GI Labs

ClinicalTrials.gov registration number NCT04820322

Brief title: Comparison of the Postprandial Glycemic and Insulinemic Response After a Fibersym Containing Cookie With a Control

Final Protocol for MGP GIL-1852 August 7, 2018

Comparison of postprandial glycemic and insulinemic response to a Cookie with or without added Fibersym after three days of pre-feeding: An acute double-blind, randomized controlled clinical trial

Comparison of postprandial glycemic and insulinemic response to a Cookie with or without added Fibersym after three days of pre-feeding: An acute double-blind, randomized controlled clinical trial

Protocol GIL-1852

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Table of Content

Study Synopsis

STUDY TITLE:	Comparison of postprandial glycemic and insulinemic response to a Cookie with or without added Fibersym after three days of pre-feeding: An acute, double-blind, randomized controlled clinical trial
STUDY NUMBER/ VERSION DATE:	GIL-1852; version: June 31, 2018
INVESTIGATORS:	GI Labs: Thomas Wolever, MD, PhD; Alexandra Jenkins, PhD
SPONSOR:	MGP Ingredients, Inc, Contact: Ody Maningat, PhD, VP Ingredients R&D and Chief Science Officer
STUDY SITE:	Glycemic Index Laboratories, Inc. (GI Labs)
STUDY OBJECTIVE(S):	Primary Objective: to compare the postprandial glucose incremental are under the curve (IAUC) after the Fibersym containing carbohydrate load with the glucose IAUC after the control meal
INTERVENTION PRODUCT	Fibersym® is a resistant modified wheat starch in which over 85% of the total starch is resistant starch as measured by AOAC method 991.43. Fibersym can easily be added to food formulations as it provides a smooth texture, neutral flavour and white color.
STUDY POPULATION	Healthy adult males or females (n=15), aged 18-75 years with BMI between 18.5 and 35 kg/m^2. Each subject will have to fulfill all inclusion criteria and will not be allowed to meet any of the exclusion criteria.
TEST MEALS:	1. Control Cookie 2. Cookie with added Fibersym The difference in the cookies is the presence of the Fibersym, meals will therefore be matched for available carbohydrate.
STUDY DESIGN AND RATIONALE	Design: acute, double blind, randomized, controlled clinical trial. Subjects will come in fasting and be given either the Control or Fibersym containing cookie. Postprandial glucose and insulin levels will be measured over 2 hours. As Fibersym is recommended to be consumed on a daily basis, for 3 days prior to each test meal visit, subjects will be given cookies to be consumed 3 times daily for 3 days, ie control cookies will be consumed for 3 days before the control cookie test meal and Fibersym cookies

	before the Fibersym cookie test meal. Each subject will be provided with enough cookies to consume 1 cookie with each meal (breakfast, lunch and dinner) over the 3 days. The Fibersym containing cookie will deliver about 29g/day of dietary fibre.
PROTOCOL SUMMARY	Participants will be recruited by GI labs from their existing subject pool through email and/or advertising posters and leaflets. Volunteers will have the study explained to them prior to providing informed consent. Visit 1: Screening: A pre-study examination will verify that subjects qualify for study inclusion. A number of parameters will be assessed: including blood pressure; weight, height, BMI, and brief medical history. Visit 2-3: Eligible subjects will be randomized using an online randomization calculator. Eligible subjects will be studied on 2 separate days over a period of 4 weeks or less. Prior to each test meal they will be provided with enough cookies to consume 3 times/day over 3 days and instructed to start consuming these 3 days before their visit. They will also be provided with a calorie appropriate, standard dinner to be consumed on the evening before their test meal The interval between successive tests will be no less than 6 days and no more than 4 weeks. On each test day, participants will come to GI Labs in the morning after a 10-12h overnight fast (except for water). Participants will be asked to maintain stable dietary and activity habits throughout their participation and refrain from drinking alcohol and from unusual levels of food intake or physical activity for 24h before each test. Before the start of the test meal, subjects will be asked whether they consumed the provided cookies over the last 3 days as instructed and the standard dinner the evening before. Subjects will be asked to complete a 3d dietary food record and symptom diary before each test visit. If any subject is not feeling well or has not complied with the preceding experimental conditions, the test will not be carried out and will be rescheduled for another day. On each test day, two fasting fingerprick blood samples will be collected at -5min and 0min. Questionnaires to record satiety and GI symptoms will be administered. Participants will then be given the test food together with 250ml of water and instructed to consume this over 15minutes. Additional blood samples will be collected 15, 30 46, 60, 90 and 120min after the start of the test meal. Satiety Questionnaires will be administered at the same time intervals. GI symptom questionnaires

	will be filled out at 2h in addition to fasting.
CRITERIA FOR EVALUATION:	EFFICACY: Primary outcome is comparison of the glucose IAUC of the Fibersym meal with the control meal. Secondary outcomes: comparison of the insulin (IAUC) of the Fibersym meal with the control meal, comparison of glucose and insulin levels at each time point and satiety scores at each time point. SAFETY: Adverse events.
STATISTICAL METHODS:	Results for all foods in a series will be compared by GLM ANOVA. After demonstrating significant heterogeneity, the significance of the differences will be tested using Tukey method to adjust for multiple comparisons
Ethics Board Approval	The investigator will be responsible for submission of the study to the Western Institutional Research Board. Prior to submission of the application, the sponsors and all co-investigators will be given the opportunity to review the application. Submission of the application will only take place if all parties agree. The Western Institutional Review Board® meets all requirements of the US Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS), the Canadian Health Protection Branch (HPB), Canadian Institutes of Health Research (CIHR) and the European Community Guidelines. Participants will not be enrolled into the study until they have had the study procedures explained to them, had a chance to ask questions, and given their voluntary consent by signing the consent form. Participants who do not understand English will not be enrolled.
Subject Selection Criteria	Inclusion criteria: 1. Male or non-pregnant females, 18-75 years of age, inclusive 2. Body mass index (BMI) between 18.5 and 35 kg/m² inclusive at screening. 3. Systolic blood pressure < 130mmHg, Diastolic Blood pressure <90mmHg. 4. Willing to maintain habitual diet, physical activity pattern, and body weight throughout the trial. 5. Subject is willing to abstain from strenuous exercise, or consume alcoholic drinks 24hours before study days. 6. Absence of health conditions that would prevent fulfillment of study requirements as judged by the Investigator on the basis

	of medical history. 7. Understanding the study procedures and willing to provide informed consent to participate in the study and authorization to release relevant protected health information to the study investigator. 8. Female subjects are willing to use a contraceptive method to avoid pregnancy during the study period. Exclusion criteria: 1. Failure to meet any one of the inclusion criteria 2. Smokers 3. Known history of diabetes, gastrointestinal, liver, kidney, or cardiovascular (including, but not limited to, atherosclerotic disease, history of myocardial infarction, peripheral arterial disease, stroke), and pulmonary disease 4. Use of medications known to influence carbohydrate metabolism, including, but not limited to adrenergic blockers, diuretics, thiazolidinediones, metformin and systemic corticosteroids within 4 weeks of the screening visit, or with any condition which might, in the opinion of Dr. Wolever either: 1) make participation dangerous to the subject or to others, or 2) affect the results. 5. Use of antibiotics within 4 weeks of start of study 6. Major trauma or surgical event within 3 months of screening. 7. Unwillingness or inability to comply with the experimental procedures and to follow GI Labs safety guidelines. 8. Known intolerance, sensitivity or allergy to any ingredients in the study products. 9. Extreme dietary habits, as judged by the Investigator (i.e. Atkins diet, very high protein diets, etc). 10. Change in body weight of >3.5kg within 4 weeks of the screening visit. 11. History of cancer in the prior two years, except for non-melanoma skin cancer. 12. Exposure to any non-registered drug product within 30 d prior to screening. 13. Pregnancy or breastfeeding 14. Any history of an eating disorder (e.g., anorexia nervosa, bulimia nervosa, binge eating) diagnosed by a health professional

1. Background and Rationale

Consumption of whole grains have been recommended by most health agencies to increase dietary fibre intake with the ultimate goal to help maintain a healthy body weight and improve insulin sensitivity. Despite these recommendations, most individuals do not meet the recommended 25–35 g per day. Therefore, innovative ideas to increase dietary fibre intake are needed. One approach is to incorporate either by substituting the carbohydrate in a food or by adding isolated fibers to products. MGP Ingredients had developed several resistant starches including, Fibersym® RW, a resistant starch 4 (RS4), which are easily incorporated into foods and would help increase the dietary fiber content of food products, however, RS4 is not included among the eight dietary fibre sources recently approved by FDA.

The FDA defines dietary fiber as “non-digestible soluble and insoluble carbohydrates (with 3 or more monomeric units), and lignin that are intrinsic and intact in plants; isolated or synthetic non-digestible carbohydrates (with 3 or more monomeric units) determined by FDA to have physiological effects that are beneficial to human health." The list of currently approved fibers under the new FDA food labeling regulations that has a compliance date of January 1, 2020 includes RS2 but not RS4.
Clinical research studies have demonstrated a broad range of health benefits after consumption of RS including attenuation of postprandial blood glucose and insulin levels, improving the profile of the microbiota, reduction in colon cancer and increased fat oxidation and mineral absorption (Higgins et al, 2004; Jenkins et al, 1998, 2000; Robertson et al, 2005; So et al, 2007, Topping et all, 2003).
Several different forms of RS have been developed, these include RS1 which is composed of starch granules embedded in indigestible plant material, RS2 is native granular starch with a B-type x-ray pattern, RS3 is crystallized starch and maltodextrins made by alternate cooking/cooling processes on starchy materials and finally, RS4 is chemically modified starch typically through esterification, crosslinking or transglycosylation.

The majority of the studies demonstrating a reduction in postprandial glucose and insulin levels kept the total carbohydrate of the meals the same, ie they achieved the attenuation of the glucose by substituting the available carbohydrate with the resistant starch (Haub et al, 2010) but not all (Al-Tamimi et al, 2010). The last trial suggests that RS4xl may differ from the other RS in that it may be inherently physiologically active itself, not unlike the viscous fibres.

Fibersym® is a resistant modified wheat starch in which over 85% of the total starch is resistant starch as measured by AOAC method 991.43. Fibersym can easily be added to food formulations as it provides a smooth texture, neutral flavour and white color. It is meant to be consumed on a regular basis and doses up to 40g/day can be tolerated. The effect of the Fibersym containing products on postprandial glucose and insulin levels when compared to a control meal containing the same amount of available carbohydrate is not known. This study therefore investigates the effect of the acute effect of control or Fibersym cookie matched for available carbohydrate after 3 day habituation.

2. Study Objectives

2.1 Primary objective

- To compare the 2 hour postprandial glucose incremental area under the curve (IAUC) after the Fibersym containing carbohydrate load with the control meal

2.2 Secondary objectives

- To compare the 2hour postprandial insulin incremental area under the curve (IAUC) after the Fibersym containing carbohydrate load with the control meal
- To compare the individual postprandial glucose and insulin responses at each time point after the Fibersym containing carbohydrate load with the control meal
- To compare the GI symptoms after the three days of pre-feeding of Fibersym cookies with the control meal
- To compare the satiety scores after the Fibersym containing carbohydrate load with the control meal
- SAFETY: GI symptoms and Adverse events.

3. Subject Selection

3.1 Type and number of subjects

Fifteen (15) healthy adult males or non-pregnant females recruited from the pool of subjects who have previously participated in studies at GI Labs and have given permission to be contacted to be recruited for future studies or using online advertising and/or posters. Each subject will have to fulfill all inclusion criteria and will not be allowed to meet any of the exclusion criteria.

3.2 Inclusion Criteria

- Male or non-pregnant females, 18-75 years of age, inclusive
- Body mass index (BMI) between 18.5 and 35 kg/m² inclusive at screening.
- Systolic blood pressure < 130mmHg, Diastolic Blood pressure <90mmHg.
- Willing to maintain habitual diet, physical activity pattern, and body weight throughout the trial.
- Subject is willing to abstain from strenuous exercise, or consume alcoholic drinks 24hours before study days.
- Absence of health conditions that would prevent fulfillment of study requirements as judged by the Investigator on the basis of medical history.
- Understanding the study procedures and willing to provide informed consent to participate in the study and authorization to release relevant protected health information to the study investigator.

- Female subjects are willing to use a contraceptive method to avoid pregnancy during the study period.

3.3 Exclusion Criteria

- Failure to meet any one of the inclusion criteria
- Smokers
- Known history of diabetes, gastrointestinal, liver, kidney, or cardiovascular (including, but not limited to, atherosclerotic disease, history of myocardial infarction, peripheral arterial disease, stroke), and pulmonary disease
- Use of medications known to influence carbohydrate metabolism, including, but not limited to adrenergic blockers, diuretics, thiazolidinediones, metformin and systemic corticosteroids within 4 weeks of the screening visit, or with any condition which might, in the opinion of Dr. Wolever, the president of GI Testing, either: 1) make participation dangerous to the subject or to others, or 2) affect the results.
- Use of antibiotics within 4 weeks of start of study
- Major trauma or surgical event within 3 months of screening.
- Unwillingness or inability to comply with the experimental procedures and to follow GI Labs safety guidelines.
- Known intolerance, sensitivity or allergy to any ingredients in the study products.
- Extreme dietary habits, as judged by the Investigator (i.e. Atkins diet, very high protein diets, etc).
- Change in body weight of >3.5kg within 4 weeks of the screening visit.
- History of cancer in the prior two years, except for non-melanoma skin cancer.
- Exposure to any non-registered drug product within 30 d prior to screening.
- Pregnancy or breastfeeding
- Any history of an eating disorder (e.g., anorexia nervosa, bulimia nervosa, binge eating) diagnosed by a health professional

3.4 Withdrawal Criteria

- Withdrawal of consent for any reason
- During the course of the study, the development of an injury or illness or initiation of use of a medication which, in the opinion of Dr. Wolever, makes the subject's continued participation dangerous to the subject or to others, or which may affect the results.
- Failure to follow GI Labs safety guidelines
- Repeated failure to attend at scheduled visits
- Repeated failure to follow the protocol

4. Study Design and Procedures

The study is double-blind with a randomized, cross-over design.

4.1 Procedures

Visit 1: Participants willing to be considered will be invited to come to the research centre to have the study procedures explained to them and be given a copy of the consent form which they may either sign then, take away to sign at a later date, or decline to participate. Participants will be encouraged to ask any questions they may have and not to sign the consent form until all of their questions have been answered to their satisfaction. Those who consent to participate will come to the research centre for a pre-selection visit when subject eligibility will be determined. A number of parameters will be assessed: including blood pressure; weight, height, BMI, and brief medical history.

Visit 2-3: Eligible subjects will be randomized using an online randomization calculator. Eligible subjects will be studied on 2 separate days over a period of 4 weeks or less. Prior to each test meal they will be provided with enough cookies to consume 3 times/day over 3 days and instructed to start consuming these 3 days before their visit. They will also be provided with a calorie appropriate, standard dinner to be consumed on the evening before their test meal. The interval between successive tests will be no less than 6 days and no more than 4 weeks. On each test day, participants will come to GI Labs in the morning after a 10-12h overnight fast (except for water). Participants will be asked to maintain stable dietary and activity habits throughout their participation and refrain from drinking alcohol and from unusual levels of food intake or physical activity for 24h before each test. Before the start of the test meal, subjects will be asked whether they consumed the provided cookies over the last 3 days as instructed and the standard dinner the evening before. Subjects will be asked to complete a 3d record of supplement consumption and whether they consumed the standard evening meal, in addition to a 3d symptom diary before each test visit. If any subject is not feeling well or has not complied with the preceding experimental conditions, the test will not be carried out and will be rescheduled for another day. On each test day, two fasting fingerprick blood samples will be collected at -5min and 0min. Each sample will consist of 2 vials, one for glucose analysis and one for insulin analysis (4—8 drops of blood each). Questionnaires to record satiety and GI symptoms will be administered. Participants will then be given the test food together with 250ml of water and instructed to consume this over 15minutes. Additional blood samples will be collected 15, 30 46, 60, 90 and 120min after the start of the test meal. Satiety Questionnaires will be administered at the same time intervals. GI symptom questionnaires will be filled out at 2h in addition to fasting.

4.2 Study Flow Chart

Visits / Procedures	Screening		TEST VISITS			
	V1	3 day prefeeding	V2 Test meal	7 day wash out	3 day prefeeding	V3 Test meal
Informed Consent Process and Informed Consent Form Signature	X					
Subject's demographic data	X					
Inclusion and exclusion criteria	X					
Subject's eligibility	X					
Anthropometry	X		X			X
Check of dietary compliance		X	X		X	X
Record of supplement consumption		X			X	
Check of concomitant medications	X		X			X
2 Fasting blood samples			X			X
Consumption of test food			X			X
Postprandial blood samples 15, 30, 45, 60, 90 and 120min after starting to eat		X	X		X	X
GI Symptom Questionnaire		X	X		X	X
Satiety Questionnaire			X			X
Check of adverse events	X		X		X	X

4.3 Test Foods

There will be two test foods:

1. Control Cookie
2. Cookie with added Fibersym

The difference in the cookies is the presence of the Fibersym, meals will therefore be matched for available carbohydrate. Both test meals will be consumed with 250ml of water.

During the 3-day pre-feeding period, subject will consume 9 cookies per day with the aim to provide approximately 29g of fibre per day from the Fibersym cookies. For the test breakfasts, the subject will consume approximately 3 cookies containing 50g available carbohydrate. The Fibersym cookies will

deliver approximately 10g of fibre. Once the cookies are baked they will be sent out for macronutrient analysis and the final weight of the cookies fed will be adjusted accordingly.

Table 1: Approximate composition of the test meals*

	Approx. # cookies	Weight (g)	Protein (g)	Fat (g)	Total carbohydrate (g)	Dietary Fibre (g)	Available carbohydrate (g)
Control Cookie	3	90	3.4	10.5	50.2	0.2	50
Fibersym cookie	3	100	3.4	10.5	60.2	10.2	50

** Once the cookies are baked they will be sent out for macronutrient analysis and the final weight of the cookies fed will be adjusted accordingly.*

4.4 Standard Evening meal

All subjects will be asked to consume a standard evening meal which will be provided by GI Labs and consist of a frozen dinner, eg Stouffers Teriyaki Chicken bowl

4.5 GI Tolerability

GI tolerability will be assessed using a Physical Comfort Questionnaire (Appendix 2). Subjects will be asked to complete the Questionnaire before they start consuming the test food and every day during the 3 day pre-feeding period. During the test day, they will fill it out before consuming the test breakfast at 0min and again at 2h.

Participants mark either “yes” or “no” after each marker of physical comfort. If they mark “yes” they are instructed to rate the severity of the side-effect on a 100 mm VAS and to provide any comments they feel are necessary. The physical comfort scale includes bloating, belching, diarrhea, flatulence, nausea, headache, and a category for “other”. In the “other” category, participants will be asked to specify what they mean by “other” and rate the severity using the 100 mm line.

4.6 Satiety

Subjective measurements of palatability, motivation to eat and physical comfort will be assessed using visual analog scales (VAS) (Appendix 3) at the same time points blood samples are collected. Each of the questions on the VAS is a 100 mm line anchored at each end with opposing statements (Rogers and Blundell 1979). For instance, fullness is assessed with the following statement on the left side of the line “not full at all” with the following statement to the right side of the line “As full as I

have ever felt". Participants make a vertical mark on the line at a point that they felt reflects their feelings at the moment the test was taken. Scores will be assessed by measuring the distance between the intersection of the mark on the line and the left end of the line (see Appendix 3).

The Motivation to Eat questionnaire includes 4 questions:

Q1: How strong is your desire to eat? ("very weak" to "very strong")

Q2: How hungry do you feel? ("not hungry at all" to "as hungry as I have ever felt")

Q3: How full do you feel? ("not full at all" to "as full as I have ever felt")

Q4: How much do you think you could eat now? ("nothing at all" to "a large amount")

Average appetite score is calculated as a summary measure using the following equation:

$$\text{Average appetite} = [Q1 + Q2 + Q4 + (100 - Q3)]\ 4$$

Since Question 3 assesses fullness, it has opposite anchors at each end of the 100 mm line compared to the other 3 questions. Therefore, Q3 is subtracted from 100 in the equation to adjust for this difference.

4.7 Randomization

Eligible subjects will be randomized using an online randomization calculator. Orders will be assigned to subjects in the order they attend the first visit after being recruited.

4.8 Subject Recruitment

Participants will be recruited from the pool of participants at GI Laboratories who have indicated that they are willing to be contacted and asked if they wish to participate in new studies or through online advertisements and posters.

4.9 Selection of participants

The procedure for obtaining informed consent is described in Section 7.1. Volunteers who consent to participate will come to the research centre for a pre-selection visit when subject eligibility will be determined.

4.10 Biochemical Analysis *(note the biochemical analysis method for glucose analysis may change)*

Blood collection tubes will be labeled with the subject's ID, visit date, test meal code, GI Labs protocol number (GIL-1852) and time of collection. After blood collection the tubes containing blood for glucose analysis will be rotated to mix the blood with the anti-coagulant and then placed in a refrigerator until the last blood sample in the set has been collected; after 3 hours the set of 10 tubes will be bundled together with a rubber band and placed in a -20°C freezer until analysis which will be performed within 3 days. Glucose analysis will be performed within 5 days using either the Vitros 350 Chemistry System (Vitros 350 Chemistry System, Ortho Clinical Diagnostics, Raritan, NJ) or a YSI 2300 Stat glucose/lactate analyser (YSI, Inc. Yellow Springs, OH). Analytical coefficient of variation (CV) for

glucose will be calculated by measuring the 0min sample 2 times; typical values range for analytical CV for glucose in our hands is <2%.

The microvette tubes containing blood for insulin will be left a room temperature to allow the blood to clot, centrifuged and the serum transferred to labeled polypropylene tubes and stored at -20°C prior to analysis of insulin. Insulin levels will be measured using the Human Insulin EIA Kit (Alpco Diagnostics, catalog # 80-INSHU-E10.1ii). The typical CV for serum insulin in our hands is about 7%.

5. Data Analysis

5.1 Calculations

The incremental areas under the blood glucose and serum insulin response curves (iAUC), ignoring area below fasting, will be calculated using the trapezoid rule (Wolever et al, 1986, 2004). Fasting glucose and insulin will be taken to be the mean of the concentrations in the 2 fasting samples.
GI symptoms and Satiety calculations – to be added

5.2 Statistical Analysis

No interim analyses are planned. All summaries of demographics, baseline characteristics, efficacy and safety will be performed after all subjects complete both periods and the data collection and query processes are finalized.

Descriptive Statistics: All continuous data will be summarized by number of subjects assessed, mean, standard deviation (SD), median and range (minimum and maximum values). Demographic and baseline characteristics to be summarized include gender; ethnicity; height (m); weight (kg); body mass index (BMI) (kg/m2) and blood pressure (mmHg).

Data will be analyzed using General Linear Model analysis of variance (GLMANOVA). After demonstration of significant heterogeneity, the individual means will be compared using Tukey's test to adjust for multiple comparisons. The criterion for statistical significance will be a 2-tailed $p<0.05$.

6. Study Product

6.1 Blinding, Packaging and Labelling

The product label will display the subject number, subject initials, product ID, ingredients statement, GIL repacked date, expiration date, researcher name and telephone number, investigational use statement, and allergy warnings (if needed). Study Product Intake Logs will be completed upon dispensation of study product to each subject.

6.2 Dispensing

It is the responsibility of the Investigator or his designee to ensure that study product is only provided to study participants. The specific serving size for each product will be provided to each subject.

7. Ethical Issues

7.1 Informed Consent

The investigator will be responsible for submission of the study to the Western Institutional Research Board. Prior to submission of the application, the sponsor will be given the opportunity to review the application. Submission of the application will only take place if both parties agree. The Western Institutional Review Board® meets all requirements of the US Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS), the Canadian Health Protection Branch (HPB), Canadian Institutes for Health Research (CIHR) and the European Community Guidelines. Participants will not be enrolled into the study until they have had the study procedures explained to them, had a chance to ask questions, and given their voluntary consent by signing the consent form. Participants who do not understand English will not be enrolled.

7.2 Confidentiality

Information from the studies may be submitted to the sponsor for its use, and may be sent to the Canadian Therapeutic Products Directorate (TPD) and to the U.S. Food and Drug Administration (FDA), Department of Health and Human Services and the Western International Review Board® (WIRB®). Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. The results of this research study may be presented at meetings or in publications; however, subject identity will not be disclosed in those presentations.

7.3. Participant Withdrawal Criteria

The Investigator may elect to withdraw the participant from the study or the participant may withdraw from the study at any time. Reasons for withdrawing include, but are not limited to:

- Study product never consumed
- Participant was lost to follow-up
- Participant did not follow study procedures
- Participant elected to withdraw from the study for any reason
- Investigator elected to remove participant from the study for any reason
- Subject takes longer than the specified time to complete the study

In the case of premature withdrawal, all planned assessments for the end of the study visit will be completed. The subject's CRF will be completed including the final assessment. The date and main reason for the premature withdrawal will be clearly documented in the subject's file and written down on the CRF

7.4 Adverse Event Reporting

An adverse event is any symptom, injury, illness, or medical/surgical procedure whether planned or not or whether associated with the study foods or not. Adverse events will be assessed at each visit and recorded in the Case Report Forms. Adverse events will be evaluated for duration, severity, seriousness, and causal relationship to the food items provided in the study by the study physician who will decide if any action is required and provide referral, treatment, and/or follow-up as appropriate until resolved, judged to no longer be clinically significant, or if a chronic condition, until fully characterized. Research staff will record the final outcome and resolution date of the event wherever possible. The action taken and the outcome will be recorded in the Case Report Form.

- It is anticipated that participants enrolled in the study will be clinically managed without the need to add medications or to change the dosage(s) assigned to their current medications. In the event that additional medication is required, or an increase in their medication dosage is warranted, these changes will be recorded as adverse events.

- Investigators are required to report adverse events that fit the following criteria within 10 working days of the time the investigator becomes aware of them:

- Event is Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, or the Investigator Brochure; and (b) the characteristics of the subject population being studied.
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

If the adverse event is clearly not related to the study drug, device, procedures, or washout process, it would not represent a risk to other subjects in the research or a “problem” for the study and, therefore, does not have to be reported to WIRB.

The Principal Investigator, Dr. Thomas Wolever, will be informed within 48 hrs of the nature of the reportable AE and the treatment allocation of the participant in whom it occurred by sending a copy of the AE report via email (thomas.wolever@utoronto.ca).

7.5 Risks

No adverse events related to ingestion of the RS4 tested in this study have been reported. However, there may be rare occurrences of study product intolerance, as manifested by gastrointestinal symptoms (such as crampy gas, bloating, or watery stools), eczema, rashes, or other signs of allergy.

7.6 Dispensing

It is the responsibility of the Investigator or his designee to ensure that study product is only provided to study participants.

7.7 Source documents and archiving

All documents relating to the study will be kept by the investigator: the original informed consent form, source documents, copy of the CRF, copy of the accountability of products administered, copy of the WIRB (ethics committee) approval and correspondence with the partner. The investigator will authorize direct access to the source documents during monitoring. As required by Canadian law, documents will be kept by the investigator for at least 25 years after the closure of the study.

8. Study Management

8.1 Source documents and archiving

All documents relating to the study will be kept by the investigator: the original informed consent form, source documents, copy of the CRF, copy of the accountability of products administered, copy of the WIRB (ethics committee) approval and correspondence with the sponsor.
The investigator will authorize direct access to the source documents during monitoring. As required by Canadian law, documents will be kept by the investigator for at least 25 years after the closure of the study.

9. References

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Appendix 1– Fibersym Nutritional Data

MGP

TECHNICAL DATA

100 Commercial St., Atchison, KS 66002 USA • 800.255.0302 • www.mgpingredients.com

Fibersym® RW

U.S. Patent No. 5855946

Product Description

Fibersym® RW is a resistant wheat starch that typically delivers greater than 85% (d.b.) Total Dietary Fiber (AOAC Method 991.43). **Fibersym® RW** has a low water-holding capacity that allows for enhanced crispness and ease in formulating higher levels of inclusion to achieve labeling benefits. Providing a smooth texture, neutral flavor and white color, **Fibersym® RW** is a nearly invisible source of fiber. **Applications include bakery products, pasta and nutritional food products to boost fiber content, snack foods and batter products to enhance crispness, breakfast cereals to increase bowl life and maintain crispness, and nutritional products targeting controlled glucose release.**

Property	Typical Value	Test Method
Total Dietary Fiber	85% min. (dry basis)	AOAC 991.43
Appearance	Fine powder	Visual
Color	White to off-white	Visual
Odor	Bland	Sensory
Moisture*	< 12%	AACC 44-15
pH	4.5 – 6.5	25% Solids
Ash	3.0% maximum	AACC 08-03
Protein, % (N x 5.7 As is)	0.5% maximum	AACC 46-30 Combustion

*The moisture content can vary depending on environmental conditions during storage.

Microbiological		
Aerobic Plate Count	10,000 cfu/g maximum	AOAC 990.12
Mold and Yeast	200 cfu/g maximum	AOAC 997.02
Escherichia coli	< 10 / g	AOAC 991.14
Salmonella spp.	Negative in 375 grams	AOAC 2003.09

Packaging, Storage, and Shelf Life

Fibersym® RW is packaged in multi-ply Kraft bags with a net weight of 50 lbs. (22.7 kg) or 25 kg (55.1 lbs). Various tote sizes and bulk also available. Typical bulk density (packed) is 48 lbs./cubic ft. (769 g/L). The product should be stored in a cool, dry, and sanitary area to achieve maximum stability. Shelf life is two (2) years from the date of manufacture when stored under these conditions.

Ingredient Labeling Statement

Modified Wheat Starch. (**Fibersym® RW** is Phosphated distarch phosphate wheat starch with CAS Number 977043-58-5 and INS Number 1413.)

Disclaimer Statement

Total dietary fiber meets the above specification at point of manufacture. Additional processing may affect the fiber content of products containing any resistant starch. Due to the nature of the testing procedure, TDF results may vary between laboratories, and it is crucial to use the temperature of 100°C as specified in the AOAC 991.43 test for best reproducibility. Final fiber content may differ from software-based calculations and it is better determined by testing.

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TECHNICAL DATA

100 Commercial St., Atchison, KS 66002 USA • 800.255.0302 • www.mgpingredients.com

FIBERSYM® RW
TYPICAL NUTRITIONAL DATA

Nutrient Information (per 100 grams)	
Water	10.5
Calories, insoluble fiber subtracted*	39
Protein (grams) (Nx5.7)	0.15
Total Fat by GC (grams)	0.5
Saturated Fat (grams)	0.2
Monounsaturated Fat (grams)	0.04
cis-cis Polyunsaturated Fat (grams)	0.23
trans Fat (grams)	0.00
Carbohydrates (grams) (by calculation)	87.6
Total Dietary Fiber (grams) (as-is) †	80
Soluble Fiber (1g)	
Insoluble Fiber (79g)	
Ash (grams)	1.25
Calcium (milligrams)	21.8
Iron (milligrams)	<1.0
Sodium (milligrams)	308
Cholesterol (milligrams)	<1.0
Potassium (milligrams)	<3.0

Sugars by HPLC (per 100 grams)	
Total Sugar	0.0
Fructose	<0.1
Glucose	<0.1
Sucrose	<0.1
Maltose	<0.1
Lactose	<0.1

Vitamins	
Vitamin D, Total	<1 ug/100g
Vitamin A, Retinol	<100 IU/100g
Vitamin C	1.19 mg/100g

This product is not produced with added sugars.

* Per 21 CFR 101.9(c)(1)(i)(c)

† Note: Total Dietary Fiber on a dry basis (db) is typically > 90%, with a minimum db specification of 85%.

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Approved: DAW
Page 1 of 1

Appendix 2: Physical Comfort Questionnaire

GI Labs	20 Victoria Street, 3rd Floor Toronto ON Canada M5C 2N8 Tel 416-861-0506 www.gilabs.com	SUBJECTIVE PHYSICAL COMFORT
Subject Initials	Subject Number	GIL #

Test Meal _____ Date: Time _____

(dd/mm/yyyy)

Symptoms	*SEVERITY*	*Comment*
Bloating	Low _____ High	
Belching	Low _____ High	
Nausea	Low _____ High	
Diarrhea	Low _____ High	
Flatulence	Low _____ High	
Other (specify) _____	Low _____ High	

Appendix 3: Satiety Questionnaire

HUNGER

How hungry are you?

Not at all hungry _____ Extremely hungry

mm:

FULLNESS

How full are you?

Not at all full _____ Extremely full

mm:

DESIRE TO EAT

How strong is your desire to eat?

Not at all strong _____ Extremely strong

mm:

PROSPECTIVE FOOD CONSUMPTION

How much food do you think you could eat?

None at all _____ A large amount

mm: