

CLAIMS

1. A method for measuring gut permeability of a subject, the method comprising:
 - orally administering a solution comprising a fluorescent contrast agent that is absorbable by a healthy gut to the subject;
 - using a light source to irradiate a location on the skin on a body part of the subject using light radiation, such that the light radiation causes at least a portion of the solution which has leaked out of the gut of the subject into the bloodstream of the subject to fluoresce;
 - using a transcutaneous sensing device to periodically detect the intensity of the fluorescence of the solution at said location to obtain fluorescence data of said intensity as a function of time;
 - normalising the fluorescence data to obtain normalised data of said intensity as a function of time; and
 - analysing said normalised data to determine the gut permeability of the subject by calculating one or more of:
 - a) the first peak value of said intensity;
 - b) the integral of said intensity with respect to time;
 - c) the product of the first peak value of said intensity and the time at said peak value;
 - d) the product of: the first peak value of said intensity, and the time at a point past the time of said first peak value;
 - e) the time at which the first peak value of said intensity occurs; or
 - f) the first peak value of said intensity divided by the time at which said peak value occurs.
2. A method as claimed in claim 1, wherein the solution comprises water or juice.
3. A method as claimed in any of the preceding claims, wherein the contrast agent comprises a dye, for example fluorescein, methylene blue or fluorescein isothiocyanate conjugated dextran, or salts thereof, or combinations thereof.
4. A method as claimed in any of the preceding claims, wherein the transcutaneous sensing device has an acquisition time and the light source has an excitation power, and wherein the fluorescence data is normalised based on said acquisition time and said excitation power.

5. A method as claimed in any of the preceding claims, wherein the transcutaneous sensing device begins taking periodic measurements before the solution is administered to the subject, such that the periodic detection of the intensity of the fluorescence of the solution begins before the solution is administered to the subject, to obtain a background signal to be used in the step of normalising the fluorescence data.
6. A method as claimed in any of the preceding claims, wherein the light source comprises a light emitting diode or a laser.
7. A method as claimed in any of the preceding claims, wherein the transcutaneous sensing device comprises one or more photodiodes, phototransistors and/or fibre-optic probes and is configured to be worn on and/or around said body part of the subject.
8. A method as claimed in any of the preceding claims, wherein in the step of using the transcutaneous sensing device to periodically detect said intensity of the fluorescence, measurements are recorded by said transcutaneous sensing device at least once per minute.
9. A method as claimed in any of the preceding claims, wherein said body part is a finger, wrist, arm or earlobe.
10. A method for measuring gastric emptying rate of a subject, the method comprising:
 - orally administering a test meal comprising a fluorescent contrast agent that is absorbable by a healthy gut to the subject;
 - using a light source to irradiate a location on the skin on a body part of the subject using light radiation, such that the radiation causes at least a portion of the fluorescent contrast agent in the test meal which has been emptied from the stomach of the subject and has entered the bloodstream of the subject to fluoresce;
 - using a transcutaneous sensing device to periodically detect the intensity of the fluorescence of the fluorescent contrast agent in the test meal at said location to obtain data of said intensity as a function of time;
 - normalising the fluorescence data to obtain normalised data of said intensity as a function of time; and

analysing said normalised data to calculate the percentage of the test meal which is remaining in the stomach of the subject as a function of time, based on the intensity as a function of time divided by a peak value of the intensity.

11. A method as claimed in claim 10, wherein the peak value of the intensity is the value of the intensity at a first peak or at a second peak in the fluorescence data, or is a maximum value of the intensity in the fluorescence data.
12. A method as claimed in any of claims 10 to 11, wherein the test meal comprises a liquid test meal or a solid test meal.
13. A method as claimed in any of claims 10 to 12, wherein the contrast agent comprises a dye, for example fluorescein, methylene blue or fluorescein isothiocyanate conjugated dextran, or salts thereof, or combinations thereof.
14. A method as claimed in any of claims 10 to 13, wherein the transcutaneous sensing device has an acquisition time and the light source has an excitation power, and wherein the fluorescence data is normalised based on said acquisition time and said excitation power.
15. A method as claimed in any of claims 10 to 14, wherein the transcutaneous sensing device begins taking periodic measurements before the test meal is administered to the subject, such that the periodic detection of the intensity of the fluorescence of the test meal begins before the test meal is administered to the subject, to obtain a background signal to be used in the step of normalising the fluorescence data.
16. A method as claimed in any of claims 10 to 15, wherein the light source comprises a light emitting diode or a laser.
17. A method as claimed in any of claims 10 to 16, wherein the transcutaneous sensing device comprises one or more photodiodes, phototransistors and/or fibre-optic probes and is configured to be worn on and/or around said body part of the subject.
18. A method as claimed in any of claims 10 to 17, wherein in the step of using the transcutaneous sensing device to periodically detect said intensity of the fluorescence, measurements are recorded by said transcutaneous sensing device at least once per minute.

19. A method as claimed in any of claims 10 to 18, wherein said body part is a finger, wrist, arm or earlobe.
20. A method as claimed in any of claims 10 to 19, wherein the step of analysing said normalised data comprises fitting the function:

$$I(t) = (1 - Ct) \left(\frac{B_{max}}{1 + \exp\left(-k_B\left(t - t_{B\frac{1}{2}}\right)\right)} + \frac{L_{max}}{1 + \exp\left(-k_L\left(t - t_{L\frac{1}{2}}\right)\right)} \right)$$

onto the normalised data using a numerical fitting procedure such as least squares fitting;

wherein:

t represents time;

I(t) represents the normalised data of said fluorescence intensity as a function of time;

B_{max} represents the maximum value of the intensity contribution from the fluorescent contrast agent in the bloodstream of the subject as a function of time;

L_{max} represents the maximum value of the intensity contribution from the fluorescent contrast agent that has leaked into the epithelium of the skin of the subject as a function of time;

t_{B1/2} represents the time at which the intensity contribution from the fluorescent contrast agent in the bloodstream of the subject as a function of time reaches half of its maximum value;

t_{L1/2} represents the time at which the intensity contribution from the fluorescent contrast agent that has leaked into the epithelium of the skin of the subject as a function of time reaches half of its maximum value;

C represents the rate at which dye is eliminated from the body of the subject; k_B is a constant and represents the logistic growth rate of the intensity contribution from the fluorescent contrast agent in the bloodstream of the subject as a function of time; and

k_L is a constant and represents the logistic growth rate of the intensity contribution from the fluorescent contrast agent that has leaked into the epithelium of the skin of the subject as a function of time.

21. A method as claimed in claim 20, wherein the step of analysing said normalised data further comprises calculating the amount of dye that has emptied from the stomach of the subject as a function of time, $S(t)$, wherein $S(t) = B(t) + B(t)Ct$, wherein $B(t)$ represents the intensity contribution from the fluorescent contrast agent in the bloodstream of the subject as a function of time.

22. A method as claimed in claim 21, wherein the step of analysing said normalised data further comprises calculating the percentage of the test meal which is remaining in the stomach of the subject as a function of time, R_{pc} , wherein:

$$R_{pc} = 100 \times \left(1 - \frac{S(t)}{S(t_{peak})} \right)$$

and wherein $S(t_{peak})$ represents the value of $S(t)$ at the time at which a final peak is observed in the normalised data of said intensity as a function of time.

23. A method as claimed in claim 20, wherein the step of analysing said normalised data further comprises calculating the percentage of the test meal which is remaining in the stomach of the subject as a function of time, R_{pc} , wherein:

$$R_{pc} = 100 \times \left(1 - \frac{B(t)}{B_{max}} \right)$$

and wherein $B(t)$ represents the intensity contribution from the fluorescent contrast agent in the bloodstream of the subject as a function of time.

24. A method as claimed in any of claims 10 to 19, wherein the step of analysing said normalised data comprises calculating the percentage of the test meal which is remaining in the stomach of the subject as a function of time, R_{pc} , wherein:

$$R_{pc} = 100 \times \left(1 - \frac{I(t)}{I(t_{peak1})} \right)$$

and wherein $I(t)$ represents the normalised data of said intensity as a function of time;
and

t_{peak1} represents the time at which the first peak is observed in said intensity as a function of time.