REVIEW

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Pharmaceutical product development technologies based on the biopharmaceutical classification system

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Poor solubility and poor permeability account for many pharmacokinetic failures and about thirty percent of drug molecules are rejected due to pharmacokinetic failures. When poor pharmaceutical properties are discovered in development, the cost of bringing a potent, but poorly absorbable molecule to the product stage by formulation can become very high. Fast and reliable *in vitro* prediction strategies are needed to filter out problematic molecules at the earliest stage of discovery. This communication will consider recent developments in physiochemical profiles used to identify molecules with physical properties related to good oral absorption. FDA's biopharmaceutical classification system (BCS) is an attempt to rationalize the critical components related to oral absorption and utilization of these principles for selection of a suitable technology to serve the interests of the early stages of drug discovery.

1. Introduction

The biopharmaceutics classification system (BCS) proposed by the FDA as a Bioavailability-Bioeqvalence (BA/BE) regulatory guideline allows the estimation of three major factors: dissolution, solubility and intestinal permeability. The biopharmaceutical classification system is used for correlating *in vitro* drug dissolution and *in vivo* bioavailability recognizing that drug dissolution and gastro intestinal permeability are the fundamental parameters controlling the rate and extent of drug absorption. The core idea in BCS is an *in vitro* transport model, centrally embracing permeability and solubility, with qualifications related to pH and dissolution. In principle the framework of the BCS could serve the interests of the early stages of discovery research. The BCS can be rationalized by considering Fick's first law, applied to membranes. When molecules are introduced on one side of a lipid membrane barrier and no such molecules are on the other side, passive diffusion will drive the molecules across the membrane. When a certain simplifying assumption is made, the flux equation in Fick's law reduces simply to a product of permeability and solubility. Many other measurable properties are closely related to permeability and solubility. Permeability is a kinetic parameter related to lipophilicity (as indicated by partition and distribution coefficient, log P and log D) relation of lipophilic molecules by the membrane (which is related to lipophilicty and may predict pharmacokinetic volumes of distribution) influence the characterization of permeability. The unstirred water on both sides of the membrane barrier can impose limits on permeability. Solubility is a thermodynamic property, and is closely related to dissolution (Dressman et al. 2001; Löbenberg and Amidon 2000). The analysis uses a transport model and human permeability results for estimating *in vivo* drug absorption to illustrate the primary importance of solubility and permeability on drug absorption.

2. Need for BCS

The most widely applied dissolution test methods for products are based on the USP's apparatus I (basket) or II (paddle) at agitation rates of 100 and 50 rpm, respectively. Typically 900 ml of aqueous dissolution media are used. Historical data suggests that *in vitro* dissolution methods are generally sensitive to formulation factors that affect drug dissolution process and often it is observed that two products that exhibit some dissolution differences, *in vitro*, may provide similar drug concentration time profiles in blood. These observations suggest that for many products, dissolution *in vivo* may not be the rate-limiting process. The observed variability in blood level profiles may be due to variability in the physiological processes and not due to minor dissolution differences in products being tested (Waterbeemd 1998). Possible causes for such differences may include; 1) inappropriate specification (dissolution test conditions, primarily media composition, and acceptance criteria), (2) presence of an excipient that may alter drug absorption. Experience gained through development of traditional *in vitro – in vivo* correlations (e.g., level A, B, or C correlations) for IR products containing poorly soluble drugs and for extended release products suggests a significant degree of formulation dependency or specificity associated with such correlations. Therefore, for products that are likely to exhibit slow *in vivo* dissolu-

tion, *in vitro – in vivo* correlations need to be established and their predictive performance verified through experimentation. Future research in this area should address how to *a priori* identify dissolution test conditions that yield robust *in vitro – in vivo* correlations that are applicable to a wide range of formulations (Dressman et al. 2000).

If the regulatory utility of dissolution tests for immediate release products are to be expanded, their reliability must be improved by considering the mechanistic relationships between drug dissolution, physicochemical characteristics of drugs, gastrointestinal physiology and absorption or permeation processes. To this effect BCS provides, with minimal reliance on *in vivo* pharmacokinetic data, a rational mechanistic frame work for developing reliable dissolution tests for assessing bioequivalence. The BCS also provides a means for identifying when dissolution *in vivo* is likely or not likely to be rate-limiting and allows for managing risks associated with reliance on *in vitro* dissolution for bioequivalence assessment.

3. Biopharmaceutical drug classes

1. Class 1: High solubility-high permeability drugs
2. Class 2: Low solubility-high permeability drugs
3. Class 3: High solubility-low permeability drugs
4. Class 4: Low solubility-low permeability drugs

Based on this classification (Table 1), suggestions are made for setting standards for *in vitro* drug dissolution testing methodology which will correlate with the *in vivo* process. This methodology must be based on the physiological and physicochemical properties controlling drug absorption. The analysis points out conditions that will have no IVIV correlation (Table 2). The fundamental starting point for analysis is

$$J_w = P_w C_w \qquad \text{(Eq. 1)}$$

where

J_w $(X_1Y_1Z_1t)$ is the flux (mass/area/time) through the intestinal wall at any position and time,

P_w $(X_1Y_1Z_1t)$ is the permeability of this (complex) membrane,

C_w $(X_1Y_1Z_1t)$ is the drug concentration at the membrane (intestinal) surface.

Table 1: Biopharmaceutical classification system

	High solubility	Low solubility
High permeability	**Class-1 (Amphiphilic)** Diltiazem Labetolol Captopril Enalapril Metoprolol Proranolol Phenylalanine Antipyrin **1** Glucose L-Dopa	**Class-2 (Lipophilic)** Flurbiprofen Naproxen Diclofenac Piroxicam Carbamazepine Phenytoin Verapamil Ketoprofen **2** Desipramine Itraconazole
Low permeability	**Class-3 (Hydrophilic)** Famotidine Cimetidine Ranitidine Hydrochlorothiazide Atenolol Acyclovir **3** Nadolol	**Class-4** Terfenadine Furosemide Cyclosporine **4**

Table 2: *In vitro-in vivo* correlation (IVIVC) expectation for immediate release products based on biopharmaceutical class

Class	Solubility	Permeability	IVIVC Expectation
I	High	High	IVIV correlation if dissolution rate is lower than the gastric emptying rate, otherwise limited or no correlation.
II	Low	High	IVIV correlation expected if the ***in vitro*** dissolution rate is similar to the ***in vivo*** dissolution rate, unless the dose is very high.
III	High	Low	Absorption (permeability) is rate determining and limiting
IV	Low	Low	Limited or no IVIV correlation expected

This is the Fick's law applied to membrane and applied to each point along the membrane. It is assumed that sink condition (drug concentration equals zero) exists for the drug inside this complex membrane and that P_w is an effective permeability (Shah et al. 1995).

Using molecular size and hydrogen bonding, a fresh view can be taken on the BCS, providing a better insight into its physiochemical meaning (Avdeef 2001). High molecular weight and low polar surface area result in poorly soluble and poorly permeable compounds (class-4). Compounds with high polar surface area and high hydrogen bonding capacity are poorly absorbed despite of favorable solubility (class-3). Compounds with a low molecular weight i.e. below 200, are capable by using the para cellular route for absorption. This potentially make them well absorbed (class-1) but exception need to be better understood. Most drugs fall in the group of well absorbed, but often poorly soluble compounds. So for both properties, permeability and solubility, it appears that molecular size and hydrogen bonding play a major role. Thus, these should be considered as the true fundamental properties (Fig. 1).

3.1. Class-1 system

For many drugs, neither solubility nor permeability is limiting within the target regions of the gastrointestinal tract appropriate to the desired input function. Thus the major challenge from a drug delivery perspective for this category of drugs is to achieve the target release profile associated with a particular pharmacokinetic and/or pharmacodynamic profile presented in Fig. 2. Clearly the vast majority of currently available and marketed oral controlled release products fall into this classification. Formu-

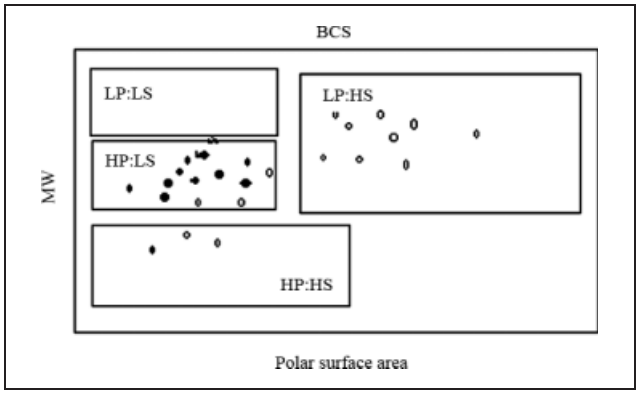

Fig. 1: The BCS projected on a molecular size/H-bonding plot. Tentatively rounded rectangles are drawn to locate the four BCS classes

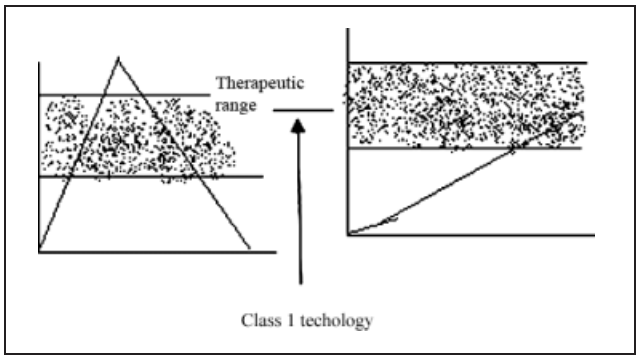

Fig. 2: Solubility and permeability are not limiting for class 1 drugs, the goal is to change drug exposure

lation approaches include both control of release rate and also certain physicochemical properties of drug, such as dependence of solubility.

Although there are no fundamental solubility or permeability limitations for drugs in this category there are a number of solubility/permeability considerations, particularly in the context of controlled release dosage form development. These considerations include:

- The appropriate choice of *in vitro* dissolution conditions to best match the physicochemical properties of the drug and drug delivery to the technology being employed.
- An understanding of the *in vivo* transit and integrity of the dosage form within the GI tract, including different conditions such as fasted or fed states.
- The regional permeability characteristic and other associated limitation to absorption, such as transporter system (e.g. the P-glycoprotein system) and metabolism system such as cytochrome (Cyt) P-450 system and more particularly the CYP-3A4 system.

3.1.1. Multiunit technologies

Nanotechnology approaches to improve the solubility of hydrophobic drugs

Nanozome Nanocrystal technology (Elan Corporation, Ireland) reduces a drug to extremely small particles (< 400 nm in diameter) using a specialized milling technique. A suspension of the insoluble drug in a stabilizing solution, consisting of GRAS stabilizers and other excipients, is used for the milling process to prevent aggregation of the resulting nanoparticles and also serves to increase the dissolution rate of the nanoparticles by acting as a surfactant within the GI tract. Additionally, Nano-Crystal technology serves as a platform for targeting drugs to specific anatomical sites or to control delivery over time. Once the nanocrystal form of the insoluble drug has been transformed into a physically more stable form, it can be incorporated into other drug delivery systems such as oral controlled-release or highly concentrated parenteral solutions. Recently, Elan obtained marketing approval from FDA for a tablet form of American Home Products Corporation's drug Rapamune, which represents the first approval for a drug presentation containing Nanocrystal technology. Rapamune is indicated for the prevention of organ rejection in kidney transplant patients, and the new tablet provides easier administration and storage than the currently marketed Rapamune oral solution (Verma et al. 2001).

Table 3: Technologies for class I drugs

Technology	Description	Size range
Multi unit		
NANOZOMS	Micron/submicron particles	0.5–5 μm
BEODAS	Small microparticles	5.0–10 μm
PHARMAZOME	Microparticles	10–500 μm
SODAS	Coated beads in a capsule	0.5–2 μm
IPDAS	Compressed coated beads in a rapidly disintegrating tablet	0.5–2 μm
PRODAS	Miniature tablets in a capsule	2–4 mm
Single monolithic		
MXDAS	Erodible matrix tablet	6–30 mm
DUREDAS	Erodible multilayer tablet	6–30 mm
MODAS	Non disintegrating coated	6–30 mm

Nanoparticulate technologies

NanoCrystal (Elan, US): NanoCrystal drug particles (< 1,000 nm) produced by wet-milling and stabilised against agglomeration through surface adsorption of stabilisers; applied to NMEs eg aprepitant/reformulation of existing drugs eg sirolimus.

Biorise (Eurand, Dayton): Nanocrystals/amorphous drug produced by physical breakdown of the crystal lattice and stabilised with biocompatible carriers (swellable microparticles or cyclodextrins).

IDD (SkyePharma, England): Insoluble Drug Delivery: micro-nm particulate/droplet water-insoluble drug core stabilised by phospholipids; formulations are produced by high shear cavitation or impaction.

CAP (BioSante, Illinois): Calcium Phosphate-based nanoparticles: for improved oral bioavailability of hormones/proteins such as insulin; also as vaccine adjuvants.

NAB (American Bioscience, US): Nanoparticle Albumin-Bound technology: injectable suspension of biocompatible protein with drug improves solubility/removes need for toxic solvents; e.g. paclitaxel-albumin nanoparticles.

Nanoedge (Baxter, US): Nanoedge technology: drug particle size reduction to nanorange by platforms including direct homogenisation, microprecipitation, lipid emulsions and other dispersed-phase technology.

Nanostructuring technologies

BioSilicon (pSivida, UK): Drug particles are structured within the nano-width pores of biocompatible BioSilicon microparticles, membranes or fibres; gives controlled release/improves solubility of hydrophobic drugs.

NanoGate (iMEDD Burlingame): Silicon membrane with nano-width pores (10–100 nm) used as part of an implantable system for drug delivery and biofiltration.

NLC8 (PharmaSol, Easton, MA): Nanostructured Lipid Carriers: nanostructured lipid particle dispersions with solid contents produced by high-pressure homogenisation; lipid-drug conjugate nanoparticles provide high-loading capacity for hydrophilic drugs for oral delivery (Saffie-Siebert et al. 2005).

Beodas or Bioerodable Enhanced Oral Drug Absorption System (Elan Corporation, Ireland) is an oral microparticulate drug delivery technology designed for the delivery of macromolecules and is based on the entrapment of ac-

tive pharmaceutical entities in a range of submicron sizes within biodegradable polymer matrices. Further modifications to the BEODAS platform technology have the potential for targeted delivery and enhanced absorption of pharmaceutical entities that normally are not amenable to oral administration (Verma and Garg 2001).

Pharmzomes or Microparticulate Drug Delivery Technology (Elan Corporation, Ireland) consists of combinations of polymers and drugs in the size range of 5 to 125 μm. Each microparticle is a micromatrix of drug embedded uniformly throughout an insoluble polymer and is produced by either a spray drying or emulsion technique. By varying the amount and nature of the polymer used to form the micro particle, this technology allows controlled- and/or delayed-release of drug from the formulation. In addition, this technology also can be used for taste masking because it acts as a means of physically preventing a drug from going into solution in the mouth and coming into direct contact with taste receptors. For the purpose of palatability, 125 mm is set as the upper limit for Pharmazomes because these particles have a gritty feeling that may be unacceptable to consumers. Pharmazomes can be subsequently incorporated into a variety of delivery systems like chewable tablets, effervescent tablets, and oral ready-made aqueous and non-aqueous suspensions, reconstituable powders, and unitdose sachet or sprinkle systems. Products using Pharmazome technology are currently approved in Japan, Europe, and Central and South America and include twice-daily theophylline.

Sodas or Spheroidal Oral Drug Absorption System (Elan Corporation, Ireland) is a multiparticulate drug-delivery technology and consists of controlled-release beads that can be produced in the range from 1 to 2 mm in diameter. Each bead begins as an inert core onto which the drug is applied, followed by a number of layers of soluble and insoluble polymers combined with other excipients to produce the rate-controlling layer. Drug release from these beads occurs by a diffusion process. Within the GI tract, the soluble polymers dissolve, leaving pores within the outer membrane. Fluid then enters the core of the beads and dissolves the drug. The resultant solution diffuses out in a controlled, predetermined manner allowing for prolongation of the *in vivo* dissolution and absorption phases. The immediate environment of the drug within the seed core can be manipulated by use of excipients to ensure optimal stability and solubility. These controlled-release beads can be packaged into a capsule or compressed into a tablet to produce the final dosage form. Products utilizing SODAS technology are approved and marketed throughout Europe, the US, and Japan and include once-daily diltiazem and once-daily verapamil.

Benefits of SODAS: The maintenance of angina control was assessed in a multicenter (three sites), randomized, double-blind, parallel-group study. Patients with stable angina pectoris receiving twice-daily sustained-release (SR) diltiazem were switched to equivalent doses of once-daily controlled-delivery (CD) diltiazem or to diltiazem SR. Patients who were switched from diltiazem SR to diltiazem CD ($n = 28$) experienced a 5% increase in time to termination ($p = 0.0004$) on the exercise tolerance test (ETT), as well as an 8% improvement in time to onset of angina ($p < 0.0001$) on the ETT. A similar trend was observed in patients randomized to diltiazem SR ($n = 7$), which suggested a training effect, and, therefore, equal efficacy between diltiazem SR and diltiazem CD. During exercise testing in the diltiazem SR baseline phase, 77% of the patients did not experience angina, whereas 60% of the patients did not experience ST-segment depression. Following transfer to diltiazem CD, 79 and 61% of patients, respectively, remained angina- and ST-segment depression free. No significant changes in the number of angina attacks, nitroglycerin use, or any hemodynamic-related parameters were observed following transfer to diltiazem CD. Eleven percent of the patients receiving diltiazem CD experienced treatment-related adverse events, which were limited to headache and abdominal pain; these adverse events did not lead to discontinuation of treatment. These findings suggest that patients whose angina is controlled with twice-daily diltiazem SR can be safely and effectively switched to an equivalent daily dose of the once-daily diltiazem CD (Savard et al. 1995).

IPDAS or Intestinal Protective Drug Absorption System (Elan Corporation, Ireland) is a multiparticulate tablet technology that has been developed to enhance the gastrointestinal tolerability of potentially irritant or ulcerogenic drugs. Unlike other tablet formulations, IPDAS is composed of numerous high-density controlled release beads. Each bead is manufactured by a two-step process that involves the initial production of a micromatrix of drug embedded in polymer and the subsequent coating of this micromatrix with time-release coatings that are transformed into a rate-limiting semipermeable membrane *in vivo*. After ingestion, the tablet rapidly disintegrates and beads are dispersed into the stomach and subsequently pass into the duodenum and along the GI tract in a controlled and gradual manner, independent of the feeding state. Drug release from each bead occurs by a diffusion process through the micromatrix and subsequently through the pores in the rate controlling semipermeable membrane. The intestinal protection of IPDAS is by virtue of the multiparticulate nature of the formulation, which ensures wide dispersion of irritant drug throughout the GI tract. The controlled-release characteristics of the individual bead avoid the high concentrations of drug being released locally and absorbed systemically.

An immediate-release granulate also can be included in the tablet and may be required for a fast onset of action. IPDAS products are approved worldwide, and Elan's Naprelan product (once-daily naproxen sodium) is sold in the US market (Gaston. 1996).

Benefits of Elan's IPDAS® Technology:

- High density multiparticulate formulation,
- Intestinal protection from irritant drugs (eg NSAIDs),
- Advantages of multiparticulate in a tablet form,
- Controlled Release through process of diffusion,
- Fast onset if required.

IPDAS®, Intestinal Protective Drug Absorption System, was initially developed as part of the development process for Elan's proprietary naproxen formulation, Naprelan®. The objective was to develop a once daily controlled release system that would have a fast onset of action and reduced gastric irritancy. IPDAS® delivery system can also be employed to confer the advantages of multiparticulate technology, in a tablet dosage form. The IPDAS® technology is composed of numerous high density controlled release beads, which are compressed into a tablet form.

Once an IPDAS® tablet is ingested, it rapidly disintegrates and disperses beads containing a drug in the stomach, which subsequently pass into the duodenum and along the gastrointestinal tract in a controlled and gradual

manner, independent of the feeding state. Release of active ingredient from the multiparticulates occurs through a process of diffusion either through the polymeric membrane and or the micromatrix of polymer/active ingredient formed in the extruded/spheronized multiparticulates. The intestinal protection of IPDAS® technology is by virtue of the multiparticulate nature of the formulation, which ensures wide dispersion of irritant drug throughout the gastrointestinal tract.

Naprelan®, which is marketed in the United States and Canada, employs the IPDAS® technology. This innovative formulation of naproxen sodium is a unique controlled release formulation indicated both for acute and chronic pain (Elan Corporation).

PRODAS®, Programmable Oral Drug Absorption System is a multiparticulate technology, which is unique in that it combines the benefits of tabletting technology within a capsule. PRODAS is presented as a number of minitablets combined in a hard gelatin capsule. PRODAS is a very flexible technology, which can be used to pre-program the release rate of a drug. It is possible to incorporate many different minitablets, each one formulated individually and programmed to release drug at different sites within the gastro-intestinal tract. It is also possible to incorporate minitablets of different sizes so that high drug loading is possible. In its most basic form, PRODAS involves direct compression of an immediate release granulate to produce individual minitablets. These minitablets are subsequently packaged into hard gelatin capsules, which represent the final dosage form. A more beneficial use of the technology, however, is in the production of controlled release formulations. In this case the incorporation of various polymer combinations within the granulate delays the release rate of drug from each of the individual minitablets. These minitablets may subsequently be coated with controlled release polymer solutions to provide additional delayed release properties. PRODAS technology can achieve equivalent bioavailability to reference multiple dose product in a once daily formulation, show minimum peak to trough ratio at steady state, show minimal food impact and facilitate pulsed/programmed release to different sites in the GI tract. Additionally, PRODAS technology, by incorporating minitablets with different release rates, can display the characteristics of a number of different conventional dosage forms namely (i) immediate release component will mimic the conventional formulation ensuring that the once daily formulation is as fast acting; (ii) delayed release can provide site/regional release and food resistance and (iii) sustained release component provides additional controlled release/protection. A case study is reported to highlight the attributes of PRODAS technology:

In collaboration with a multi-national pharmaceutical firm Elan employed PRODAS technology to orchestrate precise control of an agent, which is conventionally dosed four times daily, to facilitate once daily dosing. Elan developed the controlled release dosage form despite a number of significant technical challenges, and a full dossier for regulatory submission was prepared. Typical equipment involved multi-tip tableting, tablet coating and multi-station capsule filling. PRODAS is an advanced technology with full scale-up and manufacturing capability available at Elan's Athlone site. However, due to the emergence of significant clinical implications with the drug itself, the commercial viability of the product was suddenly reduced, and the PRODAS formulation was not submitted for regulatory approval. A number of biostudies were carried out over the course of the development work, which clearly illustrates the attributes of the PRODAS dosage form as evidenced from Figs. 3a and 3b that clearly demonstrate smooth sustained plasma levels, minimal effect of food on the plasma profile and predictability and reliability of the dosage form (Elan drug technology news). PRODAS is not affected by the presence of food in the GI tract. This is a patient friendly dosage form, leading to increased compliance as the dose can be administered irrespective of the fed or fasting state.

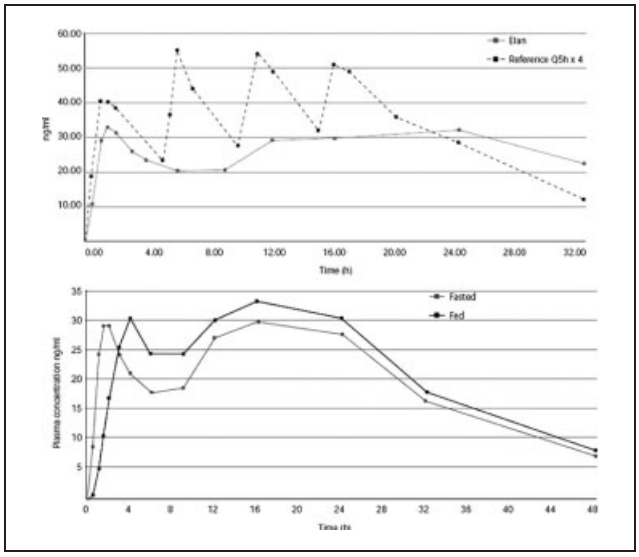

Fig. 3: PRODOS Technology, Sustained plasma profile, 3b. PRODOS Technology, Effect of food, Fed vs. Fasted state

CODAS™ technology. In certain cases immediate release of drug is undesirable. A delay of drug action may be required for a variety of reasons. Chronotherapy is an example of when drug release may be programmed to occur after a prolonged interval following administration. Elan's drug delivery technology can be tailored to release drug after a predetermined delay. The CODAS drug delivery system enables a delayed onset of drug release, resulting in a drug release profile that more accurately compliments circadian patterns.

Elan's Verelan® PM represents a commercialized product using the CODAS technology. The Verelan PM formulation was designed to begin releasing Verapamil approximately four to five hours post ingestion. This delay in release is introduced by the level of release controlling polymer applied to the drug loaded beads. The release controlling polymer is a combination of water soluble and water insoluble polymers. As water from the gastrointestinal tract comes in contact with the polymer coat beads, the water soluble polymer slowly dissolves and the drug diffuses through the resulting pores in the coating. The water insoluble polymer continues to act as a barrier, maintaining the controlled release of the drug. When taken at bedtime, this controlled onset extended release delivery system enables a maximum plasma concentration of Verapamil in the morning hours, when blood pressure normally rises from its overnight low (Elan Corporation, case study).

The CODAS technology gives rise to attributes that directly benefit individual drugs:

- delivery profile designed to compliment the circadian pattern of blood pressure,

- controlled onset, extended release delivery system,
- rate of release essentially independent of pH, posture and food,
- "Sprinkle" dosing by opening the capsule and sprinkling the contents on food.

3.1.2. Single monolithic technologies

Duredas or Dual Release Drug Absorption System (Elan Corporation, Ireland) utilizes bilayer-tableting technology, which has been specifically developed to provide two different release rates or dual release of a drug from a single dosage form. The tablets are prepared by two separate direct-compression steps that combine an immediate-release granulate (for rapid onset of action) and a controlled-release hydrophilic matrix complex within one tablet. The controlled-release matrix remains intact and slowly absorbs fluid from the GI tract, which causes the matrix to expand and transforms the hydrophilic polymers into a porous, viscous gel that serves as a barrier between the drug and the surrounding fluid. As the gel continues to expand, fluid penetrates further into the dosage form, dissolving the drug and allowing the resulting solution to diffuse out in a controlled manner. A further extension of the Duredas technology is the production of controlled-release combination dosage forms whereby two different drugs are incorporated into the different layers, and the drug release of each is controlled to maximize the therapeutic effect of the combination. Again both immediate-release and controlled-release combinations of the two drugs are feasible.

Modas or Multiporous Oral Drug Absorption System (Elan Corporation, Ireland) is surrounded by a non-disintegrating, timed-release coating, which after coming in contact with gastrointestinal fluid is transformed into a semi-permeable membrane through which the drug diffuses in a rate-limiting manner (United State Patent: 6,174,873). The tablet consists of a core of active drug plus excipients. This is then coated with a solution of insoluble polymers and soluble excipients. After ingestion, the fluid of the gastrointestinal tract dissolves the soluble excipients in the outer coating leaving just the insoluble polymer, thereby forming a network of tiny, narrow channels connecting fluid from the GI tract to the inner drug core of water-soluble drug. This fluid passes through these channels into the core, dissolves the drug and a resultant solution of drug diffuse out in a controlled manner to the outside. The addition of excipients, such as buffers can help produce a microenvironment within the tablet that facilitates more predictable release rates and absorption. Examples of MODAS products developed by Elan include Bron-12 (a 12 hour multicomponent over-the-counter [OTC] cough and cold product) and once-daily potassium chloride.

Benefits of MODAS: The bioavailability of a new sustained-release potassium chloride (KCl) tablet, designed for once-a-day dosing, was compared to a KCl elixir using urinary excretion data. The study utilized 25 male volunteers dosed in a crossover design in a dietary/activity-controlled environment. The regimens consisted of a total of 80 mEq of potassium in three equally divided doses of elixir every 6 h and a single 80 mEq dose using four 20 mEq sustained-release (SR) tablets. The mean time to maximum rate of potassium urinary excretion was 2.2 h for the first elixir dose and 5.5 h after the SR tablet ($P < 0.01$), thereby supporting the prolonged-release properties of this formulation. After correction for baseline urinary potassium excretion, the mean total 24 h urinary potassium excretion was 42.18 mEq for the elixir and 40.41 mEq for the SR tablet. The results indicated that the absorption pattern from the SR tablet was equal to three doses of KCl elixir dosed 6 h apart (Betlach et al. 1987).

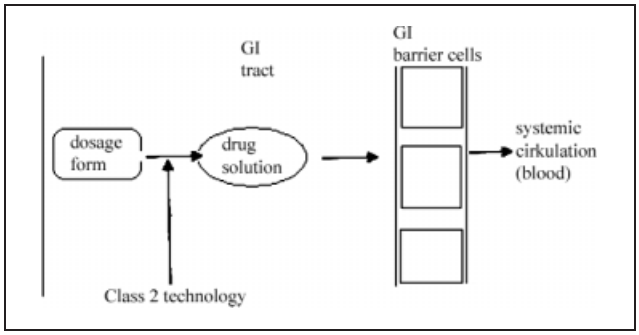

Fig. 4: Solubility/permeability considerations for class 2 drugs

3.2. Class-2 system

This classification relates to the situation in which solubility or dissolution (in general or on o regional basis with in the GIT tract) is limiting and thus significantly affects absorption and bioavailability. Many distinct technology approaches are employed to address class-2 problems for immediate release dosage forms (Fig. 4). These approaches include classical micronisation, stabilization of high energy states (including lyophilized fast melt system) inclusion of surfactants, formulation as emulsion or micro-emulsion systems and use of complexing agents such as cyclodextrins. The problem in the context of extended release dosage forms relates not only to the primary formulation approach required to improve solubility properties but also to the incorporation of this approach in to a final dosage forms that provides for extended release and an associated pharmacokinetic profile. A number of approaches particularly those are not emulsion based, represent the opportunity for solid oral dosage form presentation and potentially manipulation and presentation as an extended release system (if permeability is not limiting).

Indas or Insoluble Drug Absorption System (Elan Corporation, Ireland) addresses the problem of poor solubility by manipulating the physicochemical characteristics of a drug to create a high-energy adsorbate that demonstrates enhanced solubility. This high-energy adsorbate is subsequently combined with Elan's other controlled absorption technologies to deliver the required plasma profile. The drug in question, usually crystalline in nature, is converted into an amorphous form by a combination of energy, excipients, and unique processing procedures. Once the drug is converted into the desirable physical form, an adsorption process utilizing a novel polymer cross-linked tech-

Table 4: Technologies for class 2 drugs

Technology	Description
INDAS	Stabilized, high energy form (crystallization to amorphous) Solid dispersion
SODAS	Microemulsion
EMDAS	Stabilized, submicron size
NANODAS	reduction

nology prevents recrystallization and stabilizes the resulting high-energy complex. The combination of the change in the physical state of the drug coupled with the solubilizing characteristics of the excipients employed ensures that the solubility of the active ingredient is enhanced. Nifelan, a once-daily nifedipine formulation, is based on this technology and is marketed in Europe and Southeast Asia.

Benefits of INDAS – Case study: Nifelan, a sustained-release formulation of nifedipine, is a new antihypertensive agent. However, its effect on peripheral vascular resistance and left ventricular mass is still controversial. The antihypertensive efficacy and safety of nifelan in 20 patients with mild to moderate essential hypertension was evaluated. After 2 weeks of a placebo-qualifying phase, the eligible patients were entered into an 8-week active treatment period in which nifelan was given 10–40 mg once-daily with gradual titration. Seventeen patients (8 men, 9 women; age range 43–72 years, mean 52 years) completed the entire study. The mean sitting systolic and diastolic blood pressures were significantly reduced ($p < 0.0001$) by 13.8 mmHg and 9.6 mmHg, respectively, with a mean nifelan dose of 27.1 $\pm$ 2.7 mg per day, while the heart rate remained unchanged (75.9 $\pm$ 1.3 vs. 73.6 $\pm$ 0.9 beats per minute, p = NS). Four patients (20%) reported side effects necessitating termination of nifelan treatment in 2 patients because of intolerance. One patient was found to be poorly compliant and withdrew prematurely from the study for unknown reasons without complaints of adverse effects. Echocardiographic left ventricular mass index was significantly reduced from 104.2 $\pm$ 4.6 g/m^2 to 96.6 $\pm$ 5.2 g/m^2 ($p < 0.05$), and the left ventricular diastolic function evaluated by E/A ratio showed a trend toward improvement from 0.97 $\pm$ 0.06 to 1.10 $\pm$ 0.07 (p = 0.06). Both forearm hemodynamic parameters showed favorable changes from baseline to the end of the study (forearm blood flow, 3.39 $\pm$ 0.28 vs. 4.04 $\pm$ 0.31 ml/100 ml/min, $p < 0.05$; forearm vascular resistance, 37.75 $\pm$ 4.95 vs. 28.73 $\pm$ 3.34 mmHg/ml/100 ml/min, $p < 0.05$). The lipid profiles followed trends toward favorable changes after treatment (high density lipoprotein, 51.8 $\pm$ 3.0 vs. 54.4 $\pm$ 3.3 mg/dl, p = NS; low density lipoprotein, 146.1 $\pm$ 8.8 vs. 139.9 $\pm$ 10.6 mg/dl, p = NS). Hematological and biochemical parameters did not change at the end of treatment. It was concluded that once-daily nifelan as monotherapy was safe and effective in Chinese patients with mild to moderate essential hypertenson. Regression of left ventricular mass and reversal of unfavorable forearm hemodynamics were observed in these patients after short-term therapy (Chang et al. 1998).

3.3. Class-3 system

The principle barrier in class-3 system is the effective permeability of the GI tract to the target drug. These targets include the transcellular flux of drug, paracellular flux via opening of the tight junctions, promotion of carrier mediated transport via established transport system and/or inhibition of excretory P-glycoprotein mediated efflux system. In addition although it is not a barrier for transport, the presence of degradative enzyme system such as the CYP-3A4 system within the GI tract also represents a significant barrier that may be achieved by manipulating the site or rate of exposure or perhaps by incorporating functional agents in to the dosage form to modify the metabolic activity of these enzyme system.
The class-3 system involves emerging technologies that attempt to address the fundamental limitation of absolute

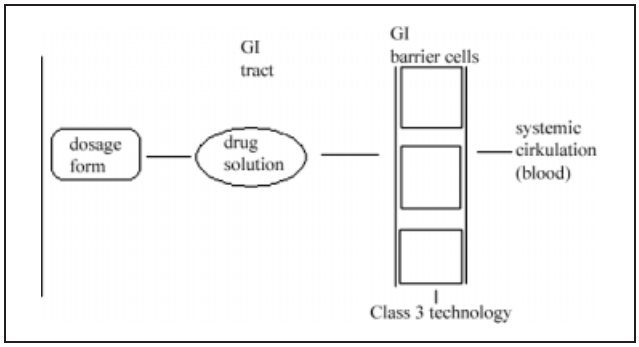

Fig. 5: Solubility/permeability considerations for class 3 drugs

or regional permeability (Fig. 5). Because of the nature of these biological systems the technology in turn represents more fundamental drug delivery approaches in terms of altering the biological system in a transient and specific manner. A broad range of technology is currently under investigation to achieve optimal bioavailability. It is clear that class-1 and/or class-2 technology, alone or combined are not adequate to address these fundamental limitation, so class-3 technologies are being developed. These technologies represent new systems that in many cases involve the development techniques and characterization in addition to the drug delivery aspects.

LOCDAS or Localized Drug Absorption System (Elan Corporation, Ireland) is a novel targeted oral drug delivery technology. This technology utilizes targeting ligands that specifically bind to certain absorption sites located on the apical surface of the epithelium cells of the human GI tract. These ligands are attached to coated microparticles of protein and peptide drugs that serve to protect their contents from the hostile environment of the GI tract. These are subsequently packaged in enteric-coated capsules that deposit the particles at appropriate sites of absorption within the GI tract, example particles for oral delivery of peptides and proteins (Grove 2007).

3.4. Class-4 system

Fortunately, class-4 compounds are the exception and are rarely developed or reach the market. Nonetheless a number of examples of class-4 drugs do exist. Taxol for example, is currently available only in an injectable form, and even then it requires the inclusion of significant solubility enhancing components (such as cremaphor) that have safety implications in the parenteral formulation. Solving class-4 drug delivery requirements will be achieved through a combination of class-2 and class-3 technologies. Class-4 drugs will benefit from the significant progress and improvements that already have been achieved in the other technology categories.

Table 5: Technologies for class 3 drugs

Technology	Description
VACDAS	Oral vaccine system; bio-degradable micron/submicron system; M-cell targeting/adjutants
LOCDAS	GI receptor targeting and activation; biodegradable submicron particles targeted to GI receptors
PROMDAS	Novel absorption promoters
GRDAS	Gastro retentive system
Smart Pill	Device/dosage form system

4. Conclusion

It is obvious that BCS is a fundamental system in pharmaceutical sciences that gives an idea about solubility characters, which ultimately affect the bioavailability of a particular drug.

Numerous techniques have been developed to increase the solubility of drugs but in formulation of dosage forms, the BCS system is useful. This system proposed by FDA as a Bioavaibility-Bioequivalence regulation basically helps to set the standards for *in vitro* drug dissolution testing methodology which ultimately arrows *in vivo* bioavailability and biological action of a drug.

References

Avdeef A (2001) Physicochemical profiling (solubility, permeability and charge state) (2001) Curr Topic Med Chem: 277–351.

Betlach CJ, Arnold JD, Frost RW, Leese PT, Gonzalez MA (1987) Bioavailability and Pharmacokinetics of a New Sustained-Release Potassium Chloride Tablet. Pharm Res 4 : 409–411.

Chang KC, Cherng WJ (1998) Once-daily nifedipine sustained release (nifelan) on forearm vascular resistance and regression of left ventricular hypertrophy in patients with mild to moderate essential hypertension. Med J 21: 28–36.

Dressman JB, Reppas C (2000) *In vitro – In vivo* correlation for lipophilic poorly water soluble drugs. Eur J Pharm Sci 11: 73–80.

Dressman J, Butler J, Hempenstall J, Reppas C (2001) The BCS: Where do we go from here? Pharm Technol: 68–76.

Devane J (1998) Oral drug delivery technology: Addressing the solubility/permeability paradigm. Pharm Technol: 68–80.

Elan drug technology news (21 april 2004) Elan nanosystems licenses Nanocrystal^{TM} technology to Aventis.

Gaston G (1996) A double-blind randomized, parallel-group study of the pharmacokinetics and onset of action of naprelan in patients following oral surgery. Am J Orthop 25: 37–41.

Grove CF (2007) www. Freepatent.com.

Löbenberg GL, Amidon R (2000) Modern bioavailability, bioequivalence and biopharmaceutics classification system. New scientific approaches to international regulatory standards. Eur J Pharm Biopharm 50: 3–12.

Saffie-Siebert R, Ogden J, Parry-Billings M (2005) Drug Discovery World Summer: 71–76.

Shah PV, Amidon LG, Lennernas H, Crison RJ (1995) A theoretical basis for a biopharmaceutical drug classification: The correlation of *in vitro* product dissolution and *in vivo* bioavailability. Pharma Res 3: 413–420.

Savard D, Lenis J, Juneau M, Jacob C (1995) Clinical efficacy and safety of once-daily diltiazem in patients with stable angina. J Cardiovasc Pharmacol 26: 85–9.

Verma S, Garg RK (2001) Current status of drug delivery technologies and future directions. Pharm Technol 25: 1–14.

Waterbeemd HVD (1998) The fundamental variables of the biopharmaceutics classification system (BCS): a commentary. Eur J Pharm Sci 7: 1–3.

Wrenn Jr, Simeon M, Danville CA (1998) Oral administration of adenosine analogs. United States Patent: 6,174,873.