

DELIVERY SYSTEMS AND DEVICES

FIELD OF THE INVENTION

5 The present invention relates to a product which is capable of the release of one or more active ingredients. Ideally, the product is used as a delivery system and/or a delivery device that is suitable for consumption by humans and/or animals. The invention also relates to a method of preparing said product. Inventive uses of said product are also disclosed herein.

10 BACKGROUND OF THE INVENTION

Gastroretentive drug delivery systems have been developed to address issues arising from the poor gastric absorption and bioavailability of certain orally-administered drugs and other active ingredients. Gastroretentive drug delivery systems can also be used for improving the absorption and bioavailability of certain orally-administered drugs in the upper small intestine.

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A gastroretentive drug delivery system allows an orally-administered drug or other active ingredient to be retained in the upper gastrointestinal tract (e.g. the stomach) for a longer period of time than that afforded by the usual timeline of digestion, thereby increasing the amount of drug or active ingredient absorbed (e.g. in the stomach or upper GIT).

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Migrating motor complexes (or migrating myoelectric complex or migratory motor complex or migratory myoelectric complex or MMC) are waves of electrical activity that sweep through the stomach and small intestines in a regular cycle during fasting. These motor complexes trigger strong, bursting peristaltic waves, also known as housekeeping waves which facilitate transportation of indigestible substances such as bone, fibre, and foreign bodies from the stomach, through the small intestine, past the ileocecal sphincter, and into the colon. The MMC waves occur every 45–180 minutes during the interdigestive phase (i.e., between meals) and are responsible for the rumbling experienced when hungry.

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30 Therefore, to be retained in the stomach for any length of time beyond this, a gastroretentive drug delivery system must be sufficiently mechanically robust to survive the forces exerted by the muscles in the stomach, for example during phase III interdigestive migrating motor complexes as well as the general peristaltic cycles of stomach muscles.

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Existing gastroretentive drug delivery systems are based on various technologies, including floating systems (FTS), high-density systems (HDS), mucoadhesive systems (MCS),

magnetic systems (MAGS), and expandable systems (EXS). A brief summary of each of these systems is summarised below. However, the reader is directed to the following review article for a greater understanding: 'Features and Facts of a Gastroretentive Drug Delivery System-A Review'; Turk J Pharm Sci. 2022 Aug; 19(4): 476–487.

A commercial example of a MCS includes Xifaxan® (Rifaximin) developed by Lupin (India). Commercial examples of EXS include: The Acccordian Pill® developed by Intec Pharma Ltd., Lyndra's LYNX™ drug delivery platform, or Depomed's AcuForm™ platform.

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Floating systems (FTS) either contain a cavity or a gas-generating agent to provide a product which is buoyant within the stomach and thus floats. However, such systems suffer from inadequate mechanical properties and thus are rapidly broken down by the MMC waves of the stomach. Additionally, a FTS is known to exit the stomach earlier than desired making such systems unsuitable for an orally-administered drug or other active ingredient to be retained in the upper gastrointestinal tract for a long period of time.

High-density systems (HDS) use weight as a retention mechanism. Thus, to ensure the gastric residence of a drug in the stomach, its density must exceed that of the normal stomach contents (1.004 g/mL). Because these systems place a lack of emphasis on the mechanical properties, the gastroretention time of these systems is generally short (up to 25h as reported) as it depends on the size of the formulation. However, the size of the formulation is limited by the requirement of oral dosage form. Additionally, as discussed in 'Nanomaterials: An Improvised Drug Delivery System through the Gastroretentive Drug Delivery System'; Mater. Proc. 2023, 14(1), 63, HDS involves the use of heavy materials with a formulation strategy of coating it with heavy materials or mixing it with iron powder, zinc oxide, or barium sulfate, which allows the formulation to settle in the stomach and retard action due to the high density of the formulation. The formulation of this system is challenging, and no such marketed formulation exists.

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Mucoadhesive systems (MCS) use its adhesive properties to target a drug to a specific region of the body for an extended period of time (e.g., the mucosa of the stomach). For this, bioadhesive or mucoadhesive polymers are typically used such as those described in 'Features and Facts of a Gastroretentive Drug Delivery System-A Review'; Turk J Pharm Sci. 2022 Aug; 19(4): 476–487. However, as set out in this review article, the gastroretentive time of a mucoadhesive system is typically short with one reported example having gastric retention of 6 hours. Further drawbacks also include: the high humidity conditions of the

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stomach which can decrease the bioadhesion of the MCS; and MCS also comes with higher risk of adhesion to the oesophagus which may lead to collateral lesions. See: Current State and Future Perspectives on Gastroretentive Drug Delivery Systems Pharmaceutics 2019, 11(4), 193.

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Magnetic systems (MAGS) include magnetic particles within the orally-administered drug device and an extracorporeal magnet to anchor the device. MAGS may potentially exhibit long gastroretention times but require extracorporeal accessory equipment. Furthermore, the long term of use of magnets and the resulting force applied to the stomach wall by the
10 MAGS are not well understood and may cause undesirable side effects.

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Expandable systems (EXS) are devices that expand in volume in the gastric environment, for example by swelling or unfolding to a volume large enough to prevent the device from exiting the stomach. Further information of this type of system can be found in the following review article: Current State and Future Perspectives on Gastroretentive Drug Delivery Systems Pharmaceutics 2019, 11(4), 193.

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An expandable system must reach a size greater than the diameter of the pylorus (preferably $\geq 25\text{mm}$, further preferably $> 30\text{mm}$) in a short period of time (within 45 minutes, preferably within 30 minutes, further preferably within 10 minutes). Cassilly et al. in "Twenty-four hour ambulatory antroduodenal manometry in normal subjects (co-operative study)" Neurogastroenterol. Motil. 2008. 12, 231–238, studied the stomach emptying of a SmartPill™ and their work shows a strong correlation between the occurrence of interdigestive MMC phase III and the exit of the nondigestive pills. For a SmartPill™ ($>7\text{mm}$ diameter), the exiting
25 was at 261 ± 22 min (first phase III MMC @ 239 ± 23 min) with an approx. 300 kcal meal. When administered with only water, the gastric residence time was at 92 ± 44 min (first phase III MMC @ 87 ± 30 min). For nondigestive particles smaller than 7mm, early exiting without phase III MMC is experienced (Stotzer et al. Neurogastroenterol Motil. 2000; 12, 415-9).

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Thus, any expandable gastroretentive drug delivery system needs to have a diameter in the stomach much greater than 7mm (preferably $\geq 25\text{mm}$, further preferably $> 30\text{mm}$) in order to be retained within the stomach for any length of time. Further, it is necessary for such a drug delivery system to achieve this size within a matter of minutes from swallowing.

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However, existing swellable devices in particular tend to suffer from conflicts between the swelling rate and the mechanical properties – faster-swelling devices have sub-standard

mechanical properties which result in accelerated degradation of the device by the MMC waves of the stomach. Once degraded to a small enough size, the swellable device is removed from the stomach by the MMC waves. Some expandable systems (particularly unfolding systems) exhibit long gastroretention times, but these require high temperature treatment during the manufacturing process, which limits the active ingredients that can be used therein. In addition, as set out in Current State and Future Perspectives on Gastroretentive Drug Delivery Systems *Pharmaceutics* 2019, 11(4), 193, expandable systems have a few limitations such as difficulty in storing easily hydrolysable, biodegradable polymers; being difficult to manufacture and may not be cost-effective; difficulty in maintaining the structural integrity; and may cause bowel obstruction, intestinal adhesion, and gastropathy.

Finally, known swelling systems and/or expandable systems in the art include double-network hydrogels and superporous hydrogels (SPHs). Such systems are discussed in, for example: 'Features and Facts of a Gastroretentive Drug Delivery System-A Review'; *Turk J Pharm Sci.* 2022 Aug; 19(4): 476–487.

Superporous hydrogels have a porous hydrophilic cross-linked structure which is hard and brittle when dried, and insoluble in water. When immersed in aqueous media, a SPH can absorb the aqueous fluids up to many times their own weight, to swell in size and to become soft yielding gel materials. SPHs typically have a three-dimensional network made from hydrophilic polymeric material with numerous pores.

In 2017, Liu *et al.*, developed a double-network hydrogel dispersed with lumefantrine (an antimalarial drug) which had the effect of doubling the release time of the free form (*Nat Commun* 8, 124 (2017)). This system was also tried with insulin, rifampicin and dimethyl sulfoxide and showed a size-dependent *in vitro* release rate. Despite this system achieving an average stomach retention time of 9 days in pigs, its commercial applications are limited due to its swelling rate; to achieve gastroretention, the endoscopically inserted pre-swelled hydrogel with a size of $\Phi 2.8\text{cm} \times 5\text{cm}$ and volume of 22 ml was used for the *in vivo* pig tests. Therefore, this device is not suitable for oral dosage.

In 2014, Nagpal *et al.* loaded a SPH, which had been made using a gas blowing method to generate the plurality of pores, with verapamil HCl as a model drug to demonstrate proof-of-concept as a drug delivery system (*Int J Pharma Investig*, 3, 131 (2013)). Their tests revealed an initial burst release of verapamil in the first hour before continued release for the next 24

hours. However, creating SPHs through gas blowing results in random pore creation and so the resulting hydrogels have insufficient mechanical strength and limited gastroretention time.

WO 2019/016560 A1 discloses a process for producing a SPH via a freeze-drying process which results in an SPH that achieves a fast rate of swelling and excellent high swelling volume. This disclosure also discloses a multi-component product formulation in a “core-shell” format at page 10, lines 5 to 12. In a preferred embodiment, a first component (which is a SPH according to the disclosure of WO 2019/016560 A1) is used to form the “shell” and a second component (which is one or more slow swelling and non-super porous hydrogels) is used to form the “core”.

WO 2021/069751 A1 discloses a process for producing a SPH via a freeze-drying process which results in an SPH that results in improved processability in addition to a fast rate of swelling and excellent high swelling volume. The disclosure also teaches a SPH for use in an oral dosage formulation in which one or more pharmaceuticals and/or nutraceuticals are incorporated within an oral dosage formulation as an additional separate ingredient to the plasticised hydrogel material. In one embodiment, the one or more pharmaceuticals and/or nutraceuticals maybe an additional separate ingredient to the SPH, or in an alternative embodiment, the one or more pharmaceuticals and/or nutraceuticals may be part of the structure of the hydrogel material. In those instances where the one or more pharmaceuticals and/or nutraceuticals may be part of the structure of the hydrogel material, the pharmaceutical and/or nutraceutical may be attached to one or more of the hydrophilic polymer chains which form the hydrogel material.

Therefore, this disclosure only makes specific reference to an oral dosage formulation in which the one or more pharmaceuticals and/or nutraceuticals may be attached to one or more of the hydrophilic polymer chains which form the SPH; there is disclosure or teaching in this prior art where the one or more pharmaceuticals and/or nutraceuticals may be located in a multi-component product formulation, e.g., in a “core-shell” format. In particular, there is no disclosure of the preparation of such a multi-component product, or any data to disclose the effectiveness of the release of one or more pharmaceuticals and/or nutraceuticals from such a multi-component product, particularly in a gastric environment. It is also not known from this prior art whether the one or more pharmaceuticals and/or nutraceuticals must be included in the “shell” or the “core” in such a multi-component product in order to achieve long term retention in the gastric environment and enable effective release of one or more pharmaceuticals and/or nutraceuticals.

The present invention therefore aims to overcome the aforementioned disadvantages of the known art.

In particular, the aim of the present invention is to provide a novel product which is capable of the release of one or more active ingredients, in an environment, ideally when subject to a gastric environment. Ideally, the novel product will therefore function as a delivery system and/or a delivery device, and preferably have a gastroretention time of 12 hours or greater in the gastric environment to allow for prolonged delivery of an active ingredient such as a pharmaceutical and/or a nutraceutical. The approach of the present invention will therefore contrast prior art products which have gastroretention times of less than of 12 hours and thus enables an increased amount of active ingredient to be absorbed by the gastric environment such as the stomach.

The methods the present invention will also enable efficient and cost-effective production of the product. In addition, the methods of the present invention will avoid high temperatures, allowing temperature-sensitive active materials (such as biologics) to be loaded onto the product, contrasting prior art approaches as discussed above.

The present invention achieves these aims by providing a product which is capable of the release of one or more active ingredients, in which the product comprises a superporous hydrogel structure, and in which the superporous hydrogel structure comprises a core region comprising one or more active ingredients. Ideally, the product is a multi-component product, typically having a shell region and a core region (i.e., a "core-shell" format).

Advantageously, as the product comprises a hydrogel material (i.e., a superporous hydrogel structure) which is ideally prepared by freeze-drying, this enables long gastroretention times by its mechanical robustness, high volume swelling ratio, and high swelling rate. Indeed, the long gastroretention times provided by the product of the present invention allow for the one or more active ingredients to be delivered to and retained in an environment, preferably a gastric environment (e.g., the stomach) for at least 12 hours, preferably at least 24 hours (preferably, up to 7 days, ideally up to 14 days), improving their absorption. In addition, because the product comprises a hydrogel material (i.e., a superporous hydrogel structure) the product (preferably acting as a delivery system and/or delivery device, ideally for a drug or vitamin) will typically break down and exit the body. Furthermore, the product is compatible with a wide range of active ingredients as such as pharmaceuticals and/or nutraceuticals as discussed below. The product is ideally used as a gastroretentive delivery system for one or more active pharmaceutical ingredients as discussed in detail below.

The term “superporous hydrogel” (SPH) as used herein means a porous hydrophilic cross-linked structure which is hard and brittle when dried, and insoluble in water. When immersed in aqueous media, a SPH can absorb the aqueous fluids up to many times their own weight, to swell in size and to become soft yielding gel materials. SPHs typically have a three-dimensional network made from hydrophilic polymeric material with numerous pores.

The average pore diameter of a newly-formed SPH (i.e., a SPH that has not been subjected to a compression step) is ideally from greater than 100 μm up to about ≤ 3 mm, optionally up to about ≤ 2 mm, further optionally up to about ≤ 1 mm.

Preferably, a superporous hydrogel has a pore structure wherein the pores of the pore structure have an average maximum dimension of at least 100 μm .

It will be appreciated that, the broad term “superporous hydrogel” may comprise “compressed superporous hydrogels” or “uncompressed superporous hydrogels” or both compressed and uncompressed superporous hydrogels. A compressed superporous hydrogel is a superporous hydrogel which has been subject to a compressive force suitable to collapse at least some of the pores of the superporous hydrogel structure. An uncompressed superporous hydrogel is a superporous hydrogel which has not been subject to such a force.

Preferably, the product comprises a compressed superporous hydrogel. Compressed superporous hydrogels can be readily distinguished from uncompressed superporous hydrogels by a variety of techniques including, for example, scanning electron microscopy. Indeed, as discussed below, Figures 23 and 24 depict the visual differences between the porous structure of a compressed and an uncompressed superporous hydrogel.

The term “maximum dimension” is a parameter that is measured using scanning electron microscopy (SEM) and is defined as half of the perimeter of a cross section of a single pore of the pore structure of a superporous hydrogel as defined herein. Therefore, if any cross section of a single pore, as depicted by SEM, has a perimeter of 200 μm or greater, then that pore has a maximum dimension of at least 100 μm .

The term “average maximum dimension” refers to a mean average of a sample of measurements made in accordance with the definition of the term “maximum dimension”. In

one embodiment, the average maximum dimension is a mean average of a sample of at least 10 pores, preferably at least 10 adjacent or interconnected pores.

Preferably, the pores of the pore structure have an average maximum dimension of at least 150 μm , optionally at least 200 μm or at least 250 μm .

Preferably, the pores of the pore structure of the superporous hydrogel have a maximum dimension of between $>10\mu\text{m}$ and 5mm. More preferably, the superporous hydrogel comprises a compressed structure having pores which have a maximum dimension of between $>10\mu\text{m}$ and 3mm, optionally between $>30\mu\text{m}$ and 2.1mm.

Optionally, the superporous hydrogel comprises an uncompressed structure having pores which have a maximum dimension of between $>100\mu\text{m}$ and 5mm, optionally between $>200\mu\text{m}$ to 3mm.

For the avoidance of doubt, the "maximum dimension" and "average maximum dimension" are defined in the same way for both compressed and uncompressed superporous hydrogels.

However, where the product comprises an uncompressed superporous hydrogel, the pores of the pore structure of the uncompressed superporous hydrogel will preferably further exhibit an average pore diameter of 100 μm or greater. Further preferably, the pores of the pore structure have an average pore diameter of at least 150 μm , optionally at least 200 μm or at least 250 μm .

As used herein, the term "average pore diameter" is defined as the longest straight line wall-to-wall dimension on any cross-section of the pore. That is, a pore is considered to have a pore diameter of 100 μm if the longest straight line wall-to-wall dimension of any cross section of that pore is 100 μm . For example, in the case where the pores of the superporous hydrogel are substantially spherical, the term "pore diameter" refers to the true diameter of the pores. Alternatively, in the case where the pores of the superporous hydrogel have a substantially elliptical cross-section, the term "pore diameter" refers to the major axis of the elliptical cross-section. It will be appreciated that the above shapes are provided for example only.

It will be appreciated that the pore size definitions above relate to a product according to the present invention. It will be further appreciated that, if a product according to the present invention is submerged in a fluid comprising water, for example simulated gastric fluid or water, the pores may increase in size. A preferred simulated gastric fluid may comprise a

mixture of salt solution (e.g., sodium chloride, ideally 0.2 wt%) and acid solution (e.g., hydrochloride acid, ideally pH 1-2).

Preferably, the superporous hydrogel structure comprises one or more selected from an
5 interpenetrating network structure, a semi-interpenetrating network structure, and a simple cross-linked structure. Ideally, the superporous hydrogel structure comprises an interpenetrating network structure.

As used herein, the term "core region" means a substantially central portion of a hydrogel
10 structure which includes a hydrogel material region and/or does not include a hydrogel material region. Optionally, the core region includes a void or cavity region and/or includes one or more active ingredients and/or one or more excipients. Therefore, the one or more active ingredients and/or one or more excipients are ideally associated (directly or indirectly) with a core region of the superporous hydrogel structure.

15 Preferably, the one or more active ingredients may be located and/or held by the core region of the superporous hydrogel structure (e.g., held within the core region), without being chemically joined (e.g., bonded) to a part of the core region of the superporous hydrogel structure itself (e.g., without using a covalent chemical bond). This includes for instance
20 without being chemically attached to one or more of the hydrophilic polymer chains which preferably form the superporous hydrogel structure. The term "chemically joined" refers to the instance of a covalent bond resulting from a chemical reaction and therefore any electrostatic (e.g., ionic) or other charge-based interactions (e.g., van der Waals attractions) are not included within this meaning. Indeed, it is possible that an active ingredient that is
25 not chemically bonded to the hydrogel material may, for instance, form an electrostatic interaction with hydrogel material.

Alternatively, or additionally, the one or more active ingredients may be located and held by the core region of the hydrogel material (e.g., held within the core region), without being
30 physically joined (e.g., bonded) to the hydrogel material itself (e.g., without the use of adhesive to join the one or more active ingredients to the hydrogel material itself).

Ideally, the one or more active ingredients maybe located and held (partially or completely) within the core region of the superporous hydrogel structure. For instance, the one or more
35 active ingredients maybe held within the core region by the elastic action or nature of the superporous hydrogel material.

Preferably, substantially all of the one or more active ingredients is located within the core region of the superporous hydrogel structure. That is, the one or more active ingredients are preferably substantially absent from a region which is not the core region (such as a shell region of the superporous hydrogel structure, or a shell region of the product). It will be appreciated that this limitation applies prior to any subsequent use of the product (i.e., prior to any optional ingestion by a patient). Advantageously, this results in a product where the release rate of the active ingredient is more consistent.

Preferably, the core region may further comprise one or more further components in addition to the one or more active ingredients. For instance, this may include one or more excipients which are discussed in greater detail below.

As used herein, the term "shell region" means a portion of the hydrogel structure which is around the outside of the core region. In particular, the "shell region" may partially or completely surround the "core region" to provide a "core-shell" structure.

Superporous hydrogel material is preferably used for the shell region. Therefore, in one embodiment, the product comprises a superporous hydrogel structure, in which the superporous hydrogel structure includes a shell region and a core region, in which the shell region includes a superporous hydrogel material, and in which the core region includes one or more active ingredients. That is, superporous hydrogel material is included in the "shell region" and one or more active ingredients are included in the "core region". However, as set out above, the "core region", is not solely limited to the one or more active ingredients and may also include a region which includes superporous hydrogel material and/or a region that does not include superporous hydrogel material (e.g., a void or cavity region). Additionally, the "shell region" could include one or more further components in addition to the superporous hydrogel material.

Preferably, the superporous hydrogel structure comprises a shell region at least partially enclosing the core region, at least a portion of the shell region of the superporous hydrogel structure comprises substantially no active ingredient. Further preferably, all of the shell region of the superporous hydrogel structure comprises substantially no active ingredient. It will be appreciated that this limitation applies prior to any subsequent use of the product (i.e., prior to any optional ingestion by a patient). Advantageously, this results in a product where the release rate of the active ingredient is more consistent.

Preferably, the core region comprises a body discrete from the superporous hydrogel structure. That is, the core region comprises a body comprising one or more active ingredients wherein said body is not a continuation of the surrounding superporous hydrogel structure. The body may or may not further comprise a hydrogel structure and/or a superporous hydrogel structure. However, in the case where the body comprises a hydrogel structure and/or a superporous hydrogel structure, the structure of the body does not form a single, continuous porous structure with the surrounding superporous hydrogel structure. Preferably, the shell region at least partially surrounds the body. Ideally, the shell region entirely surrounds the body.

The body may further comprise one or more excipients. Preferable one or more excipients (optionally two or more excipients) may include but not be limited to permeation enhancers, filler materials, binders, diluents, buffering agents, thickener or gelling agents, stabilizers, solubilizers, surfactants, disintegrants, lubricants, glidants, colorants, contrast agents (for radiographic imaging), preservatives, suspending agents, emulsifiers, film formers or coatings, antioxidants, tonicity modifiers, release modifiers, radioactive materials, and combinations of these.

The body may optionally be in a solid state, a liquid state, or a mixture of a solid and a liquid.

Preferably, the core region comprises one or more cavities which are ideally substantially empty of hydrogel material prior to being loaded with one or more active ingredients. Ideally the one or more cavities are loaded with one or more active ingredients. A "cavity" as used herein is intended to mean any empty space within a hydrogel material which is not considered a 'pore' of the hydrogel structure. That is, the term "cavity" does not include any of the plurality of pores inherent to the structure of a hydrogel, produced by chemical or physical means during the one or more processing steps, and instead refers to empty space which has been intentionally created by separate means (e.g., by use of a specific mould or by making an incision in the hydrogel). Therefore, the term may also include a "pocket", a "pouch", a "chamber", a "void" or the like.

After a compression step, the one or more cavities may have dimensions of $< 25\text{mm} \times < 10\text{mm} \times < 10\text{mm}$. However, prior to a compression step, the one or more cavities may have dimensions of up to $35\text{mm} \times 35\text{mm} \times 35\text{mm}$. Ideally, prior to a compression step, the one or more cavities may have dimensions of around $20\text{mm} \times 20\text{mm} \times 20\text{mm}$. Thus, dimension could be from about $10\text{mm} \times 10\text{mm} \times 10\text{mm}$ to about $35\text{mm} \times 35\text{mm} \times 35\text{mm}$ prior to a compression step.

In one embodiment, after a compression step, the one or more cavities will accommodate a cylindrical or sphere-shaped tablet that is optionally about 25mm long and has a diameter of about 8mm.

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Preferably, the core region, and optionally the one or more cavities, may further comprise one or more excipients which are discussed in greater detail below.

The core region may comprise one or more cavities, and ideally the one or more cavities may be loaded with two or more active ingredients, or in some cases, three or more active ingredients. The two or more active ingredients, or in some cases, three or more active ingredients may each be the same active ingredient but contained within separate delivery vehicles such as capsules or pills, for instance. Alternatively, the cavity may contain a first active ingredient and a second active ingredient (optionally a third active ingredient), in which the first active ingredient is different from the second active ingredient (optionally the third active ingredient is different from the first and second active ingredient).

The core region may comprise two or more cavities, or in some cases, three or more cavities. Each of the two or more cavities, or each of the three or more cavities may be loaded with one or more active ingredients. In one embodiment, the core region may comprise two or more cavities, in which one of the two or more cavities is loaded with a first active ingredient and another of the two or more cavities is loaded with a second active ingredient. In this instance, the first active ingredient may be the same or different from the second active ingredient. Thus, in one embodiment, all of the two or more cavities, or optionally all of the three or more cavities, may each comprise different active ingredients.

Preferably, the total volume of the one or more cavities is $\geq 0.17 \mu\text{L}$ and $\leq 2 \text{ mL}$. As used here, the term "total volume" refers to the combined volume of the one or more cavities. Optionally, the one or more cavities have a maximum combined volume of at least $100 \mu\text{L}$ and $\leq 3 \text{ mL}$, optionally $\leq 2 \text{ mL}$, and further optionally $\leq 1 \text{ mL}$. Optionally, the one or more cavities have a maximum combined volume of at least $\geq 0.17 \mu\text{L}$ and $\leq 3 \text{ mL}$, further optionally $\leq 1 \text{ mL}$.

In one preferred embodiment, the total volume of the one or more cavities is $> 4.2 \mu\text{L}$ and $\leq 2 \text{ mL}$. It will be appreciated in this preferred embodiment that this will not overlap with the pore size of a preferred superporous hydrogel which comprises a compressed structure having pores which have a maximum dimension of $> 100 \mu\text{m}$ to 1 mm .

Additionally, the one or more cavities may comprise one or more passageways which allow for fluid communication from an opening on a side of the product to the one or more cavities. A passageway could be considered as a corridor between an opening on a side of the product and the one or more cavities within a substantially central portion of the superporous hydrogel structure. Advantageously, such one or more passageways permit easy loading of the one or more cavities with the one or more active ingredients. Thus, the one or more passageways preferably includes an opening on a side of the product to permit easy loading of the one or more cavities with one or more active ingredients. Ideally, such passageways are present prior to loading of the one or more cavities with one or more active ingredients during the manufacture of the product of the present invention. This is because such passageways may be sealed or closed off following the loading of such one or more cavities with one or more active ingredients. In one embodiment, the opening is closed after the one or more cavities are loaded with one or more active ingredients. The opening and/or the passageway may be closed by installation of a plug, preferably comprising biologically inert material and glue; by sealing, optionally by use of glue, thread or staples; by the elastic action of the superporous hydrogel material; by application of a compressive force, optionally after a freeze-drying treatment; or by any other means available to the skilled person.

The shell region may comprise one or more incisions. These one or more incisions may have been made to the shell region of the hydrogel material to enable one or more active ingredients be loaded into the core region.

Preferably, the superporous hydrogel comprises a compressed structure having pores which have a maximum dimension of between $>100\mu\text{m}$ and 5mm . More preferably, the superporous hydrogel comprises a compressed structure having pores which have a maximum dimension of between $>100\mu\text{m}$ and 2mm , optionally $>100\mu\text{m}$ and 1mm .

As used herein the term "capable of the release of one or more active ingredients" means that the one or more active ingredients included in the product are released within an environment, preferably the gastric environment after ingestion. Preferably, this release occurs by diffusion or dissolution of the active ingredient through the plurality of pores which expand in size as a result of the superporous hydrogel swelling within the gastric environment. Preferably, substances or particles with a diameter of $\leq 500\mu\text{m}$ may freely release from the core region once the superporous hydrogel has swollen. In some instance, substances or particles with a diameter of up to $200\mu\text{m}$ may freely release from the core region once the

superporous hydrogel has swollen. In one embodiment, a diameter could be from about 200µm to about 500µm, or from about 300µm to about 500µm.

As used herein, the term “active ingredient” means any active ingredient selected from the group consisting of pharmaceutical ingredients, nutraceutical ingredients, and combinations thereof.

The term “pharmaceutical ingredient” as used herein is intended to include any active component which provides an effect on a human or animal to treat a condition. Such active components are known in the art as “active pharmaceutical ingredients” (APIs). Also included within the scope of the term “pharmaceutical ingredient” are radiopharmaceuticals which are suitable for use in a human or animal to treat or to diagnose a condition.

The term “nutraceutical ingredient” as used herein is intended to include any food supplement or ingredient, mineral, or vitamin which gives health enhancing benefits when ingested by a human or animal. For the avoidance of any doubt, a nutraceutical ingredient as defined herein also includes within its scope a probiotic ingredient, a prebiotic ingredient, yeasts, a symbiotic ingredient, antioxidants, phytochemicals, fatty acids, and amino acids.

Preferably, the active ingredient as a nutraceutical ingredient comprises a vitamin.

The term “probiotic” as used herein is intended to mean “live microorganisms which when administered in adequate amounts confer a health benefit on the host”.

The term “prebiotic” as used herein is intended to mean ‘nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacterial species already established in the colon, and thus in effect improve host health’.

The term “symbiotic” as used herein is intended to mean ‘mixtures of probiotics and prebiotics that beneficially affect the host by improving the survival and implantation of live microbial dietary supplements in the gastrointestinal tract of the host’ (Andersson et al., 2001).

The definition of “probiotic”, “prebiotic” and “symbiotic” are defined to be consistent with that reported by the World Health Organisation in October 2001, which is a recognised body which would be understood by the skilled person at the filing date of this application. In particular, reference is made to page 5, section 3, and pages 20 to 21, section 8.4 of the report published

by the World Health Organisation of a Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria which took place 1-4 October 2001.

- 5 Preferably, the one or more active ingredients are suitable to be released in the stomach, optionally with one or more excipients such as one or more permeation enhancers. Optionally, the one or more active ingredients may have a narrow absorption window in the upper GI tract. The one or more active ingredients may, in some embodiments, be subject to losing their therapeutic effect (e.g., by degradation) in the intestine (e.g., the colon and/or
- 10 the small intestine). Alternatively or additionally, the one or more active ingredients may cause negative or harmful effects if they are released in the intestine (e.g., the colon and/or the small intestine). An example of an active ingredient which may cause negative or harmful effects if released in the intestine includes antibiotics for treating helicobacter pylori (H. pylori).
- 15 Optionally, the one or more active ingredients may be thermolabile and/or heat sensitive.

Optionally, the one or more active ingredients may be suitable for use to treat a disease for which appetite regulation and/or any weight loss resulting from appetite regulation are not a negative side-effect. Preferably, the one or more active ingredients may be suitable for use

20 to treat a disease for which appetite regulation and/or any weight loss resulting from appetite regulation enhance the therapeutic effect of the one or more active ingredients.

Optionally, the one or more active ingredients may comprise one or more large molecules with a molecular weight of greater than 1000 g/mol. These large molecules may optionally

25 not be releasable from a microporous or mesoporous system, but are able to be released through the pores of a superporous hydrogel.

In one embodiment, the pharmaceutical ingredient and/or nutraceutical ingredient may be selected from one or more of the group consisting of a small molecule, a peptide, a protein,

30 an oligonucleotide, one or more cells (e.g., probiotics and/or yeasts), and an oligopeptide. Preferably, the pharmaceutical ingredient and/or the nutraceutical ingredient may be selected from one or more of the group consisting of a small molecule and a peptide.

A preferable peptide may include a glucagon-like peptide, in particular a glucagon-like peptide

35 receptor agonist such as semaglutide.

A preferable small molecule may have a molar mass of less than 500 g/mol, ideally less than 250 g/mol, and preferably from about 125 g/mol to about 250 g/mol.

Preferably, the active ingredient as a pharmaceutical ingredient comprises a drug.

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A preferable active ingredient may be selected from obesity related drugs, particularly with one or more modes of action including but not limited to regulating appetite, increasing energy expenditure, modulation of gut hormones, modulation of gut microbiota and reduction of fat absorption.

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Highly preferably, the pharmaceutical ingredient may be one or more selected from the group consisting of Metformin (N,N-dimethylbiguanide), Carbidopa (N-amino- α -methyl-3-hydroxy-L-tyrosine monohydrate), Levodopa (L-3,4-dihydroxyphenylalanine) and Semaglutide.

15 Metformin is often sold under the name Glucophage® and is a first-line medication for the treatment of type 2 diabetes, particularly for humans who are overweight. It is also used to treat polycystic ovary syndrome.

Carbidopa is often sold under the name Lodosyn™ and is for the treatment of Parkinson's disease. Levodopa is often sold under the names such as Sinemet™, Pharmacopa™, Atamet™, and Stalevo™. It is also for the treatment of Parkinson's disease.

25 Semaglutide is often sold under the names Ozempic™, Rybelsus™, and Wegovy™. Semaglutide is a GLP-1 peptide (in particular a GLP-1RA peptide) (i.e., similar to the hormone: glucagon-like peptide-1) and is used to treat type 2 diabetes, by managing blood glucose levels in a human, and obesity.

30 In one highly preferred embodiment, the pharmaceutical ingredient comprises a glucagon-like peptide, in particular a glucagon-like peptide receptor agonist such as semaglutide, and preferably is used together with one or more permeation enhancers such as salcaprozate sodium (SNAC, sodium 8-(2-hydroxybenzamido)octanoate).

Alternatively, a preferred nutraceutical ingredient comprises a cobalt-containing or iron-containing food supplement, which is preferably a vitamin. In particular, a highly preferred nutraceutical ingredient comprises vitamin B12 (also known as cobalamin). In one embodiment, when the nutraceutical ingredient comprises vitamin B12, it may be used with

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or without permeation enhancers such as salcaprozate sodium (SNAC, sodium 8-(2-hydroxybenzamido)octanoate).

5 The one or more pharmaceutical ingredients and/or one or more nutraceutical ingredients may be used in combination with one or more excipients. These may service the purpose of introducing further or increased stabilisation to one or more pharmaceutical ingredients and/or one or more nutraceutical ingredients, or enhancing the therapeutic properties of such one or more pharmaceutical ingredients and/or one or more nutraceutical ingredients.

10 Preferably, the product comprises one or more excipients which are located in the core region of the product. Optionally, the one or more active ingredients may be mixed, optionally intimately mixed, with one or more excipients, with the mixture located in the core region of the product. Preferably, the shell region does not comprise one or more excipients.

15 As explained above, the one or more cavities may further comprise one or more excipients.

In some instances, two or more excipients may be used together with the one or more pharmaceutical ingredients and/or the one or more nutraceutical ingredients.

20 Preferable one or more excipients (optionally two or more excipients) may include but not be limited to permeation enhancers, filler materials, binders, diluents, buffering agents, thickener or gelling agents, stabilizers, solubilizers, disintegrants, lubricants, glidants, colorants, contrast agents (for radiographic imaging), preservatives, suspending agents, emulsifiers, film formers or coatings, antioxidants, tonicity modifiers, release modifiers, and combinations
25 of these.

A most preferable excipient includes one or more permeation enhancers. As used herein a "permeation enhancer" means a chemical compound that improves the absorption of one or more active ingredients ideally across the gastric mucosa. A preferable permeation enhancer
30 includes salcaprozate sodium (SNAC, sodium 8-(2-hydroxybenzamido)octanoate).

Ideally, the product of the present invention is capable of the release of one or more active ingredients in an environment, preferably a gastric environment (e.g., the upper gastrointestinal tract, particularly the stomach), preferably for a prolonged period of time.
35 Preferably this will be 12 hours or greater, more preferably at least 24 hours and in some cases, up to 7 days, and in other cases up to 14 days. Therefore, the present invention will ideally provide a product which can be used as a delivery system, or a delivery device, which

is suitable for treatment of humans and/or animals. Preferably, this product will be suitable for oral dosage. Preferably, this product will be capable of retention in the stomach (i.e., gastroretention) for 12 hours or greater, more preferably at least 24 hours and in some cases, up to 7 days, and in other cases up to 14 days.

5

To exhibit long gastroretention times of 12 hours or greater, at least 24 hours, up to 7 days, or up to 14 days, the product will preferably have mechanical characteristics in the gastric environment which prevent early exit of the product from the stomach. As such, the product preferably exhibits an engineering stress at the point of breaking (measured using a force meter calibrated in pressure units) of at least 100N, ideally at least 300N, after immersion in simulated gastric fluid for one hour. Additionally or alternatively, the product optionally also exhibits an engineering stress at the point of breaking (measured using a force meter calibrated in pressure units) of at least 100N, further optionally at least 300N, after immersion in simulated gastric fluid for 7 days.

15

Preferably, the product is fatigue resistant and can withstand >1800 cycles of 10-20N compression repeats in 37°C SGF. In one embodiment, the product is fatigue resistant and can withstand >9000 cycles of 10-20N compression repeats in 37°C SGF. In one embodiment, the product is fatigue resistant and can withstand >25200 cycles of 10-20N compression repeats in 37°C SGF. The compression repeats are preferably performed using the compression plate of a mechanical tester to apply a compressive force on the product until 10-20N is reached. After 10-20N is reached, the compression plate moves away from the product, ceasing to apply a compressive force to the product, and completing a cycle. A product is considered to be fatigue resistant (i.e., to withstand the cycles of compression repeats) if it can recover its original shape and mechanical properties at and/or after the final cycle of compression.

25

Preferably, the product exhibits a maximum true stress at the point of breaking (measured using a force meter) of at least 50kPa, ideally at least 200kPa, after immersion in simulated gastric fluid for one hour. Additionally or alternatively, the product optionally also exhibits a maximum true stress at the point of breaking (measured using a force meter) of at least 50kPa, further optionally at least 200kPa, after immersion in simulated gastric fluid for 7 days.

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Preferably, the product comprises a superporous hydrogel structure formed by freeze-drying. In particular, it is preferred that the product comprises a superporous hydrogel structure having a pore structure formed by freeze-drying. A superporous hydrogel structure having a pore structure formed by freeze-drying exhibits an improved pore structure when compared

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to a superporous hydrogel structure having a pore structure formed by other methods, such as gas blowing. The pore structure of a superporous hydrogel is formed by a freeze-drying process as follows: the liquid reaction mixture (i.e., an initial mixture of monomers and, preferably, cross-linking agents) adopts a regular solvation arrangement during polymerisation for thermodynamic reasons. Then, during the freeze-drying process, this water is frozen in place and then sublimed out of the hydrogel, resulting in the formation of thin polymeric wall structure (i.e. pores) with certain size and distribution in the areas which previous contained ice crystals. These pores are often adjacent to, or adjoined with, neighbouring pores and often separated by only a thin polymer wall between pores. Thus, the pore structure of the resultant superporous hydrogel structure is formed during the freeze-drying process. That is, the hydrogel is made superporous by the freeze-drying process.

In contrast, superporous hydrogel structures having a pore structure formed by other methods, for example gas blowing, have different pore structures and distribution patterns. The pores of a superporous hydrogel formed by gas blowing are often usually separated and independent, with large volumes of polymer material separating each pore.

A pore structure formed by freeze-drying imparts improved mechanical properties onto the superporous hydrogel, as discussed above, and consequently allows a superporous hydrogel structure formed by freeze-drying to exhibit longer gastroretention time than a superporous hydrogel structure formed by other methods, such as gas blowing.

Ideally, the product comprises a superporous hydrogel structure having a pore structure formed by freeze-drying without the use of gas-blowing agents. Advantageously, the product therefore has a regular pore structure as described above.

Alternatively, the product may comprise a superporous hydrogel structure formed by a blowing agent, a foaming agent or other foaming means as discussed below. Further alternatively, the product may comprise a superporous hydrogel structure formed by 3D-printing. The product may also comprise a superporous hydrogel structure formed by a freezing step followed by a drying step which is one or more selected from the group consisting of supercritical drying, vacuum drying, microwave drying, conventional heat drying, and combinations of these. The product may also comprise a superporous hydrogel structure formed by freeze-thawing. Alternative methods may also include salt-leaching or solvent-casting methods.

Preferably, the superporous hydrogel comprises a structure which includes a mixture of hydrophilic polymers that are cross-linked by virtue of one or more cross-linking agents.

Preferably, the mixture of hydrophilic polymers comprise one or more hydrophilic polymers made from an alkenyl amide-containing monomer, preferably acrylamide, and a polysaccharide. Ideally, the acrylamide-containing monomer comprises acrylamide and the polysaccharide comprises alginate.

The hydrophilic polymers and/or copolymers may be derived from naturally occurring polymers and monomers, from synthetic polymers and monomers, or from mixtures of naturally occurring and synthetic polymers and monomers.

Preferably, the one or more hydrophilic polymers include hydroxylated polymers, and further preferably, the hydrophilic polymers are selected from C₁-C₆-alkylcelluloses, hydroxy-C₁-C₆-alkylcelluloses, hydroxy-C₁-C₆-alkyl-C₁-C₆-alkyl-celluloses. Highly preferred polymers include alginate-containing compounds, such as sodium alginate or alginic acid, and chitosan.

Preferably, the one or more hydrophilic polymers include polymers made by the polymerisation and/or copolymerisation of one or more monomers selected from C₁-C₆-alkenyl amides (e.g. to make polyacrylamide) and C₁-C₆- alkenyl acids (e.g. to make acrylic acid). Highly preferred polymers include poly(acrylamide), poly(2-acrylamido-2-methyl-1-propanesulfonic acid) and poly(N-isoacrylamide). Most preferably, the one or more hydrophilic polymers comprise polyacrylamide.

It is particularly advantageous that the superporous hydrogel structure is derived from one or more hydrophilic polymers and/or copolymers which are at least in part derived from an amine-containing monomer and/or an alkenyl amide-containing monomer and/or an acryloyl-containing monomer, preferably together with one or more polysaccharides.

Preferably, one or more of the hydrophilic polymers and/or copolymers are derived from one or more amine-containing monomers and/or alkenyl amide-containing monomers and/or acryloyl-containing monomers, and/or polymers selected from polyacrylamide, poly(N-isopropylacrylamide), and polyacrylic acid.

Preferably, the one or more polysaccharides include alginate-containing compounds, such as sodium alginate or alginic acid, and chitosan.

Ideally, the superporous hydrogel structure is derived from polyacrylamide and sodium alginate.

- 5 Ideally, the superporous hydrogel comprises a cross-linked structure by virtue of one or more cross-linking agents. That is, ideally the superporous hydrogel comprises a plurality of polymer chains, wherein each polymer chain is linked to one or more other polymer chains by one or more cross-linking agents to provide a cross-linked structure. The one or more cross-linking agents preferably crosslink the polymer chains by chemical means (e.g.,
10 covalent bonds) and/or physical means (e.g., electrostatic attraction).

Preferably, the one or more cross-linking agents comprises a salt of a divalent metal cation such as barium, calcium, magnesium, and iron. A preferred cross-linking agent comprises a salt of a divalent metal cation selected from calcium and/or barium. Exemplary cross-linking
15 agents are one or more selected from the group consisting of calcium sulfate, calcium chloride, and barium sulfate.

Alternatively or additionally, the one or more cross-linking agents comprise one or more acryloyl groups, and/or one or more acrylamide groups, and/or one or more amine groups,
20 and/or one or more olefinic groups, and/or one or more aldehyde groups. Particularly preferably, the one or more cross-linking agents include an amine-reactive bifunctional crosslinker and/or a multiolefinic crosslinker. Very preferably, the one or more cross-linking agents comprise one or more acryloyl groups and/or one or more acrylamide groups. Ideally, the one or more cross-linking agents comprise one or more acrylamide groups.

25 The one or more cross-linking agents are preferably selected from monofunctional aldehydes such as acetaldehyde or formaldehyde, bifunctional aldehydes such as glutaraldehyde or glyoxal, N,N'-bis(acryloyl)cystamine (BAC), N,N'-bis(acryloyl)cystine (BISS), N,N - methylenebis(acrylamide) (MBA), ethyleneglycoldiacrylate (EGDA),
30 poly(ethyleneglycoldiacrylate) (PEGDA), ethyleneglycoldimethacrylate (EDGDMA), N,N'- ethylenebisacrylamide (EBAA), and polyethyleneimine (PEI). Preferably, the cross-linking agent comprises N,N'-bis(acryloyl)cystamine (BAC) or N,N -methylenebis(acrylamide) (MBA). Ideally, the cross-linking agent comprises N,N'-bis(acryloyl)cystamine (BAC).

- 35 In a particularly preferred embodiment, the superporous hydrogel comprises a cross-linked structure by virtue of two or more cross-linking agents. Preferably, a first cross-linking agent comprises one or more divalent metal salts and a second cross-linking agent comprises one

or more cross-linking agents. Particularly preferably, a first cross-linking agent comprises calcium and/or calcium ions and a second cross-linking agent comprises N,N'-bis(acryloyl)cystamine (BAC) or N,N'-methylenebis(acrylamide) (MBA). Ideally, a first cross-linking agent comprises calcium sulfate and a second cross-linking agent comprises N,N'-bis(acryloyl)cystamine (BAC).

Preferably, the product comprises a swelling force which is released when exposed to gastric fluid to result in a swollen hydrogel having a diameter of $\geq 25\text{mm}$ within 30 minutes, ideally $\geq 30\text{mm}$ within 30 minutes. This diameter is greater than that of the pylorus of a patient so the product will not exit the stomach.

Preferably, the pores of the pore structure have an average maximum dimension of $\geq 250\mu\text{m}$ after immersion in simulated gastric fluid for one or more hours. Very preferably, the pores of the pore structure have an average maximum dimension of $\geq 450\mu\text{m}$, optionally $\geq 600\mu\text{m}$, after immersion in simulated gastric fluid for one or more hours. Ideally, the pores of the pore structure have an average maximum dimension of $\geq 700\mu\text{m}$ after immersion in simulated gastric fluid for one or more hours.

Optionally, the pores of the pore structure have a maximum dimension of between $>100\mu\text{m}$ and 5mm after immersion in simulated gastric fluid for one or more hours. Further optionally, the the pores of the pore structure have a maximum dimension of between $>100\mu\text{m}$ and 3mm after immersion in simulated gastric fluid for one or more hours.

As used herein, simulated gastric fluid has a pH of 1-2 and comprises a mixture of salt solution (e.g., sodium chloride, ideally 0.2 wt%) and acid solution (e.g., hydrochloride acid).

In a further aspect, the present invention seeks to provide a facile, cost effective and reliable method for making a product which can ideally be used as a delivery system or delivery device that is suitable for consumption by humans and/or animals. Thus, the present invention also provides, in another aspect, a method of preparing a product which is capable of the release of one or more active ingredients, and which has a superporous hydrogel structure preferably formed by freeze-drying, in which the superporous hydrogel structure comprises a core region comprising one or more active ingredients, and in which the method comprises:

- a) loading the core region with one or more active ingredients, either prior to, or after freeze drying.

Preferably, the one or more active ingredients comprise those defined above.

Preferably, the product produced by the method defined herein is a product according to the present invention. Therefore, features which apply to the product above may apply equally to the product produced by the method defined herein.

Preferably, the pore structure of the superporous hydrogel structure is formed by freeze-drying. Ideally, the pore structure of the superporous hydrogel structure is formed by freeze-drying without the use of gas-blowing agents. Advantageously, the resulting product therefore has a regular pore structure as described above.

Preferably, step a) comprises loading one or more active ingredients into the core region such that substantially all of the one or more active ingredients is located in the core region. That is, preferably the one or more active ingredients are loaded into the core region such that the one or more active ingredients are substantially absent from a region which is not the core region (such as a shell region of the superporous hydrogel structure, or a shell region of the product). Therefore, it is preferred that the one or more active ingredients are not loaded by immersion of a hydrogel and/or a superporous hydrogel in an aqueous solution comprising one or more active ingredients.

Preferably, the one or more active ingredients are loaded in the core region of the superporous hydrogel structure (e.g., held within the core region), without being chemically joined (e.g. bonded) to a part of the core region of the superporous hydrogel structure itself (e.g., without using a strong covalent chemical bond). This includes for instance without being chemically attached to one or more of the hydrophilic polymer chains which preferably form the superporous hydrogel structure.

Optionally, step a) comprises loading the core region with one or more active ingredients together with one or more excipients either prior to, or after freeze drying. As set out above, a most preferable excipient includes one or more permeation enhancers.

Preferably, the method of present invention comprises either:

- (i) in the case of loading the core region with one or more active ingredients prior to freeze drying;
 - a. providing an initial hydrogel comprising a core region;

- b. loading the core region of the initial hydrogel with one or more active ingredients; and
 - c. freeze-drying the resulting product of step (b) to form a superporous hydrogel structure comprising a core region loaded with one or more active ingredients; or
- 5
- (ii) in the case of loading the core region with one or more active ingredients after freeze drying;
 - a. providing an initial hydrogel comprising a core region;
 - b. freeze-drying the initial hydrogel to form a superporous hydrogel structure
- 10
- c. loading the core region of the superporous hydrogel structure with one or more active ingredients to form a superporous hydrogel structure comprising a core region loaded with one or more active ingredients.

15 Preferably, prior to freeze-drying in either of method (i) or (ii), the method comprises a step wherein the initial hydrogel is subjected to a washing treatment, ideally using a washing fluid. Such a treatment may take 1 day or more, 7 days or more, such as ideally from 7 to 14 days, or in some cases up to 21 days. Such a treatment may also include optional flushing steps, or optional steps of replacing the washing fluid during the course of the washing treatment.

20 A washing fluid may comprise acid, base, salt, distilled water and/or a gastric fluid (including simulated gastric fluid). A preferred washing fluid has a pH of around 1-2. This may be a region of the mould which is square-like, cylindrical or spherical. In one embodiment, this is not the region which projects outwardly of the initial hydrogel structure. A preferred simulated

25 gastric fluid may comprise a mixture of salt solution (e.g., sodium chloride, ideally 0.2 wt%) and acid solution (e.g., hydrochloride acid, ideally pH 1-2).

Preferably, in the case of loading the core region with one or more active ingredients prior to freeze drying, in which the method further comprises:

- 30 a. polymerising a mixture of monomers and/or polymers around one or more central moulds in the presence of a cross-linking agent to form an initial hydrogel;
- b. demoulding the resulting product of step (a) to provide the initial hydrogel with a core region comprising one or more cavities;
- 35 c. loading the one or more cavities of the initial hydrogel with one or more active ingredients; and

- d. freeze-drying the resulting product of step (c) to form a superporous hydrogel structure having a core region comprising one or more cavities loaded with one or more active ingredients.

5 The further preferred features of step (a) are discussed below (e.g., polymerisation etc).

Preferably, the initial hydrogel is not a superporous hydrogel. That is, preferably the pores of the pore structure of the initial hydrogel have an average maximum dimension of less than 100 μm . Therefore, the purpose of the freeze-drying step is, at least in part, to provide a
10 superporous hydrogel (i.e., a hydrogel wherein the pores of the pore structure have an average maximum dimension of at least 100 μm).

Preferably, the polymerisation of step a) is carried out within an external mould that may be cylindrical, spherical, square-like, or rectangular in shape. The central mould may then be
15 reversibly or irreversibly attached to one internal face of the external mould, optionally the inside of the "top" or "lid". Thus, the central mould acts to shape the initial hydrogel such that one or more cavities and one or more passageways and one or more openings are formed.

Preferably, the central mould comprises one or more structures which extend through or are
20 present within a section of the initial hydrogel in use. In particular, the one or more structures are preferably spherical, cylindrical-like, square-like, or rectangular-like in shape to permit the formation of one or more cavities and/or one or more passageways. Such a central mould may therefore be referred to as a cavity-making device and/or a passageway making device.

25 In one embodiment, the central mould may comprise at least a portion of an elongate structure to permit the formation of one or more passageways to the one or more cavities. The elongate structure may be a structure comprising an internal diameter from 100 μm to 40mm, preferably from 1mm to 10 mm, and more preferably from 1 to 5 mm. Ideally, the structure is cylindrical-like, preferably made of polypropylene. This ideally provides one or
30 more passageways having a narrow diameter, for instance from 100 μm to 40mm, preferably from 1mm to 10 mm, and more preferably from 1-5 mm. Ideally, the elongate structure has substantial straight section extending along an axis.

In the case of using an elongate structure as the central mould, it is desirable for the elongate
35 structure to project outwardly from a central region of the initial hydrogel (associated with the one or more cavities) to a region outside of the initial hydrogel structure, in order to provide an opening on a side of the initial hydrogel to the one or more cavities. This advantageously

enables the one or more passageways to have fluid communication between the one or more cavities and the opening allowing for loading of one or more active ingredients to the one or more cavities. The opening may have a narrow diameter, for instance from 100µm to 40mm, preferably from 1mm to 10 mm, and more preferably from 1-5 mm.

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In one embodiment, the central mould may comprise a two-part structure which may include two regions having distinct shapes. One region may be square-like, cylindrical-like or spherical-like whilst the other region may be elongate having a rectangular-like or cylindrical-like shape. Such regions may associate with each other in use to permit the formation of one or more passageways to the one or more cavities.

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In a preferred embodiment, at least a part of the central mould may be dissolvable upon contact with a washing fluid such as acid, base, salt, distilled water or a gastric fluid (including simulated gastric fluid). A preferred washing fluid has a pH of around 1-2. This may be a region of the mould which is square-like, cylindrical or spherical. In one embodiment, this is not the region which projects outwardly of the initial hydrogel structure. A preferred simulated gastric fluid may comprise a mixture of salt solution (e.g., sodium chloride, ideally 0.2 wt%) and acid solution (e.g., hydrochloric acid, ideally pH 1-2).

15

Therefore, step b) may further comprise the use of a washing treatment, ideally using a washing fluid to dissolve at least a part of the central mould. Such a treatment may take 1 day or more, 7 days or more, such as ideally from 7 to 14 days, or in some cases up to 21 days. Such a treatment may also include optional flushing steps, or optional steps of replacing the washing fluid during the course of the washing treatment.

25

Step b) may also comprise two steps in which a first step i) comprises the use of a washing treatment to dissolve at least a part of the central mould which is dissolvable and then a second step ii) which comprises demoulding the resulting product of step (i) from the remaining parts which are non-dissolvable.

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The part of the mould which is dissolvable and is used to form the one or more cavities may be formed from sucrose-based materials. Advantageously, such a material is dissolvable upon contact with a washing fluid.

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In an embodiment where no part of the central mould is dissolvable, step b) may further comprise, before or preferably following demoulding, the use of a washing treatment, ideally using a washing fluid. Such a treatment may take 1 day or more, 7 days or more, such as

ideally from 7 to 14 days, or in some case up to 21 days. Such a treatment may also include optional flushing steps, or optional steps of replacing the washing fluid during the course of the washing treatment.

- 5 Step b) may also further comprise, prior to demoulding, a first step i) comprising a curing treatment carried out by preferably, treatment with steam, water vapour, heat, or a combination thereof. Ideal conditions include a temperature from about 30 to 60 °C. The curing may take place for around 24 to 72 hours. Then, after demoulding, a second step ii), comprising the use of a washing treatment as discussed above.

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Step c) comprises loading the one or more cavities of the initial hydrogel with one or more active ingredients. In a preferred embodiment, the one or more cavities of the initial hydrogel are loaded with the one or more active ingredients using the one or more passageways which are ideally formed using a central mould comprising at least a portion of an elongate structure as discussed above.

15

Ideally, the one or more active ingredients are loaded in the core region of the initial hydrogel without being chemically and/or physically joined (e.g., bonded) to a part of the core region of the initial hydrogel structure itself. That is, owing to the elastic nature of the initial hydrogel and/or a narrow passageway, the one or more active ingredients are retained within the one or more cavities of the initial hydrogel.

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Step d) comprises freeze-drying the resulting product of step (c) to form a superporous hydrogel structure with a core region comprising one or more cavities.

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Optionally, the superporous hydrogel may then be treated with a compressive force to close an opening of the one or more passageways. Preferably, the superporous hydrogel may first be placed in a compressive mould to apply a compressive force, closing the opening (i.e., of the one or more passageways). The superporous hydrogel may then be treated as follows while remaining in the mould.

30

Typically, the hydrogel is first placed in a freezer at from -10°C to -50°C for at least 2 hours and up to 36 hours, preferably from 8 hours to 24 hours. Then the freeze-drying process is performed at temperature of around -50 °C. However, a temperature from about -30°C to about -50°C is acceptable. Further, the freeze-drying process is typically performed for at least 2 hours and up to 120 hours. In one embodiment, the freeze-drying process may be performed for 24 to 120 hours, ideally for 48 to 72 hours, or in some cases for 8 to 24 hours.

35

Optionally, the freeze-dried hydrogel may then be removed from the compressive mould.

Following step d), the method may also comprise the step of substantially sealing, at least a
5 part of, the one or more cavities and/or the one or more passageways after loading the one
or more cavities with one or more active ingredients. In particular, the method may include
the step of substantially sealing, preferably by compression and/or by application of an
adhesive such as biologically-inert glue, an opening on a side of the initial hydrogel which is
associated with the one or more cavities.

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In a preferred embodiment, the step of substantially sealing comprises blocking access to
the one or more cavities after loading the one or more cavities with one or more active
ingredients. In particular, an opening to one of the one or more passageways and/or the
passageway themselves may be closed by installation of one or more plugs. Ideally, the one
15 or more plugs may comprise one or more of biologically inert material and superporous
hydrogel material. Preferably, the one or more plugs comprise superporous hydrogel
material.

Adhesive and/or sealant may be applied to the one or more plugs to establish a seal with one
20 or more passageways and and/or the passageway themselves.

The method preferably comprises after freeze-drying, one or more steps selected from (i)
treating the superporous hydrogel structure to plasticise its structure; and (ii) compressing
the resulting plasticised superporous hydrogel structure to provide a compressed structure,
25 typically having pores which have an average maximum dimension of between 100µm and
5mm.

Preferably, the method comprises step (i) followed by step (ii). However, the method may
comprise step (i) or step (ii) only; or neither of steps (i) and (ii).

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In case of optional step (i), the plasticisation treatment may be carried out by use of a
plasticiser or, preferably, by treatment with steam, water vapour, heat, or a combination
thereof. Ideal plasticisation conditions include a temperature from about 30 to 60 °C at a
relative humidity of from 50-95%.

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In the case of optional step (ii), an SPH may be optionally treated with a compressive force
to yield a "compressed superporous hydrogel" (compressed SPH). This compression may

preferably be performed by a process involving one or more inserts, preferably a central insert such as a pin, wherein the insert is placed within the one or more cavities using the one or more passageways prior to compression and removed after compression to ensure that the one or more cavities are retained in the compressed SPH. The one or more inserts will ideally
5 have an elongate structure such as those of a rod, bar, pin, or pole.

By using the insert this aids a suitably sized space in the compressed SPH. Thus, the step of compression optionally includes compressing the resulting plasticised superporous hydrogel structure with an insert present in at least a portion of the one or more cavities.

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The pores of the pore structure of a compressed superporous hydrogel may have an average maximum dimension from greater than 100 μm up to about ≤ 5 mm, optionally up to about ≤ 4 mm, further optionally up to about ≤ 3 mm, further optionally up to about ≤ 2 mm, and further optionally up to about ≤ 1 mm. The pores of a compressed SPH retain similar
15 functionality to the pores of an uncompressed SPH and, when immersed in aqueous media, a compressed SPH will swell to a similar volume to a corresponding uncompressed SPH. However, a compressed SPH may have a faster swelling rate than an uncompressed SPH.

Alternatively, in the case of loading the core region with one or more active ingredients after freeze drying, in which the method further comprises:

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- a. polymerising a mixture of monomers and/or polymers around one or more central moulds in the presence of a cross-linking agent to form an initial hydrogel;
- b. demoulding the initial hydrogel to provide the initial hydrogel with a core
25 region comprising one or more cavities;
- c. freeze-drying the resulting product of step (b) to form a superporous hydrogel structure with a core region comprising one or more cavities; and
- d. loading the one or more cavities of the superporous hydrogel structure with one or more active ingredients to form a superporous hydrogel structure
30 comprising a core region loaded with one or more active ingredients.

The further preferred features of step (a) are discussed below (e.g., polymerisation etc).

Preferably, the polymerisation of step a) is carried out within an external mould that may be
35 cylindrical, spherical, square-like, or rectangular in shape. The central mould may then be reversibly or irreversibly attached to one internal face of the external mould, optionally the

inside of the “top” or “lid”. Thus, the central mould acts to shape the initial hydrogel such that one or more cavities and/or one or more passageways and/or one or more openings are formed.

- 5 Preferably, the central mould comprises one or more structures which extend through or are present within a section of the initial hydrogel in use. In particular, the one or more structures are preferably spherical, cylindrical-like, square-like, or rectangular-like in shape to permit the formation of one or more cavities and/or one or more passageways. Such a central mould may therefore be referred to as a cavity-making device and/or a passageway making device.

10

In one embodiment, the central mould may comprise at least a portion of an elongate structure to permit the formation of one or more passageways to the one or more cavities. The elongate structure may be a structure comprising an internal diameter from 100µm to 40mm, preferably from 1mm to 10 mm, and more preferably from 1 to 5 mm. Ideally, the structure is cylindrical-like, preferably made of polypropylene. This ideally provides one or more passageways having a narrow diameter, for instance from 100µm to 40mm, preferably from 1mm to 10 mm, and more preferably from 1-5 mm. Ideally, the elongate structure has substantial straight section extending along an axis.

15

- 20 In the case of using an elongate structure as the central mould, it is desirable for the elongate structure to project outwardly from a central region of the initial hydrogel (associated with the one or more cavities) to a region outside of the initial hydrogel structure, in order to provide an opening on a side of the initial hydrogel to the one or more cavities. This advantageously enables the one or more passageways to have fluid communication between the one or more cavities and the opening allowing for loading of one or more active ingredients to the one or more cavities. The opening may have a narrow diameter, for instance from 100µm to 40mm, preferably from 1mm to 10 mm, and more preferably from 1-5 mm.

25

- In one embodiment, the central mould may comprise a two-part structure which may include two regions having distinct shapes. One region may be square-like, cylindrical-like or spherical-like whilst the other region may be elongate having a rectangular-like or cylindrical-like shape. Such regions may associate with each other in use to permit the formation of one or more passageways to the one or more cavities.

30

- 35 In a preferred embodiment, at least a part of the central mould may be dissolvable upon contact with a washing fluid such as acid, base, salt, distilled water or a gastric fluid (including simulated gastric fluid). A preferred washing fluid has a pH of around 1-2. This may be a

region of the mould which is square-like, cylindrical or spherical. In one embodiment, is not the region which projects outwardly of the initial hydrogel structure. A preferred simulated gastric fluid may comprise a mixture of salt solution (e.g., sodium chloride, ideally 0.2 wt%) and acid solution (e.g., hydrochloride acid, ideally pH 1-2).

5

Therefore, step b) may further comprise the use of a washing treatment, ideally using a washing fluid to dissolve at least a part of the central mould. Such a treatment may take 1 day or more, 7 days or more, such as ideally from 7 to 14 days, or in some cases up to 21 days. Such a treatment may also include optional flushing steps, or optional steps of replacing the washing fluid during the course of the washing treatment.

10

Step b) may also comprise two steps in which a first step i) comprises the use of a washing treatment to dissolve at least a part of the central mould which is dissolvable and then a second step ii) which comprises demoulding the resulting product of step (i) from the remaining parts which are non-dissolvable.

15

The part of the mould which is dissolvable and is used to form the one or more cavities may be formed from a sucrose-based material. Advantageously, such a material is dissolvable upon contact with a washing fluid.

20

In an embodiment where no part of the central mould is dissolvable, step b) may further comprise, before or preferably following demoulding, the use of a washing treatment, ideally using a washing fluid. Such a treatment may take 1 day or more, 7 days or more, such as ideally from 7 to 14 days, or in some cases up to 21 days. Such a treatment may also include optional flushing steps, or optional steps of replacing the washing fluid during the course of the washing treatment.

25

A washing fluid may include an acid, base, salt, distilled water or a gastric fluid (including simulated gastric fluid). A preferred washing fluid has a pH of around 1-2. A preferred simulated gastric fluid may comprise a mixture of salt solution (e.g., sodium chloride, ideally 0.2 wt%) and acid solution (e.g., hydrochloride acid, ideally pH 1-2).

30

Step b) may also further comprise, prior to demoulding, a first step i) comprising a curing treatment carried out by preferably, treatment with steam, water vapour, heat, or a combination thereof. Ideal conditions include a temperature from about 30 to 60 °C. The curing may take place for around 24 to 72 hours. Then, after demoulding, a second step ii), comprising the use of a washing treatment as discussed above.

35

Step c) comprises freeze-drying the resulting product of step (b) to form a superporous hydrogel structure with a core region comprising one or more cavities. Typically, the hydrogel is first placed in a freezer at from -10°C to -50°C for at least 2 hours and up to 36 hours, preferably from 8 hours to 24 hours. Then, the freeze-drying process is performed at temperature of around -50°C . However, a temperature from about -30°C to about -50°C is acceptable. Further, the freeze-drying process is typically performed for at least 2 hours and up to 120 hours. In one embodiment, the freeze-drying process may be performed for 24 to 120 hours, ideally for 48 to 72 hours, or in some cases for 8 to 24 hours.

Preferably, following step c), the method comprises step d), loading the one or more cavities of the superporous hydrogel structure with one or more active ingredients to form a superporous hydrogel structure comprising a core region loaded with one or more active ingredients. In a preferred embodiment, the one or more cavities of the superporous hydrogel structure are loaded with the one or more active ingredients using the one or more passageways which are ideally formed using a central mould comprising at least a portion of an elongate structure as discussed above.

Ideally, the one or more active ingredients are loaded in the core region of the superporous hydrogel structure without being chemically and/or physically joined (e.g., bonded) to a part of the core region of the superporous hydrogel structure itself. That is, owing to the elastic nature of the superporous hydrogel structure and/or a narrow passageway, the one or more active ingredients are retained within the one or more cavities of the superporous hydrogel structure.

Following step d), the method preferably comprises after loading, the steps of (i) treating the superporous hydrogel structure to plasticise its structure; and (ii) compressing the resulting plasticised superporous hydrogel structure to provide a compressed structure, typically having pores which have an average maximum dimension of between $100\mu\text{m}$ and 5mm .

Further, as an intermediate step between step (i) and step (ii), the method may also comprise the step of substantially sealing, at least a part of, the one or more cavities and/or the one or more passageways after loading the one or more cavities with one or more active ingredients. Alternatively, rather than an intermediate step between step (i) and step (ii), this step maybe performed after step d), but before step (i) and step (ii).

In particular, this step may include applying an adhesive (e.g. biologically inert glue) with or without a lid to an opening on a side of the superporous hydrogel structure which is associated with the one or more cavities. Thus, the effect would be to substantially seal, at least a part of, the one or more cavities and/or the one or more passageways.

5

In a preferred embodiment, the step of substantially sealing comprises blocking access to the one or more cavities after loading the one or more cavities with one or more active ingredients. In particular, an opening to one of the one or more passageways and/or the passageway themselves may be closed by installation of one or more plugs. Ideally, the one or more plugs may comprise one or more of biologically inert material and superporous hydrogel material. Preferably, the one or more plugs comprise superporous hydrogel material.

Adhesive and/or sealant may be applied to the one or more plugs to establish a seal with one or more passageways and and/or the passageway themselves.

15

In an alternative embodiment, following step c), and prior to step d), the method may optionally comprise after freeze-drying, the steps of (i) treating the superporous hydrogel structure to plasticise its structure; and (ii) compressing the resulting plasticised superporous hydrogel structure to provide a compressed structure, typically having pores which have an average maximum dimension of between 100µm and 5mm.

20

Preferably, the method comprises step (i) followed by step (ii). However, the method may comprise step (i) or step (ii) only; or neither of steps (i) and (ii).

25

Optional steps (i) and (ii) are further discussed below.

In case of optional step (i), the plasticisation treatment may be carried out by use of a plasticiser or, preferably, by treatment with steam, water vapour, heat, or a combination thereof. Ideal plasticisation conditions include a temperature from about 30 to 60 °C at a relative humidity of from 50-95%. The treatment may be performed for 1 hour or less, 30 minutes or less, and ideally from 1 minute to 10 minutes until the superporous hydrogel structure becomes malleable.

30

In the case of optional step (ii), an SPH may be optionally treated with a compressive force to yield a "compressed superporous hydrogel" (compressed SPH). This compression may preferably be performed by a process involving one or more inserts, preferably a central insert

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such as a pin, wherein the insert is placed within the one or more cavities using the one or more passageways prior to compression and removed after compression to ensure that the one or more cavities are retained in the compressed SPH. The one or more inserts will ideally have an elongate structure such as those of a rod, bar, pin, or pole.

5

By using the insert this aids a suitably sized space in the compressed SPH. Thus, the step of compression optionally includes compressing the resulting plasticised superporous hydrogel structure with an insert present in at least a portion of the one or more cavities.

- 10 A compressed SPH may have an average maximum dimension from greater than 100 μm up to about ≤ 5 mm, optionally up to about ≤ 4 mm, further optionally up to about ≤ 3 mm, further optionally up to about ≤ 2 mm, and further optionally up to about ≤ 1 mm.

- 15 The pores of a compressed SPH retain similar functionality to the pores of an uncompressed SPH and, when immersed in aqueous media, a compressed SPH will swell to a similar volume to a corresponding uncompressed SPH. However, a compressed SPH may have a faster swelling rate than an uncompressed SPH.

- 20 After removal of the optional insert, step d) can take place which comprises loading of the one or more cavities of the compressed superporous hydrogel structure with one or more active ingredients to form a superporous hydrogel structure comprising a core region loaded with one or more active ingredients.

- 25 Following step d), the method may also comprise the step of substantially sealing, at least a part of, the one or more cavities and/or the one or more passageways after loading the one or more cavities with one or more active ingredients. In particular, the method may include the step of substantially sealing, preferably using an adhesive (e.g. biologically insert glue) and/or a lid and/or applying compressive force, an opening on a side of the superporous hydrogel structure which is associated with the one or more cavities.

30

- In a preferred embodiment, the step of substantially sealing comprises blocking access to the one or more cavities after loading the one or more cavities with one or more active ingredients. In particular, an opening to one of the one or more passageways and/or the passageway themselves may be closed by installation of a plug. Ideally, the one or more
35 plugs may comprise one or more of biologically inert material and superporous hydrogel material. Preferably, the one or more plugs comprise superporous hydrogel material.

Adhesive and/or sealant may be applied to the one or more plugs to establish a seal with one or more passageways and and/or the passageway themselves. The process may then be completed by applying a compressive force to an opening on a side of the superporous hydrogel structure to finalise the step of substantially sealing.

As set out above, further preferred features of step (a) are discussed below (e.g., polymerisation etc).

In particular, the method comprises polymerising a mixture of monomers and/or polymers in the presence of a cross-linking agent to form an initial hydrogel.

Preferably, the mixture of hydrophilic polymers comprise one or more hydrophilic polymers made from an alkenyl amide-containing monomer, preferably acrylamide, and a polysaccharide. Ideally, the acrylamide-containing monomer comprises acrylamide and the polysaccharide comprises alginate.

The hydrophilic polymers and/or copolymers may be derived from naturally occurring polymers and monomers, from synthetic polymers and monomers, or from mixtures of naturally occurring and synthetic polymers and monomers.

Preferably, the one or more hydrophilic polymers include hydroxylated polymers, and further preferably, the hydrophilic polymers are selected from C₁-C₆-alkylcelluloses, hydroxy-C₁-C₆-alkylcelluloses, hydroxy-C₁-C₆-alkyl-C₁-C₆-alkyl-celluloses. Highly preferred polymers include alginate-containing compounds, such as sodium alginate or alginic acid, and chitosan.

Preferably, the one or more hydrophilic polymers include polymers made by the polymerisation and/or copolymerisation of one or more monomers selected from C₁-C₆-alkenyl amides (e.g. to make polyacrylamide) and C₁-C₆- alkenyl acids (e.g. to make acrylic acid). Highly preferred polymers include poly(acrylamide), poly(2-acrylamido-2-methyl-1-propanesulfonic acid) and poly(N-isoacrylamide). Most preferably, the one or more hydrophilic polymers comprise polyacrylamide.

It is particularly advantageous that the superporous hydrogel structure is derived from one or more hydrophilic polymers and/or copolymers which are at least in part derived from an

amine-containing monomer and/or an alkenyl amide-containing monomer and/or an acryloyl-containing monomer, preferably together with one or more polysaccharides.

Preferably, one or more of the hydrophilic polymers and/or copolymers derived from one or
5 more amine-containing monomers and/or alkenyl amide-containing monomers and/or acryloyl-containing monomers, and/or polymers selected from polyacrylamide, poly(N-isopropylacrylamide), and polyacrylic acid.

Preferably, the one or more polysaccharides include alginate-containing compounds, such
10 as sodium alginate or alginic acid, and chitosan.

Ideally, the superporous hydrogel structure is derived from polyacrylamide and sodium alginate.

15 Ideally, the superporous hydrogel comprises a cross-linked structure by virtue of one or more cross-linking agents.

Preferably, the one or more cross-linking agents comprises a salt of a divalent metal cation such as barium, calcium, magnesium, and iron. A preferred cross-linking agent comprises a
20 salt of a divalent metal cation selected from calcium and/or barium. Exemplary cross-linking agents are one or more selected from the group consisting of calcium sulfate, calcium chloride, and barium sulfate.

Alternatively or additionally, the one or more cross-linking agents are selected from N,N'-
25 bis(acryloyl)cystamine (BAC), N,N'-bis(acryloyl)cystine (BISS), N,N'-Methylenebis(acrylamide) (MBA), ethyleneglycoldiacrylate (EGDA), N,N'-ethylenebisacrylamide (EBAA), and polyethyleneimine (PEI). Preferably, the cross-linking agent comprises N,N'-bis(acryloyl)cystamine (BAC) or N,N'-Methylenebis(acrylamide) (MBA). Ideally, the cross-linking agent comprises N,N'-bis(acryloyl)cystamine (BAC).

30 In a particularly preferred embodiment, the superporous hydrogel comprises a cross-linked structure by virtue of two or more cross-linking agents. Preferably, a first cross-linking agent comprises calcium sulfate and a second cross-linking agent comprises N,N'-bis(acryloyl)cystamine (BAC).

35 In a preferred embodiment, the product of the present invention comprises a compressed superporous hydrogel or has a compressed superporous hydrogel structure. Preferably,

such a compressed SPH will have an average maximum dimension from greater than 100 μm up to about ≤ 5 mm, optionally up to about ≤ 4 mm, further optionally up to about ≤ 3 mm, further optionally up to about ≤ 2 mm, and further optionally up to about ≤ 1 mm.

- 5 The present invention provides a method of preparing a product which is capable of the release of one or more active ingredients, and which has a superporous hydrogel structure formed by freeze-drying, in which the superporous hydrogel structure comprises a core region comprising one or more active ingredients, and in which the method comprises:
- a) loading the core region with one or more active ingredients, either prior to, or after
10 freeze drying.

Alternatively, (i.e., to using one or more cavities), the one or more active ingredients may be loaded in the core region of the superporous hydrogel structure. This may be preferably performed by forming one or more incisions in the body of the superporous hydrogel material
15 to enable one or more active ingredients be loaded therein.

The present invention also provides, in another aspect, a product which is obtainable by the method as disclosed herein.

- 20 The present invention also provides, in another aspect, the use of a product as disclosed herein, in drug delivery.

The present invention also provides, in another aspect, a pharmaceutical composition comprising a product as disclosed herein. The pharmaceutical composition may optionally
25 comprise one or more one or more excipients.

The present invention also provides, in another aspect, a method of medical treatment comprising administration of a product as disclosed herein, to a subject.

- 30 The treatment may include one or more conditions selected from gastric cancer, gastric ulcers, helicobacter infections, Parkinson's disease, polycystic ovary syndrome, metabolic diseases, obesity and obesity-related diseases, cardiovascular disease and Vitamin B12 deficiency. Preferably, the treatment may include one or more of obesity, diabetes, or non-alcoholic fatty liver disease. Very preferably, the treatment may include obesity and/or
35 diabetes. Ideally, the treatment may include obesity.

The present invention may therefore provide, in another aspect, a method of preventing or treating one or more conditions as defined herein, comprising administration of a product as disclosed herein, to a subject.

5 Preferably, the one or medical conditions are selected from gastric cancer, gastric ulcers, helicobacter infections, Parkinson's disease, polycystic ovary syndrome, metabolic diseases, obesity, obesity-related diseases, diabetes, cardiovascular disease and non-alcoholic fatty liver disease. Very preferably, the one or more medical conditions are selected from obesity, obesity-related diseases, diabetes and non-alcoholic fatty liver disease.

10

Preferably, the product is administered in an amount effective to result in a minimum gastroretention period of 24 hours.

15 Preferably, the product is administered in an amount effective to result in a minimum gastroretention period of 3 days.

Preferably, the product is administered in an amount effective to result in a gastroretention period of between 3 and 14 days.

20 Preferably, the product is administered in an amount effective to result in a swollen hydrogel having a diameter of $\geq 25\text{mm}$ within 30 minutes when the product is exposed to gastric fluid.

Preferably, the product is administered in an amount effective to result in a swollen hydrogel having a diameter of $\geq 30\text{mm}$ within 30 minutes when the product is exposed to gastric fluid.

25

Preferably, the product is administered in an amount effective to result in the release of 65% or less of the one or more active ingredients after 24 hours.

30 Preferably, the product is administered in an amount effective to result in the release of 80% or less of the one or more active ingredients after 48 hours.

The present invention also provides, in another aspect, a product as disclosed herein, for use as a medicament.

35 The present invention also provides, in another aspect, a product as disclosed herein, for use in therapy. In particular, for use in therapy in oral administration.

The present invention also provides, in another aspect, a product as disclosed herein for use in treating one or medical conditions selected from gastric cancer, gastric ulcers, helicobacter infections, Parkinson's disease, polycystic ovary syndrome, metabolic diseases, obesity and obesity-related diseases, cardiovascular disease, and Vitamin B12 deficiency. Preferably, the product may be used to treat obesity, diabetes, or non-alcoholic fatty liver disease. Very preferably, the product is for use to treat obesity and/or diabetes.

The present invention also provides, in another aspect, a superporous hydrogel material for use in treating one or medical conditions selected from gastric cancer, gastric ulcers, helicobacter infections, Parkinson's disease, polycystic ovary syndrome, metabolic diseases, obesity and obesity-related diseases, cardiovascular disease and Vitamin B12 deficiency. Preferably, the superporous hydrogel material may be used to treat one or more medical conditions selected from obesity, diabetes, or non-alcoholic fatty liver disease. Very preferably, the superporous hydrogel material may be used to treat non-alcoholic fatty liver disease.

Preferably, the superporous hydrogel material has a pore structure formed by a freeze-drying process.

The present invention also provides, in another aspect, a dosage regimen for administering a product according to the present invention to a patient suffering from one or more medical conditions, for example selected from gastric cancer, gastric ulcers, helicobacter infections, Parkinson's disease, polycystic ovary syndrome, metabolic diseases, obesity and obesity-related diseases, cardiovascular disease, and Vitamin B12 deficiency. Preferably, the present invention provides a dosage regimen for administering to a patient suffering from one or more medical conditions selected from obesity, diabetes, or non-alcoholic fatty liver disease.

Preferably, the dosage regimen comprises orally administering to the patient a first dose of a product according to the present invention in an amount which will swell to a diameter greater than that of the pylorus in less than one hour, preferably $\geq 25\text{mm}$ within 30 minutes, ideally $\geq 30\text{mm}$ within 30 minutes. Therefore, preferably the first dose is retained in the stomach of a patient for at least 12 hours, preferably at least 24 hours (preferably, up to 7 days, ideally up to 14 days). Optionally, the first dose is retained in the patient's stomach for several weeks (preferably at least 3 weeks or 4 weeks, optionally up to 10 weeks).

In a preferred dosage regimen for treating a patient, a first dose of 1 to 3 orally acceptable tablets, capsules, or delivery formulations of any suitable size, preferably 000 size capsules, comprising a product according to the present invention are administered to the patient. This is then optionally followed by a second, and optionally further subsequent doses containing
5 optionally up to 5 orally acceptable tables, capsules, or delivery formulations comprising a product according to the present invention. Preferably the optional second and optional further subsequent does contain 1, 2 or 3, orally acceptable tables, capsules, or delivery formulations comprising a product according to the present invention. The optional second and optional further subsequent doses are preferably delivered at time intervals of around at
10 least 12 hours and preferably around at least 24 hours, and highly preferably longer e.g., around 48 hours. The optional second and subsequent doses may be the same as each other and/or the same as the first dose, or different from each other.

Optionally the second dose is retained in the stomach of a patient for at least 12 hours,
15 preferably at least 24 hours or at least 48 hours, (preferably, up to 7 days). Optionally, the first dose is retained in the patient's stomach for up to 7 days (preferably at least 1 days, optionally up to 5 days).

Optionally a subsequent dose is retained in the stomach of a patient for at least 12 hours,
20 preferably at least 24 hours or at least 48 hours (preferably, up to 7 days). Optionally, the first dose is retained in the patient's stomach for up to 7 days (preferably at least 1 days, optionally up to 5 days).

Ideally the above method will also include the ingestion by the patient of one or more of: at
25 least 300Kcal of foodstuffs and at least 100ml of water, before and/or during and/or after the ingestion of the at least one of the first, second or further subsequent doses by the patient.

In many applications it will be important that each superporous hydrogel-containing product can swell to a size which is larger than the diameter of the pylorus of the patient (human or
30 animals) to ensure its retention in the stomach.

Whilst the product of the present invention is not designed to block the oesophagus or lower GI tract, it is possible that an unforeseen accident may happen. Also, it is desirable that the product can be terminated easily without the need for surgical, endoscopic or other
35 unpleasant medical interventions. The present invention combats these issues using a trigger or emergency exiting mechanism to breakdown of the product formulation into a form which is easily excreted by the patient. The 'breakdown trigger' can have variety of forms so

long as it is effective and efficient in the breakdown process and is safe to be used by the patient. Preferred breakdown triggers include electromagnetic waves (e.g. light, heat), mechanical waves (e.g. ultrasound) or chemicals.

- 5 The size of the product formulation is preferably no larger than a standard 000 capsule. The product may be inserted into a capsule, tablet or lozenge or otherwise coated in a biologically acceptable material.

BRIEF DESCRIPTION OF THE DRAWINGS

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The invention will now be described with reference to the representations in the following Figures, in which:

- 15 Figure 1A: shows a cross-sectional view of a mould containing a hydrogel material wherein the mould has a central portion which is made from a dissolvable material and attached to the lid by a thin stick;
- Figure 1B: shows a cross-sectional view of the hydrogel material of Figure 1A after its removal from the mould, wherein the hydrogel material still contains the dissolvable central portion of the mould and the thin stick;
- 20 Figure 1C: shows a cross-sectional view of the hydrogel material of Figure 1B after the central portion of the mould has been dissolved and the thin stick has been removed, leaving behind a cavity which is linked to an opening on the top surface of the hydrogel by a passageway;
- 25 Figure 2A: shows a cross-sectional view of a drug core which is about to be inserted into the cavity of the hydrogel material of Figure 1C through the opening and the passageway;
- Figure 2B: shows a cross-sectional view of the drug core and hydrogel material of Figure 2A after the drug core has been inserted into the cavity;
- 30 Figure 2C: shows a cross-sectional view of a hydrogel material several processing steps on from that of Figure 2B which has been freeze-dried, plasticised and compressed, resulting in closure of the opening and passageway;
- Figure 3A: shows a cross-sectional view of a sample of loaded, freeze-dried, plasticised superporous hydrogel inserted into a hollow open-ended cylindrical mould with two push rods, one inserted in each of the two open ends of the mould;
- 35 Figure 3B: shows a cross-sectional view of the sample of loaded, freeze-dried, plasticised superporous hydrogel inserted into a hollow open-ended cylindrical mould as

shown in Figure 4A, with the two push rods compressing the sample on opposing sides;

Figure 4A: shows a cross-sectional view of a mould containing a hydrogel material wherein the mould has a non-dissolvable central portion which is attached to the lid;

Figure 4B: shows a cross-sectional view of the hydrogel material of Figure 4A after its removal from the mould, wherein the hydrogel material comprises a cavity which is linked to an opening on the top surface of the hydrogel by a passageway;

Figure 5A: shows a cross-sectional view of a drug core which is about to be inserted into the cavity of a freeze-dried hydrogel material through an opening and a passageway;

Figure 5B: shows a cross-sectional view of the hydrogel material of Figure 5A after a drug core has been loaded into the cavity;

Figure 5C: shows a cross-sectional view of a hydrogel material several processing steps on from that of Figure 5B which has been plasticised and compressed, resulting in closure of the opening and passageway;

Figure 6: shows a graph of the % release of Vitamin B12 against time, using a buffer solution comprising sodium phosphate at a pH of 6.8, for a tablet containing 50% by weight HPMC, 22% by weight SNAC and 0.22% by weight Vitamin B12;

Figure 7: shows a graph of the % release of Vitamin B12 against time, using a buffer solution comprising sodium phosphate at a pH of 6.8, for a product having been loaded after freeze-drying which contains a drug core comprising a tablet containing 50% by weight HPMC, 22% by weight SNAC and 0.22% by weight Vitamin B12;

Figure 8: shows a graph of the % release of Vitamin B12 against time, using a buffer solution comprising sodium phosphate at a pH of 6.8, for a drug core comprising a tablet containing 60% by weight HPMC, 22% by weight SNAC and 0.22% by weight Vitamin B12;

Figure 9: shows a graph of the % release of Vitamin B12 against time, using a buffer solution comprising sodium phosphate at a pH of 6.8, for a product having been loaded before freeze-drying which contains a drug core comprising a tablet containing 60% by weight HPMC, 22% by weight SNAC and 0.22% by weight Vitamin B12;

Figure 10: shows a graph of the % release of Vitamin B12 against time, using a buffer solution comprising sodium phosphate at a pH of 6.8, for a product having

been loaded after freeze-drying which contains a drug core comprising a tablet containing 60% by weight HPMC, 22% by weight SNAC and 0.22% by weight Vitamin B12;

- 5 Figure 11: shows a graph of the diameter swelling profile against time, using simulated gastric fluid as the swelling medium, for a product having been loaded before freeze-drying which contains a drug core comprising a placebo tablet containing 30% HPMC.
- Figure 12: shows dissolution of MR tablets and combined devices. V1-3: MR Tablet, V4-6: Drug Delivery System.
- 10 Figure 13: shows mean dissolution data for MR tablets and combined devices.
- Figure 14: shows representative plasma concentration versus time plot for animals administered the MR B12 pills.
- Figure 15: shows representative plasma concentration versus time plot for animals administered the CS pills.
- 15 Figure 16: shows comparative average plasma concentration versus time plot for animals administered the MR and CS pills
- Figure 17: shows displacement curve of the drug delivery system according to the invention at 100N Load.
- Figure 18: shows force-displacement curve of the drug delivery system according to the invention at 300N Load.
- 20 Figure 19: shows Fatigue Tests for the Drug Delivery System according to the present invention;
- Figure 20: shows a schematic diagram of 'Route 1'.
- Figure 21: shows a schematic diagram of 'Route 2'.
- 25 Figure 22: shows a schematic diagram of 'Route 3'.
- Figure 23: shows a scanning electron microscope (SEM) image of the pores of a freeze-dried superporous hydrogel made according to the process of the present invention.
- Figure 24: shows a scanning electron microscope (SEM) image of the pores of a compressed superporous hydrogel made according to the process of the present invention.
- 30 Figure 25: shows a scanning electron microscope (SEM) image of the pores of a compressed superporous hydrogel made according to the process of the present invention after it has swollen after being submerged in simulated gastric fluid for 1 hour.
- 35 Figure 26: shows volume swelling data for a product according to the present invention using MBA and BaSO₄ as crosslinkers.

Figure 27: shows mechanical strength data for a product according to the present invention using MBA and BaSO₄ as crosslinkers.

SPECIFIC EXAMPLES

5

The abbreviations used herein are defined as follows:

TABLE 1

Abbreviation	Chemical
AAm	Acrylamide
AL	Alginic acid sodium salt
APS	Ammonium persulfate,
BAC	N, N' bis(acryloyl)cystamine
CaSO ₄	Calcium sulfate dihydrate
Cellulose	Cellulose
DW	Distilled water
HPMC	Hydroxypropyl methylcellulose
TEMED	N, N, N', N'-tetramethylethylenediamine
SGF	Simulated gastric fluid without pepsin (0.2%/wt sodium chloride and 0.7%/wt hydrochloric acid solution; pH=1.2)
SNAC	Sodium 8-(2-hydroxybenzamido)octanoate
IR	Instant Release
MR	Modified Release
CS	Combined System / Drug Delivery System

10 **Example 1:** The preparation of a product which is capable of the release of one or more active ingredients, and which has a superporous hydrogel structure formed by freeze-drying, and in which the superporous hydrogel structure comprises a core region comprising one or more active ingredients wherein the one or more active ingredients are loaded before freeze-drying (Route 01).

15

Hydrogel Synthesis:

25.0-50.0g (+/- 0.1g) of AAm, 6.0-20.0g (+/- 0.1g) of AL, and 99.0-132.0mg (+/- 1mg) BAC were weighed and mixed with 150-500ml of DW. The above solution was mixed together
5 with 433.0-751.0mg (+/- 1.0mg) of APS in a beaker (marked as Beaker A).

Into another beaker (marked as Beaker B) was weighed 150.0-250.0mg (+/- 1.0mg) of CaSO_4 powder, 4-10ml water and 47-82ul TEMED.

10 The solution in Beaker A was poured into with the suspension in Beaker B. The mixture was then stirred for 10-50 seconds and poured into moulds. Each mould consisted of a cylindrical polypropylene (PP) tube (10) with an internal diameter of 10-40mm and a dissolvable central mould (12) attached to a top stopper (14) by a thin stick (16), as shown in Figure 1A.

15 The samples in the PP moulds were left in an incubator (preheated to 60°C) for 1 hour. The moulds were then transferred into a humid chamber to cure for another 24-72 hours at room temperature for the completion of polymerization. The resulting gelled materials (initial hydrogel materials) were labelled as the as-prepared gels (APGs) (18).

20 The top stopper (14) was removed from the mould (see Figure 1B), and the APGs (18), still containing the dissolvable central mould (12) and thin stick (16) were removed from the tubes (10) for the next washing process.

The APGs (18) were submerged in a washing solution (at a pH of around 1-2) for 7-21 days
25 with a daily routine of flushing the samples and containers with DW as well as refreshing of the SGF. The volume of the SGF used to soak the samples was 75~150ml per gel. The dissolvable centre portion (12) dissolved during the process and the thin stick (16) was removed to yield washed APGs (20) comprising a cavity (22) in their core region and a narrow passageway (24) including an opening (26) on the top side of the washed APG as shown in
30 Figure 1C.

Loading:

The washed APGs (20) were drained from the SGF, washed with deionised water, and dried.
35 A drug core (28) comprising one or more active ingredients was then inserted through the opening (26) and the passageway (24) into the cavity (22) of each washed APG (20), as depicted in Figure 2A, to yield loaded APGs (30). Owing to the elastic nature of the APG

material and the narrow diameter of the passageway (24), the drug core was retained within the cavity (22), as depicted in Figure 2B.

Freezing & Freeze-drying:

5

Each loaded APG (30) was directly put into a PP cylindrical tube mould which compressed each loaded APG such that the opening (26) of each closed. The swollen gel inside the mould was then put into a freezer at -10°C to -50°C for 8-24 hours and then transferred into the freeze-dryer and freeze-dried at from -30°C to -50°C to produce a loaded freeze-dried superporous hydrogel (loaded freeze-dried SPH), as depicted in Figure 2C.

10

Plasticisation:

A sample of loaded freeze-dried SPH was put in the sample holder and left inside a humidity chamber at 30-60°C with a relative humidity of 50-75% for from 1 to 10 minutes until it became malleable, yielding a plasticised loaded freeze-dried SPH (31).

15

Compression:

The plasticised loaded freeze-dried SPH (31) was carefully removed from the container and squeezed into a cylindrical tube (25) and compressed with push rods (27a and 27b), each having a concave end (29a, 29b) and each inserted into opposing open ends of the cylindrical tube (25), as shown in Figures 3A and 3B, or directly moulded in a capsule mould. This compressive step yielded a loaded, compressed SPH (32).

20

A schematic diagram of Route 1 is shown in Figure 20.

25

Example 2: The preparation of a product which is capable of the release of one or more active ingredients, and which has a superporous hydrogel structure formed by freeze-drying, and in which the superporous hydrogel structure comprises a core region comprising one or more active ingredients wherein the one or more active ingredients are loaded after freeze-drying (Route 02).

30

Hydrogel Synthesis:

35

25.0-50.0g (+/- 0.1g) of AAm, 6.0-20.0g (+/- 0.1g) of AL, and 99.0-132.0mg (+/- 1mg) BAC were weighed and mixed with 150-500ml of DW. The above solution was mixed together with 433.0-751.0mg (+/- 1.0mg) of APS in a beaker (marked as Beaker A).

- 5 Into another beaker (marked as Beaker B) was weighed 150.0-250.0mg (+/- 1.0mg) of CaSO_4 powder, 4-10ml water and 47-82ul TEMED.

The solution in Beaker A was poured into with the suspension in Beaker B. The mixture was then stirred for 10-50 seconds and poured into moulds. Each mould consisted of a cylindrical
10 polypropylene (PP) tube (10) with an internal diameter of 10-40mm and a central mould (34) attached to a top stopper (14) as shown in Figure 4A.

The samples in the PP moulds were left in an incubator (preheated to 60°C) for 1 hour. The moulds were then transferred into a humid chamber to cure for another 24-72 hours at room
15 temperature for the completion of polymerization. The resulting gelled materials (initial hydrogel materials) were labelled as the as-prepared gels (APGs) (36).

As shown in Figure 4B, the top stopper (14) was removed from the mould, and the APGs (36), comprising a cavity (22) in their core region and a passageway (24) including an opening
20 (26) on the top side of the APG, were removed from the tubes (10) for the next washing process.

The APGs (18) were submerged in a washing solution (at a pH of around 1-2) for 7-21 days with a daily routine of flushing the samples and containers with DW as well as refreshing of
25 the SGF. The volume of the SGF used to soak the samples was 75~150ml per gel.

Freezing & Freeze-drying:

The expanded and acidic solution washed samples were drained from the SGF, washed with
30 deionised water and dried, and each hydrogel was directly put into a PP cylindrical tube mould which has a similar diameter to that of a swollen gel. The swollen gel inside the mould was then put into a freezer at -10°C to -50°C for 8-24 hours and then transferred into the freeze-dryer and freeze dried at from -30°C to -50°C to produce a freeze-dried superporous hydrogel (freeze-dried SPH (38)).

35

Loading:

The freeze-dried SPH (38) was loaded with a drug core (28) comprising one or more active ingredients. This was done by insertion of the drug core through the opening (26) and into the cavity (22) of the freeze-dried SPH (38), as depicted in Figure 5A, to yield a loaded freeze-dried SPH (40), as depicted in Figure 5B.

5

Sealing

A sealing mechanism was employed wherein sections were excised from additional freeze-dried SPHs to form plugs. These plugs were inserted into the passageway (24) of the primary freeze-dried SPHs to block access to the cavity (22). A sealant was applied to the peripheral surface of the plug to establish a seal with the passageway (24). The sealed assembly was then allowed to set and dry for up to 3 days at ambient temperature.

10

Plasticisation:

15

A sample of loaded freeze-dried SPH (40) was put in the sample holder and left inside a humidity chamber at 30-60°C with a relative humidity of 50-75% for from 1 to 10 minutes until it became malleable, yielding a plasticised loaded freeze-dried SPH (31).

Compression:

20

The plasticised loaded freeze-dried SPH (31) was carefully removed from the container and biologically inert bioadhesive glue was applied to the opening (26). Then, the plasticised loaded freeze-dried SPH (31) was squeezed into a cylindrical tube (25) and compressed with push rods (27a and 27b), each having a concave end (29a, 29b) and each inserted into opposing open ends of the cylindrical tube (25), as shown in Figures 3A and 3B, or directly moulded in a capsule mould. This compressive step yielded a loaded, compressed SPH (32), additionally resulting in the closure of the opening (26), as depicted in Figure 5C.

25

A schematic diagram of Route 2 is shown in Figure 21.

30

Example 3: The preparation of a product which is capable of the release of one or more active ingredients, and which has a superporous hydrogel structure formed by freeze-drying, and in which the superporous hydrogel structure comprises a core region comprising one or more active ingredients wherein the one or more active ingredients are loaded after freeze drying (Route 3).

35

This route differs to Route 2 because, in Route 3, a freeze-dried SPH is compressed and then loaded with a drug core.

Hydrogel Synthesis:

5

25.0-50.0g (+/- 0.1g) of AAm, 6.0-20.0g (+/- 0.1g) of AL, and 99.0-132.0mg (+/- 1mg) BAC were weighed and mixed with 150-500ml of DW. The above solution was mixed together with 433.0-751.0mg (+/- 1.0mg) of APS in a beaker (marked as Beaker A).

10 Into another beaker (marked as Beaker B) was weighed 150.0-250.0mg (+/- 1.0mg) of CaSO₄ powder, 4-10ml water and 47-82ul TEMED.

The solution in Beaker A was poured into with the suspension in Beaker B. The mixture was then stirred for 10-50 seconds and poured into moulds. The moulds were of
15 polyoxymethylene or acetal material with an internal diameter of 10-40mm. The mould was designed in such a way that a bridge was placed on top of the moulds. The bridge would allow the central positioning of a dissolvable central mould attached to a top stopper by a thin stick, as shown in Figure 1A.

20 The samples in the acetal moulds were left in an incubator (preheated to 60°C) for 1 hour. The moulds were then transferred into a humid chamber to cure for another 24-72 hours at room temperature for the completion of polymerization. The resulting gelled materials (initial hydrogel materials) were labelled as the as-prepared gels (APGs).

25 The top stopper was removed from the mould, and the APGs, still containing the dissolvable central mould and thin stick were removed from the tubes for the next washing process.

The APGs were submerged in a washing solution (at a pH of around 1-2) for 7-21 days with a daily routine of flushing the samples and containers with DW as well as refreshing of the
30 SGF. The volume of the SGF used to soak the samples was 75~150ml per gel. The dissolvable centre portion dissolved during the process to yield washed APGs comprising a cavity in their core region and a narrow passageway including an opening on the top side of the washed APG.

35 Freezing & Freeze-drying:

The expanded and acidic solution washed samples were drained from the SGF, washed with deionised water and dried, and each hydrogel was directly put into a PP cylindrical tube mould which has a similar diameter to that of a swollen gel. The swollen gel inside the mould was then put into a freezer at -10°C to -50°C for 8-24 hours and then transferred into the freeze-dryer and freeze dried at from -30°C to -50°C to produce a freeze-dried superporous hydrogel (freeze-dried SPH).

Plasticisation

A sample of freeze-dried SPH was put in the sample holder and left inside a humidity chamber at 30-60°C with a relative humidity of 50-75% for from 1 to 10 minutes until it became malleable, yielding a plasticised freeze-dried SPH.

Compression, Loading

The plasticised freeze-dried SPH was carefully removed from the container and squeezed into a compression tool and an acetal pin was placed through the passageway and inside the cavity of the freeze-dried SPH. The system was then compressed with the acetal pin still in the cavity with the help of the compression tool. This creates a suitably sized cavity space in the compressed SPH. The compressed freeze-dried SPH pill was loaded with a drug core comprising one or more active ingredients via the cavity. This was done by insertion of the drug core into the cavity of the freeze-dried SPH pill to yield an open loaded freeze-dried SPH pill. The opening of the compressed freeze dried SPH pills was plugged and sealed with a suitable glue. The compression was completed with push rods, each having a concave end and each inserted into opposing open ends of the cylindrical tubes and directly moulding in a capsule mould. This step yielded a loaded, compressed SPH, additionally resulting in closure of the opening.

A schematic diagram of Route 3 is shown in Figure 22.

Example 4: Dissolution test of drug delivery system products loaded with various active ingredients.

Various Vitamin B12/HPMC drug cores were loaded into superporous hydrogel structures by methods involving loading before or after freeze-drying. The dissolution of these products in 900mL of 50mM sodium phosphate buffer solution at a pH of 6.8 were then measured by a

United States Pharmacopeia (USP) Dissolution Apparatus II using the parameters set out in Table 2 below.

TABLE 2: Dissolution Test Method

5

Medium:	900 mL of 50mM Sodium Phosphate buffer pH 6.8
Apparatus	USP Apparatus II (Paddles)
Paddle Speed:	75 rpm
Temperature:	37.0°C ± 0.5 °C
Sinkers:	QSS 9 (Japanese baskets)
Sampling Time Points:	1, 2, 4, 7, 10, 12, 14, 16, 20, 24, 26, 28 Hours
Sampling Type:	Automatic through 10µm full flow filter
Sampling Volume:	1.5 mL

The results of these dissolution tests are set out in Figures 12 to 16 and in Table 3 below. “Bare tablet” examples refer to dissolution tests of bare drug cores (i.e., with no hydrogel shell).

10

TABLE 3: Dissolution Test Results

Loaded before freeze-drying, loaded after freeze-drying, or bare tablet	Drug Core Composition	Average Dissolution of 3- Core Device after 28 hours
Bare tablet	50% HPMC, 22% SNAC, 0.22% B12	88.0%
Loaded after freeze-drying	50% HPMC, 22% SNAC, 0.22% B12	60.4%
Bare tablet	60% HPMC, 22% SNAC, 0.22% B12	86.8%
Loaded before freeze-drying	60% HPMC, 22% SNAC, 0.22% B12	65.9%
Loaded after freeze-drying	60% HPMC, 22% SNAC, 0.22% B12	46.7%

These results show that products produced by either loading before or after freeze-drying exhibit acceptable dissolution data in a gastric environment.

15

Furthermore, a bare drug core (i.e., a normal tablet) will be removed from the stomach in a matter of hours, whereas a product according to the present invention will stay in the stomach for multiple days. Therefore, consulting Figures 12 and 14, only approximately 20% of the Vitamin B12 contained in the tablets will be released in the stomach for the comparative examples.

Consequently, a far greater percentage of the Vitamin B12 contained in a product of the present invention will be released while the product is in the stomach and thus more Vitamin B12 will be absorbed by the body.

10

Example 5: In vitro dissolution profile of B12-loaded drug delivery system (2)

Vitamin B12/HPMC drug cores were loaded into superporous hydrogel structures by methods involving loading after freeze-drying. The dissolution of these products in 900mL of 50mM sodium phosphate buffer solution at a pH of 6.8 were then measured by a United States Pharmacopeia (USP) Dissolution Apparatus II using the parameters set out in the Table below.

15

TABLE 4: Dissolution Test Method:

Medium:	900 mL of Sodium Phosphate buffer pH 6.8
Apparatus	USP Apparatus II (Paddles)
Paddle Speed:	75 rpm
Temperature:	37.0°C ± 0.5 °C
Sinkers:	Client supplied
Sampling Time Points:	1, 2, 4, 6, 8, 12, 16, 24, 36, 48 Hours
Sampling Type:	Automatic through 10µm full flow filter
Sampling Volume:	1.5 mL

20

As shown by Figure 13, individual dissolution release profiles show good consistency between each vessel, the drug delivery system (CS) has vastly improved variability in its release profile against previous work. Mean dissolution results show that drug delivery system release (CS) is slower than the MR tablets.

25

Example 6: Swelling performance of drug delivery system product

Four products having been prepared according to Example 1, each containing a placebo tablet containing 30% HPMC, were left in simulated gastric fluid for 90 minutes at 37°C. At 0, 10, 30, 60, and 90 minutes, each product was removed from the simulated gastric fluid, wiped to remove any simulated gastric fluid on its surface, and had its diameter measured.

- 5 Each product was then replaced in the simulated gastric fluid. The results of this are displayed in Figure 11, with the data points representing the average values and the error bars representing the standard deviation.

- Figure 11 shows that a device made according to Example 1 swells to a diameter of above 10 30mm within 30 minutes. As discussed above, this diameter is greater than that of the pylorus of the patient. Furthermore, as the swelling rate is rapid, the hydrogel device will reach this size after ingestion before MMC waves begin. Therefore, the device will not exit the stomach.

- Example 7:** Pharmacokinetic Evaluation of formulated Modified Release B12 pill in drug 15 delivery system in canine model

Study Protocol

- To evaluate the safety and feasibility of dosing Drug Delivery Systems in animals, a pilot 20 study was conducted. Two Male Beagle Dogs, 3 years of age weighing between 10 and 15kg were orally dosed with the Drug Delivery System as disclosed herein. The Drug Delivery System was dosed followed by administration of 150 mL of warm water. On the morning of dosing (pre-dose), the animals were deprived of their daily food allowance until 1 h post dose.

- 25 Excreta Sample Collection - Faeces were collected into polypropylene pots. The faecal samples were examined over a mesh grid or clear self-seal plastic bag to identify if the swollen superporous hydrogel was contained in the sample. Photographs were captured of the sample prior to and after examination.

- 30 Results – The dosing was performed without any incidences of chewing or biting of the pill. No adverse reactions to the administration of the Drug Delivery System were observed for the animals dosed indicating safety and tolerability. There was no impact on food consumption or animal behaviours throughout the study duration. From the faecal collection, it was observed that a section of the hydrogel was recovered on day 5 from one dog. The 35 other dog did not expel the hydrogel in the course of the study.

Example 8: Plasma concentration of B12

A study was designed to evaluate the Pharmacokinetics of Vitamin B12 in the Male Beagle Dog Following Oral Administration of 3 Different release Formulations.

5 Study Protocol

Dogs – 12 non-naive Male Beagles Dogs, 3 years of age weighing between 10-15kg

Food Consumption - Animals had access to 300 to 350 g/day of certified canine diet 5007
10 (Labdiet, PMI Nutrition International) throughout the study. On the morning of dosing (pre-dose), the animals were deprived from their daily food allowance until 3 h post dose.

Test Items – Three 1mg B12 formulations with different release profiles, Details of the formulations are specified in Table 5.

15

TABLE 5 – Formulations Evaluated in Animal Studies

PILL TYPE		Source	Composition
MR Pills (1mg B12)		Formulated by QS	1 mg B12, HPMC K200M, MCC PH102, Silica Colloidal Anhydrous, Magnesium Stearate
Drug System	Delivery	MR formulated by QS and drug delivery system assembly at OMP	OMPGEL - Interpenetrating network of Alginate and Polyacrylamide + MR formulation (composition same as above made by Route 2)
OMPGEL + 1 MR B12 (1mg B12) according to the invention.			

Route of Administration – Pills across all formulations were administered orally to dogs in a 12-hour fasted state. A group of 6 male beagle dogs will receive a single administration of 1
20 pill per dog containing 1 mg Vitamin B12 MR (Animal Numbers - 064M, 065M, 066M, 078M, 079M, 088M). A third group of 6 male beagle dogs will receive a single administration of 1 pill per dog containing 1 mg Vitamin B12 Combined System: B12 MR+OMPGEL (068M, 069M, 097M, 098M, 099M, 100M). Prior to oral dosing (approximately 30 minutes pre-dose), all animals will receive a single intramuscular (IM) administration of pentagastrin at a target
25 dose level of 6 µg/kg.

Sample Collection - Following oral administration of respective pills, blood samples (ca 1 mL) were collected from the jugular vein by venipuncture into tubes containing Lithium heparin anticoagulant. The details of the blood collection time points are in Table 5. The samples upon collection were analyzed using an Immulite 2000 XPi Immunoassay system, Siemens Healthineers using the Chemiluminescent enzyme immunoassay method. The detectable range of analysis 150-1000pg/mL.

For dogs administered the combined system, fecal samples were collected from the holding pen floor at the time intervals specified in Table 6.

TABLE 6 – Animal Study Design Details

Group	Animal No.	Blood Sample Collection Time	Excreta Collection
B12 MR	064M, 065M, 066M, 078M, 079M, 088M (Housed in 3 groups)	Predose, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 36, 48 hours post dose	N/A
Drug Delivery System, CS (OMPGEL +B12 MR) according to the present invention (made by Route 2)	068M, 069M, 097M, 098M, 099M, 100M (Individually housed)	Predose, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 36, 48 hours post dose.	0-6, 6-12, 12-24, 24-30, 30-36, 36-48, 48-60, 60-72, 72-84, 84-96, 96-120, 120-144, 144-168, 168-192, 192-216, 216-240, 240-264, 264-288, 288-312, 312-336 hours post dose

Results

Pre-dose B12 values were considered endogenous levels and were subtracted from subsequent measurements to obtain accurate analytical data.

As seen in Figure 14, a notable degree of variability was observed across all animals receiving modified-release tablets, suggesting inconsistencies in gastric transit. Additionally, some samples exhibited dual peaks, potentially indicative of faecal reingestion due to the lack of precaution of housing design.

For drug delivery system, one sample (97M) was prematurely expelled from the dog before 24 hours. Another sample (100M) had a significantly delayed deployment. Given that these two hydrogels did not align with the expected behaviour, they were considered outliers.

- 5 Plasma concentration analysis revealed that the remaining 4 samples from dogs administered the drug delivery system (OMPGEL+B12) exhibited a peak concentration at six hours (Figure 15; 16). Plasma concentration spectra from animals 068M, 069M, 098M, and 099M revealed a consistent trend, indicating that the extent of absorption was less variable. The observed consistency in drug release further supports the notion of effective gastric transit.

A comparative analysis was conducted on the two systems, plotting the averages of both the MR and CS plasma concentrations while excluding outliers.

TABLE 7 – PK Summary for the tested groups

Parameters	Modified Release	Combined System
Tmax (hr)	2	6
Cmax (pg/mL)	581	669
AUC (pg*hr/mL)	10,975	16,164

- Comparative analysis of modified-release and combined systems revealed a rightward shift in the time required to achieve peak concentration, from two to six hours. This shift aligns with the swelling kinetics of OMPGEL in a physiological environment, supporting its delayed-release function. Additionally, the combined system demonstrated slightly higher B12 concentrations compared to the modified-release system (Figure 13). The area under the curve (AUC) for the combined system exhibited a 47% increase, indicating favourable pharmacokinetic properties (Table 7). These results suggest the potential of improving bioavailability and increase in therapeutic duration.

GASTRORETENTION ESTIMATION

- In total, eight OMPGELs were administered to dogs, 87.5% of the OMPGELs exhibited a minimum gastroretention period of three days, and 62.5% demonstrated a maximum gastroretention of over 14 days with no hydrogel remains collected from faeces after 14 days. Only one system (12.5%) failed to deploy correctly (<24h).

Example 9:Mechanical Testing – I

- 5 To assess the mechanical robustness of the drug delivery system, a pre-swollen sample was secured within a 12cm x 12cm petri dish containing 50 mL of Simulated Gastric Fluid (SGF) and positioned on a Mecmesin Multitest 2.5i instrument platform. A compressive load of 100N was applied to the system at room temperature. The system successfully withstood this load, exhibiting no signs of cracking or other structural damage. This process was repeated on
- 10 three samples to ensure reproducibility amongst results (Figure 17). These findings confirm the system's unwavering stability and its suitability for prolonged gastroretention.

Mechanical Testing – II

- 15 To assess the mechanical robustness of the drug delivery system, a pre-swollen sample was secured within a 12cm x 12cm petri dish containing 50 mL of Simulated Gastric Fluid (SGF) and positioned on a Mecmesin Multitest 2.5i instrument platform. A compressive load of 300N was applied to the system at room temperature. The system successfully withstood this load, exhibiting no signs of cracking or other structural damage. This process was repeated on
- 20 three samples to ensure reproducibility amongst results (Figure 18). These findings confirm the system's unwavering stability and its suitability for prolonged gastroretention.

Fatigue Testing (FT)

- 25 The loaded drug delivery system was pre-swollen in Simulated Gastric Fluid and were positioned in a 12cm x 12cm petri dish mounted on a Mecmesin Multitest 2.5i instrument platform. The drug delivery system was subjected to 7000 cycles, 10N Load whilst maintaining a volume of 50 mL SGF in the petri-dish at room temperature. The trial was conducted to demonstrate the robustness of the drug delivery system. The complete overlap
- 30 of the load versus displacement curves from the initial cycles compared to the final cycles further confirmed the system's stability, even under prolonged and repeated stress (Figure 19). The study revealed the system's unwavering stability, even when subjected to the most demanding conditions.

- 35 Example 10: SPH pore perimeters

Figures 23 - 25 depict scanning electron microscope (SEM) images of a superporous hydrogel produced according any of Examples 1-3 in the absence of a loading step.

Figure 23 depicts a cross-section of a superporous hydrogel immediately after freeze-drying (i.e., before any compression or plasticisation processes have been conducted). The average perimeter of the pores in the cross section of the superporous hydrogel depicted in Figure 23 is 1596.0 μm , meaning that the pores of the superporous hydrogel of Figure 23 have an average maximum dimension of 798.0 μm .

Figure 24 depicts a cross-section of a compressed superporous hydrogel (i.e., a superporous hydrogel after the "compression" step of any of Examples 1-3). The average perimeter of the pores in the cross section of the compressed superporous hydrogel depicted in Figure 24 is 998.7 μm , meaning that the pores of the compressed superporous hydrogel of Figure 24 have average maximum dimension of 499.3 μm .

Figure 25 depicts a cross-section of a superporous hydrogel which has swollen after immersion in simulated gastric fluid for 1 hour. The average perimeter of the pores in the cross section of the swollen superporous hydrogel depicted in Figure 25 is 1470.1 μm , meaning that the pores of the swollen superporous hydrogel of Figure 25 have average maximum dimension of 735.1 μm .

Table 8 discloses the average pore area and the average pore perimeter for 6 samples of superporous hydrogels immediately after freeze-drying (i.e., before any compression or plasticisation processes have been conducted). The average pore area across these samples is 205365.58 μm^2 (standard deviation 136633.65 μm^2) and the average pore perimeter across these samples is 1813.79 μm (standard deviation 573.31 μm). Therefore, the average maximum dimension of the pores of the samples in Table 8 is 906.6 μm .

Table 8

Sample	Average Pore Surface Area (μm^2)	Average Pore Perimeter (μm)
Freeze-dried Sample 01	151008.37	1596.03
Freeze-dried Sample 02	370221.31	2469.60
Freeze-dried Sample 03	70015.42	1232.45
Freeze-dried Sample 04	416380.67	2682.28

Freeze-dried Sample 05	141481.06	1715.16
Freeze-dried Sample 06	83086.63	1187.19

Table 9 discloses the average pore area and the average pore perimeter for 6 samples of compressed superporous hydrogel (i.e., a superporous hydrogel after the “compression” step of any of Examples 1-3). The average pore area across these samples is 8833.97 μm^2 (standard deviation 4735.50 μm^2) and the average pore perimeter across these samples is 671.62 μm (standard deviation 188.13 μm). Therefore, the average maximum dimension of the pores of the samples in Table 9 is 385.8 μm .

Table 9

Sample	Average Pore Surface Area (μm^2)	Average Pore Perimeter (μm)
Compressed Sample 01	18625.90	998.68
Compressed Sample 02	10724.76	839.88
Compressed Sample 03	6181.93	612.73
Compressed Sample 04	5745.70	450.58
Compressed Sample 05	5204.74	536.06
Compressed Sample 06	6520.79	591.82

Table 10 discloses the average pore area and the average pore perimeter for 6 samples of a superporous hydrogel which has swollen after immersion in simulated gastric fluid for 1 hour. The average pore area across these samples is 123960.71 μm^2 (standard deviation 30453.32 μm^2) and the average pore perimeter across these samples is 1482.16 μm (standard deviation 178.22 μm). Therefore, the average maximum dimension of the pores of the samples in Table 8 is 741.1 μm .

Table 10

Sample	Average Pore Surface Area (μm^2)	Average Pore Perimeter (μm)
Swollen Sample 01	142871.59	1470.13

Swollen Sample 02	118084.49	1540.41
Swollen Sample 03	167244.38	1745.25
Swollen Sample 04	86235.06	1266.28
Swollen Sample 05	143842.55	1618.26
Swollen Sample 06	85486.18	1252.61

Example 11: N,N'-Methylenebisacrylamide (MBA) and BaSO₄ cross-linking agents

- 5 Hydrogel compositions were prepared using different MBA concentrations, ranging from 0.0065% to 0.008% of the total formulation while maintaining a constant overall crosslinker concentration.

Initial Hydrogel Synthesis:

10

25.0-50.0g (+/- 0.1g) of AAm, 6.0-20.0g (+/- 0.1g) of AL, and 10-100mg (+/- 1mg) MBA were weighed and mixed with 150-500ml of DW. The above solution was mixed together with 433.0-751.0mg (+/- 1.0mg) of APS in Beaker A. In Beaker B, 150.0-250.0mg CaSO₄ powder (+/- 1.0mg), 4-10ml water and 47-82ul TEMED were weighed. The solution in Beaker A was
15 poured into Beaker B. The mixture was then stirred and poured into moulds. Each cylindrical mould has an internal diameter of 10-40mm and a central mould attached to a top stopper by a thin stick.

20

The samples in the PP moulds were left in an incubator (25-60C) to cure for 1 hour. The moulds were then transferred into a humid chamber to cure for another 24-72 hours at room temperature for the completion of polymerization. The resulting gelled materials (initial hydrogel materials) were labelled as the as-prepared gels (APGs).

25

The top stopper was removed from the mould, and the APGs, still containing the central mould and thin stick were removed from the tubes for the next washing process.

30

The APGs were submerged in a wash solution for 7-21 days with a daily routine of flushing the samples and containers with deionized water and replacing used wash solution with fresh wash solution. The central mould was either removed or dissolved, resulting in washed APGs comprising a cavity in their core region and a narrow passageway including an opening on the top side of the washed APG.

Loading Method

The washed APGs were drained from wash solution. A drug core comprising one or more
5 active ingredients was then inserted through the opening and the passageway into the cavity
of each washed APG to yield loaded APGs. Owing to the elastic nature of the APG material
and the narrow diameter of the passageway, the drug core was retained within the cavity.

Freezing & Freeze-drying:

10 Each loaded APG was put into a freezer at -10°C to -50°C for 8-72 hours and then transferred
into the freeze-dryer and freeze-dried to produce a loaded freeze-dried superporous hydrogel
(loaded freeze-dried SPH).

Plasticisation:

15 A sample of loaded freeze-dried SPH was put in the sample holder and left inside a humidity
chamber at 30-60°C with a relative humidity of 50-95% for from 1 to 10 minutes until it became
malleable, yielding a plasticised loaded freeze-dried SPH.

Compression:

20 The plasticised loaded freeze-dried SPH was carefully removed from the container and
compressed into a pill shape. This compressive step yielded a loaded, compressed SPH.

Swelling performance

25 The swelling capacity of the hydrogels was assessed by measuring changes in diameter,
height, and mass upon immersion in simulated gastric fluid at 37°C. These results are set out
30 in Figure 26.

Concentration 1, 2, 3, 4 corresponds to 0.008%, 0.0075%, 0.007% and 0.0065% w/w
concentration of MBA in the APGs. All Samples swelled to an average of >30mm in 30min,
indicating potentials for gastroretention property.

Mechanical strength evaluation

The mechanical strength of the hydrogels was evaluated by assessing their resistance to cracking or structural failure under controlled conditions. These results are set out in Figure 27.

- 5 The samples have been compressed with 100 N force using a 500N capacity load cell. Both samples remained intact after the compression. No cracks or fractures have been induced by the compression. Sample with MBA concentration-01 (0.008% w/w MBA) showed less displacement compared to sample with MBA concentration-02 (0.0075% w/w MBA), indicating a higher compressive modulus.

CLAIMS

1. A product which is capable of the release of one or more active ingredients, in which the product comprises a superporous hydrogel structure having a pore structure formed by freeze-drying, and in which the superporous hydrogel structure comprises a core region comprising one or more active ingredients.
5
2. The product according to claim 1 wherein substantially all of the one or more active ingredients is located within the core region of the superporous hydrogel structure.
10
3. The product according to claim 1 wherein the superporous hydrogel structure comprises a shell region at least partially enclosing the core region, and at least a portion of the shell region of the superporous hydrogel structure comprises substantially no active ingredient.
15
4. The product according to any of claims 1 to 3 wherein the core region comprises a body discrete from the superporous hydrogel structure.
5. The product according to any of claims 1 to 4, in which the one or more active ingredients are held by the core region of the superporous hydrogel structure without being chemically joined to a part of the core region of the superporous hydrogel structure.
20
6. The product according to any one of claims 1 to 5, in which the superporous hydrogel comprises a structure which includes a mixture of hydrophilic polymers that are cross-linked by virtue of one or more cross-linking agents.
25
7. The product according to claim 6, in which the mixture of hydrophilic polymers comprise one or more hydrophilic polymers made from an alkenyl amide-containing monomer and a polysaccharide.
30
8. The product according to claim 7, in which the alkenyl amide-containing monomer comprises acrylamide and the polysaccharide comprises alginate.
- 35 9. The product according to any of claims 6 to 8, wherein the one or more cross-linking agents comprise one or more selected from one or more acryloyl groups, one or more

acrylamide groups, one or more amine groups, one or more olenfinic groups, one or more aldehyde groups, and one or more divalent metal ions.

10. The product according to claim 9, wherein the one or more cross-linking agents
5 comprise one or more selected from N,N'-bis(acryloyl)cystamine (BAC), and/or N'-Methylenebisacrylamide (MBA) and/or calcium ions.
11. The product according to any one of claims 1 to 9, in which the superporous hydrogel
10 comprises a compressed structure having pores which have an average maximum dimension of between 100µm and 5mm.
12. A product according to any preceding claim wherein the pores of the pore structure
have an average maximum dimension of $\geq 250\mu\text{m}$ after immersion in simulated gastric
15 fluid for 1 hour.
13. The product according to any one of claims 1 to 12, in which the core region comprises
one or more cavities (22), and the one or more cavities (22) are loaded with one or
more active ingredients.
- 20 14. The product according to claim 13, in which, prior to loading of the one or more cavities
(22) with one or more active ingredients, the one or more cavities (22) comprise one or
more passageways (24), and in which one end of the one or more passageways (24)
includes an opening (26) on a side of the product.
- 25 15. The product according to any one of claims 13 to 14, in which the total volume of the
one or more cavities (22) is $\leq 2\text{mL}$.
16. The product according to any of claims 1 to 15, in which the active ingredient comprises
one or more pharmaceutical ingredients.
- 30 17. The product according to any of claims 1 to 16, in which the active ingredient comprises
one or more nutraceutical ingredients.
18. The product according to any one of claims 1 to 17, in which the active ingredient is
35 selected from one or more of the group consisting of Metformin (N,N-dimethylbiguanide),
Carbidopa (N-amino- α -methyl-3-hydroxy-L-tyrosine

monohydrate), Levodopa (L-3,4-dihydroxyphenylalanine), a glucagon-like peptide receptor agonist such as Semaglutide, a cobalt-containing food supplement such as vitamin B12, an iron-containing food supplement, and combinations of these.

- 5 19. The product according to any of claims 1 to 18, in which the core region further includes one or more excipients.
20. The product according to claim 19, in which the one or more excipients include a permeation enhancer such as salcaprozate sodium.
- 10 21. The product according to any of claims 1 to 20, in which the product comprises a swelling force which is released when the product is exposed to gastric fluid to result in a swollen hydrogel having a diameter of $\geq 25\text{mm}$ within 30 minutes.
- 15 22. A method of preparing a product which is capable of the release of one or more active ingredients, and which has a superporous hydrogel structure having a pore structure formed by freeze-drying, in which the superporous hydrogel structure comprises a core region comprising one or more active ingredients, and in which the method comprises:
- 20 a) loading the core region with one or more active ingredients, either prior to, or after freeze drying.
23. The method according to claim 22 wherein step a) comprises loading one or more active ingredients into the core region such that substantially all of the one or more active ingredients is located in the core region.
- 25 24. The method according to claim 22 or 23 in which step a) further comprises, either:
- (i) in the case of loading the core region with one or more active ingredients prior to freeze drying;
- 30 a. providing an initial hydrogel comprising a core region;
- b. loading the core region of the initial hydrogel with one or more active ingredients; and
- c. freeze-drying the resulting product of step (b) to form a superporous hydrogel structure comprising a core region loaded with one or more active ingredients; or
- 35 (ii) in the case of loading the core region with one or more active ingredients after freeze drying;
- a. providing an initial hydrogel comprising a core region;

- b. freeze-drying the initial hydrogel to form a superporous hydrogel structure comprising a core region; and
- c. loading the core region of the superporous hydrogel structure with one or more active ingredients to form a superporous hydrogel structure comprising a core region loaded with one or more active ingredients.
- 5
25. The method according to any one of claims 22 to 24, in the case of loading the core region with one or more active ingredients prior to freeze drying, in which the method further comprises:
- 10
- a. polymerising a mixture of monomers and/or polymers around one or more central moulds (12, 16; 34) in the presence of a cross-linking agent to form an initial hydrogel;
- b. demoulding the resulting product of step (a) to provide the initial hydrogel with a core region comprising one or more cavities (22);
- 15
- c. loading the one or more cavities (22) of the initial hydrogel with one or more active ingredients; and
- d. freeze-drying the resulting product of step (c) to form a superporous hydrogel structure having a core region comprising one or more cavities (22) loaded with one or more active ingredients.
- 20
26. The method according to any one of claims 22 to 24, in the case of loading the core region with one or more active ingredients after freeze drying, in which the method further comprises:
- 25
- a. polymerising a mixture of monomers and/or polymers around one or more central moulds (12, 16; 34) in the presence of a cross-linking agent to form an initial hydrogel;
- b. demoulding the initial hydrogel to provide the initial hydrogel with a core region comprising one or more cavities (22);
- 30
- c. freeze-drying the resulting product of step (b) to form a superporous hydrogel structure with a core region comprising one or more cavities (22); and
- d. loading the one or more cavities (22) of the superporous hydrogel structure with one or more active ingredients to form a superporous hydrogel structure comprising a core region loaded with one or more active ingredients.
- 35
27. The method according to any one of claims 24 to 26, in which the step of demoulding includes a washing treatment.

28. The method according to any one of claims 22 to 27, further including, after loading, the steps of (i) treating the superporous hydrogel structure to plasticise its structure; and (ii) compressing the resulting plasticised superporous hydrogel structure to provide a compressed structure having pores which have an average maximum dimension of between 100µm and 5mm.
29. The method according to claim 28, further including prior to step (i) and (ii), the step of substantially sealing at least a part of one or more selected from one or more cavities, an opening to one or more passageways, and one or more passageways.
30. The method according to claim 29, in which the step of substantially sealing comprises the installation of a plug.
31. The method according to any one of claims 22 to 27, further including, after freeze-drying, the steps of (i) treating the superporous hydrogel structure to plasticise its structure; and (ii) compressing the resulting plasticised superporous hydrogel structure to provide a compressed structure having pores which have an average maximum dimension of between 100µm and 5mm.
32. The method according to claim 31, in which the step of compression includes compressing the resulting plasticised superporous hydrogel structure with an elongate insert present in at least a portion of one or more cavities.
33. The method according to any one of claims 25 to 26, further including, after loading the one or more cavities (22) with one or more active ingredients, the step of substantially sealing at least a part of one or more selected from the one or more cavities, an opening to one or more passageways, and one or more passageways.
34. The method according to claim 33, in which the step of substantially sealing comprises the installation of a plug.
35. A product which is obtainable by the method according to any one of claims 22 to 34.
36. Use of a product according to any one of claims 1 to 21, or claim 35, in drug delivery.

37. A pharmaceutical composition comprising a product according to any one of claims 1 to 21 or claim 35.
- 5 38. A method of medical treatment comprising administration of a product according to any one of claims 1 to 21 or claim 35, to a subject.
39. A product according to any one of claims 1 to 21 or claim 35, for use as a medicament.
- 10 40. A product according to any one of claims 1 to 21 or claim 35, for use in treating or preventing one or medical conditions selected from gastric cancer, gastric ulcers, helicobacter infections, Parkinson's disease, polycystic ovary syndrome, metabolic diseases, obesity, obesity-related diseases, cardiovascular disease diabetes, and non-alcoholic fatty liver disease.
- 15 41. A dosage regimen for administering a product according to any of claims 1 to 21 or 35 to a patient suffering from one or more medical conditions.
- 20 42. A method for treating or preventing one or medical conditions in a subject, the method comprising administering to the subject, a product according to any one of claims 1 to 21 or claim 35.
- 25 43. The method according to claim 42, wherein the one or medical conditions are selected from gastric cancer, gastric ulcers, helicobacter infections, Parkinson's disease, polycystic ovary syndrome, metabolic diseases, obesity, obesity-related diseases, diabetes, cardiovascular disease and non-alcoholic fatty liver disease.
- 30 44. The method according to any one of claims 42 to 43, wherein the product is administered in an amount effective to result in a minimum gastroretention period of 24 hours.
- 35 45. The method according to any one of claims 42 to 44, wherein the product is administered in an amount effective to result in a minimum gastroretention period of 3 days.
46. The method according to any one of claims 42 to 45, wherein the product is administered in an amount effective to result in a gastroretention period of between 3 and 14 days.

47. The method according to any one of claims 42 to 46, wherein the product is administered in an amount effective to result in a swollen hydrogel having a diameter of $\geq 25\text{mm}$ within 30 minutes when the product is exposed to gastric fluid.
- 5
48. The method according to any one of claims 42 to 47, wherein the product is administered in an amount effective to result in a swollen hydrogel having a diameter of $\geq 30\text{mm}$ within 30 minutes when the product is exposed to gastric fluid.
- 10
49. The method according to any one of claims 42 to 48, wherein the product is administered in an amount effective to result in the release of 65% or less of the one or more active ingredients after 24 hours.
- 15
50. The method according to any one of claims 42 to 49, wherein the product is administered in an amount effective to result in the release of 80% or less of the one or more active ingredients after 48 hours.