DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 14(7), 925-937 (1988)

A STUDY OF THE EFFECTS OF SUCROSE CONCENTRATION, LACQUER CONCENTRATION AND COATING TIME ON THE FORMULATION OF STABLE AND EFFECTIVE CARBENICILLIN INDANYL SODIUM MICROCAPSULES

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SUMMARY

Carbenicillin indanyl sodium, commonly known as Geocillin[R] (GC), is an orally effective derivative of carbenicillin employed in the treatment of gram negative infections of the urinary tract. GC exhibits an extremely bitter taste which affects patient compliance upon oral dosing (1). A novel coating approach allows Geocillin[R] to be prepared as a suspension for oral administration. GC is available only as a tablet.

Eudragit E100[R] [EE] is a tasteless, acid soluble cationic polymer. Encapsulation of GC with [EE] inhibited its release in the mouth, thus overcoming its bitter taste. Dissolution studies were carried out in simulated gastric fluid and simulated intestinal fluid. Three factors, viz. sucrose concentration, lacquer concentration and coating time were evaluated to arrive at an optimally acceptable formulation.

The formulation containing GC and sucrose in the ratio of 1:3, suspension coated using a 5% w/w lacquer solution for 40 mins. yielded taste free microcapsules with optimal release characteristics.

I. INTRODUCTION

Geocillin (GC), a semi-synthetic penicillin (1), is acid stable and is rapidly absorbed from the G.I. tract (2). GC hydrolyzes in

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vivo to produce carbenicillin and metabolic by-products derived from indanol (3). GC is effective in the treatment of gram-negative urinary tract infections (1, 2, 4).

GC exhibits an extremely bitter taste which affects patient compliance when an aqueous solution is administered orally (1). GC is sparingly soluble in gastric juice, but solubilizes easily in intestinal fluids. Attempts to incorporate GC in stable liquid formulations for peroral administration have not been successful (5). Currently, GC is available as tablets for peroral administration.

Synthetic cationic methacrylate polymer [EE] is soluble in gastric fluid but is insoluble in water. This polymeric lacquer is tasteless, not absorbed from the alimentary tract and is excreted unchanged (6).

Coating of commercially available micronized GC particles with [EE] would serve a twofold purpose; scarce or no release in the mouth overcoming GC's taste and odor, and adequate to complete release in the gastric medium. This was achieved by the encapsulation of GC particles within the coating material using the technique of suspension coating. The resultant coated particles were evaluated for release of GC content in simulated gastric and intestinal fluids. The three variables examined in the process were sucrose concentration, lacquer concentration and coating time. Each variable was studied and evaluated to arrive at an optimally acceptable formulation.

II. EXPERIMENTAL

GC was obtained as a gift from Pfizer, Inc. USA. All analytical grade reagents were used. Simulated gastric as well as simulated intestinal fluids were prepared according to USP/NF specifications. The analytical method reported by Bundgaard and Ilver (9) was employed for determination of GC.

A. Granulation and Coating

One gram of GC was weighed and triturated with the calculated amount of sugar in a glass mortar. Isopropyl alcohol was added dropwise with constant trituration until a mass of suitable consistency was obtained. This mass was passed through a #40 mesh sieve. The resultant granules were collected and air dried in a dessicator for 10-15 mins. until completely dry (constant weight).

The lacquer solution was prepared by dissolving the calculated weight of [EE] in acetone to obtain the required concentration in a tared beaker. The mixture was stirred at constant speed for sufficient time to ensure complete dissolution (~15-30 mins.). The final concentration of the lacquer solution was adjusted by the addition of acetone.

Dry granules, obtained from the granulation described earlier, were suspended in 50 mL of the lacquer solution of known concentration to coat the granules. The suspension coating process was conducted for a predetermined variable time. The suspension was then filtered under suction. The residue (coated granules) was air dried for 90 mins. following which the coated granules were passed through a #40 and #60 mesh sieve. The granules which passed through

a #40 mesh sieve but were retained on a #60 mesh sieve were used for the dissolution studies. These granules were then transferred to tightly closed, light resistant containers and stored in a refrigerator.

B. Content Uniformity Analysis and Dissolution Studies

Following preparation the ganulaes were subjected to content uniformity analysis. Subsequently, they were subjected to dissolution testing employing a beaker stirrer assembly. An accurately weighed sample of coated granules was initially subjected to dissolution in simulated gastric fluid followed by dissolution in intestinal fluid of the undissolved portion at preset time intervals.

III. RESULTS AND DISCUSSION

A. Adjuvant Selection Considerations

Initial investigation for the coating of GC established a need for an adjuvant prior to the coating process partly due the extremely small particle size of commercially available GC. Coating of GC may have been hindered due to the possibility of surface charges present on the micronized particles. Hence, a binder was incorporated to enhance the adhesivity of GC toward the lacquer solution, thus facilitating coating. In addition, the binder would help to increase the particle size. Sugar, with its inherent binding properties, could assist efficiently in increasing the particle size in addition to overcoming the possibility of undesired taste imparted by small amounts of uncoated drug particles.

TABLE I

Formulations Prepared With Varying Amounts of Sugar Using a) 2% w/w Lacquer Solution, and b) 5% w/w Lacquer Solution

Formulations* a	Formulations* b	GC:Sugar	Lacquer Solns. Used (% w/w) a	Lacquer Solns. Used (% w/w) b	Coating Time (min.)
$S_1L_2T_{30}$	$S_1L_5T_{30}$	1:1	2	5	30
$S_2L_2T_{30}$	$S_2L_5T_{30}$	1:2	2	5	30
$S_3L_2T_{30}$	$S_3L_5T_{30}$	1:3	2	5	30
$S_4L_2T_{30}$	$S_4L_5T_{30}$	1:4	2	5	30
$S_5L_2T_{30}$	$S_5L_5T_{30}$	1:5	2	5	30

B. Formulations With Varying Ratios of GC to Sugar

Formulations with increasing ratios of GC:sugar ranging from 1:1 to 1:5 were prepared (Table I). The granulation was coated for 30 minutes by suspension coating using a 2% w/w lacquer solution. The release of GC from each formulation was characterized in simulated gastric and intestinal fluids (Fig. 1). The cumulative amounts of GC released in simulated gastric and intestinal fluids for all batches showed essentially complete release.

With increasing ratios of GC:sugar, the availability of GC in simulated gastric fluid increased markedly. The time to reach a plateau (Tp) also increased from 10 to 20 minutes respectively. However, for the GC:sugar ratio of 1:4, there was no further increase in Tp. Formulations with GC:sugar in ratios of 1:4 and 1:5 showed relatively decreased GC availability in simulated gastric

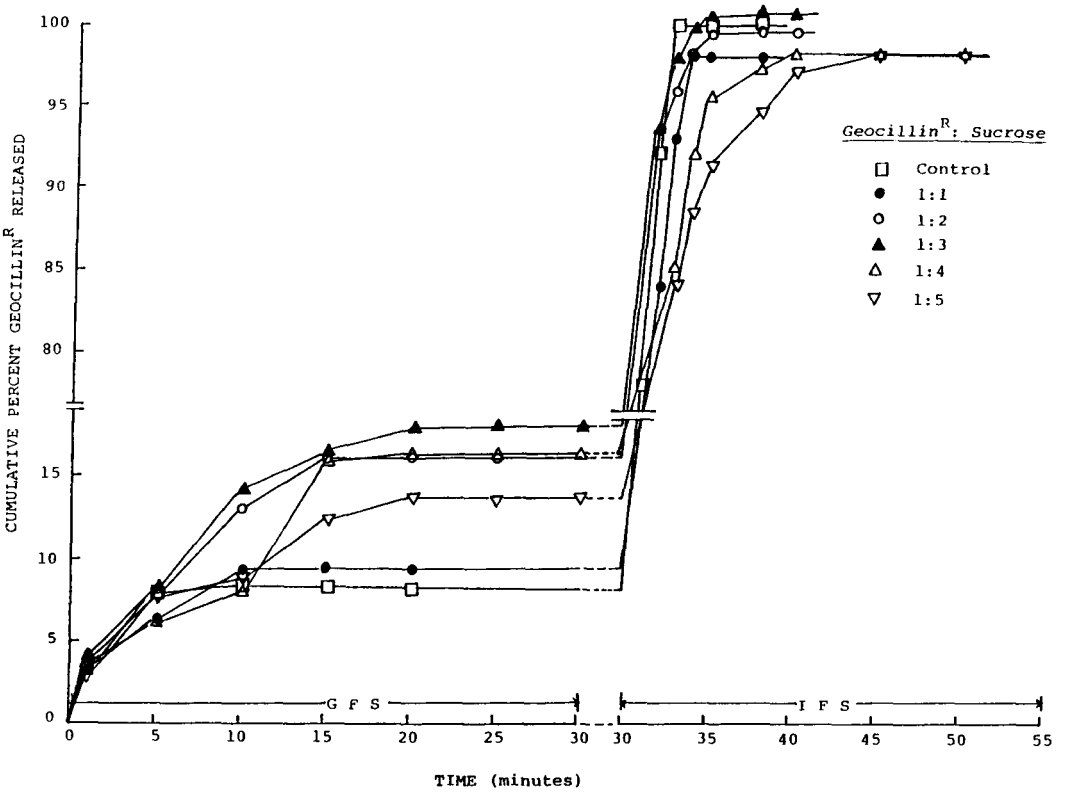

FIGURE 1

Geocillin Release Profile in Simulated Gastric Fluid (GFS) and Simulated Intestinal Fluid (IFS) from Formulations with Varying Amounts of Sucrose Using 2% w/w Lacquer Solution and a coating Time of 30 Minutes

fluid, yet maintained the Tp value. The maximum amounts of GC available in simulated intestinal fluid were relatively comparable. The Tp in simulated intestinal fluid was within 15 mins. for all formulations (Fig. 1). Hence, it can be concluded that the formulation $S_3L_2T_{30}$ exhibited maximum availability in simulated gastric and intestinal fluids within 20 mins. and 5 mins.

TABLE II

Formulations Prepared With GC:Sugar::1:3 and Varying Concentrations of Lacquer Solutions, and Coating Time

Formulations* a	Formulations* b	Lacquer Solns. Used (% w/w) a	Lacquer Solns. Used (% w/w) b	Coating Time (min.) a	Coating Time (min.) b
$S_3L_2T_{30}$	---	2	-	30	-
$S_3L_3T_{30}$	---	3	-	30	-
$S_3L_4T_{30}$	$S_3L_5T_{20}$	4	5	30	20
$S_3L_5T_{30}$	$S_3L_5T_{30}$	5	5	30	30
$S_3L_6T_{30}$	$S_3L_5T_{40}$	6	5	30	40
$S_3L_7T_{30}$	$S_3L_5T_{50}$	7	5	30	50

*Each formulation contains 1 g of GC. Symbols S, L and T represent sugar lacquer and coating time respectively. The subscripts for S, L and T indicate amount of sugar in grams, percent (w/w) lacquer concentration used and coating time in minutes respectively.

respectively. This formulation exhibited optimal characteristics for further investigation.

C. Formulations Utilizing Varying Concentrations of the Lacquer Solution

Formulations with GC:sugar ratio of 1:3 were suspension coated for 30 mins. in lacquer solutions with concentrations of [EE] ranging from from 2% w/w to 7% w/w in acetone (Table II) and subsequently, subjected to dissolution testing.

With increasing lacquer concentrations, maximum dissolution of GC in simulated gastric fluid was achieved within 20 to 25 mins. The total amount of GC released in simulated gastric fluid showed a

slight decline with increasing concentrations of lacquer attributable to the increase in thickness of the lacquer coating. Coated formulations with lacquer concentrations ranging from 2-4 % w/w exhibited a markedly bitter taste. However, formulations with 5-7% w/w lacquer concentrations exhibited no bitter taste.

The maximum dissolution of GC in simulated gastric fluid from formulations coated with lacquer concentrations in the 5-7% w/w range occurred within 25 mins. in each case. Cumulative amounts of GC in simulated gastric and intestinal fluids gave essentially complete release from the microcapsules (Fig. 2) with a Tp value within 25 mins. and 5 mins. respectively.

The formulation $S_3L_5T_{30}$ contained the lowest lacquer concentration in which minimal or no bitter taste was observed. It also provided a dissolution pattern in which a plateau was reached in 25 mins. in simulated gastric fluid followed by complete dissolution of the residue within 5 mins. in simulated intestinal fluid. As a result, formulation $S_3L_5T_{30}$ was selected for the next phase of the investigation.

D. Formulations With Varying Ratios of GC to Sugar at Lacquer Concentrations of 5% w/w in Acetone

The formulation $S_3L_5T_{30}$ was modified by varying sugar concentrations at a fixed lacquer concentration of 5% w/w in acetone (Table I). These formulations were suspension coated for 30 mins. after which they were subjected to dissolution rate determinations.

The formulations with increasing ratios of GC to sugar (1:1-1:3) yielded increasing GC availability to the simulated gastric fluid

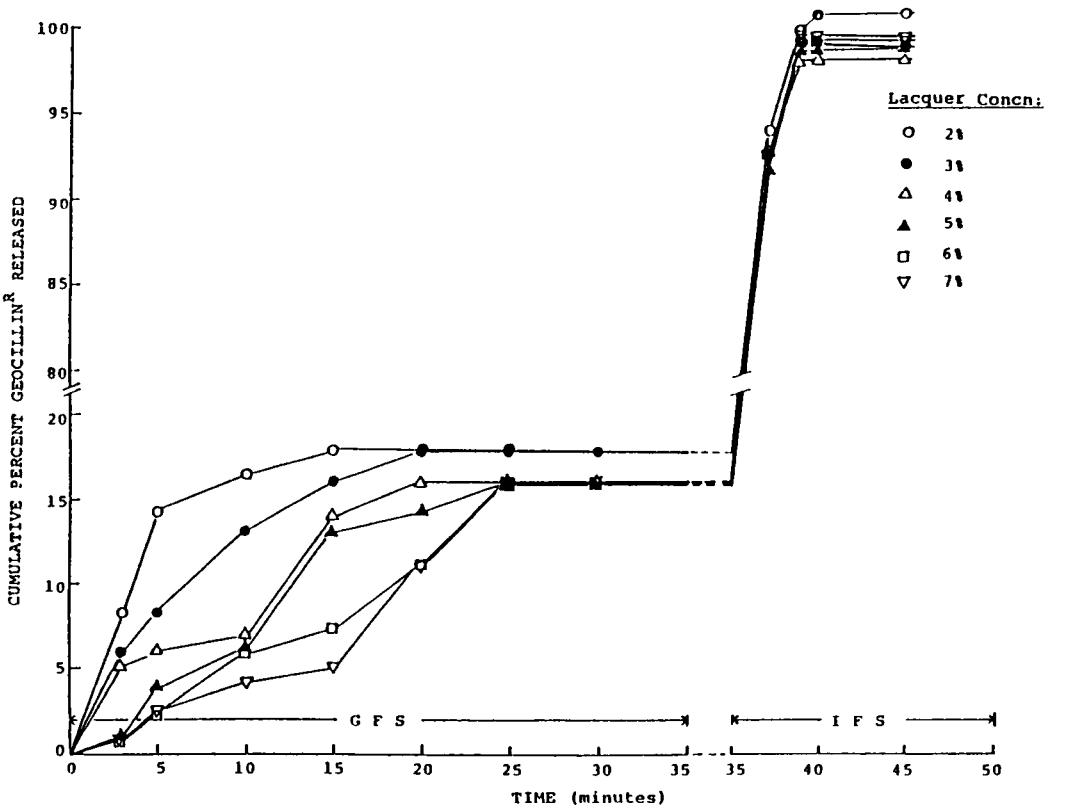

FIGURE 2

Geocillin Release Profile in Simulated Gastric Fluid (GFS) and Simulated Intestinal Fluid (IFS) from Formulations with Varying Lacquer Concentrations Using Geocillin to Sugar Ratio of 1:3 and a Coating Time of 30 Minutes

within 15-25 mins. Formulations with ratios of 1:4 and 1:5, however, yielded lower GC availability within 25 mins. in simulated gastric fluid. The Tp values in simulated gastric and intestinal fluids ranged from 15-25 mins. and 5 mins. respectively (Fig. 3). Total availability of GC to both gastric and intestinal fluids for all formulations was essentially complete. This formulation was then investigated for optimization of coating time.

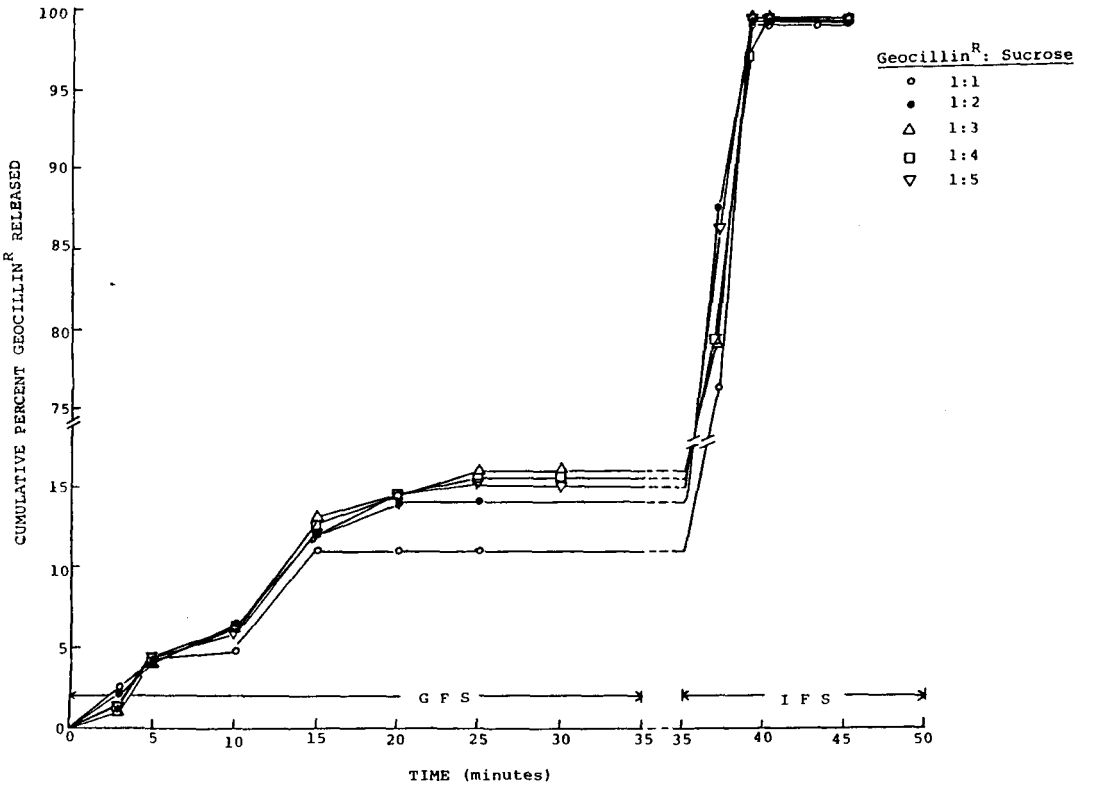

FIGURE 3

Geocillin Release Profile in Simulated Gastric Fluid (GFS) and Simulated Intestinal Fluid (IFS) from Formulations with Varying amounts of Sucrose Using 5% w/w Lacquer Solution and a Coating Time of 30 Minutes

E. Formulations With Varying Coating Time

Formulations were prepared in which the coating time was varied between 20 to 50 mins. using 5% w/w lacquer solution and a GC to sugar ratio of 1:3 (Table II) and subsequently, subjected to dissolution rate studies in both media.

The dissolution studies indicated that the Tp in simulated gastric fluid was within 25 to 30 mins. The maximum amount of GC

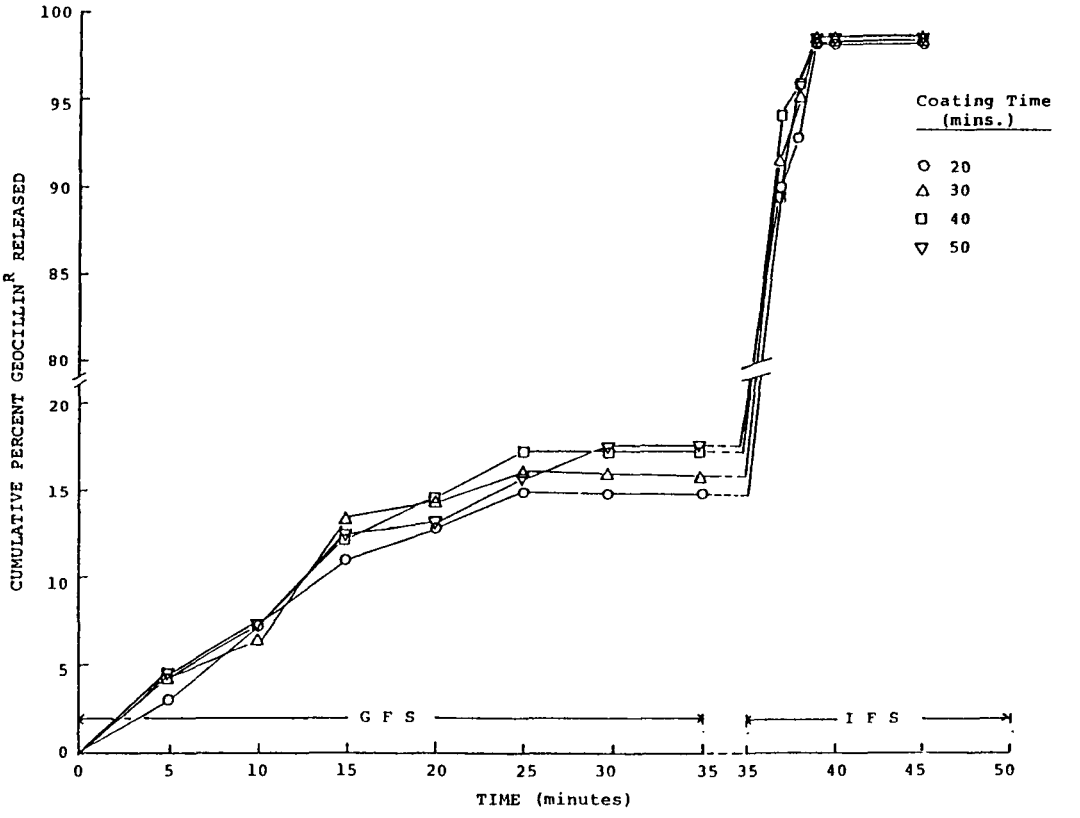

FIGURE 4

Geocillin Release Profile in Simulated Gastric Fluid (GFS) and Simulated Intestinal Fluid (IFS) from Formulations with Varying Coating Times Using Geocillin to Sucrose Ratio of 1:3 and 5% w/w Lacquer Solution

released in simulated gastric fluid increased when the coating time was increased from 20 to 30 mins. However, the formulation with a 20 minute coating time provided bitter tasting granules. When the coating time was increased from 30 to 40 mins., the maximum amount of GC released in simulated gastric fluid was significantly greater (>9%). The granules from both formulations $S_3L_5T_{30}$ and $S_3L_5T_{40}$ were

taste free. The Tp in simulated gastric fluid for both formulations was 25 mins. Increase in the coating time to 50 mins. showed no significant increase (ca. 2% additional) in the maximum amount of GC released in simulated gastric fluid. However, the Tp value increased to 30 mins.

There was no significant difference in the amount of GC released in simulated intestinal fluid for all of the formulations employed in this phase of the investigation. The time to reach plateau in simulated intestinal fluid was 4 mins. for all formulations (Fig. 4). Hence, it can be concluded that a coating time of 40 mins. provides optimal release characteristics. However, a range of 30 to 40 mins. could also be recommended.

IV. CONCLUSIONS

1] Granules composed of commercially available GC powder combined with sucrose by a wet granulation process, using isopropyl alcohol as the volatile binding solvent, provided a uniform and effective group of granules for microencapsulation.

2] Microencapsulation by the process of suspension coating provided an effective coat to mask the bitter taste of GC provided that a minimum thickness of the coat was applied.

3] GC microcapsules coated with [EE] exhibited reproducible and optimal release patterns in simulated gastric and intestinal fluids.

4] Among the various preparations of GC-sugar concentrations employed in this investigation, a ratio of 1 part w/w of GC to 3 parts of sucrose coated with a 5% w/w lacquer solution was deemed the optimal formulation for the taste vs. release rate competing factors.

5] A coating time of 30 to 40 minutes produced microcapsules with optimal taste and release rate characteristics (refer dissolution rate studies).

Finally, it is suggested that a solid in liquid suspension be investigated as a potentially ideal oral dosage form for GC.

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