

Scientific Contributions  
Series H: Inaugural Address Nr. 250

***DRUG DELIVERY:  
CREATING OPPORTUNITIES FROM PHARMACOKINETIC  
CHALLENGES***

**Prof JH Hamman**

It all starts here



NORTH-WEST UNIVERSITY  
YUNIBESITHI YA BOKONE-BOPHIRIMA  
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POTCHEFSTROOM CAMPUS<sup>®</sup>



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**SCIENTIFIC CONTRIBUTIONS** (*Wetenskaplike Bydraes*)  
**SERIES H: INAUGURAL ADDRESS: NR. 250**

***DRUG DELIVERY: CREATING  
OPPORTUNITIES FROM PHARMACOKINETIC  
CHALLENGES***

**Prof JH Hamman**

**Inaugural Address held on 31 May 2012**

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## 1. ABSTRACT

A drug faces several challenges after oral administration before the site of action is reached. The major obstacles to drug delivery after oral administration include enzymatic degradation, the physical barrier of the intestinal epithelial membrane, active efflux back into the lumen of the gastrointestinal tract and biliary excretion. As more and more drugs are developed that exhibit poor membrane permeability, the issue of drug absorption enhancement becomes increasingly important in drug research. Strategies to improve the oral bioavailability of drugs can be divided into two groups namely chemical modifications and formulation technologies. Chemical modifications include pro-drug design and or changing the structure of the drug in such a way to improve solubility or membrane permeability. Formulation technologies include the use of absorption enhancing agents, efflux inhibitors, enzyme inhibitors, mucoadhesive systems and particulate carrier systems. Absorption enhancing agents increase drug membrane permeability through different mechanisms such as tight junction regulation and efflux inhibition. Although many chemical compounds have been investigated for their drug absorption enhancing properties, some caused toxicity and damaging effects to the intestinal epithelium. However, some absorption enhancing agents have been identified that cause a reversible effect on the intestinal epithelium and thereby show potential to be included in clinically effective drug delivery systems.

## 2. UITTREKSEL

Na orale toediening staan 'n geneesmiddel baie uitdagings in die gesig voordat die plek van werking bereik kan word. Die hoofversperrings wat inwerk teen effektiewe geneesmiddelaflewering na orale toediening sluit ensiematiese afbraak, fisiese skans van die intestinale epiteelselmembraan, aktiewe efflux terug na die lumen van die gastrointestinale kanaal en galeksresie in. Soos wat meer en meer geneesmiddels met swak membraandeurlaaatbaarheid ontwikkel word, word die aspek van geneesmiddelabsorpsiebevordering meer belangrik in geneesmiddelnavorsing. Strategieë om geneesmiddels se orale biobeskikbaarheid te verbeter kan in twee groepe verdeel word naamlik chemiese modifikasies en formuleringstegnologieë. Chemiese modifikasies sluit die ontwerp van pro-geneesmiddels asook verandering van die chemiese struktuur van geneesmiddels om hul oplosbaarheid en membraandeurlaaatbaarheid te verbeter in. Formuleringstegnologieë sluit die gebruik van absorpsiebevorderaars, efluks-inhibeerders, ensiem-inhibeerders, mukoklewendesisteme en deeltjieafleweringssisteme in. Absorpsiebevorderende stowwe verhoog geneesmiddels se membraandeurlaaatbaarheid deur middel van verskillende meganismes soos byvoorbeeld regulering van digte aansluitings en efluksinhibisie. Alhoewel baie chemiese stowwe reeds ondersoek is vir hulle geneesmiddelabsorpsie bevorderende eienskappe veroorsaak sommige toksisiteit en skadelike effekte op intestinale epiteel. Absorpsiebevorderende stowwe is al geïdentifiseer wat omkeerbare effekte op die intestinale epiteel veroorsaak en daardeur die potensiaal wys om ingesluit te word by kliniese effektiewe geneesmiddelafleweringssisteme.

### 3. INTRODUCTION

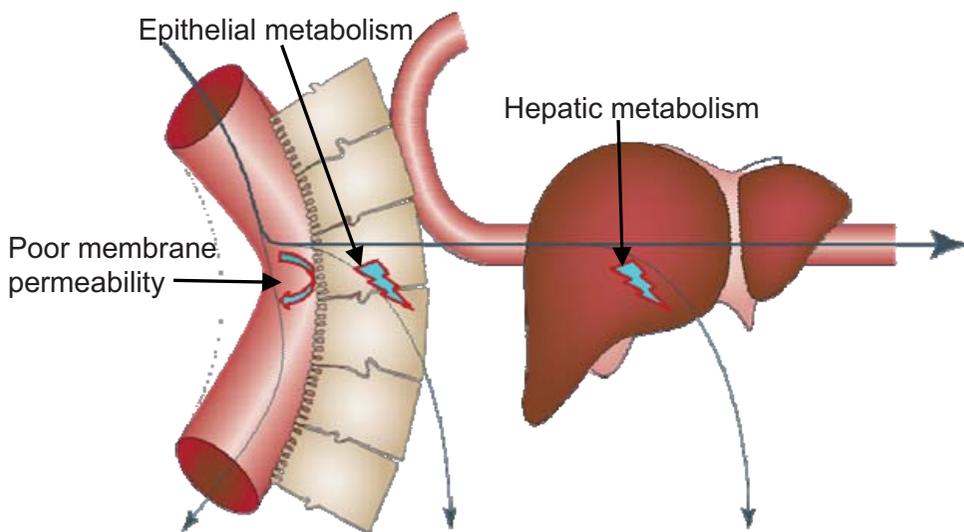
Technologies to develop new drugs are far more advanced when compared to those available for effective systemic delivery of drugs, especially for drugs with physicochemical properties that limit membrane transport and those that are susceptible to pre-systemic metabolism. Drug discovery and production technologies such as recombinant DNA techniques, solid state peptide synthesis and combinatorial chemistry contributed to the fast progress made in this field of research. Ironically, many drug molecules that are now developed and produced on a large scale through these advanced technologies cannot be delivered orally in sufficient amounts. The main constraints that limit oral delivery of these drugs include poor solubility, degradation in the gastrointestinal tract, metabolism in the epithelium and in the liver as well as poor permeability across the membranes of the intestinal epithelial cells (Hamman *et al.*, 2005).

The issue of drug delivery becomes progressively important as more and more poorly absorbable drugs are developed. The development of innovative drug delivery systems remains an important issue to produce clinically successful formulations for these poorly absorbable drugs. These advanced drug delivery systems will have to utilize different approaches such as biological systems (e.g. active transporters) to ensure effective drug delivery (Morishita and Peppas, 2012).

The strategies that have been utilized to enhance drug absorption can be divided into three main groups namely pro-drugs, physicochemical modifications and formulation strategies. More than one strategy is often applied together since more than one barrier is usually simultaneously responsible for the poor absorption of drugs (Gomez-Orellana, 2005).

## 4. PHARMACOKINETIC CHALLENGES

If a drug has a very low bioavailability that is typically below 20% of the administered dose, it is likely that insufficient drug will become available at the site of action to produce a pharmacological response. In addition, low bioavailability causes high inter- and intra-subject variability that makes prediction of the pharmacologic and toxic effects of a given dose very difficult especially for drugs with narrow therapeutic indices (Aungst, 2000). Some of the potential challenges that may affect drug delivery after oral administration are illustrated in Figure 1.



**Figure 1:** Illustration of some of the potential pharmacokinetic challenges that may affect drug bioavailability when a drug is administered orally that is intended for systemic delivery (Adapted from Dickens and Van de Waterbeemd, 2004).

## 4.1 Poor membrane permeability

A balance between hydrophilic and lipophilic properties is needed for a drug to cross the intestinal epithelial membrane after oral administration because the plasma membranes act as a semi-permeable barrier to the passage of molecules based on their physico-chemical properties. Four physicochemical parameters have been identified that are associated with both aqueous solubility and intestinal permeability, which include the hydrogen bonding capacity in terms of both H-bond donors and acceptors, lipophilicity and size of the molecule (Table 1). Drug molecules with a molecular size above 500 Da usually experience difficulty in terms of membrane permeability by means of passive diffusion. The phospholipid bilayer nature of the plasma membrane is responsible for restricting the movement of large hydrophilic drugs across the epithelial cells (Lipinski *et al.*, 2001; Lipinski, 2004).

**Table 1:** Physicochemical parameters required for acceptable aqueous solubility and membrane permeability according to the 'rule of five' (Lipinski *et al.*, 2001; Lipinski, 2004).

| Physicochemical parameter                              | Value      |
|--|------------|
| Molecular weight                                       | $\leq 500$ |
| Partition coefficient (Log P)                          | $\leq 5$   |
| H-bond donors (expressed as the sum of OH's and NH's)  | $\leq 5$   |
| H-bond acceptors (expressed as the sum of N's and O's) | $\leq 10$  |

There is only one type of occluding junction between epithelial cells that represents the barrier for the paracellular absorption pathway (i.e. through the intercellular spaces), namely the tight junctions (Schumacher and Schumacher, 1999). The tight junctions act as a gate by selectively allowing small hydrophilic molecules to pass through the intercellular spaces, but block the passage of larger hydrophilic molecules. They also act as a fence by forming an intra-membrane diffusion barrier that restricts the mixing of apical and basolateral membrane components. This fence function is directly responsible for the maintenance of polarity of the enterocytes (Ward *et al.*, 2000).

## **4.2 Efflux**

ATP binding cassette (ABC) transporters (e.g., P-gp and multi-drug resistance-associated protein-2 (MRP2)) are located in different organs such as the intestinal epithelium, human liver, kidney or the endothelium of blood capillaries of the brain. These transporters are responsible for actively transporting molecules from within the epithelial cells back into the lumen of the gastrointestinal tract. It has been shown that drug efflux transporters, acting alone or together with drug metabolising enzymes, play a significant role in oral drug bioavailability (Breedveld *et al.*, 2005; Hellum and Nilsen, 2008).

## **4.3 Metabolic degradation**

The primary site of metabolism for xenobiotics is the liver, but other sites of metabolism include skin, lung, kidneys and the gastrointestinal tract. The most common drug metabolism action is performed by a large class of enzymes called the Cytochrome P-450 enzyme system (Janda and Fagan, 2010).

Enzymatic degradation of drugs may occur at the different sites in the gastrointestinal tract, which include the following (Lee and Yang, 2001):

- in the fluids of the gastrointestinal tract lumen,
- in the microvilli of the enterocytes by means of membrane-bound enzymes of the brush-border,
- within the cytoplasm of the enterocytes,
- by colonic microflora.

Although peptides and proteins in the diet need to be metabolized in the intestine to be absorbed as amino acids, it is important that peptide and protein drugs be transported intact to the site of action in order to exert their pharmacologic actions (Hamman *et al.*, 2005).

#### **4.4 Interplay between efflux and metabolism**

The concerted effect by efflux transporters and metabolic enzymes presents a complex mechanism by which a drug's bioavailability is restricted. This interplay occurs due to overlap in substrate specificity between metabolizing enzymes and efflux transporters and has been identified as a complicating factor in drug-drug and herb-drug interactions (Benet *et al.*, 2004; Zhang *et al.*, 2009).

## **5. STRATEGIES TO OVERCOME PHARMACOKINETIC CHALLENGES**

### **5.1 Formulation technologies**

Effective oral drug delivery is becoming increasingly important due to the fact that more and more drugs are developed with poor solubility and bioavailability properties. This limited oral bioavailability is especially applicable to biotechnology-based drugs with peptide and protein structures, which are now produced in large quantities at relatively low cost (Lemmer and Hamman, 2012).

Formulation technologies to improve the oral delivery of poorly absorbable drugs include the use of dosage forms that protect the drug from pre-systemic degradation, dosage forms that remain at the absorption site in close contact with the absorption membrane as well as those that improve drug bioavailability through the use of excipients capable of increasing membrane permeability (Hamman *et al.*, 2005).

#### **5.1.1. Absorption enhancing agents**

Absorption enhancing compounds reversibly remove or temporarily disrupt the intestinal barrier with minimal tissue damage, thus allowing drug molecules to penetrate the epithelial cells and enter the blood and/or lymph circulation (Muranishi, 1990). The properties of an ideal absorption enhancing agent include compatibility with the drug to be delivered, a rapid response, a predictable duration of action, its effect should result in therapeutic drug plasma levels, the effect should be completely reversible, specificity for the drug to be delivered, should not exhibit any systemic or toxic

effects and should not irritate or damage the membrane (Fix, 1996; Junginger *et al.*, 1998).

A relatively large number of chemically diverse compounds have already been investigated for their ability to enhance drug permeability across the intestinal epithelium. Although intestinal drug absorption enhancement has been correlated with acute epithelial damage in some cases, there is evidence that certain drug absorption enhancing agents can increase intestinal drug absorption in a reversible way without causing significant damage or exerting toxic effects (Whitehead *et al.*, 2008).

A summary of different absorption enhancing agents and their respective mechanisms of action are given in Table 2.

**Table 2:** Intestinal drug absorption enhancers and their mechanisms of action (Aungst, 1993; Hamman *et al.*, 2005).

| <b>Absorption enhancer</b>  | <b>Mechanism of action</b>   |
|---|--|
| <b>Salicylates:</b><br>Sodium salicylate<br>Salicylate ion  | Increasing cell membrane fluidity, decreasing concentration of non-protein thiols, prevention of protein aggregation or self-association                                       |
| <b>Fatty acids:</b><br>Medium chain glycerides<br>Long chain fatty acid esters (palmitoylcarnitine)           | Paracellular (e.g. sodium caprate dilates tight junctions) and transcellular (epithelial cell damage or disruption of cell membranes)  |
| <b>Bile salts:</b><br>Sodium taurocholate, sodium taurodeoxycholate, sodium taurodihydrofusidate              | Disruption of membrane integrity by phospholipid solubilisation and cytolytic effects, reduction of mucus viscosity  |
| <b>Surfactants:</b><br>Sodium dodecyl sulfate, sodium dioctyl sulfosuccinate                                  | Membrane damage by extracting membrane proteins or lipids, phospholipid acyl chain perturbation  |
| <b>Chelating agents:</b><br>Ethylene diamine tetraacetic acid (EDTA), ethylene glycol tetraacetic acid (EGTA) | Complexation of calcium and magnesium (tight junction opening)   |
| <b>Complexation:</b><br>Cyclodextrins   | Increase aqueous solubility and dissolution rate   |
| <b>Ion pairing:</b><br>Counterion   | Ionised drug and counterion form a more lipophilic ion pair that can partition into the membrane.  |
| <b>Toxins and venom extracts:</b><br>Zonula occludens toxin (ZOT)<br>Melittin (bee venom extract)             | Interaction with the zonulin surface receptor induces actin polymerisation (tight junction opening)<br>$\alpha$ -helix ion channel formation, bilayer micellisation and fusion |
| <b>Efflux pump inhibitors:</b><br>First, second and third generation P-gp inhibitors                          | Blocking the drug binding site on P-gp, interference with ATP hydrolysis and altering integrity of cell membrane lipids  |
| <b>Anionic polymers:</b><br>Poly(acrylic acid) derivatives  | Combination of enzyme inhibition and extracellular calcium depletion (tight junction opening)  |
| <b>Cationic polymers:</b><br>Chitosan salts<br>N-trimethyl chitosan chloride                                  | Combination of mucoadhesion and ionic interactions with the cell membrane (tight junction opening)   |

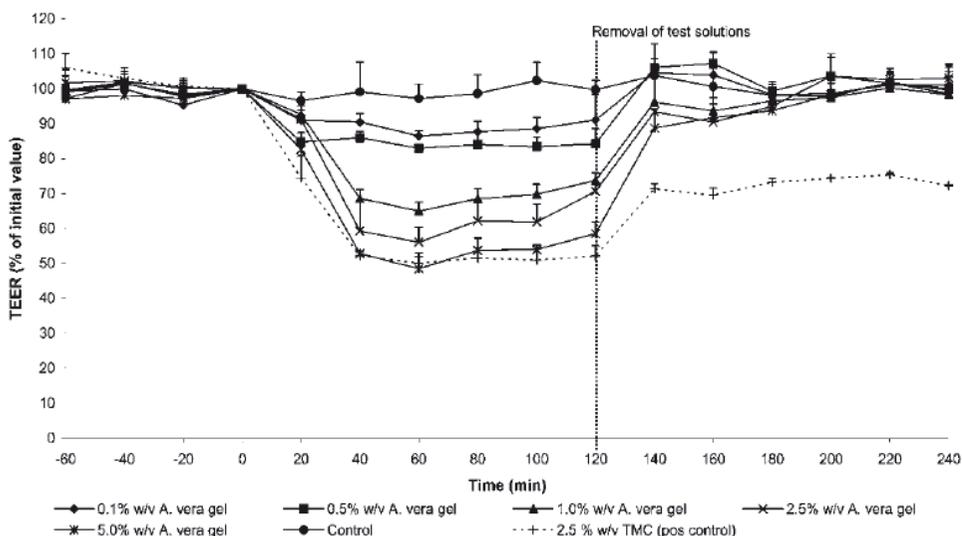
Although absorption enhancing agents exert their effects via many different mechanisms, only those that open tight junctions and inhibit efflux transporters will be discussed in more details in this document.

### **5.1.1.1 Opening of tight junctions**

Cationic polysaccharides such as chitosan can interact with the anionic components of the glycoproteins (i.e. sialic acid) on the surface of the intestinal epithelial cells due to its net positive charge. This interaction with the cell membrane results in a structural reorganization of tight junction-associated proteins, which is followed by enhanced transport through the paracellular pathway (Schipper *et al.*, 1997). Other polysaccharide containing materials of natural origin that have been found to open tight junctions as indicated by reduction in the transepithelial electrical resistance of epithelial cell monolayers as well as enhanced transport of model compounds include the gel material of *Aloe vera*, *Aloe ferox* and *Aloe marlothii* (Chen *et al.*, 2009; Lebitsu *et al.*, 2012; Beneke *et al.*, 2012).

Since certain intestinal inflammatory diseases such as irritable bowel syndrome are characterised by increased paracellular permeability, it was hypothesised that the abnormally leaky colonic epithelium allows bacterial fragments to penetrate into the sub-epithelial spaces that cause an inflammatory response from macrophages and monocytes residing in the lamina propria. The use of paracellular permeation enhancers may therefore cause local intestinal inflammation similar to that observed in irritable bowel syndrome. The challenge in finding a successful paracellular permeation enhancer is therefore to demonstrate that the transient and reversible opening of tight junctions does not result in increased exposure to intestinal bacteria or their by-products (Ward *et al.*, 2000).

The effect of *A. vera* gel on the transepithelial electrical resistance of Caco-2 cell monolayers was completely reversible indicating that the tight junctions reverted back to their original state after removal of the gel materials from the cell monolayers (Figure 2). The *A. vera* gel material therefore showed very high potential to act as an absorption enhancer that may prevent adverse effects due to uptake of unwanted compounds such as toxins and bacterial fragments.



**Figure 2:** TEER of Caco-2 cell monolayers plotted as a function of time after incubation with *A. vera* gel (Chen *et al.*, 2009).

### 5.1.1.2. Efflux transporter inhibitors

Inhibition of efflux transporters such as P-glycoprotein (P-gp) in the intestine can increase the oral bioavailability of drugs that are substrates for these efflux transporters. P-gp efflux inhibition can occur by different mechanisms such as blocking the drug-binding site (i.e. competitively, non-competitively or

allosterically), by interfering with ATP hydrolysis and by altering the integrity of cell membrane lipids (Varma et al., 2003).

Efflux transporter inhibitors are classified into three generations based on their specificity and affinity. First-generation P-gp inhibitors are pharmacologically active substances and these compounds have limited use due to the relatively high concentrations required for P-gp inhibition. Examples include the calcium channel blocker verapamil and the immunosuppressant cyclosporin A. Second-generation P-gp inhibitors lack pharmacological activity and exhibit higher P-gp affinity. Examples include the D-isomer of verapamil and dexverapamil. Third-generation P-gp inhibitors are currently being developed, which are highly potent and selective inhibitors of P-gp (Varma *et al.*, 2003). Marula has shown potential to act as a third generation efflux inhibitor (Tarirai *et al.*, 2012).

Many inhibitors of P-gp also act as inhibitors of metabolising enzymes such as cytochromeP450 co-enzymes. Examples of compounds that show overlap in their inhibition profiles include verapamil, diltiazem, felodipine and nifedipine as well as cortisol, prednisone and progesterone. Co-administration of these inhibitors provides the possibility to maximise the oral bioavailability of drugs that are substrates for for both efflux and metabolising systems (Hunter and Hirst, 1997).

### **5.1.2 Enzyme inhibitors**

This approach is based on the inclusion of an enzyme inhibitor into the dosage form that can reduce pre-systemic metabolism of the active pharmaceutical ingredient. Ideally, the enzyme inhibitor must be specific and should only work where the drug is metabolised for the time that the drug is located at that position. For this to be possible, the enzyme

inhibitor must be kept in close proximity of the drug until it has passed the site of metabolism. Furthermore, inhibition of enzymes in the gastrointestinal tract seems more practically feasible than in the liver due to systemic effect that may be elicited in the latter case. This approach is most applicable to protein and peptide drugs due to the availability of specific peptidase and protease inhibitors (Aungst, 1993).

Attempts to overcome the enzymatic barrier alone provide only limited success for the improvement of bioavailability of peptide drugs (Touitou, 1992). This can be explained by the fact that more than one factor is often simultaneously responsible for the low bioavailability of a particular peptide drug. Most polypeptides exhibit both instability and membrane permeation problems (Bernkop-Schnurch, 2000).

The use of enzyme inhibitors in long-term therapy seems to be problematic due to possible side effects, disturbance of the digestion of nutritive proteins and stimulation of protease secretion as a result of feedback regulation (Bernkop-Schnurch, 1998).

### **5.1.3 *Mucoadhesive systems***

Bioadhesion is defined as the attachment of a synthetic or biological macromolecule to a biological surface. When the drug delivery device adheres specifically to the mucus layer, it is termed mucoadhesion and if it adheres to the cells, it is referred to as cytoadhesion (Vasir *et al.*, 2003). Mucoadhesive delivery systems have several advantages for drug delivery such as a prolonged gastrointestinal residence time, an intimate contact of the delivery system with the mucosal membrane to provide a high concentration gradient as a driving force for passive drug absorption as well as minimum luminal drug degradation, localisation of the delivery system at the absorption window of the particular drug and

providing a basis for functioning of drug absorption enhancers and enzyme inhibitors (Bernkop-Schnurch, 2005).

Unfortunately, gastrointestinal mucoadhesive systems have not yet fulfilled their initial expectation to retain or localise drug delivery systems at a specific region. This inability to remain at the site of adhesion for extended periods of time is due to the relatively high natural turnover rate of the mucus and sloughing of epithelial cells (Kompella and Lee, 2001).

#### **5.1.4 Particulate carrier systems**

Although particles in the size-range of up to 10  $\mu\text{m}$  are taken up intact across the intestinal wall, the efficiency of this process seems to be very low and bulk uptake of compounds via this mechanism (especially through Peyer's patches) is unlikely to be achieved (Swenson *et al.*, 1992).

Liposomes are micro-vesicles consisting of concentric spherical phospholipid bilayers that can encapsulate hydrophilic molecules into their aqueous core spaces. These drug delivery systems have many advantages such as biocompatibility and they are pharmacologically inert with very little toxic effects and don't cause immunogenic reactions. The greatest disadvantage of conventional liposomes is their rapid elimination by the reticulo-endothelial system. To overcome this problem, surface-modified liposomes were developed by attachment of flexible hydrophilic polymers such as poly(ethylene glycol) (Torchillin and Lukyanov, 2003).

## **5.2 Chemical modifications**

### **5.2.1 Pro-drugs**

A pro-drug is defined as a pharmacologically inactive chemical derivative of a parent drug that must undergo enzymatic transformation within the body to become pharmacological active and has improved delivery properties over the parent molecule (Greenwald *et al.*, 2003).

The pro-drug approach can be used to produce a soluble derivative of a water insoluble compound. The pro-drug dissolves in the luminal fluids and diffuses to the membrane where it is converted to the parent drug in close proximity of the membrane by membrane bound enzymes. Since the parent drug is more lipophilic, it will permeate more easily across the epithelial membrane. This is an example where the pro-drug approach increases both the polarity and hence solubility as well as the membrane permeability of a compound (Lipka *et al.*, 1996).

### **5.2.2 Structural modifications**

To improve membrane permeation, the drug structure can be modified to increase its lipophilicity or to reduce the molecular weight or by replacing hydrogen bonding groups (Aungst, 1993). Chemical modification that results in an increase in lipophilicity of a polypeptide molecule is called lipidisation (Wang *et al.*, 2003), which seems to be a reasonable approach for the successful development of an oral peptide delivery system (Shen, 2003).

The covalent attachment of polyethylene glycol (PEG) to amino groups in therapeutically useful polypeptides is termed PEGylation and has been shown to improve their biological

properties (Roberts *et al.*, 2002). An example where PEGylation has been applied to insulin is hexyl-insulin monoconjugate-2 (HIM2). This polyethylene glycol conjugate is one of the first successfully delivered insulin forms via the oral route to show acceptable bioavailability (~5%) and satisfactory glucose-lowering effects (Cefalu, 2004).

Chemical modifications that can be used to protect a peptide drug from pre-systemic degradation range from simple chemical group additions that protect the target bond from enzymatic attack to its complete replacement or by modifying the peptide's conformation in such a way that the molecule is not recognised by the enzyme of concern (Pauletti *et al.*, 1997).

### **5.2.3 Peptidomimetics**

A peptidomimetic resembles a target protein that contains some synthetic elements to reduce enzymatic degradation and to optimise biological activity (Pauletti *et al.*, 1997). The design of peptidomimetics includes strategies ranging from replacement of only one atom up to the design of more complex mimetics that are capable of showing secondary structural elements of peptides (Swenson and Curatolo, 1992).

## **6. CONCLUSIONS**

Many new hydrophilic drug candidates and peptide drugs would become available for oral administration if their bioavailability could be increased so that therapeutic levels are reached in the systemic circulation. Oral administration is still the most popular and acceptable route of drug administration that underpins good patient compliance. The

topic of drug absorption enhancement therefore continues to be an important issue in drug development and research.

Several formulation and chemical modification techniques have been investigated to enhance the intestinal absorption of poorly absorbable drugs. Some of these techniques that were discussed include the co-administration of absorption enhancers, enzyme inhibitors, the preparation of pro-drugs, structural modifications of drugs, microparticulates and mucoadhesive devices. Many materials of natural origin showed potential to act as reversible drug absorption enhancing agents through opening of tight junctions or inhibition of efflux transporters such as chitosan, gel and whole leaf extracts of different aloe species and certain fruit such as marula.

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