileum, and quantitative mass balance studies using [^{14}C]-bexagliflozin have shown that colonic absorption is minimal (Zhang *et al. Xenobiotica*. 2019 Aug 27:1-11. doi: 10.1080/00498254.2019.1654634). Because of the potential practical incompatibility of using an extended release tablet while aiming for most drug release to occur high in the small intestine, tablets of the ~~invention~~ disclosure advantageously include an adaptation that can help to retain them in the stomach. A large part of the extended release of bexagliflozin can thus occur in the stomach, permitting absorption of the drug to occur at the desired location in the small intestine, thereby providing an advantageous pharmacokinetic profile. Tablets with gastric retention adaptations have been shown to function well *in vivo* even though bexagliflozin is unstable in the prolonged presence of acid, and is susceptible to acidic decomposition.

[0015] Various adaptations can be used to help retain a tablet of the ~~invention~~ disclosure in the stomach, including but not limited to: (i) inclusion of an effervescent excipient, which can provide buoyancy during gaseous release in stomach acid; (ii) rapid gastric dispersal into multiple granules or pellets, thereby avoiding expulsion of the complete tablet from the stomach in a single event; (iii) the use of low density excipients to provide a buoyant or floating tablet; and/or (iv) the inclusion of a mucoadhesive in the tablet. These four approaches can be used individually or together to provide advantageous tablets for delivery of bexagliflozin.

[0016] According to a fourth ~~aspect~~example, the disclosure~~invention~~ provides an extended release tablet that contains bexagliflozin and a mucoadhesive. Ideally, this tablet has a density below that of gastric contents. It can also be effervescent (particularly when in contact with gastric acid) and/or it can disperse into multiple granules or pellets when it comes into contact with gastric acid.

[0017] According to a fifth ~~aspect~~example, the disclosure~~invention~~ provides a solid oral dosage form, typically an extended release tablet, that contains bexagliflozin and that in an *in vitro* dissolution test in simulated gastric fluid (see below) releases ≤17% of its bexagliflozin after 1 hour and releases ≥80% after 8 hours. In one ~~embodiment~~example, it releases between 20-45% (inclusive) of its bexagliflozin after 3 hours,

and/or between 45-75% (inclusive) of its bexagliflozin after 5 hours. This tablet can be from a manufacturing batch of tablets which pass the formal dissolution acceptance criteria discussed below.

[0018] According to a sixth ~~aspect~~example, the disclosure~~invention~~ provides a solid oral dosage form, typically an extended release tablet, that contains bexagliflozin and that in an *in vitro* dissolution test in simulated gastric fluid (see below) has a f_2 value of >50 when compared to a reference tablet, wherein f_2 is proportional to the decimal logarithm of one plus the mean squared error:

$$f_2 = 100 - 25\log_{10}(1 + n^{-1}\sum_{i=1}^{n}(R_i - T_i)^2)$$

[0019] where: n is number of time points at which dissolution is measured; R_i is the dissolution percentage of a reference tablet at the i-th timepoint; and T_i is the dissolution percentage of the solid oral dosage form at the i-th timepoint;

[0020] and where the reference tablet is an extended release tablet that contains bexagliflozin and that, in an *in vitro* dissolution test in simulated gastric fluid, releases ≤17% of its bexagliflozin at 1 hour, releases ≥80% at 8 hours and, optionally, releases between 20-45% (inclusive) of its bexagliflozin at 3 hours and/or 45-75% (inclusive) of its bexagliflozin at 5 hours. Three suitable reference tablets are disclosed in more detail below as reference tablets (a) to (c), where tablet (c) is preferred. The value of n is preferably at least 3 *e.g.* between 4-8.

[0021] According to a seventh ~~aspect~~example, the disclosure~~invention~~ provides a batch of extended release bexagliflozin tablets wherein, upon administration to a cohort of healthy fasted subjects, a first representative sample set of tablets from the batch provides on one occasion a first mean logarithm of C_{max} and a first mean logarithm of $AUC_{0\text{-}t}$, and a second representative sample of tablets from the batch produces on a different occasion a second mean logarithm of C_{max} and a second mean logarithm of $AUC_{0\text{-}t}$, and wherein the differences between the first and second mean logarithms of C_{max} and between the first and second mean logarithms of $AUC_{0\text{-}t}$ both exhibit 90% confidence intervals having endpoints which lie between -0.22314 and +0.22314. Details on assessing these parameters are given in the section 'Bioequivalence' below *e.g.* the use of a random crossover study in a suitable test population, *etc.* Ideally each tablet in the batch contains 5 mg, 10 mg, or 20 mg of bexagliflozin.

[0022] According to an eighth ~~aspect~~example, the disclosure~~invention~~ provides a batch of extended release bexagliflozin tablets wherein, upon administration to a cohort of healthy subjects each provided on one occasion a single tablet from a first representative tablet sample set in the fasted state, and on a different occasion a single tablet from a second representative tablet sample set in the fed state (*e.g.,* 30 minutes following a standard high fat, high calorie meal, as described in the section 'Bioequivalence' below and references therein), the mean differences in $\ln(C_{max})$ and $\ln(AUC_{0\text{-}t})$ (created by subtracting the values for the logarithms of C_{max} and the logarithms of $AUC_{0\text{-}t}$ for the fasted state from the values for the logarithms of C_{max} and the logarithms of $AUC_{0\text{-}t}$ for the fed state) both exhibit a 90% confidence interval with endpoints which lie between -0.22314 and +0.58779. Ideally each tablet in the batch contains 5 mg, 10 mg, or 20 mg of bexagliflozin.

[0023] According to a ninth ~~aspect~~example, the disclosure~~invention~~ provides a batch of extended release bexagliflozin tablets wherein, upon administration to a cohort of fasted healthy subjects each provided on one occasion a single tablet from a first representative tablet sample set without any prior dosage of a parenteral GLP-1 receptor agonist, and on a different occasion a single tablet from a second representative tablet sample set 30 minutes following an approved dosage of a parenteral GLP-1 receptor agonist, the mean differences in $\ln(C_{max})$ and $\ln(AUC_{0-t})$ (created by subtracting the values of the logarithms of C_{max} and the logarithms of AUC_{0-t} for the first sample set from the values of the logarithms for the second sample set) both exhibit a 90% confidence interval with an upper bound of less than 0.69315. Ideally each tablet in the batch contains 5 mg, 10 mg, or 20 mg of bexagliflozin.

[0024] According to a tenth ~~aspect~~example, the disclosure~~invention~~ provides a batch of extended release bexagliflozin tablets wherein, upon administration to a cohort of healthy subjects each provided on one occasion a single tablet from a first representative tablet sample set in the fasted state, and on a different occasion, a single tablet from a second representative tablet sample set in the fed state (*e.g.,* 30 minutes following a standard high fat, high calorie meal as described in the section 'Bioequivalence' below), the differences created by subtracting the values for the T_{max} for the fasted state from the values for the T_{max} for the fed state exhibit a median that is less than or equal to 3.5 hours. The median difference is the difference for which 50% of the subjects have values above the median and 50% of subjects have values below the median; for example in an ordered listing of the differences, for an odd number of subjects (*e.g.,* 2n +1 subjects), the median is the difference for the subject in the list midpoint, (subject n +1), and for an even number of subjects (*e.g.,* 2n subjects), the median is the arithmetic average of the differences for the two subjects flanking the midpoint (subjects n and n+1). Ideally each tablet in the batch contains 5 mg, 10 mg, or 20 mg of bexagliflozin.

[0025] According to an eleventh ~~aspect~~example, the disclosure~~invention~~ provides a solid oral dosage form, typically an extended release tablet, that contains bexagliflozin and that provides a first plasma C_{max}, a first AUC_{0-t} and a first T_{max} in fasted subjects, and provides a second plasma C_{max}, a second AUC_{0-t} and a second T_{max} in fed subjects, wherein (i) the ratio of the second divided by the first C_{max} is between 0.8 and 1.8; (ii) the ratio of second divided by the first AUC_{0-t} is between 0.8 and 1.8; or (iii) the ratio of second divided by the first T_{max} is between 0.8 and 3.0.

[0026] As explained below, the properties defined for such a tablet will typically be measured after administration of representative specimens of a batch of which that tablet is an exemplar. Thus a batch of tablets of the eleventh ~~aspect~~example can provide a first geometric mean plasma C_{max}, a first geometric mean AUC_{0-t} and a first median T_{max} in fasted subjects, and provides a second geometric mean plasma C_{max}, a second geometric mean AUC_{0-t} and a second median T_{max} in fed subjects, wherein (i) the ratio of the second divided by the first geometric mean C_{max} is between 0.8 and 1.8; (ii) the ratio of second divided by the first geometric mean AUC_{0-t} is between 0.8 and 1.8; or (iii) the ratio of second divided by the first median T_{max} is between 0.8 and 3.0.

[0027] According to a twelfth ~~aspect~~example, the disclosure~~invention~~ provides a solid oral dosage form, typically an extended release tablet, that contains bexagliflozin and that provides a first plasma C_{max}, a first AUC_{0-}

$_t$ and a first T_{max} in subjects not previously administered a parenteral GLP-1 receptor agonist, and provides a second plasma C_{max}, a second AUC_{0-t} and a second T_{max} in subjects previously administered a parenteral GLP-1 receptor agonist, wherein (i) the ratio of the second divided by the first C_{max} is between 0.8 and 2.0; (ii) the ratio of second divided by the first AUC_{0-t} is between 0.8 and 2.0; or (iii) the ratio of second divided by the first T_{max} is between 0.8 and 3.0.

[0028] As explained below, the properties defined for such a tablet will typically be measured after administration of representative specimens of a batch of which that tablet is an exemplar. Thus a batch of tablets of the twelfth ~~aspect~~example can provide a first geometric mean plasma C_{max}, a first geometric mean AUC_{0-t} and a first median T_{max} in subjects not previously administered a parenteral GLP-1 receptor agonist, and provides a second geometric mean plasma C_{max}, a second geometric mean AUC_{0-t} and a second median T_{max} in subjects previously administered a parenteral GLP-1 receptor agonist, wherein (i) the ratio of the second divided by the first geometric mean C_{max} is between 0.8 and 2.0; (ii) the ratio of second divided by the first geometric mean AUC_{0-t} is between 0.8 and 2.0; or (iii) the ratio of second divided by the first median T_{max} is between 0.8 and 3.0.

[0029] The disclosure~~invention~~ also provides methods for treating patients as discussed in more detail below.

BRIEF DESCRIPTION OF DRAWINGS

[0030] Figure 1 shows the geometric mean plasma concentration (ng/mL) of bexagliflozin in fasted subjects as a function of time post-dose (hours). Closed circles (●) show data for 20 mg capsules, whereas the other symbols are for 15 mg tablets XR5 (▼), XR8 (Δ), or XR11 (○).

[0031] Figure 2 shows the geometric mean plasma concentration (ng/mL) of bexagliflozin in fasted subjects who received 10 mg (●), 15 mg (○), or 30 mg (▼) tablets.

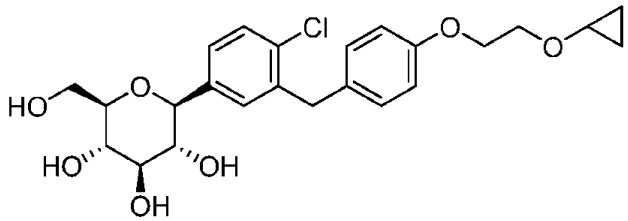
[0032] Figure 3 shows the % of bexagliflozin released (ordinate) after 1 hour (♦), 3 hours (■), 5 hours (▲), or 8 hours (X) in an *in vitro* dissolution test. The tablets had been stored for up to 60 months (abscissa) at 25 °C (Fig. 3A) or 30 °C (Fig. 3B). The graph shows measured means with a line of regression.

DETAILED DESCRIPTION OF THE INVENTION

[0033] The invention provides extended release tablet formulations that provide improved pharmacokinetic properties for bexagliflozin when compared to capsule formulations.

Bexagliflozin

[0034] Bexagliflozin is a SGLT2 inhibitor in the *C*-aryl glucoside class and has formula (I):



(I)

CLAIMS

~~1. An extended-release tablet comprising bexagliflozin.~~

~~2.~~1. An extended-release tablet that contains bexagliflozin and a mucoadhesive.

~~3. An extended-release tablet that contains bexagliflozin and~~The tablet of claim 1, that, in an *in vitro* dissolution test in simulated gastric fluid, releases ≤17% of its bexagliflozin after 1 hour and releases ≥80% after 8 hours~~.~~

~~4. The tablet of claim 3~~, for example, wherein the tablet releases between 20-45% of its bexagliflozin after 3 hours, and/or between 45-75% of its bexagliflozin after 5 hours~~.~~

~~5.~~2. ~~The tablet of claim 4~~, for example wherein the tablet releases (a) between 45-72% of its bexagliflozin after 5 hours (b) between 50-70% of its bexagliflozin after 5 hours (c) between 49-69% of its bexagliflozin after 5 hours or (d) between 48-68% of its bexagliflozin after 5 hours.

~~6.~~3. The tablet of ~~any one of~~ claim~~s~~ ~~3-5~~2, wherein the *in vitro* dissolution test is performed with a United States Pharmacopoeia (USP) Apparatus 1 at 50 rpm with 900 mL of 0.1 N HCl at 37 ± 0.5 °C.

~~7. The tablet of any preceding claim, from a batch of tablets which releases bexagliflozin *in vivo* to provide a geometric mean plasma bexagliflozin C_{max} in an appropriately constituted cohort of fasted human subjects that is at least 125,000× lower per milliliter than the tablet's total bexagliflozin content.~~

~~8. An extended-release tablet~~The tablet of claim 1, that provides a plasma bexagliflozin C_{max} of ≤ 8 ng/mL per mg of bexagliflozin in the tablet in a fasted subject having a body mass greater than 60 kg~~.~~

~~9.~~4. ~~The tablet of claim 8~~, for example, wherein (i) the tablet contains 10 mg bexagliflozin and the C_{max} is ≤80 ng/mL, (ii) the tablet contains 20 mg bexagliflozin and the C_{max} is ≤160 ng/mL, or (iii) the tablet contains 40 mg bexagliflozin and the C_{max} is ≤ 320 ng/mL.

~~10.~~5. The tablet of any preceding claim,

(a) which provides a bexagliflozin plasma concentration 24 hours after administration of ≥10 ng/mL; and/or

(b) which releases bexagliflozin *in vivo* to provide a T_{max} in a fasted human subject which is between 2 and 6 hours; and/or

(c) which contains 20 mg bexagliflozin and provides an AUC_{0-t} in a fasted human subject which is between 600-1200 ng h mL^{-1}, for example, wherein the tablet provides AUC_{0-t} between 650-1150 ng h mL^{-1}; and/or

(d) which contains 20 mg bexagliflozin and provides an $AUC_{0-\infty}$ in a fasted human subject which is between 675-1275 ng h mL^{-1}, for example, wherein the tablet provides $AUC_{0-\infty}$ between 750-1200 ng h mL^{-1}; and/or

(e) which contains 20 mg bexagliflozin and provides a plasma C_{max} in a fasted human subject which is between 80-150 ng/mL, for example, wherein the tablet provides a plasma C_{max} between 85-145 ng/mL or between 95-140 ng/mL.

~~11. The tablet of any preceding claim, which releases bexagliflozin *in vivo* to provide a T_{max} in a fasted human subject which is between 2 and 6 hours.~~

~~12. The tablet of any preceding claim, which contains 20 mg bexagliflozin and provides an AUC_{0-t} in a fasted human subject which is between 600-1200 ng h mL^{-1}.~~

~~13. The tablet of claim 12, wherein the tablet provides AUC_{0-t} between 650-1150 ng h mL^{-1}.~~

~~14. The tablet of any preceding claim, which contains 20 mg bexagliflozin and provides an $AUC_{0-\infty}$ in a fasted human subject which is between 675-1275 ng h mL^{-1}.~~

~~15. The tablet of claim 14, wherein the tablet provides $AUC_{0-\infty}$ between 750-1200 ng h mL^{-1}.~~

~~16. The tablet of any preceding claim, which contains 20 mg bexagliflozin and provides a plasma C_{max} in a fasted human subject which is between 80-150 ng/mL.~~

~~17. The tablet of claim 16, wherein the tablet provides a plasma C_{max} between 85-145 ng/mL or between 95-140 ng/mL.~~

~~18.~~6. The tablet of any preceding claim, wherein the tablet provides bexagliflozin plasma concentrations in which the ratio of the median C_{max} to the median C_{min} is less than 10.

~~19.~~ The tablet of any preceding claim, which is an extended-release tablet that contains 20 mg bexagliflozin and that, in an *in vitro* dissolution test performed with a United States Pharmacopoeia (USP) Apparatus 1 at 50 rpm with 900 mL of 0.1 N HCl at 37 ± 0.5 °C, releases ≤17% of its bexagliflozin after 1 hour, releases between 20-45% of its bexagliflozin after 3 hours, releases between 45-75% of its bexagliflozin after 5 hours, and releases ≥80% of its bexagliflozin after 8 hours~~.~~

~~20.~~7. ~~The tablet of claim 19, which~~, for example, wherein the tablet releases (a) between 45-72% of its bexagliflozin after 5 hours (b) between 50-70% of its bexagliflozin after 5 hours (c) between 49-69% of its bexagliflozin after 5 hours or (d) between 48-68% of its bexagliflozin after 5 hours.

~~21.~~ The tablet of claim ~~19 or claim 20~~7 which, in a fasted human subject, provides an AUC_{0-t} which is between 600-1200 ng h mL^{-1}, provides an $AUC_{0-\infty}$ which is between 675-1275 ng h mL^{-1}, and provides a plasma C_{max} which is between 80-150 ng/mL~~.~~

~~22.~~8. ~~The tablet of claim 21, which~~, for example, wherein the tablet provides AUC_{0-t} between 650-1150 ng h mL^{-1}, provides $AUC_{0-\infty}$ between 750-1200 ng h mL^{-1}, and provides a plasma C_{max} between 95-140 ng/mL.

~~23.~~9. The tablet of any one of claims ~~7~~ 4 to ~~22~~8, wherein the fasted human subject is a healthy young adult Caucasian subject with a body mass between 60-100 kg.

~~24. The tablet of any preceding claim, which (i) has a density below that of gastric fluid and/or (ii) effervesces when in contact with gastric fluid.~~

~~25.~~10. The tablet of any preceding claim, wherein bexagliflozin is in the form of a crystalline solid.

~~26.~~11. The tablet of any preceding claim,

(a) comprising a monolithic matrix in which bexagliflozin is dispersed within solid excipient(s) which comprise a water-insoluble substance, for example, wherein the water-insoluble substance is glyceryl dibehenate, for example, wherein the tablet includes 30-35% by weight glyceryl dibehenate; and/or

(b) wherein the tablet includes a solubilizer, for example, wherein the solubilizer comprises a poloxamer, such as poloxamer 188, for example, wherein the tablet includes 10-12% by weight poloxamer 188; and/or

(c) wherein the tablet includes a filler, for example, wherein the tablet includes lactose and/or microcrystalline cellulose, for example, wherein the tablet includes 11-13% by weight lactose and/or 18-20% by weight microcrystalline cellulose; and/or

(d) wherein the tablet includes a glidant and/or a lubricant, for example, wherein the tablet includes magnesium stearate and/or colloidal silicon dioxide, for example, wherein the tablet includes 1.5-2.5% by weight magnesium stearate and/or 1.0-1.5% by weight colloidal silicon dioxide; and/or

(e) wherein the mucoadhesive is a polyethylene oxide, for example, wherein the tablet includes 16-20% by weight polyethylene oxide having an average molecular weight of approximately 900,000 or greater.

~~27. The tablet of claim 26, wherein the water-insoluble substance is glyceryl dibehenate.~~

~~28. The tablet of claim 27, including 30-35% by weight glyceryl dibehenate.~~

~~29. The tablet of any preceding claim, wherein the tablet has a density below 1.04 g/cm^3 and can float in simulated gastric fluid.~~

~~30. The tablet of any preceding claim, wherein the tablet includes a solubilizer.~~

~~31. The tablet of claim 30, wherein the solubilizer comprises a poloxamer, such as poloxamer 188.~~

~~32. The tablet of claim 31, including 10-12% by weight poloxamer 188.~~

~~33. The tablet of any preceding claim, wherein the tablet includes a filler.~~

~~34. The tablet of claim 33, wherein the tablet includes lactose and/or microcrystalline cellulose.~~

~~35. The tablet of claim 34, including 11-13% by weight lactose and/or 18-20% by weight microcrystalline cellulose.~~

~~36. The tablet of any preceding claim, wherein the tablet includes a glidant and/or a lubricant.~~

~~37. The tablet of claim 36, wherein the tablet includes magnesium stearate and/or colloidal silicon dioxide.~~

~~38. The tablet of claim 37, including 1.5-2.5% by weight magnesium stearate and/or 1.0-1.5% by weight colloidal silicon dioxide.~~

~~39. The tablet of any preceding claim, wherein the tablet includes a mucoadhesive.~~

~~40. The tablet of claim 39, wherein the mucoadhesive is a polyethylene oxide.~~

~~41. The tablet of claim 40, including 16-20% by weight polyethylene oxide having an average molecular weight of approximately 900,000 or greater.~~

~~42.~~ The tablet of any preceding claim, wherein the tablet has a coating surrounding a core~~.~~

~~43.~~12. ~~The tablet of claim 42~~, for example, wherein the coating (i) comprises polyvinyl alcohol and (ii) is present at between 2.5-3.5% of the core's weight.

~~44.~~13. The tablet of any preceding claim, wherein the tablet has a hardness between 20-100 N and/or a friability of ≤1% by weight.

~~45. A tablet, for instance a~~The tablet of any preceding claim, comprising: bexagliflozin; glyceryl dibehenate; polyethylene oxide; lactose; poloxamer 188; microcrystalline cellulose; colloidal silicon dioxide; and magnesium stearate; and optionally having a coating comprising polyvinyl alcohol~~.~~

~~46.~~14. ~~The tablet of claim 45, having~~, for example, wherein the tablet has the following composition per tablet: bexagliflozin, between 5-50 mg; glyceryl dibehenate, between 100-140 mg; polyethylene oxide, between 50-75 mg; lactose, between 40-50 mg; poloxamer 188, between 40-45 mg; microcrystalline cellulose, between 60-80 mg; colloidal silicon dioxide, between 4-5 mg; and magnesium stearate, between 6-9 mg; optionally also having 10-12 mg of the coating.

~~47. A batch of tablets which include an amount of bexagliflozin between 5-50 mg wherein, when tablets are assessed in an *in vitro* dissolution assay conducted in USP Apparatus 1 charged with 900 mL of 0.1 N HCl and stirred at a rate of 50 rpm with the temperature maintained at 37 ± 0.5 °C, from which 10 mL is extracted at 1, 3, 5 and 8 hours after being added to the HCl, at least one of the following criteria is satisfied: (i) six tablets of the batch are analyzed and all six tablets release ≤17% of their bexagliflozin after 1 hour, release between 20-45% of their bexagliflozin after 3 hours, release between 45-75% of their bexagliflozin after 5 hours, and release ≥80% of their bexagliflozin after 8 hours; (ii) six tablets did not satisfy criteria (i), but the average bexagliflozin release for those six tablets and six further tablets is ≤17% after 1 hour, between 20-45% after 3 hours, between 45-75% after 5 hours, and ≥80% after 8 hours, and the bexagliflozin release seen by all twelve tablets falls no more than 2 mg outside these release criteria; or (iii) twelve tablets did not satisfy criteria (ii), but the average bexagliflozin release for those twelve tablets and twelve further tablets is ≤17% after 1 hour, between 20-45% after 3 hours, between 45-75% after 5 hours, and ≥80% after 8 hours; not more than 2 of the 24 tablets are more than 10% outside each of the ranges of ≤17% after 1 hour, between 20-45% after 3 hours, between 45-75% after 5 hours, and ≥80% after 8 hours; and none of the tablets is more than 20% outside each~~

of the ranges of ≤17% after 1 hour, between 20-45% after 3 hours, between 45-75% after 5 hours, and ≥80% after 8 hours.

48. The batch of claim 47, wherein the tablets release (a) between 45-72% of its bexagliflozin after 5 hours (b) between 50-70% of its bexagliflozin after 5 hours (c) between 49-69% of its bexagliflozin after 5 hours or (d) between 48-68% of its bexagliflozin after 5 hours.

49. A batch of extended release bexagliflozin tablets which include an amount of bexagliflozin between 5-50 mg wherein:

(a) upon administration to an appropriately constituted cohort of healthy fasted subjects, a first representative sample set of tablets from the batch provides on one occasion a first mean logarithm of the C_{max} and a first mean logarithm of the AUC_{0-t}, and a second representative sample of tablets from the batch produces on a different occasion a second mean logarithm of the C_{max} and a second mean logarithm of the AUC_{0-t}, and wherein the differences between the first and second mean logarithms of the C_{max} and between the first and second mean logarithms of the AUC_{0-t} both exhibit 90% confidence intervals, the endpoints of which lie between -0.22314 and +0.22314.

(b) upon administration to an appropriately constituted cohort of healthy subjects each provided on one occasion a single tablet from a first representative tablet sample set in the fasted state, and on a different occasion a single tablet from a second representative tablet sample set in the fed state, the mean differences in $\ln(C_{max})$ and $\ln(AUC_{0-t})$ both exhibit a 90% confidence interval, the endpoints of which lie between -0.22314 and +0.58779;

(c) upon administration to an appropriately constituted cohort of fasted healthy subjects each provided on one occasion a single tablet from a first representative tablet sample set without any prior dosage of a parenteral GLP-1 receptor agonist, and on a different occasion, a single tablet from a second representative tablet sample set 30 minutes following an approved dosage of a parenteral GLP-1 receptor agonist, the mean differences in $\ln(C_{max})$ and $\ln(AUC_{0-t})$ both exhibit a 90% confidence interval wherein the upper bound of the interval is less than 0.69315; and/or

(d) upon administration to an appropriately constituted cohort of healthy subjects each provided on one occasion a single tablet from a first representative tablet sample set in the fasted state, and on a different occasion, a single tablet from a second representative tablet sample set in the fed state, the differences created by subtracting the values for the T_{max} for the fasted state from the values for the T_{max} for the fed state exhibit a median that is less than or equal to 3.5 hours.

54. The batch of any one of claims 47 to 49, wherein the amount of bexagliflozin is 20 mg.

55. A tablet of the batch of any one of claims 47 to 50.

56. The tablet of claim 51, comprising: one or more release-controlling agents; one or more matrix or membrane modifiers; one or more solubilizers; one or more glidants, lubricants and/or flow aids; one or more disintegrants; one or more fillers; one or more binders; one or more density modifiers and/or effervescent components; one or more colorings; one or more flavorings; one or more anti-oxidants; and/or one or more mucoadhesives.

~~57.~~15. ~~A solid oral dosage form~~The tablet of claim 1, that contains bexagliflozin and that provides a first geometric mean plasma C_{max}, a first geometric mean AUC_{0-t} and a first median T_{max} in fasted subjects, and provides a second geometric mean plasma C_{max}, a second geometric mean AUC_{0-t} and a second median T_{max} in fed subjects, wherein (i) the ratio of the second divided by the first geometric mean C_{max} is between 0.8 and 1.8; (ii) the ratio of second divided by the first geometric mean AUC_{0-t} is between 0.8 and 1.8; or (iii) the ratio of second divided by the first median T_{max} is between 0.8 and 3.0.

~~58.~~16. ~~A solid oral dosage form~~The tablet of claim 1, that contains bexagliflozin and that provides a first geometric mean plasma C_{max}, a first geometric mean AUC_{0-t} and a first median T_{max} in subjects not previously administered a parenteral GLP-1 receptor agonist, and provides a second geometric mean plasma C_{max}, a second geometric mean AUC_{0-t} and a second median T_{max} in subjects previously administered a parenteral GLP-1 receptor agonist, wherein (i) the ratio of the second divided by the first geometric mean C_{max} is between 0.8 and 2.0; (ii) the ratio of second divided by the first geometric mean AUC_{0-t} is between 0.8 and 2.0; or (iii) the ratio of second divided by the first median T_{max} is between 0.8 and 3.0.

~~59.~~17. The ~~solid oral dosage form~~tablet of claim ~~53~~15 or claim ~~54~~16, which is a tablet comprising 20 mg bexagliflozin.

~~60.~~18. Use of ~~A method for treating a subject suffering from diabetes or its symptoms, comprising a step of administering to the subject~~ the tablet of any one of the preceding claims ~~1-46, 51-52, or 55~~in the manufacture of a medicament for the treatment of diabetes or its symptoms.