

[Home](#) > Oral-Absorption-Enhancing Drug-Delivery Technology

## Oral-Absorption-Enhancing Drug-Delivery Technology

The authors examine an oral-absorption-enhancement technology based on surface-active materials to increase apical membrane fluidity *in vitro*.

Apr 01, 2011

By [John S. Fox](#) [1], [Thomas W. Leonard](#) [2], [Edwin G. Walsh](#) [3]

Pharmaceutical Technology

Volume 35

Intestinal-absorption enhancers to improve the oral delivery of poorly permeable drug compounds have been studied since the 1960s. The approaches taken to increase absorption of these types of compounds have varied considerably in the years since Windsor et al. demonstrated that ethylenediaminetetraacetic acid increased absorption of heparin in rats and dogs (1). Strategies have included using surface-active agents, such as surfactants, steroidal detergents, acylcarnitines, and alkanoylcholines, liposomes, mucoadhesive polymers, prodrug modification, nano- and microparticles, modifications of known bacterial intestinal toxins, *n*-acetylated  $\alpha$ -amino acids and *n*-acetylated non- $\alpha$ -amino acids, ultrasound, iontophoresis, and bioadhesive intestinal patches.



SEAN RUSSEL

Several factors have inhibited the commercial development of technologies to improve bioavailability. Concerns include toxicity, the preservation of epithelial barrier function, inter- and intra-subject variability, and the ability to deliver adequate therapeutic levels over a sustained period. Other concerns are the requirement for large amounts of expensive active payloads, the lack of reliable and predictive animal models, and the inability to incorporate the enhancer technology into practical, stable, and reproducible solid-dose formulations amenable to commercial scale manufacturing.

### Oral absorption enhancement technology

GIPET (a registered trademark of Merrion Pharmaceuticals) is an oral-absorption-enhancement technology platform that has advanced to clinical evaluation. This enhancer system has increased the oral bioavailability of several types of low-permeability compounds safely in man. Although absorption-enhancement technology focuses primarily on low-permeability drugs, it also can improve the bioavailability of some moderately permeable drug compounds, thus resulting in lower intra- and inter-subject variation and improved pharmacokinetic (PK) profiles.

Significant technical hurdles exist when formulating with enhancer systems. Co-release of the promoter and the active compound at appropriate relative concentrations adjacent to the epithelium of the small intestine is necessary to generate sufficiently mixed micelles to increase absorption. The GIPET technology consists of three formats containing surface-active materials to achieve absorption in the small intestine. The first format, GIPET I, is an enteric-coated tablet consisting of the surface-active materials in powder form combined with a drug in select ratios by weight. The second, GIPET II, consists of microemulsions of oil and surfactant with a drug in an enteric-coated gel capsule (hard or soft). The third format, GIPET III, consists of a mixture of fatty-acid derivatives in an enteric-coated gel capsule. All three GIPET platforms have been tested in humans. The *in vivo* results for all three formats show that the technology platform is suitable for oral delivery of a wide range of molecule classes.

**Barriers to intestinal absorption.** There are many gastrointestinal (GI) tract barriers to the absorption of small hydrophilic and macromolecules, including peptides and proteins. These barriers include the low pH in the stomach and the enzymatic milieu of the stomach and small intestine, both of which may result in the degradation of the compound before it reaches the wall of the GI tract. If the compound survives these conditions, it moves to the diffusion barriers of the mucus gel layer, consisting of an unstirred water layer and a layer produced by a mixture of sloughed-off epithelial cells and GI fluids.

The diffusion barriers discriminate on the basis of lipophilicity and charge. Once through these diffusion barriers, the compound must pass through the epithelial cell layer lining the gut wall. The tight junctions (TJ) between cells of this layer form a barrier to the uncontrolled absorption of noxious luminal xenobiotics (i.e., the gate function), and maintain epithelial polarity (i.e., the fence function). The pore radius of the TJ (ranging from 3 to 11 Å depending on the region of the GI tract) prevents the passage of molecules with molecular weights in excess of approximately 500 Da. Small hydrophilic molecules may alternatively pass through the cell monolayer via carrier-mediated transporters on the apical membrane as an alternative to low-capacity paracellular flux *via* tight junctions. Only relatively lipophilic molecules diffuse through the cell membrane to pass transcellularly into the systemic circulation. Transcellular migration across the intestinal epithelial monolayer does not represent an unrestricted passageway for a molecule because it faces potential metabolism within the cell (i.e., primary metabolism by Cytochrome P450), or it may be ejected back out to the luminal surface by efflux pumps, including the permeability glycoprotein (P-glycoprotein) and breast-cancer-resistant proteins. Absorption *via* the small-intestine blood supply means that the drug will go to the liver *via* the hepatic portal vein, where it may be metabolized (i.e., the first-pass effect) and eliminated from the body. Overcoming these barriers requires specialized technology to produce safe and effective oral delivery.

### GIPET technology platform

**Product-development process.** The *in vitro/in situ* studies on absorption enhancers typically are performed using cell monolayers, isolated tissue, or perfused rodent-intestinal segments using mixed solutions of the enhancer and test compound. Although such studies may produce useful data to compare compounds, they are not

helpful in developing effective clinical dosage forms. Thus, *in vivo* studies in an appropriate species are needed to confirm the effects of enhancers in a drug-product formulation.

In working with the GIPET platform, Merriam Pharmaceuticals uses a preclinical animal model to produce reliable and predictive data to evaluate candidate compounds and suitable enhancers to take into the clinic. In the product-development pathway, cannulated beagle dogs are used for duodenal instillation to evaluate the effectiveness of GIPET systems to enhance specific drug products and GIPET enhancers. The specific steps are as follows:

- Proof of concept: The active pharmaceutical ingredient (API) is evaluated in solution versus various formulations of the API and enhancer in solution
- Formulation development: The emphasis is on optimizing dissolution and confirming stability
- Phase I/II trials: Human PK and pharmacodynamic (PD) data are generated to match oral availability, biomarker, or clinical endpoints
- Phase III development: The focus of the Phase III program is to develop an appropriate abbreviated new drug application package to be filed under Sec. 505 (b)(2).

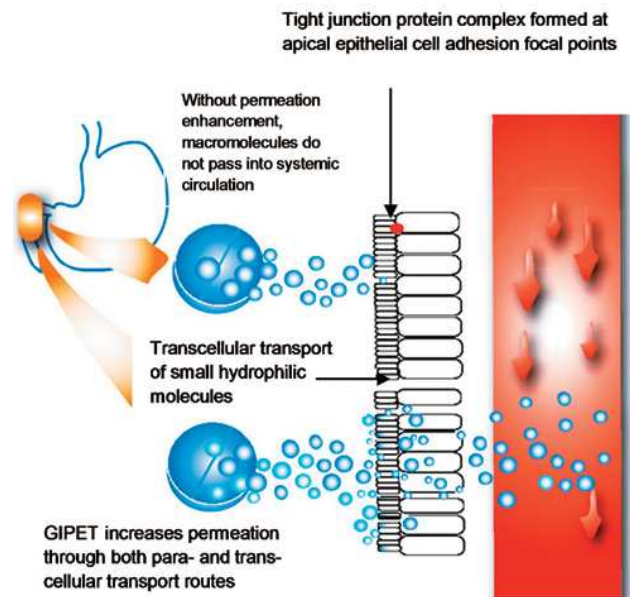


Figure 1: Barriers to the intestinal absorption of hydrophilic and/or macromolecular compounds.

This model is designed to mimic human intestinal handling of the enteric-coated GIPET dosage form and the co-release of the drug and permeation enhancer in the duodenum and jejunum (see Figure 1). Delivery to the same site *via* the duodenal cannula decreases variability, thus increasing the sensitivity of the model and enabling accurate projections of drug/enhancer combinations and dose ranges for evaluation in clinical studies. Use of a larger species enables multiple PK samples to be taken from the same animal for each test formulation and for multiple test formulations for evaluation in the same group of animals, which also increases the power of discrimination between systems. The GIPET technology platform uses conventional

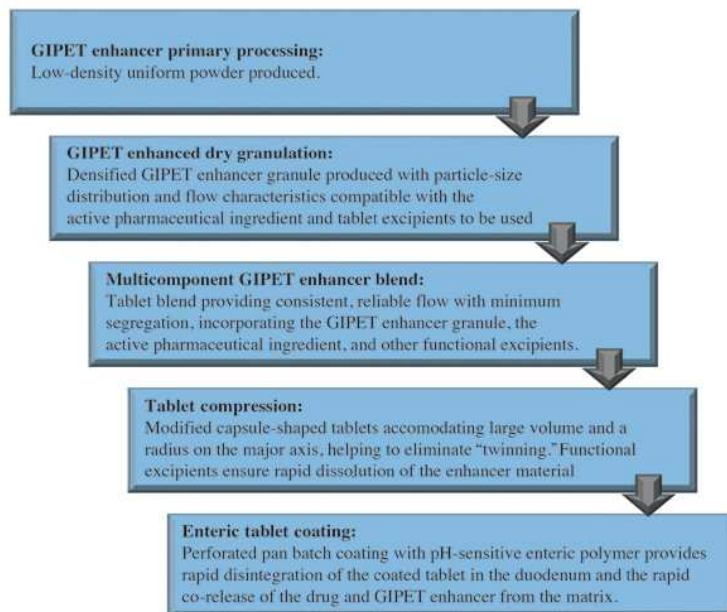


Figure 2: GIPET (Merriam Pharmaceuticals) manufacturing process.

solid oral dosage manufacturing equipment to allow for efficient technology transfer, scale-up, and use of high throughput equipment. The GIPET I technology produces a compressible powder form (see Figure 2), which can be blended, compressed, and coated as per conventional tablet excipients, thereby allowing for many formulation-development options with various molecule types. A legitimate concern with intestinal

**Mechanism of action.** GIPET enhancers are surface-active materials and can act as mild surfactants, thereby increasing apical membrane fluidity *in vitro* and increasing the transcellular transport of normally excluded molecules. *In vitro*, they also have been shown to increase the paracellular transport route by contracting cytoskeletal actin filaments, which results in the opening of the TJ, thereby allowing for increased permeation of hydrophilic compounds (2, 3). GIPET materials form mixed micelle vesicular structures above their critical micelle concentration. At higher concentrations (i.e., their critical vesicle concentration), they form multilamellar micelle structures, also known as liquid crystals (4). Micelles and vesicles are dynamic structures, constantly forming and reforming under the influence of the changing environment of the intestine. It is probable that the active compound is entrapped within these mixed micelle structures via physical or electrochemical interaction. As a result of the intimate mix and co-release of the enhancer and drug from these systems, the latter may exhibit more lipophilic properties, thereby enabling larger or more highly charged molecules to cross the membrane. Incorporation into such structures also protects drug molecules prone to enzymatic degradation. GIPET enhancers also may inhibit efflux pumps (5).

Irrespective of the route of transport across the epithelial monolayer, maintaining concentrations of GIPET at the gut wall above the critical micelle concentration for longer time periods results in greater drug absorption. As a result, the drug payload and enhancer must be co-released at the target region of absorption in sufficient quantities to achieve therapeutically relevant systemic availability. GIPET achieves this condition by using enteric-coated tablets (GIPET I) or gelatin capsules (GIPET II and III) to synchronize release of drug and enhancer.

**Safety studies.** The enhancer excipients used in GIPET were developed due to their known safety as approved food additives. Several regulatory bodies have reviewed the data on safety and concluded that the materials in GIPET formulations have low toxicity potential (6). Phase I and II studies showed that exposures could be given safely on a repeated basis.

**Table I: Timing of effect of GIPET I on human intestinal permeability using urinary excretion of polar sugars as a surrogate marker.**

Group	LMER (CV)	N	Statistics
A. Sugars	0.02 + 0.01 (66.3)	24	-
B. GIPET I 20 min before sugars	0.03 + 0.01 (70.4) *	22	P < 0.01
C. GIPET I 40 min before sugars	0.02 + 0.01 (38.9)	22	NS
D. GIPET I 60 min before sugars	0.02 + 0.01 (31.9)	23	NS
E. Sugars	0.02 + 0.00 (29.5)	22	NS

LMER is lactulose-to-mannitol urinary excretion ratio. CV = Coefficient of variation. GIPET is a registered trademark of Merrion Pharmaceuticals. Treatments were 0.5 g GIPET I in a 15-mL solution administered via perfusion tube to the jejunum in the presence and absence of 2 g mannitol/5 g lactulose /9 g glycerol administered as 100-mL solution orally at different time intervals. Statistical significance was assessed by a paired t-test against group A. Group B was statistically different from baseline if two high responding outliers were removed from the analysis. NS is not significant. Data supplied by Dr. S.J. Warrington, Hammersmith Medicines Research, Hammersmith Hospital, London, UK.

Table I: Timing of effect of GIPET I on human intestinal permeability using urinary excretion of polar sugars as a surrogate marker.

absorption-promoting technologies is the impact on general intestinal permeability. Although the clinical experience thus far has not suggested that this concern is an issue *in vivo*, intestinal-permeability studies were carried out in human subjects after intrajejunal administration of GIPET I, followed by tracer molecules with low oral absorption largely restricted to the paracellular route. The aim was to establish intestinal permeability recovery time in the presence of typical components of a GIPET formulation. The polar sugar, mannitol (molecular weight of 182.17 g/mol), is absorbed paracellularly across the gut and is excreted unchanged in the urine. Oral bioavailability of mannitol is approximately 25%, and this amount appears in the urine because it is freely filtered and not reabsorbed by renal tubules. Another polar disaccharide sugar, lactulose (molecular weight of 342.30 g/mol), also is absorbed paracellularly, but only to a level of 1% due to its larger molecular radius. The ratio of the urinary excretion is a well-established noninvasive indicator of human intestinal paracellular permeability *in vivo* (7). When the intestinal barrier function is compromised, the urinary lactulose-to-mannitol excretion ratio (LMER) increases because lactulose absorption is preferentially increased. In an open-label, partially randomized study using up to 24 human subjects, the marker molecules were given orally at 20, 40, or 60 min following intrajejunal instillation of GIPET I. The combined data showed that only when the sugars were administered 20 min after the fatty acid, the urinary LMER ratio increased (see Table I). Therefore, in subjects receiving three separate doses of GIPET I, the effect of the agent on intestinal permeability was very small (Aspirin has been reported to increase permeability as much as 40 times more than GIPET)(8). The observed increases were reversed quickly (i.e., no effect at 40 min). The three doses of GIPET I were considered safe and well tolerated in the human subjects. **Phase I clinical studies.** Although rodent and canine oral delivery

Table II: Phase I oral bioavailability data with GIPET.				
Drug (molecular weight, g/mol)	GIPET	Reference	Oral bioavailability (%)*	Fold- increase over control**
Alendronate (323)	I	Fosamax (oral)	8.4	5
Desmopressin (1069)	II	SC	2.4	13
LMWH† I (approx. 4500)	I	SC	9.0	-
LMWH† II (approx 6000)	I	SC	8.0	-
Antisense I (6350)	I	IV	4.9	-
Antisense II (7284)	I	IV	6.9	-

GIPET is a registered trademark of Merriion Pharmaceuticals. Fosamax is a registered trademark of Merck & Co. SC is subcutaneous; IV is intravenous.  
 \* % oral bioavailability refers to the bioavailability of these compounds using GIPET, relative to the parenteral dosage form.  
 \*\* Fold-increase over control is the improvement in oral bioavailability resulting from the GIPET formulation, relative to an unenhanced oral control.  
 † LMWH is low molecular-weight heparin.

Table II: Phase I oral bioavailability data with GIPET.

data with absorption-promoting technologies can be impressive, significant differences in the intestinal physiology of species suggest that the only true species model for humans is human (9). Studies to date of GIPET in man have focused on different types of Biopharmaceutics Classification Scheme (BCS) Class III compounds, including small-molecule bisphosphonates (e.g., alendronate and zoledronate), a polysaccharide (e.g., low molecular-weight heparin, and peptides (e.g., desmopressin and acyline). All Phase I clinical studies showed a significant increase in oral bioavailability where absorption in control patients was negligible and showed that the GIPET platform can deliver therapeutic levels of these BCS Class III molecules (see Table II). The preclinical and clinical development results for one model molecule, acyline, are presented. Acyline, a decapeptide, is a gonadotropin-releasing hormone

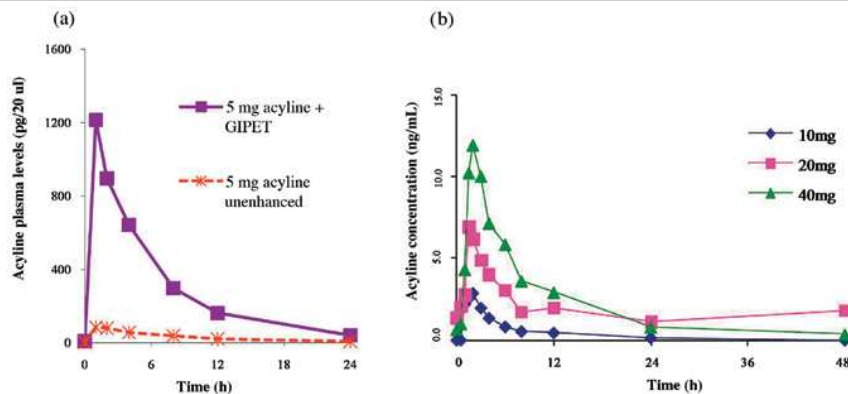


Figure 3: Acyline serum levels achieved: Figure 3(a) shows results from a preclinical dog model; Figure 3(b) shows results from Phase I clinical studies for GIPET-enhanced acyline.

(GnRH) antagonist that suppresses luteinizing hormone and testosterone in man. It has the potential to treat hormone-dependent conditions, such as prostate and breast cancer, or to treat benign conditions, such as endometriosis. However, for therapeutic use, it currently has to be injected, which limits its clinical utility. Also, acyline is difficult to formulate as an injectable because it tends to form a gel. This gel results in a sustained-release injection, which is not always desirable to maximize therapeutic benefit. As a result, there is a clinical need for orally active GnRH antagonists, such as acyline. Proceeding from positive data in the preclinical dog model, the authors investigated GIPET-enhanced oral acyline in eight healthy men (18–55 years of age) in a PK and PD study (see Figure 3). Oral acyline was administered on three occasions, each separated by one week. The subjects received progressively increasing doses of 10, 20, and 40 mg of GIPET-acyline after an overnight fast and continued to fast for four hours post dose. Blood for the measurement of serum-luteinizing hormone, follicle-stimulating hormone (FSH), testosterone, and acyline was obtained before each dose of GIPET-acyline and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 48 h and 7 days after each dose. Complete blood counts and comprehensive metabolic panels were obtained 24 h after each dose for assessment of safety.

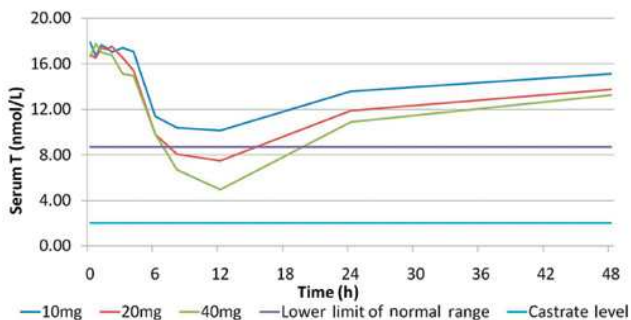


Figure 4: Testosterone levels following administration of 10-, 20-, and 40-mg GIPET-enhanced acyline tablets. GIPET is a registered trademark of Merriion Pharmaceuticals.

Results showed that mean serum acyline concentrations rose immediately after oral administration with all three doses and were undetectable in all subjects 48 h after dosing, except for one subject in the 40-mg group. Due to the large degree of variability between subjects, there were no significant differences in the PK parameters between doses. Acyline was not detected in the serum of any subject seven days after dosing (see Table III). Serum LH, FSH, and testosterone were



significantly suppressed by all doses of GIPET-acyline after 6 h, with maximum suppression 12 h post dose. The average suppression of serum FSH 12 h post-dose was  $28 \pm 5\%$  compared to  $70 \pm 10\%$  suppression of serum LH. The difference is most likely due to the fourfold greater serum half-life of FSH compared to LH (320 versus 80 min). The suppression of testosterone closely matched that of LH, with levels below the lower limit of the normal range ( $< 8.4$  nmol/L) 12 h after the 40-mg dose (see Figure 4). A repeat dose study of GIPET-acyline showed a similar PK profile with no

**Table III: Oral acyline pharmacokinetic parameters.**

Dose (mg)	10	20	40
$C_{max}$ (ng/mL)	$15.3 \pm 10.3$	$20.7 \pm 18.6$	$17.1 \pm 12.7$
$T_{max}$ (h)	$1.6 \pm 0.7$	$7.7 \pm 16$	$2.3 \pm 1.2$
$AUC_{0-24}$ (ng h/mL)	$61 \pm 48$	$175 \pm 188$	$100 \pm 87$
$T_{1/2}$ (h)	$7.4 \pm 3.1$	$9.2 \pm 6.3$	$10.7 \pm 3.2$

All data are means  $\pm$  standard deviation.

$C_{max}$  is concentration after dosing.  $T_{max}$  is time of maximum concentration.  $AUC_{0-24}$  is area-under-the-curve, 0–24 h,  $T_{1/2}$  is terminal half-life.

Table III: Oral acyline pharmacokinetic parameters. accumulation of drug. The acyline Phase I clinical studies clearly showed the clinical potential for this advanced drug-delivery platform.

#### Conclusion

The GIPET technology is an advanced-stage permeation enhancement oral drug-delivery platform based on enhancers that have been studied in cells, tissues, rodents, dogs, and humans to demonstrate their ability to promote drug absorption, safety, reversibility, and mechanism of action. The technology is suitable for a wide range of different molecule types as evidenced by the preclinical and clinical studies showing enhanced intestinal absorption.

#### Acknowledgments

The authors thank David Brayden, professor at the University College Dublin in Ireland for critical reading of the manuscript. The authors also want to acknowledge that the work of Edwin Walsh is funded by an Irish Research Council for Science, Engineering and Technology (IRCSET)–Industry Partnership between the Irish Government and Merriam Pharmaceuticals.

**Edwin G. Walsh**, BSc, is a PhD student at the School of Veterinary Medicine and Conway Institute, University College Dublin, in Dublin, Ireland. **Alan P. Cullen**, MSc, is preclinical development manager, **John S. Fox**, PhD, MBA, is chief development officer, and **Thomas W. Leonard\***, RPh, PhD, is vice-president and chief scientific officer, all at Merriam Pharmaceuticals, 219 Racine Drive, Suite D, Wilmington, NC 28403, tel. 910.799.1847, fax 910.395.1843, [leonard@merriampharma.com](mailto:leonard@merriampharma.com) [4]

**References** 1. E. Windsor and G.E. Cronheim, *Nature* **190** (4772), 263–264 (1961).

2. M. Hayashi, M. Tomita, and A. Awazu, *Adv. Drug Deliv. Rev.* **28** (2), 191–204 (1997).

3. T. Lindmark, T. Nikkila, and P. Artursson, *J. Pharmacol. Exp. Ther.* **275** (2), 958–964 (1995).

4. H. Huang and R.E. Verall, *J. Solution Chem.* **26** (2) 135–162 (1997).

5. Y. Lo and J. Huanh, *Biochem. Pharmacol.* **59** (6), 665–672 (2000).

6. JECFA, *29th Report of the Joint FAO/WHO Expert Committee on Food Additives*, WHO Technical Report Series No. 733 (1986).

7. L. Blomquist, *Gastroenterol.* **32** (8), 805–812 (1997).

8. A.J. Ryan, R-T. Chang, and C.V. Gisolfi, *Med. & Sci. in Sports & Exerc.* **28** (6), 698–705 (1996).

9. T.T. Kararli, *Biopharm. Drug Dispos.* **16** (5), 351–380 (1995).

© 2015 Advanstar Communications, Inc. All rights reserved. Reproduction in whole or in part is prohibited. Please send any technical comments or questions to our webmasters.

**Source URL:** <http://www.pharmtech.com/oral-absorption-enhancing-drug-delivery-technology>

#### Links:

- [1] <http://www.pharmtech.com/john-s-fox>
- [2] <http://www.pharmtech.com/thomas-w-leonard>
- [3] <http://www.pharmtech.com/edwin-g-walsh>
- [4] <mailto:leonard@merriampharma.com>