

## DRUG DELIVERY

## A once-a-month oral contraceptive

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Poor patient adherence to oral contraceptives is the predominant cause of failure of these therapies, leading to unplanned pregnancies that can negatively affect female health worldwide. To improve patient adherence, we developed an oral contraceptive that is administered once a month. Here, we describe the design and report in vivo characterization of a levonorgestrel-releasing gastric resident dosage form in pigs.

## INTRODUCTION

Female contraceptives provide women an autonomous means for spacing pregnancies, controlling family size, and maintaining health (1). Female contraceptives can be used to avoid pregnancies in women whose health can be deleteriously affected by child bearing (2, 3). These interventions enable spacing of pregnancies, which can help support the health of both the infant and the mother. In addition to the benefits to female health, family planning provides women an opportunity to pursue an education and/or employment, generating confidence and economic independence (1). Hence, the impact of female contraceptives on global good cannot be underestimated.

Several methods for hormonal contraception exist including subcutaneous implants, intrauterine devices, vaginal rings, transdermal patches, injectables, and oral pills (4). Implantable devices such as Nexplanon and Implanon are polymeric systems that can provide drug release up to ~3 years, after which they are surgically removed (5, 6). Several intrauterine hormonal devices such as Mirena, Liletta, Kyleena, and Skyla are available, which provide protection for 3 to 6 years (7–10). Injectable formulations such as Depo-Provera contain poorly soluble drug microcrystals that slowly dissolve in extracellular fluid and provide sustained serum concentrations for ~3 months (11). Shorter-term protection (~1 month) can be obtained with vaginal rings (NuvaRing) or transdermal patches (Ortho Evra) (12, 13). Tablets have the shortest duration and need to be taken daily. In addition to these commercial products, several other exciting avenues for providing long-term contraception are being pursued. These include injectable polymeric microparticles made from poly(lactide-co-glycolide) and poly(caprolactone) that release drug by polymer degradation and drug diffusion. In situ-forming drug depots that are made by injecting drug, polymer, and a safe organic solvent

have also been described (14). Last, microneedles are also being developed as a pain-free means of administering long-term contraceptives (15). These technologies underscore the value long-acting contraceptives add to society.

Daily oral pills are favored by a sizeable fraction of the population (16–19), possibly because of their ease of use, opportunity for self-administration, and rapid resumption of fertility upon discontinuation. However, the effectiveness of oral contraception is compromised because of a lack of patient adherence. A multinational survey has revealed that over a 3-month interval, nearly 40 to 50% of women missed at least one dose. A similar percentage of women reported to have taken the medication at the wrong time (19). Consequently, the chance of pregnancy in women using oral contraceptive pills is ~9% per year (20). Hence, there is a need to identify methods of improving adherence in the patient population that prefers oral pills.

Patient adherence to medications can be increased by reducing dosing frequency (21). Adherence to monthly therapies is greater than adherence to weekly and daily therapies (22). Hence, an orally administered long-acting contraceptive could improve patient adherence in the population that prefers pills. Unfortunately, orally administered drug delivery systems have a short gastrointestinal transit time, providing a limited interval for drug delivery. To address this issue, we have developed a gastric resident dosage form that can be placed in a gelatin capsule to enable oral administration. This dosage form, once ingested, expands and resides in the stomach for extended periods (23–25), providing drug release for 3 weeks with a hormone-free period, which would be associated with the recognized breakthrough bleeding that would also serve as a reminder for the next monthly dose. Using this dosage form, we have shown 1- to 2-week-long delivery of anti-infectious disease agents previously (23, 25); however, month-long delivery of contraceptives has yet to be achieved.

## RESULTS

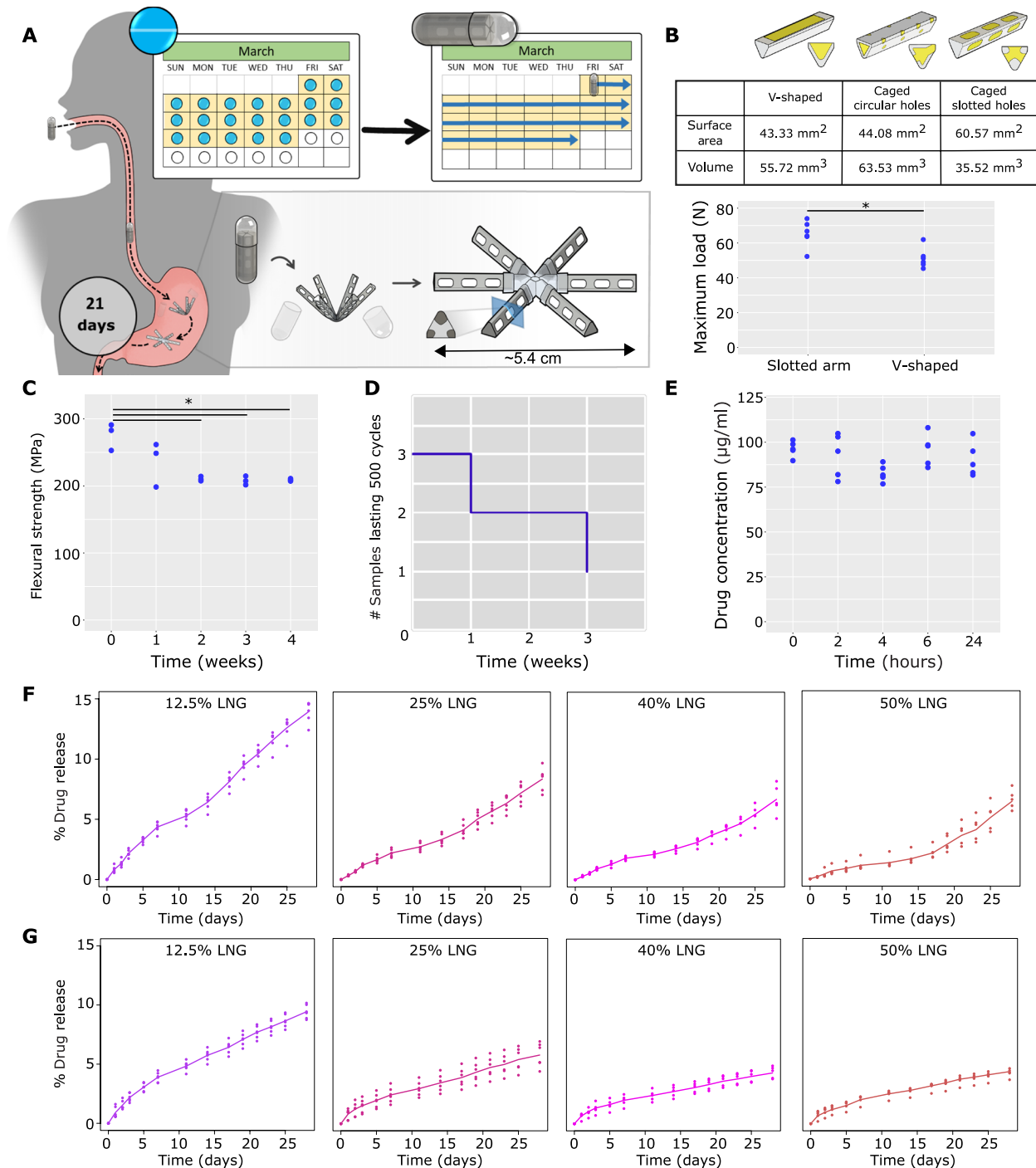
## Dosage form design, mechanical properties, and drug release

A schematic depicting the strategy for month-long contraceptive delivery using a gastric resident dosage form is shown in Fig. 1A. The dosage form consists of six polymeric arms joined by an elastomeric core that allows for folding into a capsule to facilitate oral administration. Upon dissolution of the capsule shell within the stomach, the dosage form recoils and assumes a size larger than that of the pylorus; the span of the dosage form is ~5.4 cm, whereas the diameter of the human pylorus is reported to be ~1.7 to 1.9 cm (26). The arms

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**Fig. 1. Concept and in vitro characterization of an oral, long-acting contraceptive.** (A) Schematic design of the oral gastric resident dosage form. The dosage form can be loaded with levonorgestrel (LNG) and folded into a capsule for ingestion; the dosage form recoils upon dissolution of the capsule in the stomach. (B) Various designs for the arms. The V-shaped arm was used to load drug matrices made of poly(sebacic anhydride). Poly(dimethylsiloxane) (PDMS)-based matrices were loaded in the caged arm. The “slotted arm” design was used because of the higher surface area. The slotted arm design showed higher fracture force than V-shaped arms ( $n = 6$ ;  $*P < 0.05$ , Student’s  $t$  test). (C) Flexural strength of the Sorona 3015G NC010 arms when incubated in simulated gastric fluid (SGF) for 4 weeks, evaluated using a three-point bending test. Circles represent individual measurements.  $*P < 0.05$ , one-way analysis of variance (ANOVA) and post hoc Bonferroni. (D) The interface between Sorona 3015G NC010 (arms) and Elastollan 1185A10 (elastomeric core) polymers was evaluated using a cyclic cantilever test. The number of samples remaining intact after 500 cycles is shown. Three samples were evaluated at each time point. (E) Stability of levonorgestrel in SGF at 37°C evaluated using high-performance liquid chromatography. Circles represent individual measurements ( $n = 5$ ). Release of levonorgestrel from matrices made of (F) poly(sebacic anhydride) and (G) PDMS in SGF over 4 weeks. Drug loading ranged from 12.5 to 50%. Circles represent individual measurements, and the line indicates average drug release ( $n = 5$  to 6).

consist of two parts: an outer sleeve made of a rigid polymer that provides mechanical integrity (structural polymer) and a drug-polymer matrix within the sleeve that releases drug over extended periods (Fig. 1A). The length, width, and height of the arms are 19, 3.5, and 3.2 mm, respectively.

Given the prior use of poly(dimethylsiloxane) (PDMS) in sustained-release products of contraceptives (7), we decided to use PDMS-based polymer matrices for sustained release of levonorgestrel. In addition, we used poly(anhydride)-based matrices previously applied in weekly oral formulation systems (23). Poly(sebacic anhydride)-based matrices were loaded onto arms that had V-shaped grooves in them (Fig. 1B). PDMS matrices slipped out from this arm geometry; hence, two caged geometries were pursued for loading these matrices: one containing circular holes and one containing slotted holes (Fig. 1B). Because of the higher surface area afforded by the slotted holes, we pursued this design further.

We first compared the mechanical properties of V-shaped arms used in our previous design (23) and the caged arms made using a thermoplastic polymer, Sorona 3015G NC010 (Fig. 1B). In a three-point bending test, the caged arms had a significantly higher fracture force than V-shaped arms ( $65.6 \pm 7.5$  N,  $n = 6$  versus  $51.7 \pm 5.8$  N,  $n = 6$ ;  $P < 0.05$ , Student's *t* test).

The dosage form is meant to reside in the stomach for nearly 1 month. We were therefore interested in understanding the mechanical stability of the polymer at low pH. Solid arms made of Sorona 3015G NC010 were placed in simulated gastric fluid (SGF) for various times, and their mechanical strength was analyzed using a three-point bending assay. The flexural strength of the arms was reduced after 2 weeks of incubation in SGF [ $P < 0.05$ , one-way analysis of variance (ANOVA) and post hoc Bonferroni test]. There was a ~25% reduction in flexural stress over 4 weeks ( $276 \pm 20$  MPa versus  $209 \pm 2$  MPa,  $P < 0.05$ , one-way ANOVA and post hoc Bonferroni test) (Fig. 1C). Despite this, the arms retained sufficient rigidity appropriate for incorporation in the dosage forms. We then tested the stability of the interface between the material used to make the central elastomer (Elastollan 1185A10) and the arms of the dosage form (Sorona 3015G NC010) using a cyclic cantilever test. Over a 3-week period, there was progressive weakening of the interface (Fig. 1D). However, one of three interfaces remained stable after the harsh 3-week treatment, and we therefore focused on this combination of materials for prototyping. An image of the gastric retentive dosage form is shown in fig. S1.

The gastric retentive dosage form resides in the stomach and releases drug over extended periods. Hence, stability of the drug at acidic pH is required. We analyzed the stability of levonorgestrel in SGF for 24 hours and observed no significant degradation ( $96.3 \pm 4.3$   $\mu$ g/ml,  $n = 5$  versus  $90.4 \pm 9.6$   $\mu$ g/ml,  $n = 5$ ;  $P = 0.122$ , Student's *t* test) (Fig. 1E).

We then synthesized poly(sebacic anhydride) and PDMS matrices loaded with increasing amounts of levonorgestrel and analyzed drug release in vitro (Fig. 1, F and G). Drug release occurred at a near-constant rate from both matrices, and it was affected by the type of polymer matrix and amount of drug loaded. For both poly(sebacic anhydride) and PDMS matrices, drug release was most rapid at lowest drug loading. For poly(sebacic anhydride) matrices, drug release from the formulation loaded with 12.5% drug was ~1.7-fold higher than that from the formulation loaded with 25% drug ( $13.9 \pm 0.9\%$ ,  $n = 6$  versus  $8.4 \pm 1.0\%$ ,  $n = 6$  over 28 days;  $P < 0.05$ , one-way ANOVA and post hoc Bonferroni). There was no significant difference between

the fraction of drug released from matrices loaded with 40 and 50% drug ( $6.2 \pm 1.1\%$ ,  $n = 5$  versus  $6.4 \pm 0.8\%$ ,  $n = 6$ , over 28 days;  $P = 0.75$ , one-way ANOVA and post hoc Bonferroni). Similar trends were observed for PDMS drug matrices. In general, drug release from PDMS matrices was slower than that from poly(sebacic anhydride) matrices. At a drug loading of 12.5%, there was ~1.5-fold lower drug release from the PDMS formulation as compared to the poly(sebacic anhydride) formulation ( $9.4 \pm 0.6\%$ ,  $n = 6$  versus  $13.9 \pm 0.9\%$ ,  $n = 6$ , over 28 days;  $P < 0.05$ , one-way ANOVA and post hoc Bonferroni). Hence, the rate of drug release could be modified by altering the drug loading and the type of polymer.

### Pharmacokinetics in a large animal model

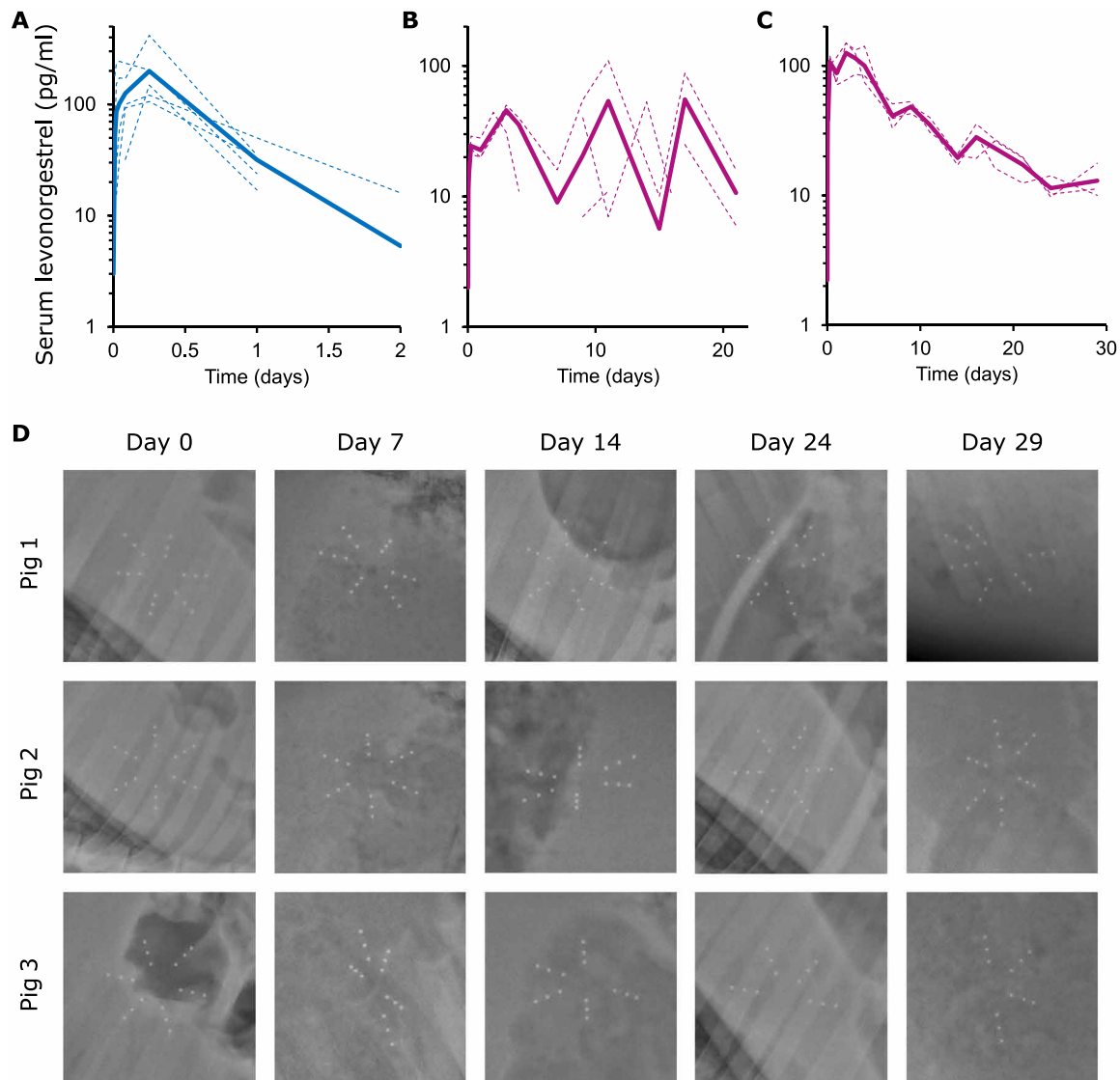
We then analyzed the oral pharmacokinetics of levonorgestrel dosed as an immediate-release tablet (Levora tablets) or in the gastric resident dosage form. The serum concentration of levonorgestrel in pigs treated with Levora tablets is shown in Fig. 2A. The drug was rapidly released and absorbed from the tablets, yielding a maximal serum concentration of  $199 \pm 56$  pg/ml ( $n = 5$ ). In most pigs, the maximum concentration was reached 6 hours after administration. Twenty-four hours after dosing, the average concentration fell to 16% of the maximum concentration ( $32 \pm 6$  pg/ml,  $n = 5$ ), and by 48 hours, the average concentration was reduced to  $5 \pm 4$  pg/ml ( $n = 5$ ). The serum concentrations that we observed in pigs were markedly lower than those observed in humans (27), possibly because of physiological differences between these species.

We then analyzed the pharmacokinetics of levonorgestrel administered using a gastric resident dosage form. We tested two formulations: one loaded with three arms of poly(sebacic anhydride) and three arms of PDMS (long-acting formulation-1; Fig. 2B) and the other containing six arms loaded with PDMS (long-acting formulation-2; Fig. 2C).

Using long-acting formulation-1, we observed a maximal concentration of  $55 \pm 18$  pg/ml ( $n = 3$ ) on day 17 (Fig. 2B). We also observed concentrations of  $45 \pm 2$  pg/ml ( $n = 3$ ) and  $54 \pm 29$  pg/ml ( $n = 3$ ) on days 3 and 11, respectively. In other words, concentrations nearing the maximal concentration were observed at different times during the study, suggesting slow and more prolonged release.

The pharmacokinetics of levonorgestrel when dosed using the long-acting formulation-2 is shown in Fig. 2C. We observed a maximum concentration of  $126 \pm 24$  pg/ml ( $n = 3$ ) on day 2. On day 3 [1 day after time to maximal concentration ( $t_{\max}$ )], the concentration was maintained at 90% of the maximum concentration. In comparison, in the animals treated with the tablet, serum concentration was reduced to 16% of the maximum concentration 1 day after  $t_{\max}$ . We detected drug in serum up to 29 days after administration of long-acting formulation-2, when the average serum concentration was  $13 \pm 2$  pg/ml ( $n = 3$ ). Over the course of the experiment, we observed detectable drug concentrations in all three animals.

A series of x-rays for the three animals treated with long-acting formulation-2 are shown in Fig. 2D. The dosage forms were retained in the stomach for the entirety of the experiment. Two of the possible 18 arms of the three dosage forms were detached and exited the stomach during the study. One arm was lost by day 7 and one by day 24. Although two arms were lost from the dosage form in pig 3, the dosage form was retained in the stomach, and consistent drug concentrations were observed.



**Fig. 2. Oral pharmacokinetics of levonorgestrel tablet and gastric resident dosage form in pigs.** The serum concentrations of levonorgestrel when administered as (A) tablet ( $n=5$ ), (B) long-acting formulation-1 ( $n=3$ ), and (C) long-acting formulation-2 ( $n=3$ ). Dark lines indicate average serum concentrations, and dotted lines show serum concentrations for individual animals. (D) X-ray images showing gastric resident dosage forms containing long-acting formulation-2 loaded with metallic beads as x-ray contrast agent.

## DISCUSSION

Contraceptive drugs provide women a means to space and/or avoid pregnancy, which can support their health and that of their children. To be effective, consistent drug levels must be maintained for prolonged periods, making the efficacy of these drugs dependent on patient adherence. To reduce the onus on the patient, several injectable and implantable long-acting contraceptives have been developed and approved for clinical use. None of these systems are administered via the oral route, which remains the most widely used route of drug administration. Hence, a long-acting contraceptive that can be orally administered would be highly desirable. Here, we report the design and preliminary testing of an oral dosage form that provides month-long delivery of a contraceptive drug, levonorgestrel. This dosage form fits in a 000 capsule to enable oral administration and recoils in the stomach to assume a size larger than the pylorus. This latter property enables the dosage form to reside in the stomach, where it releases levonorgestrel. To develop this platform, several barriers

needed to be overcome. First, the migrating motor complex, intended to remove the contents of the stomach, can break and dislodge the gastric retentive dosage form. Second, the acidic gastric contents may degrade the drug. Last, to achieve consistent serum drug levels, the drug must be released at a near-constant rate in an environment that shows considerable diurnal variations. To address the issue of gastric residence, we chose materials and geometries that were highly durable and evaluated their performance using a series of mechanical tests. To enable protection of drug from the gastric environment and sustained release, we encapsulated the drug in polymer matrices. These formulations released drug by robust mechanisms such as drug diffusion and hydrolysis, enabling us to achieve near zero-order release in vitro and consistent serum concentrations in vivo in a large animal model.

We tested the pharmacokinetics of levonorgestrel delivered using two formulations loaded onto the gastric resident dosage form. The first formulation (long-acting formulation-1) contained half the drug loaded into a PDMS matrix and the other half loaded into a poly(sebacic



anhydride) matrix. The second formulation (long-acting formulation-2) had the entirety of the drug loaded into a PDMS matrix. Formulation-2 produced a peak concentration on day 2, after which concentrations slowly declined throughout the study. In contrast, formulation-1 produced comparable concentrations on days 3, 11, and 17, and changes in serum concentration were not unidirectional. Moreover, formulation-1 produced lower (undetectable at some time points) concentrations than formulation-2. Further pharmacokinetic-pharmacodynamic studies (experiments and/or simulations) evaluating efficacy and safety may aid in identifying lead formulations for clinical translation.

During weekly x-ray imaging of three pigs dosed with one dosage form each, we observed that 2 of the 18 arms detached from the dosage form body within 30 days after ingestion. It is likely that the amount of drug delivered and gastric retention would be adversely affected if more arms were lost or if arms were lost early. Loss of arms at later times during the dosing period, when most of the drug is released, will not affect the efficacy of the system. Choice of materials and manufacturing technique is essential in avoiding disassembly.

For clinical translation, some challenges need to be addressed. Currently, the passage of the dosage form from the stomach is via non-user-controlled mechanisms. Programmed exit of the dosage form from the stomach may be achieved by inclusion of tough materials that disintegrate in the presence of chemical or thermal stimuli (23, 28, 29) and pH-sensitive linkers to maximize safety in the setting of inadvertent transit across the pylorus (23, 25). Passage of the dosage form from the body was not studied here; although pigs are recognized as having gastric anatomy comparable in dimension to humans, transit times are recognized to be slower (25, 30). Intestinal passage time will not be important to serum drug levels if the dosage form has released all of its contents. This can be achieved by decoupling the length of drug release from the residence. For example, longer residence with fixed shorter release times ensures consistent drug dosing across subjects. Future successful human translation will require further development in dogs and humans with a focus on further optimal material selection for retention of the dosage form for the desired period and complete drug release in the prescribed period. Additional studies will be needed to test the contraceptive efficacy of this dosage form, which was not evaluated in these studies.

To overcome the economic and cultural barriers in low-income countries, a long-acting contraceptive should have several key features. We believe that the orally administered long-acting contraceptive described here satisfies several of these considerations. These include (i) opportunity for self-administration, (ii) drug administration by the oral route, (iii) circumvention of the need for clinical procedures for dosage form removal, and (iv) maintenance of privacy. Hence, our technology stands to benefit a large patient population that prefers oral medication or is in regions of the world where self-medication is the only means to chronic therapy.

## MATERIALS AND METHODS

### Study design

The goal of this study was to develop a gastric resident dosage form that can be orally administered, be retained in the stomach for ~1 month, and release the contraceptive drug, levonorgestrel, during this time. The gastric resident dosage form consisted of six arms connected via a central elastomer that allowed for the folding of the dosage form in the capsule and its recoil upon dissolution of the capsule. The arms of the dosage form were loaded with drug-polymer

matrices. In vitro testing was conducted to select optimal materials to advance to the in vivo stage. In vitro characterization included mechanical tests that helped identify materials that could endure the harsh gastric environment and drug release studies that helped in the selection of lead formulations.

Gastric retentive dosage forms were produced using materials and designs identified in our in vitro analysis and tested in a swine model. The swine model was chosen because of its similarity to the human gastrointestinal tract. All animal studies were approved by the Committee on Animal Care at the Massachusetts Institute of Technology. In the swine model, we tested the gastric retention of our dosage form. In addition, we conducted pharmacokinetic studies to compare delivery of levonorgestrel using a commercial tablet and the gastric resident dosage form.

### Manufacturing of gastric resident drug delivery systems

Gastric retentive dosage forms were manufactured as described before (23, 24) with minor changes. The arm casings of the dosage form were manufactured from Sorona 3015G NC010 using a microcompounder and an injection molder as described in the Supplementary Materials. Two geometries were created to allow loading of the PDMS and poly(sebacic anhydride)-based matrices. For poly(sebacic anhydride)-based matrices, a V-shaped groove was created in the Sorona3015G NC010 arms. To achieve this, the injection-molded arms were mounted, with the bottom faced up, to a custom milling fixture on the Othermill computer numerical control (CNC) machine (Bantam Tools, USA) and then milled. The CNC machine was controlled by a computer-aided machine (CAM) code generated from the designs made in SolidWorks CAD software (Dassault Systèmes, France) and HSMWorks CAM software add-on (Autodesk, USA). For loading PDMS matrices, a caged arm structure was used. To create the caged arm structure, the arms were milled using the CNC machine and two custom three-dimensionally printed fixtures. The caged designs were converted into CAM code and used to execute the milling of each side of the arms. The same fixture mentioned above was also used to mill the bottom face, and another fixture was used to mill out the two side faces of the arm. The holes milled into the arms were 1.7 mm by 4.5 mm rectangles.

We then melted Elastollan 1185A10 in the central part of the PDMS negative molds at 245°C. On melting, arms, placed in the peripheral parts of the negative molds, were pushed into the polymer melt to allow for overmolding. Once all the arms were pushed into the melted central polymer, the molds were removed from the oven and cooled to room temperature.

On the next day, polymer matrices [PDMS or poly(sebacic anhydride)] containing 25% levonorgestrel were filled into the cavities of the arm casing of the dosage form. Polymer matrices were prepared in the cavities of the arms using the manufacturing process used for the in vitro studies (described in the Supplementary Materials). Before casting the PDMS matrix, the slotted cage design arms were masked with tape to prevent leakage of the polymer drug. After filling the PDMS matrix and before curing, 1-mm radiopaque steel balls were inserted in each cavity, totaling to 3 in each arm and 18 in total for radiograph monitoring. After curing, the tape mask was removed, and excess polymer drug was cleaned up. We report here pharmacokinetic results of two experiments. In one experiment, three arms were loaded with PDMS-based formulation, and the other three contained poly(sebacic anhydride)-based formulation. In the second experiment, all six arms were loaded with PDMS-based formulations.

### Oral pharmacokinetics of levonorgestrel in pigs

All animal studies were approved by the Committee on Animal Care at the Massachusetts Institute of Technology. We compared the pharmacokinetics of levonorgestrel administered as an immediate-release tablet (Levora, 600 µg of drug per pig) or in sustained-release dosage forms (~33 mg of drug per pig) in female Yorkshire pigs (30 to 80 kg). Pigs were fed daily in the morning and in the evening, with a diet consisting of pellets (Laboratory Mini-Pig Growler Diet, 5081), with a midday snack consisting of various fruits and vegetables.

At the time of dosing, the pigs were sedated with Telazol (5 mg/kg), xylazine (2 mg/kg), and atropine (0.04 mg/kg). An endoscopic overtube was placed into the stomach under esophageal evaluation. The tablets, as received from the manufacturer, were placed into the stomach via the overtube. To administer the gastric resident dosage form, the dosage form was folded into a size 000 gelatin capsule. A size 000 gelatin capsule is 26.1 mm long when closed; the external diameter of the cap and body are 9.9 and 9.1 mm, respectively. The volume of the capsule is 1.37 ml. The gelatin capsule containing the dosage form was administered into the stomach of the pig via the overtube (one dosage form per animal). After treatment administration, the overtube was carefully removed. At various times, blood was drawn from the mammary vein and transferred to a BD Vacutainer serum separator tubes (Becton, Dickinson and Co.). The tubes were centrifuged (3202g, 10 min, 4°C), and the serum was collected and stored at -80°C until further analysis. Animals were radiographed under sedation at various time points.

Levonorgestrel was measured in 0.4 ml of serum by a highly specific and sensitive competitive enzyme immunoassay using reagents from Arbor Assays. Before its quantitation, levonorgestrel was extracted twice with 3.5 ml of hexane:ethyl acetate (3:2) to remove water-soluble conjugated levonorgestrel metabolites. After evaporating the organic solvents, the extracts were reconstituted in 0.3 ml of assay buffer, and 0.1 ml was transferred to a microtiter plate coated with goat anti-rabbit immunoglobulin G. Quality control samples were treated in the same manner. To generate a standard curve for the assay, different concentrations of levonorgestrel in assay buffer, ranging from 0.625 to 20 pg in 0.1 ml, were prepared and added to the plate. After adding the levonorgestrel antibody and a levonorgestrel peroxidase conjugate, the microtiter plate was shaken for 1 hour at room temperature. The contents of each well were then aspirated, and the wells were washed with buffer. This was followed by the addition of the substrate, a 30-min incubation, and the addition of a stop solution. The optical density generated from each well was read in a plate reader at 450 nm. Appropriate software was used to calculate the levonorgestrel concentration in each sample. The values were then corrected for procedural loss (11%), which was previously determined in independent serum samples using tritiated levonorgestrel. The assay sensitivity was 6 pg/ml, and the interassay coefficient of variation was 9.5, 5.5, and 7.9% at levonorgestrel concentrations of 0.38, 2.83, and 8.02 ng/ml, respectively ( $n = 13$ ).

### Statistical analyses

For all experimentation producing continuous data, individual data points are plotted. For drug release studies (Fig. 1, F and G), individual data points are shown, and a line is plotted to show average drug release. For pharmacokinetic studies (Fig. 2, A to C), serum drug concentrations for each animal are shown as dotted lines, and the average serum drug concentrations are shown as the hard line. To determine whether differences between two groups were statistically

significant, Student's  $t$  test was used. One-way ANOVA and post hoc Bonferroni was used for multiple comparisons.  $P$  value of less than 0.05 was considered statistically significant. Sample size, type of statistical test, and outcome of the test are provided at each occasion.

### SUPPLEMENTARY MATERIALS

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Materials and Methods

Fig. S1. Image of gastric resident dosage form.

Reference (31)

[View/request a protocol for this paper from Bio-protocol.](#)

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# Science Translational Medicine

## A once-a-month oral contraceptive

Ameya R. Kirtane, Tiffany Hua, Alison Hayward, Ambika Bajpayee, Aniket Wahane, Aaron Lopes, Taylor Bense, Lihong Ma, Frank Z. Stanczyk, Sierra Brooks, Declan Gwynne, Jacob Wainer, Joy Collins, Siddartha M. Tamang, Robert Langer and Giovanni Traverso

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### When less is more

Reducing the frequency at which a patient must take a medication can improve patient adherence. Kirtane *et al.* developed an ingestible gastric resident dosage form that releases the contraceptive levonorgestrel. Levonorgestrel was detected in the serum of pigs for 1 month after oral administration of a single dose. These preliminary results demonstrate progress that is an easy pill to swallow.

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