



CHALLENGES OF ORAL DRUG DELIVERY SYSTEMS

Bushra Ahmedi*¹, Anna Balaji¹ and M.S. Uma Shankar¹

¹Department of Pharmaceutics, Trinity College of Pharmaceutical Sciences, Peddapally, Karimnagar, Andhra Pradesh, India.

ABSTRACT

Advances have developed and commercialized in oral controlled release products. The significant challenges in developing controlled release formulations for drugs with poor aqueous solubility require different techniques for both solubilization and engineering of release profile. New therapeutics like peptides, proteins, oligonucleotides and vaccines demand for novel controlled release technologies. Challenges for the oral vaccines like instability and poor absorption in GIT have been overcome by lipid formulations. Developing a controlled release formulation for a water insoluble drug is challenging. Complexation and hydrogel reported as carrier for the intestinal delivery of peptides. Compression coating is an extension of tableting technology. Injection molding is a thermal process where polymer or polymer mixture is melted and injected to a mold to form a finished product eg. microneedle for transdermal delivery. Melt extrusion, injection moulding, and drug coating provides flexibility to design oral controlled release formulations. Controlled release delivery of poorly soluble compounds could be pursued through several approaches with combination of solubilization. Formulation designs with computer modeling help to achieve desired release profile of drugs. It is optimistic that oral dosage form of biopharmaceuticals including proteins, peptides, vaccines and nucleotides will become reality eventually with the advancement of the novel technologies. Diabetes mellitus is a common disease and its complications leads to excess morbidity, mortality, loss of independence and reduced quality of life. Diabetes mellitus is responsible for major health care problems and costing billions of dollars annually. Novel approaches for insulin delivery are explored, including oral, nasal, rectal, transdermal, pulmonary, uterine, ocular delivery and subcutaneous implants. Making needles needless is gaining widespread prominence over the disadvantages of subcutaneous route. The oral route is most acceptable and convenient route of drug administration for chronic therapy. Extensive investigations are being conducted to achieve successful control of blood glucose by the oral delivery system.

Key Words:- Challenges, Oral controlled release, Peptides and Vaccines.

INTRODUCTION

Significant challenges in developing controlled release formulations for drugs with poor aqueous solubility require both solubilization and engineering of release profile. New therapeutics under development is large molecules such as peptides, proteins, oligonucleotides, and vaccines. Their physical, chemical, and biopharmaceutical attributes demand novel controlled

release technologies to reduce barriers for oral delivery, such as instability in GI tract and poor absorption. The continuous improvement is also important regarding the decrease of cost and the increase of efficiency. The advancements include novel excipients, processes, and equipments for formulation scientists to develop oral controlled release formulation (Rao VM *et al.*, 2001).

ORAL CONTROLLED DELIVERY FOR WATER-INSOLUBLE DRUGS

Drug products have to be dissolved in GI fluids to get absorbed. For a water-insoluble drug, the absorption

Corresponding Author

Bushra Ahmedi

Email:- ahmedibushra@gmail.com

and bioavailability could be restricted in the GI tract. Strategies to formulate water insoluble drugs include salt formation, micro environmental pH control, solubilization by surfactants, complexation with cyclodextrins, solid dispersion, lipid-based formulation, and nanoparticles formulation. Strategy to be chosen is based on molecular and physical properties of a drug. It is challenging to develop a controlled release formulation for a water insoluble drug (Sotthivirat S *et al.*, 2007).

A controlled oral delivery may be needed to achieve prolonged release for a water-insoluble drug and can be achieved by solubilization and modulating the release. It is advantageous in improving efficacy, reducing side effect, or achieving a more desirable dose regimen (Lee KR *et al.*, 2008).

NEW FORMULATION DESIGNS IN ACHIEVING DESIRED RELEASE PROFILES

Many formulation designs have been pursued to achieve controlled release and minimize the effects of the GI environment. Osmotic pump drug delivery systems by Alza have many proved successes regarding those two aspects. Disintegration controlled matrix tablet (DCMT) and erodible molded multilayer tablet take an erosion approach. Bioadhesive polymers have advantages in improving gastro retentive delivery and enhancing localized therapy in GI tract. Computer modeling has significant progress to design controlled release formulations (Lee KR *et al.*, 2008).

Disintegration-Controlled Matrix Tablet

Tanaka et al developed DCMT as an erosion-based controlled release for the sustained release of solid dispersions. It contains hydrogenated soybean oil as the wax matrix with uniform distribution of solid dispersion granules. These granules are formulated with low-substituted hydroxypropylcellulose as a disintegrant. Mechanism of drug release is tablet erosion. The wax only allows the penetration of water to the surface of tablet, and triggers the swelling of the disintegrant on the surface, and subsequently tablet erosion results in the separation of granules from the tablet (fig 1). A constant rate of disintegration/erosion can be achieved by repeating the processes of water penetration and swelling/separating of solid dispersion granules (Mehramizi A *et al.*, 2007).

Erodible Molded Multilayer Tablet (Egalet)

Egalet erodible molded tablets are also an erosion-based. It has the advantage of delivering zero-order or delayed release with minimal effect from the gastrointestinal conditions. In Egalet erosion occurred in one dimensional, whereas DCMT erosion is taken place in

all three dimensions. Drug is dispersed in the matrix and the zero-order release is controlled by the rate of erosion in the two ends of tablets and surface area for erosion is constant. Egalet tablets are prepared by injection molding (IM). Egalet technology tablet contains a coat and a matrix. Drug release is controlled through the matrix part. The mode and rate of release are designed and engineered by altering the matrix, the coat, and to achieve either a zero-order release or a delayed release. The release rate of prolonged release is dependent on the erosion rate and drug concentration. The zero-order release can be easily achieved if a uniform drug concentration in the matrix and a constant erosion rate are present. Addition of polyethylene glycol could speed up the erosion. The in vivo erosion rate may be affected by GI mobility. Due to the erosion controlled delivery, the burst release effect can be minimized in the Egalet system.

On the other hand, delayed release can be fabricated by Egalet delivery system and is gaining popularity for the enhancement of local effect or chronotherapy. The release of drug is delayed in a certain period of a time in GI tract. One area applicable is to achieve colonic delivery for some therapeutic agents. The time release of the drug can match the natural rhythms of a disease such as the morning stiffness and pain experienced by arthritis patients on waking. A delayed release is achieved through three compartment tablets including a coat, a drug release matrix, and a lag component. The lag component provides a predetermined delayed release (Mehramizi A *et al.*, 2007).

Bioadhesive Oral Delivery

Bioadhesive polymers adhere to the mucin/epithelial surface and find applications in buccal, ocular, nasal, and vaginal drug delivery. It also increases the residential time of solid dosage forms in the GI tract to improve gastro retentive delivery. Bioadhesive polymers enable oral dosage forms stay close to epithelial layer and the quick flux of drugs takes place after dissolution and enhances oral absorption or improve localized therapy if the disease occurred in the GI tract.

Bioadhesion is phenomenon of the attachment of a synthetic or biological polymer to a biological tissue. The GI tract is covered by a layer of mucus and adhesion to mucosa layer is called mucoadhesion. The mechanism of mucoadhesion is not fully understood and attraction forces such as hydrogen bonding, van der Waals, and charges make polymers to have a close contact with the mucus. Many natural polymers and pharmaceutical ingredients show bioadhesive properties and polymers are carbomers, chitosan, starch, polymethacrylic acid, hydroxypropylcellulose, hydroxypropyl methylcellulose,

and sodium carboxymethylcellulose. Bioadhesive delivery provides sustained release for localized therapy. Deshpande *et al.* studied about the design and evaluation of oral bioadhesive-controlled release formulations of miglitol, intended for the prolonged inhibition of intestinal α -glucosidases and the enhancement of plasma glucagon like peptide-1 levels. Bigucci *et al.* developed Pectin-based microspheres for the colon specific delivery of vancomycin. The microspheres made of pectin and chitosan show good mucoadhesive properties (Hong *et al.*, 2008).

Computer Modeling

The biggest challenge for developing of controlled release products is in vitro–in vivo correlation and the GI tract is much more complicated than a dissolution unit. Influences from pH, food, GI mobility, regional absorption, bile salts, and gut metabolism are too complex to formulate as several simple mathematical equations and computer modeling is used. Computer simulation software is useful tools to study the drug molecules and propose target release profiles. Softwares are also applicable for deconvoluting animal and human pharmacokinetic (PK) data and for optimization. Advanced software packages like iDEA, GastroPlus, and SimCYP for modeling oral absorption are physiology-based simulation softwares (Tanaka *et al.*, 2006).

ORAL DELIVERY OF BIOPHARMACEUTICALS

Development of biopharmaceutical agents is challenging for past two decades owing to many breakthroughs in genomics and biotechnology. Hormones, growth factors, and cytokines are important therapeutic agents for curing many diseases including diabetes, anemia, and hepatitis. Monoclonal antibodies with specific molecular targets are excellent drugs for cancer and rheumatoid arthritis. Many new vaccines have been developed for challenging infectious diseases such as HIV, HCV, and HBV. Oligonucleotides such as small interferon RNA appear to be very promising as specific therapeutic agents (Tanaka *et al.*, 2006).

Challenges in Oral Delivery of Biopharmaceuticals

Though many bioactive molecules have become successful commercial products, most of them are delivered by intravenous or subcutaneous injection. The development of noninvasive administration of peptide drugs especially through oral delivery route still remains a great challenge.

Oral delivery of biopharmaceuticals is challenged by instability and poor permeability.

1. Proteins and nucleotides denatured at acidic pH in the stomach, which results in the loss of biological activities.
2. Proteases and nucleases in GI fluids degrade biopharmaceuticals.
3. Pepsin in the stomach and proteases from the pancreas cleave peptide bonds and break down active therapeutic proteins and peptides.
4. Proteins and nucleotides have poor intestinal permeability and are not absorbed due to large molecular weight and hydrophilic nature. The mucus layer in the intestinal lumen tends to bind charged molecules such as proteins and nucleotides, which also prevent oral absorption.

Approaches in Overcoming Challenges in Oral Delivery of Biopharmaceuticals

Progress has been made for oral delivery of peptides or small proteins. Several approaches are taken to improve the GI stability and enhance absorption, like enteric coating, protease inhibitors and permeation enhancers. Enteric coating of oral dosage forms avoid the release of therapeutic agents in the stomach, which reduce the denaturation caused by acidic pH and the degradation by pepsin. Enteric polymers like Eudragit S100 used in tablets, capsules, or pellets pass through the stomach without release and deliver therapeutic peptides to the small intestine or the colon. Colonic delivery is advantageous to the oral delivery of peptides or proteins due to their lower proteolysis activity and greater responsiveness to absorption enhancers (Pederson *et al.*, 2006).

Protease inhibitors (**Ex:** Aprotin, trypsin inhibitor, chymotrypsin inhibitor) reduce the enzymatic cleavage by pancreatic proteases in the intestine. Protease inhibitors are either specific enzyme inhibitors such as aprotin or trypsin inhibitors originated from animals or plants. Organic acids are also effective in inhibiting pancreatic proteases through controlling local pH, which are more active in neutral and alkaline pH than acidic PH.

Permeation enhancers (**Ex:** Acylcarnitine, salicylates, sodium cholate, long-chain fatty acids, bile salts, surfactants (Andrews *et al.*, 2009) reduce the barrier for the oral absorption of peptides. Permeation enhancers are surfactants or detergents such as sodium cholate, fatty acids, bile salts, and phospholipids. Besides from solubilizing poorly soluble peptides, absorption enhancers increase the permeability of biological membrane and fluidize the lipid membrane (Washington *et al.*, 2006).

Several Oral Delivery Systems for Biopharmaceuticals

Unigene (Fairfield) has developed an enteric-coated capsule or tablet with organic acids and

permeability enhancers mixed with a peptide (fig 2) to deliver various therapeutic peptides orally. Oral delivery system by Unigene could achieve 1–10% bioavailability for various peptides and small proteins, depending on size, charge, and structure. Capsules and tablets of salmon calcitonin, a 32-amino acid peptide for the treatment of postmenopausal osteoporosis and Calcitonin is a polypeptide hormone that regulates the metabolism of calcium and phosphorous (Takayama K *et al.*, 2009).

A significant amount of salmon calcitonin has been detected after oral dosing in rats, dogs, and humans. The C_{max} (250–3500 pg/mL) in dog and human was linear with dose from 0.33 to 4.58 mg. The phase I study in human has demonstrated that an oral dose of 0.5 mg can give a mean C_{max} of 300 pg/mL with T_{max} ranging from 90 to 180 min. Unigene has entered a phase II clinical trial. Oral formulations of therapeutic peptides, such as human parathyroid hormone, glucagon-like peptide- 1, and leuprolide, are also being developed and are in preclinical or early clinical test. There are remarkable interests in developing oral formulation for insulin and gained significant media attention (Chen ML *et al.*, 2011).

Challenges to oral insulin delivery

Generally, peptides and proteins [eg: Insulin] cannot be administered orally due to the rapid enzymatic degradation in the stomach, inactivation and digestion by proteolytic enzymes in the intestinal epithelium because of its high molecular weight and lack of lipophilicity. Their bioavailability is less than 1% and the challenge is to improve the bioavailability between 30-50%.

Enzymatic barrier

The harsh environment of GIT causes insulin degradation because of digestive processes, are designed to breakdown proteins and peptides. Insulin undergoes enzymatic degradation pepsin and pancreatic proteolytic enzymes such as trypsin and α -chymotrypsin. Insulin is subjected to various types of degradation such as acid-catalyzed degradation in the stomach, luminal degradation in the intestine and intracellular degradation. Insulin-degrading enzyme is cytosolic enzyme that degrades the Insulin. Insulin is not subjected to proteolytic breakdown by brush border enzymes and can be presented for absorption only if the enzyme attack is either reduced or defeated (Agarwal V *et al.*, 2001).

Intestinal transport of Insulin

Another major barrier for the absorption of hydrophilic macromolecules [eg: Insulin] is that they cannot diffuse across epithelial cells [lipid bilayer cell membrane] to the blood stream. It has low permeability

through intestinal mucosa. It has been found that Insulin delivery to the mid-jejunum protects Insulin from the gastric and pancreatic enzymes and release is enhanced by intestinal microflora. Various strategies have been tried to enhance absorption of Insulin in the intestinal mucosa and in some cases it is successful in overcoming this barrier (American Diabetes Association 1997).

Dosage form stability

During the development of dosage form, proteins may undergoes physical and chemical degradation. Physical degradation involves modification in the native structure and chemical degradation involves bond cleavage and may lead to new product. During formulation, proteins must be characterized to change in conformation, size, shape, surface properties and bioactivity. Different techniques like spectrophotometric techniques, X-ray diffraction, and Differential scanning calorimetry, and light scattering, electrophoresis and gel filtration are used to observe changes in conformation, size and shape (Lee VH *et al.*, 1991).

ORAL DELIVERY FOR VACCINES

Vaccination is an established therapy against various infectious diseases caused by bacteria and viruses. Vaccine is a biopharmaceutical preparation that establishes the immunity of animals or humans to a particular infectious disease. Many types of vaccines available, which include killed microorganisms, live and attenuated microorganisms, inactive toxoids, protein subunits, polysaccharide–protein conjugates, and DNA vaccines. The immunization of vaccines is mainly through parental route and there is an interest in developing oral vaccines for humans and animals due to their more desirable acceptance, avoidance of needles, easy administration, low cost (Vipond J *et al.*, 2008)

Challenges are expected for the oral immunotherapy of vaccines, such as instability and poor absorption in GIT. Various ingredients used to improve oral bioavailability, includes monosaccharide, ethyl alcohol and water vehicles, oxygen-containing metal salts, enteric coating, and poly (lactic- co-glycolic) acid microspheres.

ORAL DELIVERY FOR NUCLEOTIDES

In contrast to protein-based drugs, nucleotide-based therapeutics has not attained success despite several decades of effort in research and development. Biopharmaceuticals based on antisense RNA and the main problem is effective delivery. Nucleotide- based drugs have to enter inside cells and many protein therapeutics acts on receptors on cell surfaces.

In recent years, RNA interference (RNAi), has gained new waves of interest. Major pharmaceutical companies such as Merck, Novartis, and Pfizer are rushing to develop RNAi therapeutics. RNAi is a RNA-dependent gene silencing process in life cells found in eukaryotes and is an important cell defense against parasitic genes such as viruses and transposons. RNAi also directs gene expression and regulates development of eukaryotes. Small interference RNA (siRNA) is a class of 20–25 nucleotide-long double-stranded RNA molecules is central to RNA interference (Miroshnyk I *et al.*, 2009).

The siRNA has used for genomic studies and drug target validation recently. It is anticipated that siRNA will play a significant role in fighting against infectious diseases such as HIV, HCV, and HBV in the future. Progression of many diseases such as cancers, Alzheimer's diseases, and diabetes is related to the activity of multiple genes and is expected that turning off of a gene with a siRNA may provide a therapeutic effect to cure various diseases. The siRNA has the potential to become next generation of new therapies for many medical needs with even greater effect than the introduction of monoclonal antibodies.

NEW PLATFORM TECHNOLOGIES FOR ORAL CONTROLLED RELEASE

Oral controlled release has been advanced to controlled delivery of poorly soluble compounds and biopharmaceutical oral formulation. New technologies and novel processes are being innovated to achieve lower cost, higher efficiency and better quality. New technologies include hot melt extrusion (HME), injection molding, printing techniques, and dry coating. These new technologies will have a huge impact on formulation development of sustained release, modified release, and targeted release oral delivery systems.

Hot Melt Extrusion for Controlled Release

Hot melt extrusion (HME) is a widely used in plastic, rubber, and food industry. HME is emerging as a powerful process technology for drug delivery and is applicable to the different variety of solid dosage forms with different geometries including granules, pellets, tablets, rods, and films for oral, transdermal and implant delivery. Immediate or controlled release oral dosage forms can be produced by HME. The primary application is to make solid dispersion formulations to enhance solubility of poorly soluble compounds and has gained extensive attention.

Many commercial products launched via HME process, such as Kaletra (lopinavir/ritonavir/copovidone) tablets, Certican tablets (everolimus/HPMC), Rezulin

tablets (troglitazone/PVP), and Sporanox capsules (itraconazole/ HPMC).

HME is a single-unit operation with four stages

1. Melting of drug/polymer mix in a heated chamber;
2. Mass transport of melted mix through the barrel using a screw system;
3. Extrusion of the mixture through a die;
4. Cooling and fabricating the mixture to a designed shape.

Development of a controlled release formulation using HME involves selection of polymers, plasticizers, and releasing modulators which are compatible with a targeted drug. The drug release rate is modified through the optimization of drug load, type and level of polymers, amount of plasticizers, and quantity of releasing modulators. Polymers used need to have good thermal stability and some polymers like hydroxypropyl methylcellulose, ethylcellulose, polyethylene oxide (PEO), are suitable for HME formulation.

Injection Molding for Controlled Release

Injection molding (IM) is also a thermal process widely used in plastic industry. It shares some common features with melt extrusion, such as the mass transport of polymer using a screw and the melting process. HME produces bulk products such as sheets, rods, and tubes and IM manufacture finished products in a single step, including bottles, caps, discs, or any designed articles.

Polymer resin is supplied to a machine through a hopper and enters into the barrel, then the resin is heated to a proper melting temperature. The melted resin is injected into a mold by a reciprocating screw or a ram injector and is cooled constantly. IM is used to produce numerous medical designs in plastic parts, such as drug implants, delivery systems, and product containers. For example, polymeric microneedle for transdermal delivery (Chokshi R *et al.*, 2004).

Printing Techniques for Controlled Release

Printing techniques for controlled release is a fabulous platform but it may take long way to be applicable for market products. Inkjet printer is cheap, common consumer goods and is a complicated technical process. The printing process engages the rapid creation and release of liquid droplets with a predetermined mode. Novel delivery systems can be designed and manufactured in three dimensions. Based on inkjet technology, Hewlett-Packard is developing patch with microneedles for transdermal delivery.

Inkjet printing is also applicable in biomedical fields such as targeted gene delivery, tissue engineering,

and the development of biodegradable implants. A three-dimensional product is built by powder delivery and printing of binder solution. Thin layer of powder delivered over the surface of a powder bed and binder material is sprayed by inkjet head to join particles at defined positions. The powder bed supported by a piston is lowered to allow next layer to be printed and this layer-by-layer process proceeds until the product is finished. By thermal treatment or other curing methods, loose powder is removed, leaving the fabricated product (Nayak B *et al.*, 2008).

Dry Coating

Coating is one of the major technologies to develop controlled release formulations which include sustained release, modified release, and delayed release oral dosage forms. It is applicable to powder, granules, pellets, mini tablets, tablets, and capsules. Pan coating and fluid bed coating using solvent or latex are well established. For liquid coating, polymers, pigments, and excipients are mixed in an organic solvent or water to form a solution or dispersion and sprayed into solid dosage forms in a pan coater or a fluid bed dryer and dried by hot air.

Liquid coating has the disadvantages of significant solvent consumption, long process, and considerable energy use and there is a considerable challenge to develop very thick coating for delayed release or erosion-based controlled delivery. Dry coating has the potential to eliminate some of the drawbacks of wet coating. Powder coating and compression coating are two approaches for dry coating.

Powder coating is stemmed from metal coating and is directly applied to a solid surface. Powder coating is attained by applying fine particles which adheres solid dosage forms by electrostatic forces and forming film by heat. Thermoplastic polymers are used. Plasticizers are included to reduce the glass transition temperature, which allows the formation of film with an improved flexibility. Depending on the way of adhesion of particles onto the surface, powder coating is classified as plasticizer-dry-coating, electrostatic dry-coating, heat-dry-coating, and plasticizer-electrostatic heat-dry-coating.

For plasticizer-dry-coating, powder and a liquid plasticizer are sprayed using separate nozzles onto the dosage surface at the same time. A continuous film is formed after heat curing. Another way of adhesion of particles to solid dosage is to use heat and is called heat-dry coating, which was invented by Cerea *et al.* Polymer particles are continuously spread onto tablets in a spherulizer while heated by an infrared lamp to promote the binding and film forming (Albers J *et al.*, 2011)

Solubility enhancement by organic acids

The solubility-enhancing property of organic acids is exposed during the manufacture of customised-release (CR) dosage forms using Diffucaps® technology. The formation of acid addition compounds by using a sustained release (SR) coating membrane between the inner organic acid layer and the weakly basic drug layer (McDonnell PJ *et al.*, 2002).

DIFFUCAPS® TECHNOLOGY

Diffucaps® technology of the Time Pulsatile Release / Time Sustained Release (TPR/TSR) bead involves the preparation of:

- Drug-containing cores by drug-layering on particles
- Customised release (CR) beads by coating immediate release (IR) particles with one or more dissolution rate controlling polymers or waxes
- Combining one or more functional polymer coated Diffucaps® beads into hard gelatin or hydroxypropyl methylcellulose (HPMC) capsules (Sensit BL *et al.*, 2001).

Mechanism of drug release from TPR/TSR beads

The water-insoluble and enteric polymers are dissolved in common solvent mixture and sprayed on drug particles. These two polymers may exist as molecularly dispersed in the lag time coating membrane applied on the drug cores.

During dissolution testing in two-stage dissolution media (first two-hour dissolution testing in 700 mL of 0.1N HCl and there after testing in 900 mL of pH 6.8 buffer) (fig 3) or upon oral administration, water or body fluid is blocked as the polymeric system is impermeable in the acidic medium or gastric fluid. When the pH of the medium is changed to 6.8 or intestinal fluid selectively dissolves the enteric polymer molecules starting from the outermost membrane layer, thereby creating nanopore channels for dissolved drug to pass through. The TPR beads have no barrier coat becomes sustained with increasing thickness of the TPR coating (Levy G *et al.*, 2000).

Advantages of CR Diffucaps® drug delivery systems

Controlled-release drug delivery systems consisting of coated multiparticulates, in range of 200-600 µm particularly based on Diffucaps® technology, exhibit characteristic target release profiles, as well as target plasma concentration time profiles to be suitable for a once-daily dosing regimen (Berg JS *et al.*, 1993).

Diffucaps®, offer advantages over conventional controlled-release monolithic dosage forms such as matrix or coated tablets including osmotic delivery systems:

- Dispersed along the GI Tract for effective delivery

- Consistent GI transit time there by minimizing food effect
- Low dose dumping and reduced inter- and intra-subject variability
- Easy adjustment of multiple dose strengths and suitable for once daily dosing regimen (La Rosa JC *et al.*, 2000).

GLARS: A NOVEL INTESTINAL AND COLONIC EXTENDED-RELEASE TECHNOLOGY

The GL Pharm Tech developed a technology named GLARS (Geometrically Long Absorption Regulated System). The system entraps more gastrointestinal fluid into the dosage form at early dissolution time to give extended absorption in the colon. The triple-layered tablet was fabricated with the drug and very hydrophilic excipients are incorporated into the middle layer while highly water-retaining and swellable materials are embedded in the upper and lower layers. After oral administration, the GI fluid penetrates very quickly into the middle layer, thus the upper and lower layers concurrently swell rapidly (Fig 4). These rapidly swollen upper and lower layers enclose the lateral side of the middle layer (Bigucci F *et al.*, 2009).

The amount of water drawn into the tablet reaches about 3-5 times the weight of the tablet and can function as additional media which enables later drug release out of the dosage form when it passes into the colon. As long as the water penetrates into the tablet core, diffusion can occur. During the diffusion process the water can also move upwards and downwards, and this additional diffusion, with the diffusion of GI fluid, allows the upper and lower layers to be quickly swollen and gelled, at the same time (Gohel MC *et al.*, 2008).

Another feature is rapid enclosing of the tablet's lateral side with the upper and lower layers in a relatively short time. After closing, drug release is mainly through the enclosed lateral side, where the orange color in the middle layer is much thicker than on the other side's.

MAYNE PHARMA'S DRUG DELIVERY SYSTEMS TECHNOLOGY INCLUDES

Technology to control drug release

This enables pulsed release, extended release, and delayed release profiles. Pellet (or bead) technology allows different drug delivery profiles to be achieved by coating drug and excipient with various polymers. The drug cores are generally spheroid in shape with diameter of 300-1,700 μm . Pellets may be presented in capsule or tablet dosage forms (Gupta PK *et al.*, 1992).

Two types of process are used to generate the spheroidal shape particles:

- The first process allows drug potencies up to 90%, utilises extrusion and marumerisation to form a drug core with a polymer coat.
 - The second process is known as spheronisation, the drug particles are fixed out of a seed core (typically a sugar sphere). Drug potencies up to 60% are possible.
- For both of the processes, the desired drug release profile is achieved by coating these particles with an appropriate polymer (Notari RE *et al.*, 1987).

Technology to improve oral bioavailability SUBA™

SUBA™ is a novel technology for enhancing the bioavailability of poor water soluble drugs by using a solid dispersion of drug in various polymers. This technique shows double the oral bioavailability of itraconazole compared with the innovator product (Sporanox®) (Langer R *et al.*, 2013).

Technology to taste mask liquids and tablets CLEANTASTE™

In Cleantaste™ technology a polymer coat is applied to very small particles (25-150 μm diameters) to improve palatability and swallowing. It is also possible to improve stability or to deliver sustained release characteristics. The fine, non-gritty texture of product produced by this technology is used in orally dispersible tablet, liquid formulations and encapsulated products. Cleantaste™ acetaminophen and ambroxol have been commercialised in Australia, the US and Japan (Lipinski CA *et al.*, 1997).

SOLUMER™ TECHNOLOGY

A viable oral dosage form option for BCS class II molecules

Solubest's Solumer™, a solid dispersion approach based on spray drying that is suitable for BCS Class II APIs.

The challenge

An increasing number of compounds about 40-70% of new lead compounds are poorly and many new compounds are poor permeable. In 1993, the Biopharmaceutical Classification System (BCS) was proposed, classifies by its aqueous solubility and gut permeability. For BCS II and IV molecules, where solubility is the main limiting property, and are number of approaches including increasing surface area through particle size reduction, surface morphology modification and solid solutions (Davis SS *et al.*, 1987).

One possible solution: SOLUMER™ TECHNOLOGY

For a BCS Class I molecule, the formulation could be a simple powder-filled capsule. For a poorly water-soluble molecule, BCS Class II or IV, one such approach is Solumer™, a patented dual polymer system utilising GRAS excipients and traditional processing techniques (Wu CY *et al.*, 2005).

LIQUID-FILL HARD TWO-PIECE CAPSULES

Liquid-fill formulation is one of the fastest growing Sectors of the drug delivery, increasing at a rate of 30% per annum. This is due to the number of highly potent chemical and biological drugs development particularly for cancer treatments (Davis SS *et al.*, 1984).

Bioavailability enhancement

For drugs with low solubility or bioavailability, Encap Drug Delivery is used which include solid solutions and solid suspensions of drugs in polymeric vehicles, emulsions and self emulsifying lipidic systems. Liquid and semi-solid filled hard capsule lipidic formulations are suited to compounds with low aqueous solubility, poor permeability and low bioavailability.

Encap has expertise in the use of self-emulsifying drug delivery systems (SEDDS) and self-micro emulsifying drug delivery systems (SMEDDS) for the oral administration of drugs with poor water solubility. An example of marketed product SMEDDS type formulation is Neoral, an oral formulation of cyclosporine from Novartis (Jain GK *et al.*, 2008).

Encap has wide range of functional “bioavailability-enhancer” excipients which are fully approved from a regulatory perspective and include the screening of such excipients during pre-formulation studies. A formulation strategy for poorly soluble drugs is the use of solid solutions, incorporation of the drug substance into hydrophilic polymeric materials such as polyvinyl pyrrolidone (PVP) and polyethylene glycol (e.g. PEG 6000) can produce additional solubility enhancing effects (Rekhi GS *et al.*, 2010).

DUOCAP TECHNOLOGY

DuoCap™ is a single, oral-dosage unit that comprises a capsule-in-a-capsule with broad therapeutic applications. The inner and outer capsules contain the same active drug providing multiple release profiles, for example, an immediate release formulation from the outer capsule and a controlled-release formulation from the inner capsule. It is also possible to target the inner and outer capsule to different areas of the GI tract (small intestine or colon), with the appropriate coating.

Alternatively, the capsules may contain different actives for combination therapies (Bossart J *et al.*, 2010).

Combination therapies are currently launches of Combodart™ (GlaxoSmithKline) and Vimovo™ (Pozen/AstraZeneca). The inner capsule contains liquid, semisolid, powder or pellet formulations (Fig 5) and the outer capsule contains liquid or semi-solid formulations. Combination drugs have not been as common in the industry due to stability issues between the actives (Sako K *et al.*, 1990).

FORMULATION STRATEGY

Two principles for enhancing water solubility of the drug are

- (i) reduction of the particle size of the drug and
- (ii) Solubility-enhancing vehicles (Michel MC *et al.*, 2005).

Particle size reduction

Increasing the surface area of a solid lead to more rapid dissolution of the drug substance. Micronising equipment (e.g. fluid energy mills) can reduce particle size to 2-10 µm and there are now technologies to produce submicron ‘nanocrystals’ through precipitation (bottom up) or wet milling (top down) techniques. The drug substance can be dispensed into capsules, either as drug alone or as a powder blend (with excipients), depending on the required dose and flow properties of the milled drug substance.

Solubility-enhancing vehicles

Capsule filling machines are suitable for this purpose include the IN-CAP® (Dott Bonapace, Limbiate, Italy), suitable for powders or liquids/ semi-solids, and the CFS 1200 (Capsugel), suitable for liquids/semi-solids (Park JS *et al.*, 2011).

APPROACHES

Approaches for oral Insulin

Attempted oral Insulin delivery system

Most of the peptides after oral delivery are not bioavailable. To overcome the enzymatic and physical barriers successful oral Insulin delivery is required. For high bioavailability and developing the oral protein delivery system, three practical approaches might be helpful (Park JS *et al.*, 2011).

- Modification of physicochemical properties [lipophilicity and enzyme susceptibility].
- Addition of novel functions to macromolecules.
- Using improved carrier systems.

Insulin delivered orally either singly or in synergistic approach categorized as follows:

Enzyme Inhibitors

Insulin is degraded by enzymes and its rate of degradation is reduced by enzyme inhibitors and increases the amount of Insulin for absorption. The earliest studies in the enzyme inhibitors were carried out with sodium cholate along with aprotinin which improved Insulin absorption in rates. Significant hypoglycemic effects was observed on large intestinal administration of Insulin with camostat mesilate, bacitracin. Other inhibitors like Leupeptin, FK-448, a potent and specific inhibitor of chymotrypsin and chicken and duck ovomucoid shows significant effects (Butler JM *et al.*, 2011).

In one study, an impervious film is formed to protect Insulin from digestion in the stomach and small intestine upon polymer cross-linked with aromatic groups (Brachu S *et al.*, 2007). In the long term therapy enzyme inhibitors are not favourable because of possible absorption of unwanted proteins, disturbance of digestion of nutritive proteins and stimulation of protease secretion.

Penetration enhancers

Insulin a hydrophilic molecule is adsorbed to the apical membrane and then leads to endocytosis another therapy suggests that absorption of hydrophilic molecules is via paracellular transport. Tight junctions prevent the transport of water and aqueous soluble compounds. The absorption enhancers open tight junctions transiently allowing water soluble proteins to pass. Absorption is enhanced when product is formulated with safe excipients, includes substances like bile salts, surfactants, trisodium citrates, chelating agents like EDTA, Labrasol (Hariharan M *et al.*, 2003).

Chemical modifications

A chemical modification of peptides and proteins is another approach to enhance bioavailability by increasing its stability against enzymatic degradation or its membrane permeation. This approach is most suitable for peptides rather than proteins because of the structural complexity of proteins. For example enzymatic stability of peptides can be increased by substitution of D-Amino acids for L-Amino acids in primary structure. A diacyl derivative of Insulin maintains its biological activity and increases intestinal absorption (Kesisoglou F *et al.*, 2007).

Solution/semi-solid capsule formulations

If the drug is dissolved in a suitable vehicle then it can be filled into capsules. The main benefit is that pre-dissolving the compound overcomes the initial rate limiting step of particulate dissolution in GIT. Problem is that the drug may precipitate out of solution when the formulation disperses in the GIT, particularly if the

solvent is miscible with water (e.g. polyethylene glycol). If the drug is sufficiently lipophilic to dissolve in a lipid vehicle there is less potential for precipitation on dilution in the GIT (Rahman MA *et al.*, 2011). Also, lipidic vehicles are generally well absorbed from the GIT and in many cases this approach alone can significantly improve the oral bioavailability compared with administration of the solid drug substance, but there may be significant inter and intra-subject variation in drug uptake. In recent years, use of lipidic excipients and surfactants to produce self-emulsifying drug delivery systems (SEDDS) and self-micro-emulsifying drug delivery systems (SMEDDS) forms emulsions or microemulsions for oral drug delivery. Both SEDDS and SMEDDS use pharmaceutical surfactant excipients to achieve self-emulsification (Kanwar JR *et al.*, 2011).

Solid solutions

Solid solutions (sometimes described as solid dispersions) are molecular dispersions of the drug molecules in a polymer matrix. This approach combines two principles to enhance water solubility of a drug:

- Conversion of the drug material into its amorphous state –amorphous form dissolves easier than crystalline due to absence of ordered intermolecular bonds
- Incorporation of the amorphous drug substance in a hydrophilic polymeric matrix – a number of hydrophilic, polymeric materials has been used as solubility-enhancing matrices. For example, polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG 6000) used for preparing solid solutions containing poorly soluble drugs (Peltonen L *et al.*, 2010).

Solid solutions can be prepared by dissolving the drug compound and the polymer in a suitable volatile solvent. On removing the solvent (e.g. by spray drying) an amorphous drug-polymer complex is produced and on cooling, the drug is then trapped in an amorphous state within the water-soluble polymer matrix, thus enhancing the water solubility of the drug (Miroshnyk I *et al.*, 2011).

Solid dispersions

Solid dispersions are similar to solid solution formulations, except that the drug exists in the form of discrete particles dispersed within a polymer (Janssens S *et al.*, 2009).

Melt extrusion

This technique is an extension of the 'solid solution' approach. It consists of extruding a co-melt of the drug substance and a polymer through a heated screw to produce a solid extrudate, and then be milled to produce granules (for encapsulation or compression into tablets). A

melt extruded drug/polymer matrix is an effective method of increasing the water solubility of a poorly water-soluble drug substance. The effectiveness of this approach depends on miscibility of drug and polymer substances and exhibiting similar melting points (Zalcenstein A *et al.*, 2010).

Melt granulation

A water soluble polymer is used as a binding agent, in a powder mixture to produce a granule blend and heated to a temperature at which the polymer binding agent softens (without completely melting) which results in formation of aggregates. The granule mass is then cooled, sieved and is suitable for either encapsulation or compression into tablets. This technique has proved to be effective in enhancing water-solubility of various drugs.

Inclusion complexes such as cyclodextrins

Cyclodextrins are doughnut-shaped molecules with inside lipophilic surface and a hydrophilic surface on the outer surface of the ring. The principle behind is that the poorly soluble drug molecule fits into the inner ring and the outer hydrophilic surface of the cyclodextrin holds the complex in solution. This can be prepared by dissolving the drug and cyclodextrin in a common solvent or by solid state mixing of the materials using a high-attrition technique, such as ball milling (Hauss DJ *et al.*, 2007).

NEW MATERIALS FOR ORAL CONTROLLED RELEASE

The advancement of oral controlled release relies not only on the invention of novel processes but also of new materials. New materials with superior thermal stability are desirable for formulation development using melt extrusion and injection molding. The progress of new material invention is less than that of new processes innovation and improvement of existing materials through physical changes is a more popular option. The introduction of a new chemical entity is as challenging for the development of a new drug. It needs safety data to pass the huge regulatory problems (Yu LX *et al.*, 2002).

Ethylcellulose is widely used as a film coating agent for controlled release and is usually granular with the average particle size of 250 mm. Dow has developed a micronized version of ethylcellulose, called Ethocel FP and can be used for the formulation of matrix tablets by direct compression. Dow developed a direct compression grade of Methocel to improve flow and eliminate the wet granulation step, a type of very low viscosity hypromellose, Methocel VLV for high productivity tablet coating (Mr Gary Norman. 2011).

High-amylose sodium carboxymethyl starch, produced by spray drying, have desirable properties as sustained drug release tablet excipient for direct compression. A cross-linked high amylose, Contramid, developed by Labopharm, is free flowing; highly compressible claimed to be desirable for developing controlled release formulations with high drug loading (Lukacova V *et al.*, 2009).

Fig 1. Proposed mechanism of drug release from DCMT

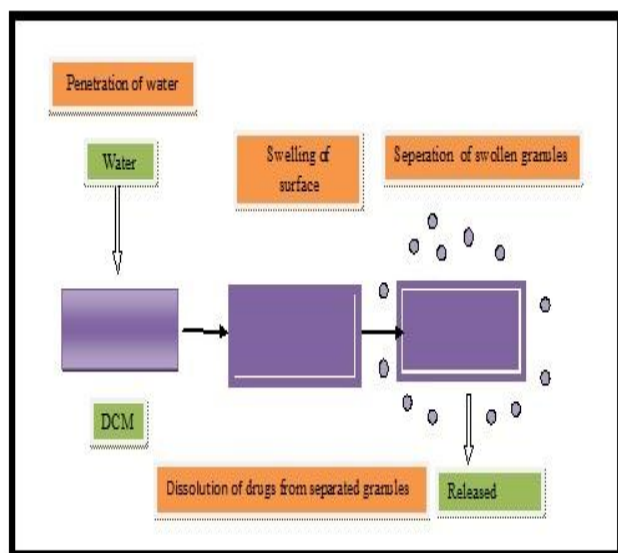


Fig 2. Oral delivery system developed by Unigene

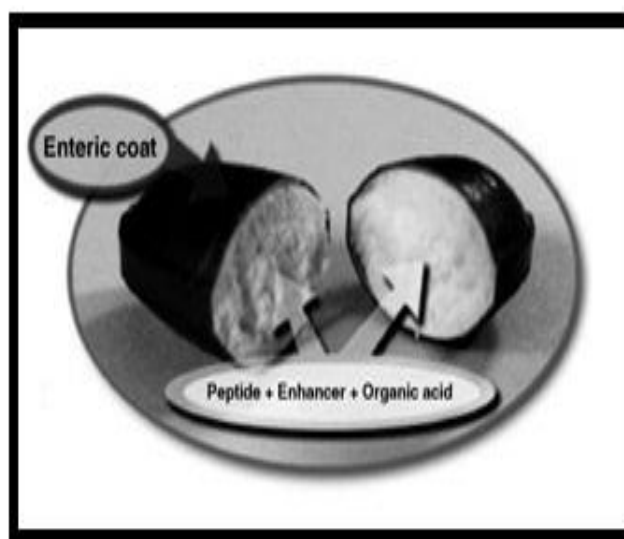


Fig 3. Diffucaps®– Customised Drug Release Bead (A) soaked in pH 1.2 or resident in the stomach and (B) soaked in pH 6.8 or in transit in the intestinal tract

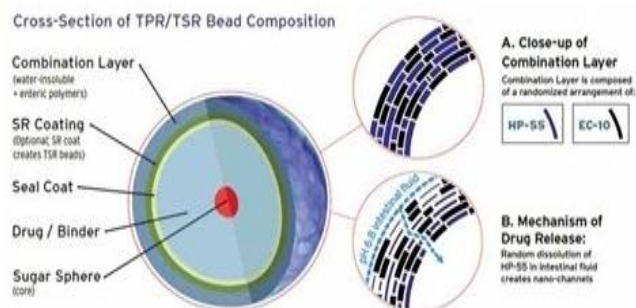


Fig 4. Triple-layered structure of GLARS and Morphological changes in GLARS upon water contact

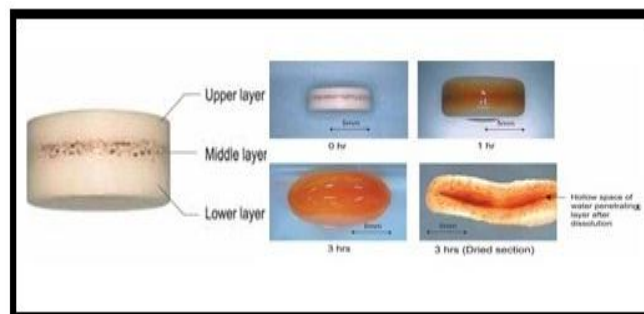


Fig 5. DuoCap: Examples of various fills



Liquid / liquid, Liquid /semi solid, Liquid /beads

CONCLUSION

Oral controlled release is being advanced in many frontiers. New technologies such as melt extrusion, injection molding, printing technologies, and dry coating provide a great opportunity and flexibility for formulation

scientists to design and develop oral controlled release formulations. The different techniques discussed above like Glars, Duocap, Unigene, Diffucaps etc may reach several challenges of oral drug delivery systems.

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