# Administration of Gelesis100 with Metformin is Safe and Under Fed Condition its Impact on Metformin Pharmacokinetics is Similar to Food Alone

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## ABSTRACT

### Background:

- Gelesis100 is a novel biocompatible hydrogel being developed for weight loss in overweight and obese subjects with or without type 2 diabetes. The Gelesis100 particles hydrate in the stomach and mix homogenously with ingested foods, creating a larger volume with a higher elasticity and viscosity of the stomach and small intestine contents. This study was undertaken to assess the effect of Gelesis100 on the bioavailability of metformin under fasting and fed conditions.

### Methods:

- Metformin hydrochloride 850 mg (immediate release tablet) was administered to 24 overweight and obese male and female subjects under fasting and fed conditions, with or without prior (30 min) oral administration of Gelesis100 2.25 g (capsule), in an open-label, cross-over fashion. Pharmacokinetic (PK) analyses of metformin including peak concentration ($C_{max}$), peak time ($T_{max}$), and extent of exposure (area under the curve "AUC") were conducted over 24 h.

### Results:

- When administered with metformin under fasting and fed conditions, Gelesis100 was safe and well tolerated. Under fasting condition, the $C_{max}$ and the AUC of metformin decreased by 37% and 32%, respectively, after prior administration of Gelesis100. Under fed condition, the decreases in the $C_{max}$ and the AUC of metformin caused by food alone were not further affected by prior administration of Gelesis100. The observed decreases in the $C_{max}$ and the AUC were 32% and 18% after food alone, and 34% and 18% after food following prior administration of Gelesis100, respectively. As expected, the $T_{max}$ of metformin was delayed approximately 1 h by food alone. Administration of Gelesis100 had no effect on the $T_{max}$ of metformin.

### Conclusions:

- Administration of Gelesis100 with metformin was safe and well tolerated. Under the fed condition, Gelesis100 affected metformin pharmacokinetics similarly to food alone. Since metformin is typically administered with food, these results demonstrate that Gelesis100 can be used safely for weight loss in metformin-treated type 2 diabetic subjects.

## BACKGROUND

- Obesity is a major predisposing factor for prediabetes, type 2 diabetes, and numerous other comorbidities. The worldwide prevalence of obesity has nearly doubled between 1980 and 2014, according to World Health Organization estimates.[1]
- Concomitant with this rise in obesity, the number of adults with diabetes worldwide has quadrupled since 1980.[2] In fact, 85% of people with type 2 diabetes are overweight or obese.[3]
- Gelesis100 is a novel, oral, non-systemic hydrogel being developed for weight loss in patients who are overweight and have obesity, and those with and without type 2 diabetes.
- Once ingested, individual Gelesis100 particles hydrate in the stomach and homogeneously with food, enhancing the volume, elasticity, and viscosity of the stomach and small intestine contents **(Figure 1)**.
  - Short-term administration of Gelesis100 increases feelings of satiety, and reduces feelings of hunger.[4]
  - Chronic administration during the 12-week First Loss of Weight (FLOW) study demonstrated that Gelesis100 was safe, well tolerated, and associated with significant loss of body weight – especially in subjects with prediabetes.[5]
- Metformin hydrochloride is the most widely-prescribed antidiabetic agent for type 2 diabetes. While it is recommended to be consumed with meals, it is known that food reduces or delays pharmacokinetic (PK) parameters related to drug absorption such as area under the curve (AUC), peak concentration ($C_{max}$), and time to maximal concentration ($T_{max}$).[4]
- Given this, and the non-systemic action of Gelesis100 within the gastrointestinal (GI) tract, the objective of this study was to assess whether prior single administration of Gelesis100 had any effect on metformin PK beyond that of food, or any effect on metformin PK under fasting conditions.


**Figure 1: Ingestion of Gelesis Capsules, and Hydration of Particles**

## SUBJECTS

- 24 healthy males and females who were overweight or had obesity (body mass index 25.0-40.0 kg/m$^2$), no concomitant diseases, no concomitant medication use, and no use of tobacco products within 3 months were enrolled in this study.

## DISCUSSION

- Metformin hydrochloride is the most widely prescribed antidiabetic agent for type 2 diabetes. Patients are instructed to take metformin with food which reduces and delays the absorption of the drug.[6] Prior PK studies of common oral hypoglycemic agents have demonstrated that bioavailability may be reduced 40-50% with co-administration of dietary fibers such as glucomannan or guar gum.[7-8] Gelesis100 shares some properties of dietary fiber (increased viscosity and elasticity of GI contents); however, the observed reductions in metformin $C_{max}$ following Gelesis100 administration were less than for dietary fibers.
- In this acute interaction study, administration of Gelesis100 prior to metformin had no effects on absorption of metformin beyond that of a high-calorie, high-fat meal. The observed 34-37% reductions in ($C_{max}$) following Gelesis100 administration under fed and fasted conditions was less than what has been previously reported following ingestion of some dietary fibers. Part of the reason for this may be due to the fact that upon ingestion, hydrated particles of Gelesis100 form a different structure that mixes homogeneously with food, compared to dietary fibers such as glucomannan which form aggregate structures.[9-10] Further, Gelesis100 particles form a hydrogel that resides exclusively within, and is excreted by, the GI system. Therefore, Gelesis100 is not metabolized by hepatic cytochrome P450 enzymes, and would not be expected to interfere with the metabolism, pharmacodynamics, or excretion of other common antidiabetic agents.
- Most importantly in this acute interaction study, co-administration of Gelesis100 with metformin was safe and well tolerated. Adverse events were mild to moderate, were similar in frequency among single and combination treatment groups, and were not assessed as being probably related to treatment. This observed safety profile is consistent with previous, chronic studies of Gelesis100 [4-5] and support its safe use for weight loss in metformin-treated patients with type 2 diabetes.

## CONCLUSIONS

- Administration of Gelesis100 with metformin was safe and well tolerated.
- Under the fed condition, Gelesis100 did not affect metformin pharmacokinetics differently than food alone.
- Since metformin is typically administered with food, these results demonstrate that Gelesis100 can be used safely for weight loss in metformin-treated patients with type 2 diabetes.

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## METHODS

- This was a single-center, randomized, open-label, 4-arm crossover study.
- Following a 10-h fast, subjects were provided single tablets of 850 mg immediate release metformin hydrochloride (Glucophage, Bristol-Myers Squibb Co, USA) with or without 2.25 g Gelesis100 (carboxymethylcellulose (CMC) cross-linked with citric acid), under fed or fasted conditions according to the treatments shown below in **Table 1**.
- All subjects completed all treatment groups in a sequential, block-randomized fashion (BACD, DCAB, ADBC, or CBDA) and were allowed 7 days of washout between treatments. The total duration of the study was approximately 3 weeks.
- Nineteen venous blood samples (3 mL each) were collected throughout the day starting prior to metformin dosing and ending at 24-h post metformin dosing.
- The following PK parameters related to metformin absorption were calculated by standard non-compartmental methods (Pharsight® Knowledgebase™ Server and WinNonlin®):
  - AUC: area under the concentration-time curve from time zero to the last non-zero metformin concentration calculated using the linear trapezoidal method
  - $C_{max}$: maximum observed metformin concentration
  - $T_{max}$: time to maximal metformin concentration
- Actual sampling time was used for the PK parameters and was calculated as the difference between the actual pre-metformin sampling time and actual post-metformin sampling time.
- Inferential statistics were performed using general linear models (GLM) procedures in SAS®. Analysis of variance (ANOVA) was performed on untransformed $T_{max}$ and on ln-transformed AUC and $C_{max}$ at the alpha level of 0.05. Factors incorporated in the model included: Sequence, Subject(Sequence), Period, and Treatment. Sequence was tested using Subject(Sequence) as the error term.
- Adverse events (AEs) were recorded and evaluated for seriousness, intensity, and relationship to Gelesis100 or metformin.

**Table 1: Metformin, Gelesis100, and Feeding Condition Treatment Assignments**

| Treatment | Metformin[1] | Gelesis100 | Feeding Condition[2] |
|---|---|---|---|
| A | ✓ | | Fasted |
| B | ✓ | ✓ | Fasted |
| C | ✓ | | Fed |
| D | ✓ | ✓ | Fed |

1. Metformin was administered 30 min after Gelesis100 in the fasted condition or after the meal in the fed condition.
2. The meal in the fed condition was high-calorie (800-1000 kcal) and high-fat (50% energy from fat).

## RESULTS

- Demographic characteristics of the 24 study subjects are provided in **Table 2.**

**Table 2. Subject Demographics**

| Demographic Variable | Mean ± SD or N (%) |
|---|---|
| Age | 47 ± 12 |
| Body Weight (kg) | 84 ± 12 |
| Height (cm) | 168 ± 8 |
| BMI (kg/m$^2$) | 30 ± 3 |
| Gender | |
| Female | 12 (50%) |
| Race | |
| White | 22 (92%) |
| Black | 2 (8%) |
| Ethnicity | |
| Hispanic or Latino | 2 (8%) |

## SAFETY AND TOLERABILITY

- When administered with metformin under fasted and fed conditions, Gelesis100 was safe and well tolerated with no serious AEs or unexpected AEs **(Table 3)**. All AEs were mild to moderate in intensity **(Table 4)**, and no AEs were regarded as being probably related to treatment **(Table 5)**.

**Table 3: AEs in Metformin and Metformin + Gelesis100-treated Subjects Under Fasted Fed Conditions**

| | Fasted | | Fed | |
|---|---|---|---|---|
| | Metformin | Metformin + Gelesis100 | Metformin | Metformin + Gelesis100 |
| N | 24 | 23 | 24 | 24 |
| Any AE | 7 (27%) | 3 (11%) | 8 (31%) | 8 (31%) |
| Any SAE | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Most Frequent AEs | | | | |
| Headache | 1 (4%) | 1 (4%) | 3 (11%) | 1 (4%) |
| Loose/soft stools | 2 (8%) | 0 (0%) | 1 (4%) | 1 (4%) |
| Abdominal pain | 2 (8%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Nasopharyngitis | 0 (0%) | 0 (0%) | 2 (8%) | 0 (0%) |

**Table 4: AE Intensity Distribution Between Metformin and Metformin + Gelesis100-Treated Subjects Under Fasted and Fed Conditions**

| | Fasting | | Fed | |
|---|---|---|---|---|
| AE Intensity | Metformin | Metformin + Gelesis100 | Metformin | Metformin + Gelesis100 |
| N | 24 | 24 | 23 | 21 |
| Mild | 6 (23%) | 2 (8%) | 8 (31%) | 8 (31%) |
| Moderate | 1 (4%) | 1 (4%) | 0 (0%) | 0 (0%) |
| Severe | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |

**Table 5: AE Causality Distribution Between Metformin and Metformin + Gelesis100-Treated Subjects Under Fasted and Fed Conditions**

| | Metformin (850 mg) | | | | Gelesis100 (2.25 g) | |
|---|---|---|---|---|---|---|
| | Fasted | | Fed | | Fasted | Fed |
| AE Causality | Without Gelesis100 | With Gelesis100 | Without Gelesis100 | With Gelesis100 | With Metformin | With Metformin |
| Unrelated | 2 (8%) | 2 (8%) | 2 (8%) | 4 (15%) | 2 (8%) | 4 (15%) |
| Remote | 1 (4%) | 0 (0%) | 2 (8%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Possible | 4 (15%) | 1 (4%) | 4 (15%) | 4 (15%) | 1 (4%) | 4 (15%) |
| Probable | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |

## METFORMIN PHARMACOKINETICS

- Pharmacokinetic parameters related to metformin absorption are provided in **Table 6** and **Figure 2**.
- Under the fed condition, the decreases in $C_{max}$ and AUC of metformin were not further affected by prior administration of Gelesis100. The respective decreases in $C_{max}$ were 32% and 34%, and the respective decreases in AUC were 18% and 18% for metformin and metformin plus Gelesis100.
- As expected, $T_{max}$ was delayed approximately 1-h by food alone ($P< 0.001$), and prior administration of Gelesis100 had no additional effect.
- Under the fasted condition, the $C_{max}$ and AUC of metformin were reduced by 37% and 32%, respectively, with prior administration of Gelesis100.

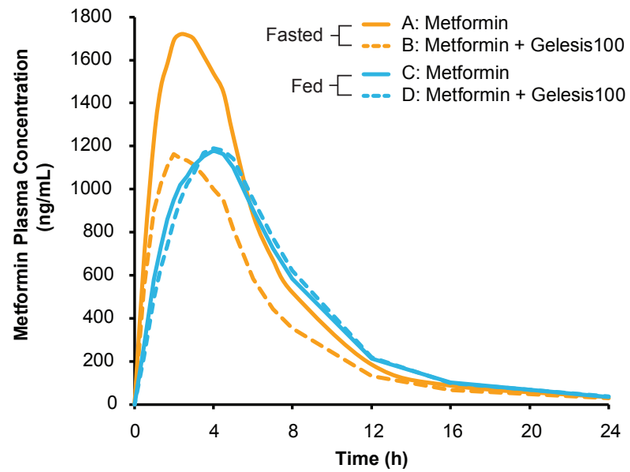


**Figure 2: Metformin Plasma Concentration by Treatment Arm.** Under the Fed Condition, Gelesis100 Had No Effect on Metformin PK Beyond That of Food Alone.

**Table 6: Metformin Pharmacokinetics**

| | Feeding Condition | | | |
|---|---|---|---|---|
| | Fasted | | Fed | |
| | Metformin | Metformin + Gelesis100 | Metformin | Metformin + Gelesis100 |
| N | 24 | 23 | 24 | 24 |
| $T_{max}$ (h) | 2.6 ± 0.8 | 2.3 ± 0.9 | 3.4 ± 1.3 | 3.8 ± 1.0 |
| $C_{max}$ (ng/mL) | 1938 ± 640 | 1228 ± 384 | 1312 ± 269 | 1270 ± 348 |
| AUC (h*ng/mL) | 11764 ± 3780 | 8039 ± 2909 | 9646 ± 2339 | 9679 ± 2615 |