Expert Opinion

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TARGIT™ technology: coated starch capsules for site-specific drug delivery into the lower gastrointestinal tract

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TARGIT™ technology (West Pharmaceutical Services) is designed for site-specific delivery of drugs in the gastrointestinal (GI) tract and, in particular, targeted release into the colonic region. A key area of application is the delivery of therapeutic agents for local treatment of lower GI diseases. The technology is based on the application of pH-sensitive coatings onto injection-moulded starch capsules. An extensive body of clinical data has been generated showing reliable *in vivo* performance of the capsules. In γ-scintigraphy studies around 90% of TARGIT capsules (n = 84) delivered their contents to the target site of the terminal ileum and colon. TARGIT-based products are in active clinical development for the treatment of conditions including inflammatory bowel diseases.

Keywords: colon, pH-sensitive coating, site-specific, starch capsule

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1. Overview of the market

The colon has been a site of interest for drug delivery for many years. A small number of drugs are currently available in rectal dosage forms and are intended for systemic delivery to overcome compliance issues or difficulties in administration associated with certain disease states. Such drugs include diazepam, diclofenac, indomethacin, morphine, chlorpromazine and ergotamine [1].

However, the current primary interest in the colon is as a site for delivery of drugs for local action; in particular, the delivery of anti-inflammatory agents for the treatment of inflammatory bowel diseases (IBDs), which encompass Crohn's disease and ulcerative colitis.

Crohn's disease is a condition associated with inflammation of the full thickness of the intestinal wall. In most patients (40 – 55%) the disease affects both the small and large intestine, and in only 15 – 25% is it confined to the colon. Ulcerative colitis is associated with inflammatory changes to the intestinal mucosa, which are confined to the large intestine. The entire large intestine may be affected or changes may be isolated to a particular region, such as the rectum. IBD is generally characterised by acute flare-ups interspersed with periods of quiescence, although the pattern of the disease varies widely between patients [2-4].

IBD is most prevalent in northern Europe and North America, where the number of affected individuals is beginning to stabilise. However, the disease incidence is continuing to rise in southern Europe, Asia and much of the developing world. The number of individuals with IBD has been estimated at around 1.4 million in the US and 2.2 million in Europe [5].

Aminosalicylates are the first line of therapy in treating IBD and are used as topical anti-inflammatories in ulcerative colitis for the induction and maintenance of remission. For acute exacerbations of the disease, rectally administered dosage

forms (e.g., corticosteroid foams, enemas and suppositories) may be used for treating local inflammation of the rectum and distal colon, and oral corticosteroids may be used for more widespread disease. Due to the possibility of causing unwanted systemic side effects, corticosteroids tend to be used over short periods (typically up to 8 weeks) for treating flare-ups [4,6,7]. An orally administered budesonide product (budesonide/Entocort™ EC, AstraZeneca), designed to provide site-specific delivery of drug into the lower small intestine, is used in the treatment of Crohn's disease and has the advantage of producing fewer side effects than oral (systemic) steroids. Entocort EC comprises enteric-coated sustained-release granules filled into a gelatine capsule [1,6]. Immunosuppressants, antibiotics and anti-TNF antibodies (e.g., infliximab) also have a role in treating IBD; in particular, Crohn's disease [7].

Detailed reviews of colonic drug delivery may be found elsewhere [8-14]. In summary, there are three primary means (alone or in combination) by which colon targeting of drugs may be achieved via the oral route of administration:

- Exploit the microflora of the colon. The microbial population of the colon provides an anaerobic (reducing) environment and also produces enzymes capable of digesting certain biodegradable polymers such as polysaccharides. Hence, delivery systems that are susceptible to chemical modification (e.g., disruption of coating) by the action of the microflora may be of utility in colonic targeting.
- pH-dependent dosage forms. Apart from the stomach, the remainder of the gastrointestinal (GI) tract is generally in the pH range 5 – 8. The pH tends to rise gradually on moving from the duodenum through the remainder of the GI tract. It reaches a peak just prior to entry into the colon, whereupon it falls in the proximal colon and gradually rises again in the distal colon. These pH characteristics may be utilised in the design of targeted colonic dosage forms based on the use of pH-sensitive polymers.
- Time-dependent dosage forms. On emptying from the stomach, the time taken for a dosage form to transit the human small intestine and reach the colon is relatively constant at around 3 – 4 h [15]. Hence, dosage forms designed to provide such a delay in drug release may be capable of colon-targeted delivery.

As mentioned earlier, aminosalicylates are a first line of treatment in IBD, especially ulcerative colitis. The active moiety in all of these compounds is mesalazine (5-aminosalicylic acid/mesalamine). Prodrugs for the oral delivery of mesalazine into the colon have been in use for many years. In particular, sulfasalazine was first described in the 1940s and comprises sulfapyridine (sulfonamide antibiotic) joined to mesalazine via an azo (-N = N-) bond. In the colon the reducing environment created by the resident anaerobic bacteria breaks the azo bond to yield the sulfapyridine and mesalazine components. Sulfapyridine is associated with side effects and other mesalazine prodrugs with better side effect profiles have been introduced in recent years (olsalazine, balsalazine) [6-9].

Dosage forms have been designed that exploit the ability of the colonic microflora to digest polysaccharides. For example, the COLAL™ system (Alizyme Therapeutics Limited) utilises a mixture of glassy amylose and ethylcellulose as a controlled-release polymer. Dosage forms coated with this polymer mixture remain intact until they reach the colon where the amylose is digested by colonic bacterial enzymes [16].

In addition to prodrugs, mesalazine has also been delivered into the colon using pH-dependent dosage forms. Enteric (or gastroresistant) coatings have been used for many years to prevent drugs being released from dosage forms into the gastric environment. The primary reason for applying such coatings is to reduce gastric side effects and/or protect drug compounds that are susceptible to degradation in the stomach environment. In such situations the enteric coating will ideally dissolve very rapidly once the dosage form has exited the stomach in order for drug to be released and absorbed in the small intestine. The use of enteric coatings with the specific aim of delivering drugs into the lower regions of the intestine is a more recent development and was driven in part by the desire to deliver mesalazine into the colon for treatment of ulcerative colitis. When delivered orally in a conventional dosage form, mesalazine will be efficiently absorbed from the upper intestine and, therefore, not available for local anti-inflammatory action in the colon. Hence, delivery systems capable of site-specific delivery of mesalazine into the lower intestines were required in order to make therapeutic use of the compound. One of the key mesalazine products is Asacol® (400 mg mesalazine tablets) (P&G Pharmaceuticals). In this product, colonic delivery is achieved by the use of Eudragit® S (Röhm Pharma, Germany): a methacrylate pH-sensitive polymer that dissolves at > pH 7. Other enteric-coated mesalazine tablets based on Eudragit L have followed; for example, Salofalk® (Dr Falk Pharma) [4,8,12].

CODES™ technology (Yamanouchi Pharmaceutical) combines a pH-sensitive polymer and a bacterially degraded component. A core tablet is produced containing drug and lactulose: a disaccharide that is digested in the colon to produce short chain fatty acids. Two coatings are applied to the core tablet: the first is an acid-soluble polymer and the second (applied over the first coating) is a gastroresistant polymer. In the small intestine the outer gastroresistant coating dissolves. When the tablet reaches the colon, lactulose is released, the tablet surface is acidified and the inner polymer coating dissolves to release drug [17].

Timed-release dosage forms have been described in the literature. For example, Pulsincap® (R.P. Scherer) is based on the use of an insoluble capsule in which the contents are sealed in place by a swelling hydrogel plug. The plug hydrates and swells when exposed to the liquid in the GI tract, and it can be engineered to swell at different rates. When it swells to a given size it is ejected from the capsule body and the capsule contents are released [18]. Time Clock™ (Zambon) is a delivery system based on a tablet coated with an eroding layer

Figure 1. Photograph of starch capsule component parts (lid and body) and assembled to form capsule.

based on hydroxypropyl methylcellulose (HPMC) and hydrophobic materials. The outer layer slowly hydrates and dissolves when the tablet enters the GI tract. The process of hydration and dissolution is essentially time dependent; hence, the layer can be designed to keep the tablet intact for the period of time it takes to reach the target region of the GI tract (e.g., colon) [19].

In addition to IBD there are other therapeutic areas for which colon targeting may be desirable or necessary, such as treatment of localised infections, treatment of irritable bowel syndrome and delivery of probiotics. There have also been suggestions of using the colon as a site for absorption of therapeutic peptides and proteins into the systemic circulation, because the environment may be more favourable for stability of these molecules than the upper intestines. For example, the relative lack of proteolytic enzymes and the relatively slow transit may make the colon a preferred target site for the oral administration of peptides and proteins. However, by virtue of molecular size, the permeability of the colonic epithelial tissues to therapeutic macromolecules is likely to be low and require some form of absorption enhancement to be of practical utility [20].

Hence, the major area of focus for colon-targeted dosage forms is, for the foreseeable future, likely to remain the delivery of drugs for local therapeutic effect. This is certainly seen to be the main area of interest for West Pharmaceutical Services' (West's) TARGIT™ technology.

2. Limitations of existing technologies

There are potential drawbacks associated with the different methods for achieving colon-specific delivery:

- Formulations that rely on colonic microflora to trigger drug release are potentially affected by inter- and intrapatient variations in the nature and number of microorganisms residing in the colon. Sources of such variations include diet, disease and drugs (e.g., antibiotics).
- Time-dependent formulations are susceptible to variable transit; in particular, variable gastric emptying due to the size and shape of the dosage form and/or state of feeding of the subject. It may be possible to overcome this drawback by applying a gastroresistant coat to the dosage form such that the time-dependent release mechanism is only triggered when the dosage form empties from the stomach.
- pH-dependent formulations often use polymer coatings that dissolve at a high pH, such as Eudragit S, which only dissolves at > pH 7. In some individuals this pH may only be reached briefly or, in some cases, not at all, which can lead to occasional excretion of intact tablets in the faeces [21].

3. TARGIT™ technology

TARGIT technology is designed to exploit the advantageous aspects of colonic delivery systems while minimising or eliminating the factors that lead to variability.

The basis of TARGIT technology is a coated injection-moulded starch capsule; hence, a description of the technology may conveniently be divided into the capsule component and the coating.

3.1 Starch capsules

3.1.1 How they are made

The starch capsules used in TARGIT are produced by a proprietary injection-moulding process, which was originally developed by Capsugel, but now exclusively licensed to West. Injection-moulded starch capsules have been described in detail elsewhere [22]. In brief, a starch-based pellet formulation is fed into the reciprocating screw of an injection-moulding machine. As the starch moves along the screw it is heated and compressed to form a melt. The melted material is fed into moulds, the moulds briefly cooled and the moulded parts ejected. The starch capsule comprises two separately moulded components: a body and a lid. In contrast to conventional hard capsules, the lid fits flush onto the body to form a continuous unit that allows for easy application of coatings (**Figure 1**). The lid is sealed onto the body by application of a thin layer of water/alcohol solution to the inner rim of the lid at the point of closure of the capsule. This process can be performed manually on a small scale or by automated means on a larger scale.

3.1.2 Properties and characteristics of starch capsules

The vast majority of hard capsules used in pharmaceutical applications are made from gelatine, although alternative materials are becoming available; for example, pullulan or HPMC gelled through the addition of other materials.

Figure 2. Photograph of production-scale machine for filling and sealing starch capsules.

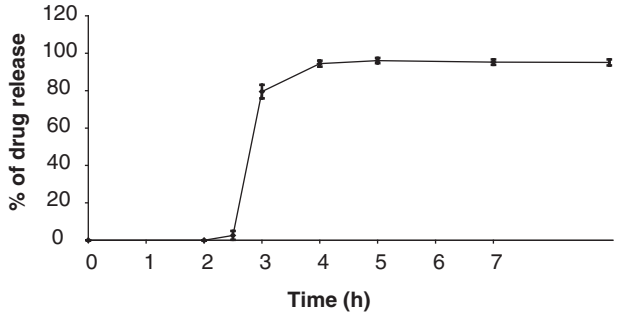

Figure 3. *In vitro* dissolution of starch capsule formulation containing drug formulated as modified-release beads (mean data ± standard deviation, n = 6). Dissolution medium was 0.1 M hydrochloric acid for first 2 h, followed by pH 7.5 phosphate buffer.

Despite the fact that they are widely accepted and inexpensive, hard gelatine capsules do have drawbacks. For example, the water content is typically in the range 13 – 16% and much of this is loosely bound and can readily migrate between the capsule shell and its contents. A reduction in solubility of the gelatine capsule shell on exposure to high temperatures and humidity is also a well-known phenomenon: often referred to as 'cross-linking' [23]. More particularly for colonic delivery, there are difficulties associated in the polymer coating of gelatine capsules; for example, the capsule shell may soften when aqueous coating preparations are applied, whereas evaporation of water from the capsule shell during coating may lead to it becoming brittle [22]. The presence of a lip between the capsule body and lid also presents problems and generally necessitates the additional step of applying a gelatine band in order to produce a continuous coating surface. Because the design of hard capsules made from materials such as HPMC and pullulan is identical to gelatine capsules, there will also be the need to apply a band prior to coating.

The flexible nature of traditional capsules means that applied coating layers need to be equally flexible to ensure that their integrity is maintained during manufacture, packing and transport, or in the event that the capsule is harshly handled.

In contrast, starch capsules have a rigid, dense construction, which is illustrated by the weight difference between starch and gelatine capsules. For example, an empty size 0 starch capsule weighs around 420 mg, whereas the same size of hard gelatine capsule weighs ~ 90 mg. Despite these structural differences, the *in vitro* and *in vivo* disintegration performance of starch and hard gelatine capsules has been shown to be equivalent [22]. Although the moisture content of starch capsules (12 – 14%) is comparable to gelatine, > 50% of this is tightly bound to the starch, and hence the potential for interactions between the capsule shell and its contents are much reduced.

The length of the starch capsule body is easily adjusted, allowing for the manufacture of capsules in a range of sizes with a universal cap.

Starch capsules are compatible with a wide range of fill materials, including powders, granules, pellets, waxes and semisolids. They may also be suitable for hydrophobic liquid fills. With regard to hot melt semisolid formulations, a waxy material with a melting point of 130°C has successfully been filled into starch capsules [24].

Commercial-scale filling of starch capsules is undertaken on purpose-modified equipment, based on a conventional capsule filler, which can fill and seal several thousand capsules per hour (**Figure 2**).

Newer generation capsules, such as those made from starch and HPMC, are more expensive to produce than their gelatine counterparts, but they will still remain a minor cost component when used as the basis of a drug delivery system.

3.1.3 Coating capsules to produce TARGIT™

To produce TARGIT, the starch capsule is coated with polymers that provide site-specific delivery into the terminal ileum and colon [101]. The preferred TARGIT coating is based on pH-sensitive (gastroresistant) polymers. A variety of polymers are available that are characterised by insolubility at gastric pH and solubility at intestinal pH. Examples of such polymers include cellulose acetate phthalate, hypromellose phthalate, polymethacrylates (e.g., Eudragit), polyvinyl acetate phthalate

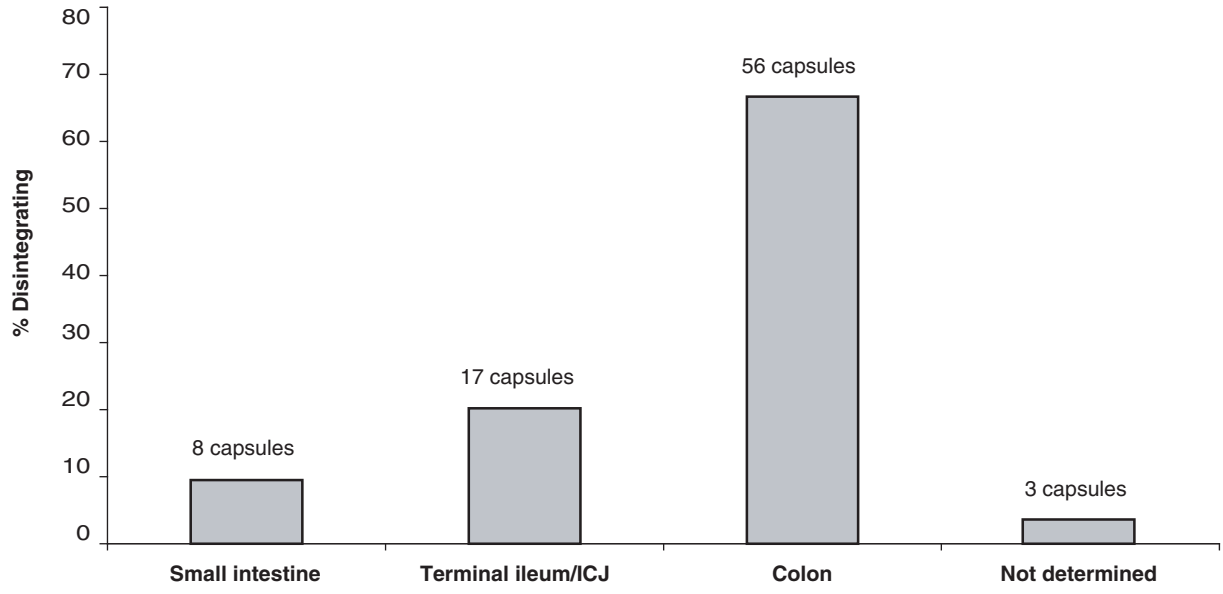

Figure 4. Regional distribution of disintegration of TARGIT™ capsules (n = 84) in gastrointestinal tract, as determined by γ-scintigraphy.
ICJ: Ileo-caecal junction.

and shellac [25]. Eudragit pH-sensitive polymers are particularly suitable, and all of the data presented in this review are based on starch capsules coated with these materials.

Eudragit L and S are anionic copolymerisation products of methacrylic acid and methylmethacrylate. The ratio of free carboxyl groups to the ester is ~ 1:1 in Eudragit L and 1:2 in Eudragit S, and these differences in structure provide the different solubility characteristics of the two polymers: Eudragit L dissolves when the pH is > 6 and Eudragit S dissolves when the pH is > 7. These polymers have monographs in the US Pharmacopeia, in which they are referred to as 'methacrylic acid copolymers', and in the European Pharmacopeia, in which they are referred to as 'methacrylic acid-methyl methacrylate copolymer (1:1)' (Eudragit L) and 'methacrylic acid-methyl methacrylate copolymer (1:2)' (Eudragit S) [25].

The preferred polymer coating used in TARGIT contains a 3:1 (by weight) mixture of Eudragit L100 and S100. Talc is also included as an anti-tack agent, and a plasticiser (e.g., dibutyl sebacate) is added to provide flexibility.

The rigid, smooth surface of the starch capsule presents an excellent coating substrate and is suitable for the application of both aqueous and non-aqueous coating preparations. The weight of the starch capsule provides a solid bed for coating processes. On a small scale TARGIT capsules can be coated efficiently using a fluidised bed apparatus such as an Aeromatic Strea-1. Pan and drum equipment is more appropriate for pilot and commercial scale coating.

3.2 How TARGIT™ works

The blend of pH-sensitive polymers used in TARGIT is specifically chosen to start dissolving at a relatively low pH to avoid the potential drawbacks associated with polymers that do not dissolve until a high pH is reached, that is, incomplete or delayed disintegration. For example, the preferred 3:1 mixture of Eudragit L100 and S100 will start to dissolve when a pH of around 6.3 is reached. Choosing a polymer coating that dissolves at such a pH should avoid the issue of the dosage form failing to disintegrate, although an appropriate coat thickness needs to be chosen to ensure that the TARGIT capsule remains intact on its passage through the small intestine. Although the thickness is typically chosen to provide delivery to the terminal ileum and ascending colon region, thicker or thinner coatings can modify the release site of TARGIT distally or proximally, respectively.

Due to the construction of TARGIT™, in which the walls of the starch capsule separate the enteric coating from the capsule contents, dissolution of the coating is essentially independent of the capsule fill. This avoids the need to reformulate the coating when changing from one drug compound or formulation to another.

Dissolution testing of TARGIT is generally performed using a paddle apparatus (USP apparatus 2, paddles set at rotation speed of 50 – 100 rpm) with the capsules being weighted by loose-coiled wire sinkers. The typical dissolution medium is 0.1 M hydrochloric acid for the first 2 h of the test to represent the stomach, after which it is replaced by a medium to represent the intestine; for example, pH 6.8 phosphate buffer. An example of an *in vitro* dissolution profile of a TARGIT formulation is shown in **Figure 3**.

3.3 Clinical profile

So far, several Phase I (volunteer) clinical studies have been conducted on TARGIT technology including γ-scintigraphy, pharmacoscintigraphy (combination of scintigraphy and drug

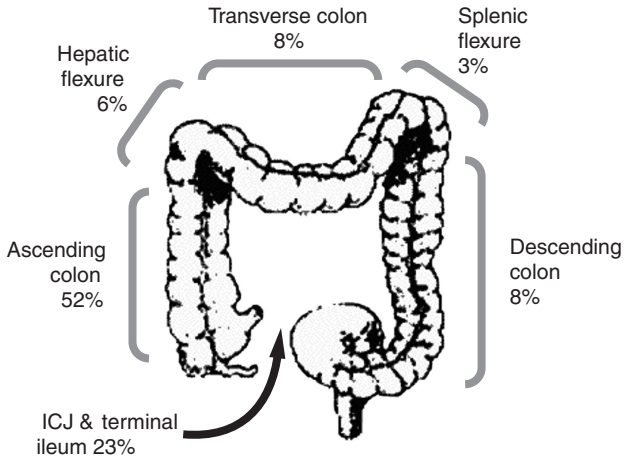

Figure 5. Distribution of disintegration of TARGIT™ capsules (n = 73) within terminal ileum and colon (γ-scintigraphy data). Data presented as percentage of capsules disintegrating in different anatomical regions.
ICJ: Ileo-caecal junction

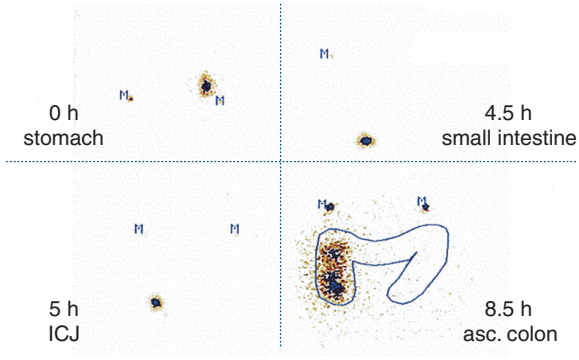

Figure 6. Selected scintigraphic images from a human volunteer following administration of a TARGIT™ capsule.
'M': Radioactive marker used to align subject for imaging.
ICJ: Ileo-caecal junction

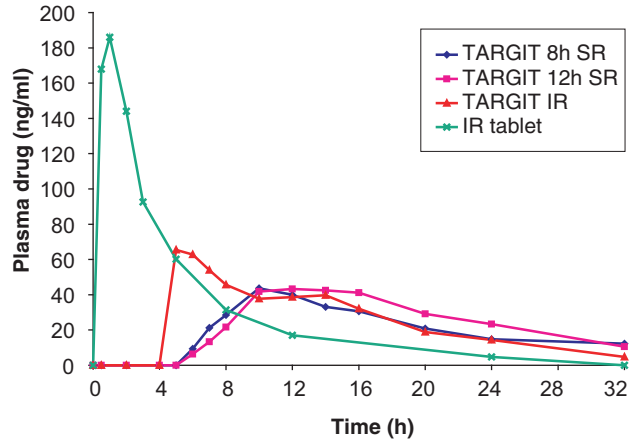

Figure 7. Mean pharmacokinetic profiles following administration of TARGIT™ and IR tablet formulations to human volunteers (n = 8) containing an experimental drug for treatment of IBD. TARGIT™ capsules contained either SR or IR beads.
IBD: Inflammatory bowel disease; IR: Immediate release; SR: Sustained release.

pharmacokinetic measurements) and pharmacokinetic investigations (no scintigraphic measurements). In these studies, around 90 volunteers have received a total of almost 300 TARGIT capsule doses.

In a number of γ-scintigraphy trials, a total of 84 TARGIT capsules have been administered to healthy human volunteers. All studies were conducted in the UK under the approval of Ethics Committees, with authority to administer radioisotopes obtained from the Department of Health, London. The capsules were radiolabelled by incorporating either indium-111 or samarium oxide into the capsule fill. γ-Scintigraphy is a well-established technique for measuring the *in vivo* movement and disintegration of dosage forms [26]. The passage of the radiolabelled capsule through the GI tract is followed by a γ-camera and a series of images collected. The intact capsule will appear on these images as a well-defined, concentrated source of radioactivity and, when it starts to disintegrate and the contents empty, this radioactivity will start to disperse accordingly.

A summary of disintegration data is provided in **Figure 4**. The clinical studies have demonstrated that TARGIT can provide highly reliable delivery into the lower GI tract, with 87% of capsules (73 out of 84) disintegrating in the target region of the terminal ileum and colon. In a small number of instances (**Figure 4**, 'Not determined') it was not possible to establish the point of disintegration accurately, typically due to the capsule disintegrating during an overnight phase between collection of scintigraphic images. The remaining capsules primarily disintegrated in the lower regions of the small intestine. The regional distribution of disintegration of the 73 capsules that disintegrated in the terminal ileum and colon is shown in **Figure 5**, and indicates that a substantial majority released their contents in the ascending (proximal) colon.

A typical series of scintigraphic images is provided in **Figure 6** and shows the intact TARGIT capsule in the stomach, small intestine and ileocaecal junction. The capsule has disintegrated in the ascending colon and its contents have widely dispersed.

In all of the clinical studies conducted so far, TARGIT capsules have been administered in the fasted state. However, because the capsule coating is resistant to disintegration in the stomach and the human small intestinal transit rate is reported to be independent of feeding state [15], TARGIT *in vivo* performance is not expected to be influenced by whether the capsule is taken on an empty stomach or after food.

Two of the TARGIT clinical studies are highlighted below.

Table 1. A summary of a selection of propietary oral drug delivery systems that may be suitable for providing colon-specific drug delivery.

Technology	Developed by	Mechanism	Comments	References
COLAL™	Alizyme	Uses glassy amylose, degraded by colonic bacteria	Phase II clinical trial completed on prednisolone	[16,201]
CODES™	Yamanouchi	Coated tablet formulation. Tablet core contains lactulose, which is degraded by colonic bacteria and triggers coat dissolution	No information on stage of development	[17]
EUDRACOL™	Röhm Pharma	Multiple units utilising Eudragit® pH-sensitive and sustained release polymers	In clinical development	[27]
OROS® technologies	Alza	In principle, it is possible to formulate osmotic tablets with delayed-release feature	Not aware of colon-targeted products being in development	[9,28]
Pulsincap®	Scherer	Insoluble capsule body with swelling plug	Development ceased	[18]
Time Clock™	Zambon	Slowly eroding coating applied to tablet	Development believed to have ceased	[19]
Enterion™	Pharmaceutical Profiles	Remote-controlled capsule device (tracked by γ-scintigraphy and triggered by external magnetic field)	Use currently confined to regional absorption studies of investigational drugs	[29]

3.3.1 Case study 1: new chemical entity for treating inflammatory bowel disease

An experimental compound under investigation for treatment of IBD was formulated into TARGIT as coated non-pareils. On release into the colon the non-pareils were designed to provide immediate release and two different rates of sustained release of the drug compound (8 and 12 h). A γ-scintigraphy study was conducted on the three TARGIT formulations (radiolabelled) with an immediate-release tablet (non-labelled) as a pharmacokinetic control. The γ-scintigraphy data showed excellent performance from TARGIT, with 23 out of 24 capsules disintegrating in the terminal ileum or colon (one capsule disintegrated more proximally). Pharmacokinetic data are provided in **Figure 7** and the delay in drug absorption from the TARGIT formulations was in accord with the scintigraphic data. In addition, the pharmacokinetic profiles were consistent with the *in vitro* dissolution profiles of the formulations. The bioavailability of drug from the TARGIT formulations was comparable with that from the immediate-release tablet.

3.3.2 Case study 2: TARGIT™–budesonide

A colon-targeted budesonide formulation is under investigation by West for the treatment of ulcerative colitis. The product is designed to provide drug for local anti-inflammatory activity in the colon and hence minimise side effects associated with systemic corticosteroid exposure. The budesonide is formulated as sustained-release non-pareils which are filled into TARGIT capsules. The formulation has completed a Phase I pharmacokinetic study in the US in which different doses of budesonide were administered in TARGIT capsules. The capsules were well tolerated and the delay in appearance of budesonide in plasma was consistent with delivery of the drug into the lower GI tract. A linear relationship was found between dose and area under the curve, and dose and C_{max}. A Phase II clinical study is being conducted that will also generate valuable data on the performance of TARGIT in a disease state. This is an important consideration in the development of a colon-targeted dosage form, as performance could potentially be influenced by changes in the colonic environment caused by the disease state and/or concomitant medications. For example, ulcerative colitis may be associated with a lower colonic pH and more rapid transit [8].

4. Alternative technologies

Table 1 provides a summary of a selection of proprietary oral drug delivery systems that may be suitable for providing colon-specific drug delivery.

5. Conclusion

TARGIT technology is based on proven concepts and materials. Performance of the coating is independent of the formulation or drug filled into the capsule and hence there is no need to modify the coating when either of these factors is changed. There is an extensive body of data confirming the ability of the coated capsules to deliver drugs into the colon. Products utilising TARGIT are in active clinical development.

6. Expert opinion

TARGIT appears to provide a simple and effective means of achieving site-specific drug delivery into the lower GI tract. The use of a coated capsule as the targeting mechanism is especially attractive because the drug formulation does not influence the dissolution of the TARGIT coating and, as a consequence, its *in vitro* and *in vivo* performance. As a result, the need for potentially lengthy and expensive reformulation work is avoided each time a new compound is incorporated into TARGIT. Diseases of the lower GI tract, such as IBD, continue to present a major challenge to medicine, and delivery technologies such as TARGIT™ may enable more effective use of existing drug compounds and provide a means of administering new compounds targeted at such conditions. The use of injection-moulded starch capsules as the basis for TARGIT offers a number of advantages over conventional capsules in terms of ease of coating, robustness and stability.

Bibliography

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

1. In: *British National Formulary*. Number 48, Pharmaceutical Press and British Medical Association, London (2004).
2. KARP CK, TARGAN SR: Ulcerative colitis. Evidence for an updated hypothesis of disease pathogenesis. In: *Mucosal Immunology*. Ogra PL *et al.* (Eds.), 2nd edition, Academic Press, San Diego (1999):1047-1053.
3. DUCHMANN R, ZEITZ M: Crohn's disease. In*: Mucosal Immunology*. Ogra PL *et al.* (Eds.), 2nd edition, Academic Press, San Diego (1999):1055-1080.
4. COURTNEY MG: The medical treatment of ulcerative colitis. In: *Ulcerative Colitis*. O'Morain CA (Ed.), CRC Press, Boca Raton (1991):139-151.
5. LOFTUS EV: Clinical epidemiology of inflammatory bowel disease: incidence, prevalence and environmental influences. *Gastroenterology* (2004) **126**:1504-1517.
6. In: *Martindale*. Sweetman SC (Ed.), 33rd edition, Pharmaceutical Press, London (2002):1205-1206.
7. NAYAR M, RHODES JM: Management of inflammatory bowel disease. *Postgrad. Med. J.* (2004) **80**:206-213.
8. WATTS PJ, ILLUM L: Colonic drug delivery. *Drug Dev. Ind. Pharm*. (1997) **23**:893-913.

•• **General review of the field of colonic drug delivery.**

9. CHOURASIA MK, JAIN SK: Pharmaceutical approaches to colon targeted drug delivery systems. *J. Pharm. Pharmaceut. Sci*. (2003) **6**:33-66.

•• **General review of the field of colonic drug delivery.**

10. YANG L, CHU JS, FIX JA: Colon-specific drug delivery: new approaches and *in vitro*/*in vivo* evaluation. *Int. J. Pharm.* (2002) **235**:1-15.

•• **General review of the field of colonic drug delivery.**

11. WILSON CG: Colonic drug delivery. In: *Modified Release Drug Delivery Technology*. Rathbone MJ, Hadgraft J, Roberts MS (Eds.), Marcel Dekker, New York (2003):217-222.
12. MUKHERJI G, WILSON CG: Enteric coating for colonic delivery. In: *Modified Release Drug Delivery Technology*. Rathbone MJ, Hadgraft J, Roberts MS (Eds.), Marcel Dekker, New York (2003):223-232.
13. MUKHERJI G, WILSON CG: Biopolymers and colonic delivery. In: *Modified Release Drug Delivery Technology*. Rathbone MJ, Hadgraft J, Roberts MS (Eds.), Marcel Dekker, New York (2003):233-242.
14. LEE WW, WILSON CG, MUKHERJI G: Time-dependent systems for colonic delivery. In: *Modified Release Drug Delivery Technology*. Rathbone MJ, Hadgraft J, Roberts MS (Eds.), Marcel Dekker, New York (2003):243-248.
15. DAVIS SS, HARDY JG, FARA JW: Transit of pharmaceutical dosage forms through the small intestine. *Gut* (1986) **27**:886-892.
16. MILOJEVIC S, NEWTON JM, CUMMINGS JH *et al.*: Amylose as a coating for drug delivery to the colon: Preparation and *in vitro* evaluation using glucose pellets. *J. Control. Rel.* (1996) **38**:85-94.
17. KATSUMA M, WATANABE S, TAKEMURA S *et al.*: Scintigraphic evaluation of a novel colon-targeted delivery system (CODES™) in healthy volunteers. *J. Pharm. Sci.* (2004) **93**:1287-1299.
18. STEVENS HNE: Pulsincap and hydrophilic sandwich (HS) capsules: Innovative time-delayed oral drug delivery technologies. In: *Modified Release Drug Delivery Technology*. Rathbone MJ, Hadgraft J, Roberts MS (Eds.), Marcel Dekker, New York, (2003):257-262.
19. POZZI F, FURLANI P, GAZZANIGA A, DAVIS SS, WILDING IR: The TIME CLOCK system: a new oral dosage form for fast and complete release of drug after a predetermined lag time. *J. Control. Rel.* (1994) **31**:99-108.
20. GOLDBERG M, GOMEZ-ORELLANA I: Challenges for the oral delivery of macromolecules. *Nat. Rev. Drug Discov.* (2003) **2**:289-295.

• **Overview of strategies for oral peptide and protein delivery.**

21. SCHROEDER KW, TREMAINE WJ, ILSTRUP DL: Coated 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. *N. Engl. J. Med.* (1987) **317**:1625-1629.
22. VILIVALAM VD, ILLUM L, IQBAL K: Starch capsules: an alternative system for oral drug delivery. *Pharm. Sci. Technol. Today* (2000) **3**:64-69.

•• **Reviews production, properties and uses of starch capsules, which are a key component of TARGIT™ technology.**

23. AUGSBURGER L: Hard and soft shell capsules. In: *Modern Pharmaceutics*. Banker

GS, Rhodes CT (Eds.), 3rd edition, Marcel Dekker, New York (1996):395-440.

24. HOWE D, GARRELL R, D'ANDREA L, IQBAL K: Development and evaluation of a hot melt formulation in enteric coated starch capsules. *AAPS Pharm. Sci.* (2001) **3**(3).

25. Rowe RC, Shesky PJ, Weller PJ (Eds.): *Handbook of Pharmaceutical Excipients*. 4th Edition, Pharmaceutical Press, London (2003).

26. WILDING IR, COUPE AJ, DAVIS SS: The role of gamma-scintigraphy in oral drug delivery. *Adv. Drug Deliv. Rev*. (2001) **46**:103-124.

27. SKALSKY B, RUDOLPH M, RENNER G: *In-vivo* evaluation of EUDRACOL™: a novel pH- and time-controlled multiple unit colonic drug delivery system. *Transactions of Controlled Release Society 31st Annual Meeting* (2004): Abstract 051.

28. WONG PSL, GUPTA SK, STEWART BE: Osmotically controlled tablets. In: *Modified Release Drug Delivery Technology*. Rathbone MJ, Hadgraft J, Roberts MS (Eds.), Marcel Dekker, New York (2003):101-114.

29. PRIOR DVL, CONNOR AL, WILDING IR: The enterion capsule. In: *Modified Release Drug Delivery Technology*. Rathbone MJ, Hadgraft J, Roberts MS (Eds.), Marcel Dekker, New York (2003):273-288.

Patents

101. WATTS PJ: Colonic drug delivery composition. International publication number WO9535100

Websites

201. http://www.alizyme.com

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