Recent Trends in Oral Drug Delivery

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Introduction

Oral drug delivery remains the most user-friendly form of drug delivery, having the highest degree of patient compliance, and is still the preferred route of drug administration. As such, drugs for chronic conditions are often administered orally for ease of long-term use. Oral drug delivery represents approximately 32% of an estimated $245 billion pharmaceutical market in the US (Viswanathan, 2004).
Many oral drugs are perceived as 'patient-friendly' for compliance, often requiring that the medication only needs to be taken once a day. The most prescribed drugs in the USA that use oral drug delivery technologies include Lipitor® (atorvastatin calcium) manufactured by **Pfizer**, and **AstraZeneca**'s Toprol-XL® (metoprolol succinate). Often, pharmaceutical, generic drug and drug delivery companies are able to apply different types of formulation technology to further develop the type of oral administration that is achieved.

The dissolution rates of drugs with poor water solubility can be greatly enhanced by techniques for producing sub-micron or nanosized drug-containing particles with high surface areas, subsequently improving their bioavailability (Rogers *et al.*, 2001). The use of absorption enhancers for the gastrointestinal (GI) tract may also improve drug bioavailability and efficacy (Aungst, 2000). Absorption rates may be altered by using controlled release formulations to increase the residence time of a drug (Huang *et al.*, 2004), and gastrointestinal site targeting can also be addressed, either as an absorption window or local therapy (Ross *et al.* 2000, Pearnchob and Bodmeier, 2003).

This technical overview aims to provide a brief summary of some of the current innovative research areas in oral drug delivery. It will focus on improved drug dissolution, absorption enhancement, novel controlled-release formulations and innovations in GI targeting.

Improvement in Drug Dissolution

It is estimated that approximately 40% of drugs currently under development have poor water solubility. In certain cases, subsequent improvements in drug dissolution may lead to enhanced bioavailability. One approach is to administer the dose in a liquid form, for example dissolved in cyclodextrin, thus the drug is already solubilised and available for absorption. According to the Noyes-Whitney equation (Costa and Lobo, 2001) the rate of dissolution is directly proportional to the surface area of a drug.
Increasing the surface area of drug particle, by significantly reducing the particle size while still maintaining a stable dry powder, will enable the drug to have a more intimate contact with GI fluids, greatly enhancing its dissolution rate. The rate can be further enhanced by coating with surfactant or stabilising excipients.
A variety of methods have been used to produce drug-containing nanosized particles for incorporation into forms of oral dosage forms. These include: precipitation techniques, such as Evaporative Precipitation into Aqueous Solution (EPAS), which prepare a stabilised and crystalline nanosized drug (Hu *et al.*, 2004a); a micronisation technique, such as the supercritical fluid-processing technique Rapid Expansion from Supercritical Solutions (RESS); mechanical milling techniques; and ultra-rapid freezing processes, for example Spray Freezing into Liquid (SFL). This technique has been used to produce stabilised amorphous nanoparticles of the poorly soluble drug danazol for oral delivery (Hu *et al.*, 2004b).

Absorption Enhancement

Absorption enhancement is a key component to the delivery of macromolecular drugs intended for oral delivery. Various types of permeation enhancers have been studied and a variety of mechanisms which improve absorption have been proposed (Thanou *et al.*, 2001). Anionic and nonionic surfactants may promote transcellular and paracelullar absorption routes, but have also been shown to demonstrate irreversible cell damage in some examples. Classes of amino acids have demonstrated increased intestinal absorption of heparin, and it is proposed that these non-toxic compounds may condense macromolecular structures to allow greater permeation of the compounds. Tight junctions, located between cells in the GI tract are the principle barrier to the passive movement of materials through the paracellular pathway. Calcium depletion by using chelating agents (e.g. EDTA, EGTA) has reportedly increased paracellular permeability by decreasing tight-junction adhesion of Ca^{2+}-dependant adhesion molecules. Fatty acids have also been shown to increase paracellular permeability; sodium caprate is used in drug formulations in Japan, Denmark and Sweden. Much recent research has focused on chitosans and their derivatives as paracellular permeation enhancers. These biocompatible compounds are able to interact with tight junctions, causing them to open while inflicting minimal damage on the integrity of cell membranes.

Controlled Release

Sustained Release

Hydrophilic gel-forming matrix tablets are commonly used for oral extended-release dosage forms. Hydroxypropylmethylcellulose (HPMC), for example, is used to prepare extended-release dosage forms, such as promethazine and acetaminophen. HPMC is considered to be pH independent and, as such, is ideal for many extended-release applications. The mechanism of drug release varies. For water-soluble drugs, drug diffuses through a gel layer that forms on the outside of the tablet as it becomes wet. Therefore, the release rate is dependent on this rate of diffusion into the surrounding media. In the case of drugs with poor water solubility, the release rate is dependent on the rate of the dissolution of the gel layer actually containing the drug.

Waxy matrix tablets may also be manufactured to obtain near zero-order release profiles in order to maintain steady physiological serum levels of drug. Water-soluble compounds can diffuse from insoluble hydrophobic matrices at a constant rate. Coatings, such as Ethocel® (Sajeev *et al.*, 2002), Eudrugit® (Pearnchob and Bodmeier, 2003), Kollicoat® (Dashevsky *et al.*, 2005), or starch acetate (Tarvainen *et al.*, 2004), can also be applied to limit the passage of water into a granule or tablet for extended drug release.

Osmotic pumps are increasingly used in oral drug delivery (Verma *et al.*, 2004). OROS® (**ALZA Corp.**), for example, can release drug for up to 24 hours. Using this type of delivery, drug release can be optimised to obtain a desired release rate that is independent of pH and other hydrodynamic conditions.

Pulsatile Drug Delivery

Many systems in the human body, such as cardiovascular, pulmonary, hepatic and renal systems, show variation in their function throughout a typical day. They are naturally synchronised to the internal body clocks and are controlled by the sleep-wake cycle. This synchronisation of individual circadian rhythms is important in the maintenance of health within the human body. Each bodily system exhibits a peak time of functionality that is in accordance with these rhythmical cycles. Similarly, disease states affect the function of some of these systems in the body and, therefore, they too exhibit a peak time of activity within a circadian rhythm.

Capsule-based delivery systems can be used to provide a wide range of drug delivery lag-times (*Table 1*). The encapsulation of a drug within a capsule means its effect on the functionality of the device and its subsequent lag-time is minimal, allowing for the inclusion of a broad spectrum of therapeutic agents. Site-specific targeting, particularly to distal regions of the GI tract, is also possible due to the robustness of these capsular devices.

Capsules may be coated with a semi-permeable or water-impervious layer. A semi-permeable coat provides the basis for an osmotically-controlled device. The pressure caused by internal swelling can be used to force the capsule open or to allow rupturing of the capsule body to deliver the drug. A water-impervious, low-density capsule may float on the gastric contents to provide a lag-time. The capsule cap may be removed by a swelling osmotic action mechanism or, in another system, a seal may be inserted into the end of the capsule body, which is removed after the desired lag-time. Another approach is the use of an erodible tablet to seal the contents of a capsule (*Figure 1*). Water in the GI tract causes the tablet's erosion over a predetermined lag-time (McConville *et al.*, 2005); this allows the contents to be expelled into the lumen for rapid dissolution.

Site-Specific Drug Delivery

Oral drug delivery can be manipulated to deliver to specific sites in the GI tract. Irritable bowel disease (IBD) conditions, such as Crohn's disease or ulcerative colitis, and bowel cancer also have the potential to be treated in this way. Conventional therapies for the treatment of IBD rely on daily administration of high doses of drug. Crohn's disease

Capsule device	Functionality
Pulsincap™	A water-impermeable capsule body with hydrogel plug. Plug length and insertion depth controls lag-time.
Egalet™	An insoluble tube with erodible plugs inserted at either end. Plugs are comprised of selected M_w PEG, waxy materials and surfactants. Composition controls lag-time.
Chronset®	An osmotically-coated active compartment within a semi-permeable cap. This swells against a rigid barrier layer and the cap is removed. Lag-time is controlled by the osmotic potential.
Time-Delayed Capsule	Water-impermeable coat on gelatin capsule with an erodible tablet. Erosion of the tablet allows water to enter the capsule, swelling of an expulsion excipient causes expulsion of the drug.
Programmable Oral Release Time (PORT) System®	A water-permeable coated gelatin capsule with an osmotic core that swells and is sealed with an insoluble wax plug. The contents swell to remove the plug. The wall thickness and composition, concentration of the osmotic contents and the length of the hydrogel plug control lag-time.
Pressure-controlled colon delivery capsule	Internally coated capsule. Drug is filled into the capsule as an oily liquid base and sealed with an insoluble waxy plug. Elevated pressure exerted by the ileocaecal junction ruptures the device to release drug into the colon.
Colon-targeted delivery capsule	Enteric outer coat dissolved in the small intestine to expose an acid soluble layer, which dissolves in the colon.
Hydrophilic sandwich capsule	HPMC layer sandwiched between a large outer gelatin capsule and a smaller inner gelatin capsule-containing drug. Erosion of the HPMC layer provides a lag-time, controlled by grade and/or thickness.

Table 1 - Capsule based pulsed delivery devices.

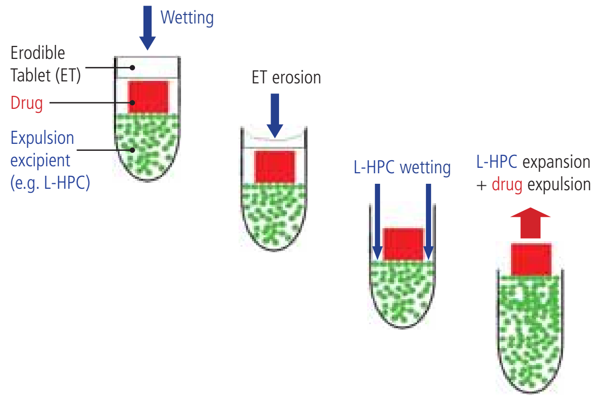

Figure 1 – The mechanism of drug release from a Time-Delayed Capsule.

is often treated with high-dose anti-inflammatory agents, which have a real potential for serious irreversible adverse effects. Localised treatment would reduce the dosage level and subsequent side-effects.
Additionally, preferential absorption of drugs has also been demonstrated for different sites of the GI tract. For example, leuprolide shows absorption variability throughout the GI tract in rats, with maximum absorption available in the colon (Zheng *et al.*, 1999).

Buccal Delivery

This site of delivery has the added advantage of avoiding first-pass metabolism, and so, considering the inefficiency of some oral medications, has the potential to reduce the dose of an administered drug and subsequent side effects. Disadvantages are that drug administration is limited to low drug-dose deliveries and there could be administration side-effects, such as atrophy at the delivery site. Additionally, the site comprises a thick membrane consisting of several layers that need to be permeated. Mucoadhesive formulations have been researched for delivery to the buccal cavity, generally with the addition of permeation enhancers such as chitosan (see above). Furthermore, it may be necessary to hide the taste of drugs and/or excipients by the incorporation of a taste-masking agent.

Gastric Targeting

Gastric retention may be valuable in modulating the delivery of a drug to a patient. Floating dosage forms consist of low-density materials or those that rapidly lower their density to enable buoyancy on the contents of the stomach to increase gastric residence times. The residence time of the dose is controlled by an increase in density or complete emptying of the stomach contents. Drug may be incorporated into low-density polyvinyl pyrrolidone, low-density hollow polycarbonate microspheres, and rapidly swelling porous hydrogel composites; all of which have demonstrated floating properties.

Targeting the Small Intestine

The small intestine is the principle section of the GI tract where absorption of molecules occurs. This part of the lumen has an extremely high surface area due to the presence of large numbers of microvilli, small protrusions on the villi (which are themselves protrusions into the lumen that aid mobility and absorption). Enteric polymeric coatings, which dissolve at the elevated pH levels of the duodenum (compared to the low pH of the stomach), may be used to target specific sites in the GI tract when a pH change occurs. However, these self-modulated systems are reliant on inter-individual uniformity of pH, and may show altered release profiles in patients with conditions such as hypochloridia.

Targeting the Colon

Site-specific delivery may be used to protect drugs such as proteins and peptides, which may be sensitive to proteolytic enzymatic degradation or a low pH associated with gastric secretions. In addition to the protective agents, drugs may be combined with various moieties to form prodrugs. These are designed to pass intact and unabsorbed in the upper GI tract, undergo a biotransformation in the colon, and then release the active drug molecule. Biotransformation is carried out by enzymatic activity, usually of bacterial origin, present in the colon.

Conclusions

Oral drug delivery remains the preferred route of drug delivery due to its non-invasive mode of delivery and its inherent good level of patient compliance. Many delivery opportunities are available using the oral route in order to obtain high systemic levels of drug that are not currently available with other routes of administration. With recent advances in oral delivery technology, many more opportunities for treatment will become available such as local therapy in the GI tract and delivery of macromolecules using mucoadhesive compounds and permeation enhancers with site-specific targeting. Pulsatile drug delivery systems may offer an opportunity to deliver drugs that exhibit chronopharmaceutical behaviour, extensive first-pass metabolism or optimal site-specific delivery in the GI tract.

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