Expert Opinion

Promoting absorption of drugs in humans using medium-chain fatty acid-based solid dosage forms: GIPET™

Thomas W Leonard†, John Lynch, Michael J McKenna & David J Brayden
†*Merrion Pharmaceuticals USA, 219 Racine Drive, Suite D, Wilmington, NC 28403, USA*

One of the most important and challenging goals in drug delivery is overcoming the poor oral absorption of high-value therapeutics that include peptides. Gastrointestinal Permeation Enhancement Technology (GIPET™) attempts to address this question by safely delivering drugs across the small intestine in therapeutically relevant concentrations. GIPET is based primarily on promoting drug absorption through the use of medium-chain fatty acids, medium-chain fatty acid derivatives and microemulsion systems based on medium-chain fatty acid glycerides formulated in enteric-coated tablets or capsules. Importantly, these excipients are generally regarded as safe and the systems are formulated in such a way that there is no change in chemical composition of the active ingredient. More than 300 volunteers have been administered GIPET formulations in 16 Phase I studies of 6 separate drugs comprising both single- and repeat-dosing regimes. Oral bioavailability of alendronate, desmopressin and low-molecular-weight heparin in humans was increased using GIPET formulations compared with unformulated controls. GIPET was well tolerated by human subjects. Using fluxes of markers of epithelial permeability, the effects of GIPET on the human intestine were shown to be rapid, short-lived and reversible *in vivo*. These data suggest that GIPET formulations have genuine potential as a platform technology for safe and effective oral drug delivery of a wide range of poorly permeable drugs.

Keywords: bisphosphonates, epithelial permeation enhancers, intestinal absorption, low-molecular weight heparin, oral peptide delivery, sodium caprate

Expert Opin. Drug Deliv. (2006) 3(5):685-692

1. Introduction

Most peptide-based molecules have properties that are not conducive to oral delivery and must be injected at significant cost and inconvenience to patients. This technology gap currently limits the usefulness of a broad range of potential therapeutics, of which peptides comprise a large component. Although there have been major advances in delivering poorly absorbable agents in humans by other routes, including the pulmonary delivery of insulin [1], oral delivery will, in most cases, be the preferred route of administration for systemic delivery. Due to a combination of improved compliance by patients and the generation of extended and entirely novel intellectual property, oral drug delivery represents a potential US$25 billion market. Some oral peptide formulations have been approved. These include a microemulsion formulation of ciclosporin, as well as a desmopressin tablet (DDAVP®; sanofi-aventis). However, these examples are exceptions that are largely based on unique physicochemical characteristics of the two peptides.

informa
healthcare

Box 1. Composition of GIPET™ solid dose oral delivery technologies.

GIPET I technology:

- Medium-chain fatty acids and salts thereof (e.g., C_{10})
- Solid dosage forms (enteric-coated tablets)

GIPET II technology:

- Mono/diglycerides of C_8 and C_{10}
- Solid dosage (enteric-coated soft gel/hard capsule shell)

GIPET III technology (preclinical):

- Novel enhancers (not disclosed)

C_8: Caprylate; C_{10}: Caprate; GIPET: Gastrointestinal Permeation Enhancement Technology™.

In 1995, Amidon *et al*. described the biopharmaceutical classification system for oral delivery of immediate release products [2]. The major outcome of the biopharmaceutical classification system was to group major drug classes according to whether they had oral delivery issues related to solubility or permeability issues, neither of these issues, or both. Technologies to address theses issues can also be described under the same headings. Thus, drugs that are insoluble but retain permeability (class II) can be better delivered with solubilising emulsion-type approaches [3], whereas soluble but poorly-absorbable drugs including most peptides (class III) are amenable to epithelial permeation enhancement [4]. There have been many attempts to promote oral absorption of poorly absorbed class III drugs over the past 15 years, but unfortunately the majority has failed. Reasons include the inability to deliver therapeutic levels by itself over a sustained period, the requirement for massive amounts of material, and safety issues regarding the long-term integrity of the intestinal epithelium. Additional pitfalls include the lack of reliable and predictive *in vivo* animal models, as well as the inability to follow through with practical and reproducible solid dose formulations amenable to scaled-up manufacturing. Achieving a successful oral formulation of a poorly absorbable drug implies that there is access to the appropriate intestinal region for a sufficient amount of time, release of intact soluble drug and an acceptable but reversible degree of epithelial cell permeability. Once the targeted pharmacokinetic and pharmacodynamic profile is achieved in humans, the formulation must have a safety profile to allow it to be given to patients on a repeated basis, perhaps for an indefinite period.

Current oral delivery technologies for class III drugs include permeation enhancers, mucoadhesive polymers, entrapment in particles and chemical conjugation. Some formulations contain combinations of the above, along with an in-built capacity to stabilise the drug against pH changes and metabolism. To the authors' knowledge, the most advanced oral technologies for drugs that are difficult to deliver in Phase II human trials are the Eligen® carrier-based approach being developed by Emipshere [5], along with the RapidMist® spray system for oromucosal delivery being developed by Generex Biotechnology [6]. A different approach developed in Phase II trials by the Nobex Corporation involves peptide conjugation to pegylated alkyl amphiphilic polymers [7]. Preclinical research of note is the use of bioadhesive peptide-entrapped nanoparticles, including those made from sebacic acid/fumaric acid (Spherics) [8], as well as mini-tablets and microparticles comprising mucoadhesive thiolated polymeric excipients (ThioMatrix) [9].

Gastrointestinal Permeation Enhancement Technology™ (GIPET™) is a proprietary solid-dose/microemulsion-based medium-chain fatty acid technology by Merrion Pharmaceuticals. This short review provides an evaluation of the technology, with a particular emphasis on previously unpublished safety and efficacy data that has been achieved in Phase I human trials. Although rodent [10] and canine [11] oral delivery data with absorption-promoting technologies can indeed be impressive, significant species differences in intestinal physiology suggest that the only true species model for humans is humans [12].

2. GIPET™

The development of GIPET technologies (Box 1) was strongly influenced by research on medium-chain fatty acid permeation enhancers. In 1991 it was shown that paracellular absorption of polar marker molecules across isolated rat colonic mucosae was increased by caprylate (C_8) and caprate (C_{10}) at selected concentrations *in vitro* [13]. Part of the mechanism of action of C_{10} in the *in vitro* human intestinal cell line Caco-2 was to dilate intestinal epithelial tight junctions at a concentration of 13 – 16 mM, thereby effecting cytoskeletal changes favouring permeation of small polar molecules [14]. By the mid-1990s it was well known that millimolar concentrations of sodium salts of C_6 (caproate), C_8, C_{10} and C_{12} (laurate) could boost the flux of hydrophilic agents [15]. When C_{10} was incorporated at higher concentrations into a rectal triglyceride base suppository containing ampicillin, there was some evidence that paracellular route enhancement might not be the dominant mechanism at the required physiological concentrations required *in vivo* [16]. Although there are the complex issues of dose-related multiple mechanisms, the potential for delivering peptides to a significant level through pharmacologically opened tight junctions remains a research area of considerable interest [17].

Although it is relatively simple to show enhanced permeation using isolated tissue mucosae or perfused rodent intestinal segments using solutions of excipients mixed with the active drug, it is an entirely another set of challenges to advance a preclinical concept to a practical solid-dose formulation that can be used in human patients. The drug must be protected from gastric acidity if it is sensitive to metabolism. Moreover, the absorption promoter and the drug should ideally be released together at the same rate and at appropriate concentrations close to the epithelium as the formulation moves down the small intestine by peristalsis. Thus, the spatial and temporal

Table 1. Phase I oral bioavailability data with GIPET™.

Drug (molecular weight, g/mol)	GIPET	% Oral bioavailability (CV%)	Fold increase over oral control
Alendronate (523)	I	8.4 (59)	5
Desmopressin (1069)	II	2.4 (124)	13
LMWH I (4400)	I	9.0 (63)	-
LMWH II (6010)	I	8.0 (40)	-

All human studies were carried out in fasted subjects. Bioavailability was calculated with reference to appropriate subcutaneous controls.
CV%: Coefficient of variation; GIPET: Gastrointestinal Permeation Enhancement Technology™; LMWH: Low molecular weight heparin.

relationships between cargo and promoter need to be optimised for delivery. Therefore, in the first format of GIPET (GIPET I), enteric-coated tablets comprising a pH-sensitive coating (e.g., Eudragit®; Röhm GmbH & Co. KG), a medium-chain fatty acid (e.g., C_{10}) and a drug in selected ratios by weight were synthesised. The second variation of the technology (GIPET II) consisted of microemulsions of mono- and diglyceride mixtures of C_8 and C_{10} entrapped with the drug in an enteric-coated soft gel capsule. Importantly, these excipients were specifically selected due to their 'generally regarded as safe' status at an individual level in other pharmaceutical formulations. In addition, C_{10} is present in milk in millimolar concentrations at a level comprising 2 – 3% of the total fatty acids [18], and it is approved as a food additive in the US and EU. GIPET I and II have been tested orally in rats, dogs and humans, primarily to establish safety profiles but also to demonstrate efficacy. Here, the authors evaluate human data from three separate Phase I clinical trials and discuss additional experiments in humans in support of the safety of the technology.

3. Phase I trials of GIPET™

GIPET has been tested in a range of doses with six poorly-absorbed drugs in a total of 16 Phase I studies. Table 1 shows the human oral bioavailability data for four of those drugs in humans. Overall, oral bioavailabilities of 5 – 13% were achieved for compounds that normally have bioavailabilities of < 1 %. Detailed pharmacokinetics from human trials are described for three specific examples: alendronate, low molecular weight heparin (LMWH) and desmopressin.

The bisphosphonate alendronate sodium is approved as both once-daily and once-weekly tablets for the treatment and prevention of postmenopausal osteoporosis in women, as well as for men requiring an increase in bone mass density. Another bisphosphonate, ibandronate sodium, was recently approved as a once-monthly oral medication. Oral bisphosphonates must be taken in the morning with a full glass of water on an empty stomach, and patients are required to remain standing for at least 30 min following administration, a regimen that impacts severely on compliance [19]. All of the current oral formulations are associated with dysphagia and oesophageal reflux. In a second disease indication, bisphosphonates such as pamidronate and zoledronic acid are used as chemotherapy for metastatic bone cancer [20]. These patients require a higher bioavailability than can currently be delivered from the oral route, and so they are injected intravenously, with some discomfort, albeit on a monthly basis. An oral formulation of bisphosphonates with significantly higher bioavailability would certainly benefit this subgroup of patients. Alendronate–GIPET I was given to a total of 16 healthy subjects as oral tablets comprising 17.5 mg active drug in a 200-mg enteric-coated GIPET-I tablet containing a selected concentration of C_{10}. Oral bioavailability was compared with that achieved with alendronate sodium 35-mg tablets, resulting in a calculation of 8.4% for alendronate–GIPET. Urinary excretion data indicated that GIPET conferred a fivefold increase in the oral bioavailability of alendronate formulations over the reference compound (Figure 1).

Subcutaneous injections of LMWH are typically used as a prophylactic anticoagulant treatment to prevent deep vein thrombosis or pulmonary embolism following hip or knee replacement surgery [21]. An oral formulation of LMWH would reduce healthcare costs, as it could be offered on an out-patient basis and would require less therapeutic monitoring than the typically prescribed standard therapy of oral warfarin. LMWH is poorly absorbed and an oral formulation would satisfy this significant medical need. LMWH–GIPET I was formulated in coated tablets containing 45,000 or 90,000 IU of LMWH with two levels of C_{10}. Oral bioavailability was compared with the standard subcutaneous dose of 3200 IU following administration to 14 – 16 normal human subjects. Mean data over time is shown in Figure 2 and the overall data are summarised in Table 2. Oral bioavailability of 3.9 – 7.6% was achieved with subcutaneous administration. With the high-dose tablet of LMWH combined with high-dose caprate, levels of an indirect plasma surrogate marker for delivery of therapeutic levels was seen in all subjects, and the responses were sustained in most subjects with a similar time course to the subcutaneous route of delivery. Oral bioavailability of 8% in humans has also been achieved using GIPET II with another LMWH, dalteparin sodium, and up to 18% oral bioavailability was seen with LMWH in dogs with GIPET III (unpublished observations, TW Leaonard).

Desmopressin is a synthetic structural stabilised peptide analogue of arginine vasopressin and it is used as an antidiuretic agent for the treatment of vasopressin-sensitive diabetes

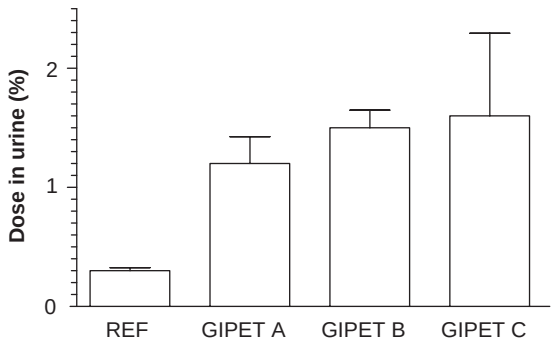

Figure 1. Urinary excretion of alendronate from a single administration of GIPET™ solid dose formulations in humans.
Groups are: REF (Fosamax® 35 mg); GIPET A (alendronate 17.5 mg with low concentrations of C_{10}); GIPET B (alendronate 17.5 mg with low concentrations of C_{10}-formulation variation of GIPET A); GIPET C (alendronate 17.5 mg with high concentrations of C_{10}). n = 16 for each group.
C_{10}: Caprate; GIPET: Gastrointestinal Permeation Enhancement Technology™.

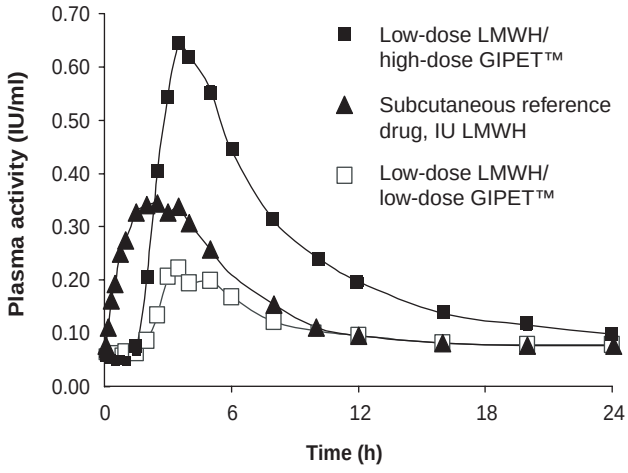

Figure 2. Plasma profile of the oral delivery of LMWH–GIPET I™ in humans. n = 14 – 16 subjects.
LMWH: Low molecular-weight heparin. GIPET: Gastrointestinal Permeation Enhancement Technology™.

insipidus, polyuria and polydypsia [22]. Oral bioavailability is low, ranging 1 – 3% and there is considerable intra-subject variation. With a direct relationship between the amount absorbed and the pharmacodynamic response, an improved oral formulation could lead to better efficacy associated with a high level of compliance. When desmopressin was formulated in a GIPET solid dose format and administered orally to 18 human subjects, a bioavailability of 2.4% relative to the subcutaneous route was measured. Notably, this value was an improvement over the 0.2% value seen in this study in subjects who were administered the currently marketed Minirin® tablet (desmopressin; Ferring Pharmaceuticals). It is worth noting that two subjects did not obtain measurable levels with the Minirin tablet. There was less variability in the GIPET tablet pharmacokinetic data than the subcutaneous route (Table 3, Figure 3).

4. Safety studies of GIPET™ in preclinical models

Pharmaceutical products that include high concentrations of medium-chain fatty acids are already marketed; one example is a C_{10}-based rectal suppository. There is well-known evidence of temporary mild abrasions associated with this product [16], but these are temporary and do not impact on long-term usage. Although the lead absorption-promoting fatty acid excipients of the GIPET technology are present in food additives and are generally regarded as safe, several GIPET safety studies were carried out in rats, dogs and humans.

There were four groups of three dogs that received daily oral doses of a GIPET I formulation comprising of C_{10} and C_{12} in ratios of 1:2 encased in gelatin capsules for up to 14 days. Doses were 0.1, 0.3 and 0.9 g/kg/day, given as 2, 6 and 18 tablets, respectively. Empty gelatin capsules were administered an equal number of times as the highest dose. Only at the highest dose was emesis seen in some dogs ~ 1 h after administration, whereas occurrence was occasional and limited in other groups. The high-dose group also appeared to show a decrease in food consumption, resulting in loss of up to 0.5 kg in weight, although this is likely to have been due to the 18 tablets ingested each day. No unusual findings were seen for any dogs in any other group with respect to ECG, haematology, serum biochemistry and urinalysis. Gastrointestinal tissue histology revealed no micro- or macroscopic changes in any of the groups.

A 1-week dose-ranging study comprising 0.33, 0.66 and 1.0 g of C_{10} per day for 7 days, was also carried out. Although lipid-rich faeces were detected, all of the animals gained weight and no adverse events were apparent. A further safety study was carried out in three groups of eight dogs using enteric-coated or uncoated immediate-release GIPET I tablets containing high concentrations of C_{10} and LMWH. No adverse events (unusual behaviour or altered physiological functions) were reported in the 16 dogs that received the GIPET I tablets.

A total of three groups of four dogs received daily oral doses of a size 12 gelatin capsules containing 0.4, 2.0 and 4.0 g GIPET II microemulsion per animal for 7 days. There was no evidence of clinical pathology, histopathology or body weight changes at these dose levels. In addition, a 28-day GIPET II/desmopressin study was also carried out in dogs. There were no overt toxicological changes, although salivation was seen in some animals. These canine data sets with GIPET II were consistent with that seen for GIPET 1, namely that solid dose formulations containing high concentrations of medium-chain fatty acids could be given to dogs on a daily basis without any signs of toxicity. In summary, the five separate canine daily tolerance studies revealed very encouraging safety data for selected components of the GIPET I and II technology.

Published literature generally reveals the extensive safe use of C_{10} as an absorption promoter in several species. In Imai *et al.*, 0.1% C_{10} was administered intra-colonically to rats with a solution of salmon calcitonin and histology revealed a

Table 2. Phase I oral bioavailability data: LMWH–GIPET™ I.

PK	Low/low	High/high	Subcutaneous reference
Oral bioavailability (%)	3.9 ± 3.5	7.6 ± 4.8	NA
Coefficient of variation (%)	89.1	62.9	NA
Number of responders with levels > 0.1 IU/ml (%)	60 (9/15)	100 (14/14)	100 (16/16)
Number of responders with levels > 0.1 IU/ml for > 6 h (%)	13 (2/15)	71 (10/14)	81 (13/16)
Total duration > 0.1 IU/ml (h)	2.6 ± 3.6	10.6 ± 5.4	7.1 ± 1.3

GIPET: Gastrointestinal Permeation Enhancement Technology™; High/high: High-dose tablet of LMWH (Parnarpain®) combined with high-dose caprate; LMWH: Low molecular weight heparin; Low/low: Low-dose tablet of low molecular weight heparin combined with low-dose caprate; NA: Not available; PK: Pharmacokinetic parameters.

Table 3. Phase I oral bioavailability data: desmopressin–GIPET™ II.

Treatment	AUC (CV%)	Relative bioavailability (CV%)
Desmopressin–GIPET (200 µg, p.o. capsule)	840 ± 729 (87%)	2.4 ± 2.9 (125%)
Desmopressin (Minrin®; Ferring Phamaceuticals) (200-µg p.o. tablet)	159 ± 383 (241%)	0.2 ± 0.2 (122%)
Desmopressin (4-µg s.c. reference drug)	539 ± 517 (96%)	Not available

n = 18 in each group.
CV%: Coefficient of variation; GIPET: Gastrointestinal Permeation Enhancement Technology™.

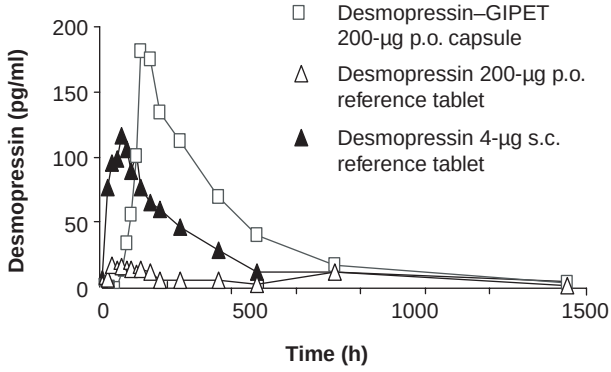

Figure 3. Plasma profile of the oral delivery of desmopressin–GIPET™ II in humans. n = 18 subjects.
GIPET: Gastrointestinal Permeation Enhancement Technology™.

normal colonic mucosa 9 h later [23]. Vervarcke *et al.* described the use of C_{10} as a promoter of antigen uptake by African catfish [24]. No adverse outcomes were reported from what is a particularly sensitive species. Raoof *et al.* provided further evidence of the safety of hydroxy propyl methyl cellulose-coated C_{10}/antisense tablets in beagle dogs [25]. There were ~ 0.33 g of C_{10} that was used in each tablet and the dogs received three per day orally for 7 days. The key safety data were that clinical chemistry and blood biochemistry was normal. The dogs tolerated the formulation well and there was normal weight gain. Canine intestinal issues were also judged to be normal following macroscopic examination at postmortem. These data are in stark contrast to some studies using *in vitro* human intestinal tissue culture monolayers where cell viability, measured by MTT assay, was reduced upon exposure to 10 mM sodium caprate [26]. The relevance of these *in vitro* models in predicting toxicity *in vivo* seems highly questionable, as the monolayers are in a static system, and are devoid of protective mucous and have a negligible cell turnover.

There are several studies describing antipathogenic effects of C_{10} and other medium-chain fatty acids. These were demonstrated to be bacteriostatic at high concentrations against *Helicobacter pylori* [27]. In addition, one mechanism of action of the agent is to prevent expression of key regulator genes in salmonella for promoting invasion of intestinal epithelia [28]. In an *in vivo* study with chickens, incorporation of medium-chain fatty acids including C_{10} in feed at a level of 3 g/kg feed appeared to protect chickens from colonisation by *Salmonella enterica* [28]. Finally, capric acid has also been shown to have antifungal activities on *Microsporium gypsum* mycelia and spores *in vitro* [29].

5. Safety studies of GIPET™ in clinical studies

Phase I studies on the six drugs described here comprised 800 exposures to a solid dosage form for GIPET in 300 volunteers. In some studies, individuals have been safely dosed up to six times with GIPET formulations. A legitimate concern about the use of intestinal absorption-promoting technologies is that the epithelium may not have time to recover before the next dose. Although the clinical experience thus far has not suggested that this is an issue *in vivo*, intestinal permeability studies were carried out in human subjects following

Table 4. Timing of effect of C_{10} on human intestinal permeability using urinary excretion of polar sugars as a surrogate marker.

Group	LMER (CV %)	n	Statistics
A. Sugars	0.02 ± 0.1 (66.3)	24	-
B. C_{10} 20 min before sugars	0.03 ± 0.1 (70.4)*	22	$p < 0.01$
C. C_{10} 40 min before sugars	0.02 ± 0.1 (38.9)	22	NS
D. C_{10} 60 min before sugars	0.02 ± 0.1 (31.9)	23	NS
E. Sugars	0.02 ± 0.0 (29.5)	22	NS

Treatments were C_{10} 0.5 g in 15-ml solution administered via perfusion tube to the jejunum in the presence and absence of mannitol 2 g /lactulose 5 g /glycerol 9 g administered as 100-ml solution orally at different time intervals. Statistical significance was assessed by paired t-test against group A. Group B was statistically different from baseline if two high responding outliers were removed from the analysis. Data from SJ Warrington, Hammersmith Medicines Research, Hammersmith Hospital, London.

C_{10}: Caprate; CV%: Coefficient of variation; LMER: Lactulose:mannitol urinary excretion ratio; NS: Non-significant.

intra-jejunal administration of C_{10} followed by sugar molecules whose oral absorption is typically low and largely restricted to the tight junction route. The aim was to establish intestinal permeability recovery time in the presence of a typical fatty acid component of GIPET in a dose designed for the formulation. The polar sugar, mannitol (molecular weight 164 g/mol), is absorbed paracellularly across the gut and is excreted unchanged in the urine. Oral bioavailability of mannitol is ~ 25% and this amount is retrieved in the urine, as it is freely filtered and not reabsorbed by renal tubules. Another polar disaccharide sugar, lactulose (molecular weight 342), is also absorbed paracellularly, but only to a level of 1% due to its larger molecular radius. The ratio of the two agents in urine is a well-established non-invasive indicator of human intestinal permeability *in vivo* [30].

When the tight junctions are open or if the epithelium forms a less restrictive barrier, the urinary lactulose:mannitol excretion ratio should be increased, as the lactulose should be absorbed more easily. In an open-label partially randomised study using up to 24 human subjects, the marker molecules, mannitol (2 g) and lactulose (5 g) were given orally at 20, 40 or 60 min following intra-jejunal instillation of 0.5 g C_{10}. The data showed that only when the sugars were administered 20 min after the fatty acid was the urinary lactulose:mannitol excretion ratio increased (Table 4). Thus, in the subjects receiving three separate doses of C_{10}, the effect of the agent on intestinal permeability was temporary and that increases in permeability were reversed at 40 and 60 min. Importantly, the three intra-jejunal doses of 0.5 g C_{10} was generally safe and well tolerated in the human subjects. Furthermore, studies testing the effects of C_{10} on increasing intestinal [^{14}C]-PEG absorption in dogs were similarly suggestive of only a temporary effect of this major component of GIPET (data not shown). These data are not surprising, as 17 billion enterocytes are normally replaced every day and the entire epithelium of the small intestine is replaced every 5 days in humans [31].

Having established that the effects of major GIPET components on the intestinal permeability are temporary, an additional concern was that the formulation might permit bystander absorption of pathogens from the lumen. However, to the authors' knowledge, decades of clinical experience with several NSAIDs with the potential to damage the intestinal epithelium does not suggest that such agents leave individuals prone to either increased microbe absorption or opportunistic enteric infections. The lack of a potentially damaging physiological response from any co-absorbed material in cases of overt gut pathology and ulceration induced by some NSAIDS appears encouraging. Nonetheless, use of GIPET or any other absorption-promoting technology in subjects with inflammatory bowel disease would clearly be inadvisable.

6. Conclusion

GIPET is a maturing technology that has shown significant efficacy in human Phase I oral delivery studies of drugs that normally must be injected. The data show that a range of drugs of different structure can be delivered to therapeutic levels using two different solid dose GIPET formulations. The wide variety of poorly absorbed drug types that have now shown efficacy in Phase I trials through the use of the GIPET oral delivery formulations suggest that the delivery system is a platform technology that can be adapted for a range of biotechnology cargoes. Importantly, Phase I trials using 300 subjects revealed no toxicity of concern and, in addition, this was also manifest in subjects receiving multiple doses of GIPET. Additional human studies revealed that the absorption-promoting effects of GIPET were transient and complete in < 1 h. These data provided additional arguments suggesting that the absorption promoter and the active ingredient need to be formulated as an enteric-coated solid dosage form in which the ingredients are gradually co-released together to temporarily promote absorption as the formulation moves along the epithelium of the upper small intestine. In contrast to GIPET, simple mixing of solutions of promoters and active agents is therefore unlikely to be effective *in vivo*, as co-localised release is not present.

7. Expert opinion

One of the lessons from the GIPET development programme is that there is no substitute for human data. More than 100 other oral delivery technologies have suggested potential in rodent studies, but only a few of them like GIPET actually make it to clinical trials. Apart from species differences in intestinal physiology [12], erroneous assumptions can also be made with regards to allosteric scaling of dosage [32], not to mention the additional challenge of redesigning the dosage form. Furthermore, there is little doubt that human intestinal monolayers have their limitations as prescreens for the *in vivo* use of absorption promoters [33]. Although the tight-junction opening effect of medium-chain fatty acid ingredients was apparent from early Caco-2 studies [14], higher concentrations and additional mechanisms could not be tested *in vitro*, as these monolayer systems are not robust enough in comparison with the human intestine *in vivo*. This is hardly surprising, as the human intestine is normally quite able to cope with regular doses of very challenging and occasionally noxious stimuli (typically food and drink). Perhaps it is just as well that GIPET appears not to operate exclusively through a tight junction-opening mechanism *in vivo*, as there is a strongly held view that this route of uptake represents only a small fraction of the intestinal epithelial surface area and therefore may offer limited uptake capacity for poorly absorbable biopharmaceuticals [34].

Conflict of interest disclosure

D Brayden is a consultant to Merrion Pharmaceuticals Ireland Ltd.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. QUATTRIN T: Inhaled insulin: recent advances in the therapy of Type 1 and 2 diabetes. *Expert Opin. Pharmacother.* (2004) 5(12):2597-2604.
2. AMIDON G, LENNERNAS H, SHAH VP, CRISON J: A theoretical basis for a biopharmaceutic drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. *Pharm. Res.* (1995) 12(3):413-420.

•• Seminal paper outlining the basis of the Biopharmaceutics Classification System for immediate-release drugs, which ultimately led to important FDA guidances on biowavers for certain *in vivo* studies.

3. TENJARLA S: Microemulsions: an overview and pharmaceutical applications. *Crit. Rev. Ther. Drug Carrier Syst.* (1999) 16(5):461-521.
4. THANOU M, VERHOEF JC, JUNGINGER H: Oral drug absorption enhancement by chitosan and its derivatives. *Adv. Drug Deliv. Rev.* (2001) 52(2):117-126.
5. KIDRON M, DINH S, MENACHEM Y *et al.*: A novel per-oral insulin formulation: proof-of-concept study in non-diabetic subjects. *Diabet. Med.* (2004) 21:354-357.
6. POZZILLI P, MANFRILI S, COSTANZA F *et al.*: Biokinetics of buccal spray insulin in patients with Type 1 diabetes. *Metabolism* (2005) 54(7):930-934.
7. CHIN CM, GUTIERREZ M, STILL JG, KOSUTIC G: Pharmacokinetics of modified oral calcitonin product in healthy volunteers. *Pharmacotherapy* (2004) 24(8):994-1001.
8. SANTOS CA, FREEDMAN BD, GHOSN S, JACOB JS, SCARPULLA M, MATHIOWITZ E: Evaluation of anhydride oligomers within polymer microsphere blends and their impact on bioadhesion and drug delivery *in vitro*. *Biomaterials* (2003) 24(20):3571-3583.
9. BERNKOP-SCHNURCH A: Thiomers: a new generation of mucoadhesive polymers. *Adv. Drug Deliv. Rev.* (2005) 57(11):1569-1582.

• A newer absorption-promoting technology based on the relatively new field of mucoadhesive thiolated polymers conjugated to peptides.

10. SALAMA NN, FASANO A, THAKAR M, EDDINGTON ND. The impact of ΔG on the oral bioavailability of low bioavailable therapeutic agents. *J. Pharm. Exp. Ther.* (2005) 312:199-215.
11. LEE YH, LEESMAN JD, MAKHEY V *et al.*: Regional oral absorption, hepatic first-pass effect, and non-linear disposition of salmon calcitonin in beagle dogs. *Eur. J. Pharm. Biopharm.* (2000) 50(2):205-211.
12. KALARLI TT: Comparison of the gastrointestinal anatomy, physiology, and biochemistry of humans and commonly used laboratory animals. *Biopharm. Drug Dispos.* (1995) 16(5):351-380.

•• This paper remains the most referenced review on comparative gastrointestinal physiology.

13. SAWADA T, OGAWA T, TOMITA M, HAYASHI, M, AWAZU S: Role of paracellular pathway in non-electrolyte permeation across rat colon epithelium enhanced by sodium caprate and sodium caprylate. *Pharm. Res.* (1991) 8(11):1365-1371.
14. ANDERBERG EK, LINDMARK T, ARTURSSON P: Sodium caprate elicits dilatations in human intestinal tight junctions and enhances drug absorption by the paracellular route. *Pharm. Res.* (1993) 10(6):857-864.
15. LINDMARK T, NIKKILA T, ARTURSSON P: Mechanisms of absorption enhancement by medium chain fatty acids in intestinal epithelial Caco-2 cell monolayers. *J. Pharmacol. Exp. Ther.* (1995) 275(2):958-964.

• A thorough study of the intercellular mechanisms medium chain fatty acids use to open tight junctions.

16. LINDMARK T, SODERHOLM JD, OLAISON G, ALVAN G, OCKLIND G, ARTURSSON P: Mechanism of absorption enhancement in humans after rectal administration of ampicillin in suppositories containing sodium caprate. *Pharm. Res.* (1997) 14(7):930-935.
• An important paper demonstrating that the *in vitro* mechanism of tight junction opening by fatty acids may not pertain *in vivo*. This also highlights the ability of the gastrointestinal tract to repair itself quickly.
17. SALAMAT-MILLER N, JOHNSTONE TP: Current strategies used to enhance the paracellular transport of therapeutic polypeptides across the intestinal epithelium. *Int. J. Pharm.* (2005) 294(1-2):201-216.
18. SODERHOLM JD, OMAN H, BLOMQUIST L, VEEN J, LINDMARK T, OLAISIN G: Reversible increase in tight junction permeability to macromolecules in rat ileal mucosa *in vitro* by sodium caprate, a constituent of milk fat. *Dig. Dis. Sci.* (1998) 43(7):1547-1552.
19. CRAMER JA, AMONKAR MM, MAYUR M, HEBBORN A, ALTMAN R: Compliance and persistence with bisphosphonate dosing regimens among women with postmenopausal osteoporosis. *Curr. Med. Res. Opin.* (2005) 21(9):1453-1460.
20. GORDON DH: Efficacy and safety of intravenous bisphosphonates for patients with breast cancer metastatic to bone: a review of randomized, double-blind, Phase III trials. *Clin. Breast Cancer* (2005) 6(2):125-131.
21. MERLI G: Anticoagulants in the treatment of deep vein thrombosis. *Am. J. Med.* (2005) 118(Suppl. 8A):13S-20S.
22. VAVRA I, MACHOVA A, HOLECEK V, CORT JH, ZAORAL M, SORM F: Effect of a synthetic analogue of vasopressin in animals and in patients with diabetes insipidus. *Lancet* (1968) 1(7549):948-952.
23. IMAI T, SAKAI M, OHTAKE H, AZUMA H, OTAGIRI M: Absorption enhancing effects of glycyrrhizin induced in the presence of capric acid. *Int. J. Pharm.* (2005) 294(1-2):11-21.
24. VERVARCKE S, OLLEVIER F, KINGET R, MICHOEL A: Oral vaccination of African catfish with *Vibrio anguillarum* O2: effect on antigen uptake and immune response by absorption enhancers in lag time coated pellets. *Fish Shellfish Immunol.* (2004) 18(2):125-133.
25. RAOOF AA, CHIU P, RAMTOOLA Z *et al.*: Oral bioavailability and multiple dose tolerability of an antisense oligonucleotide tablet formulated with sodium caprate. *J. Pharm. Sci.* (2004) 93(6):1431-1439.
• Literature that outlines safe and relatively efficacious *in vivo* effects of solid-dose formulations of sodium caprate is limited, but this study is the most comprehensive attempt.
26. RAIMON J, TORMALEHTO S, YRITYS K, JUNGINGER HE, MONKKONEN J: Effects of various absorption enhancers on transport of clodronate through Caco-2 cells. *Int. J. Pharm.* (2003) 261(1-2):129-136.
27. PETSCHOW PW, BATEMA RP, FORD LL: Susceptibility of *Helicobacter pylori* to bactericidal properties of medium-chain monoglycerides and free fatty acids. *Antimicrob. Agents Chemother.* (1996) 40(2):302-306.
28. VAN IMMERSEEL F, DE BUCK J, BOYEN F *et al.*: Medium chain fatty acids decrease colonisation and invasion through *hil*A suppression shortly after infection of chickens with *Salmonella enterica* serovar enteridis. *Appl. Environ. Microbiol.* (2004) 70(6):3582-3587.
29. CHADEGANIPOUR M, HAIMS A: Antifungal activities of pelargonic and capric acid on *Microsporium gypsum*. *Mycoses* (2001) 44:109-112.
30. BLOMQUIST L, BARK T, HEDENBORG G, NORMAN A: Evaluation of the lactulose/mannitol and ^{51}Cr-ethylenediaminetetraacetic acid/^{14}C-mannitol methods for intestinal permeability. *Scand. J. Gastroenterol.* (1997) 32(8):805-812.
31. WIDMAIER EP, RAFF H, STRANG KT: In: *Vander, Sherman and Luciano's Human Physiology: The Mechanisms of Body Function (9th edn)*. McGraw Hill Publisher, NY, USA (2004):570-571.
32. RIVIERE JE, MARTIN-JIMENEZ T, SUNDLOF SF, CRAIGMILL AL: Interspecies allometric analysis of the comparative pharmacokinetics of 44 drugs across veterinary and laboratory animal species. *J. Vet. Pharmacol Ther.* (1997) 20(6):453-463.
33. BRAYDEN D, CREED E, O'CONNELL A, LEIPOLD H, AGARWAL R, LEONE-BAY A: Heparin absorption across the intestine: effects of sodium *N*-[8-(2-hydroxybenzoyl) amino]caprylate in rat *in situ* intestinal instillations and in Caco-2 monolayers. *Pharm. Res.* (1997) 14(12):1772-1779.
• One of the first papers examining the Emisphere technology at the level of biological mechanism using *in vitro* and *in vivo* models. Showed limitations of Caco-2 in absorption-promoting studies.
34. MRSNY RJ: Modification of epithelial tight junction integrity to enhance transmucosal absorption. *Crit. Rev. Ther. Drug Carrier Syst.* (2005) 22(4):331-418.
•• A definitive review of the up-to-date knowledge on tight junction structure. This paper also provides a pertinent analysis of potential safety concerns that may need to be addressed by biotechnology companies seeking approval of products comprising of intestinal absorption-promoting technologies.

Affiliation

Thomas W Leonard[†1] PhD,
John Lynch[2] BComm,
Michael J McKenna[3] PhD &
David J Brayden[4] PhD
[†]Author for correspondence
[1]VP and Chief Scientific Officer, Merrion Pharmaceuticals USA, 219 Racine Drive, Suite D, Wilmington, NC 28403, USA
Tel: +1 910 799 1847;
Fax: +1 910 395 1843;
E-mail: tleonard@merrionpharma.com
[2]Chief Operating Officer, Merrion Pharmaceuticals, Ireland, Biotechnology Building, Trinity College, Dublin 2, Ireland
[3]Chief Executive Officer, Merrion Pharmaceuticals USA, Wilmington, NC, USA
[4]Associate Professor, UCD Conway Institute, University College Dublin, Belfield, Dublin 4, Ireland