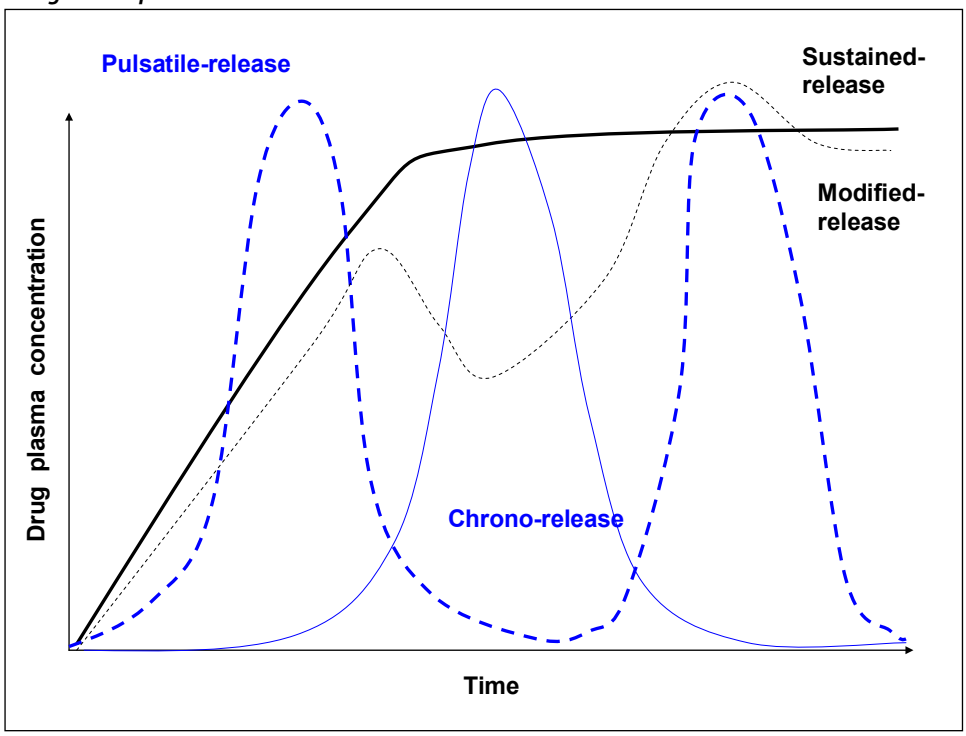
Delivery specialists have devised controlled-release platforms that provide a variety of drug plasma profiles including: sustained-release (SR), modified-release (MR), pulsatile-release (PR) and chrono-release profiles. The characteristics of each profile are summarised in Figure 1.1.2.

Figure 1.1.2: Drug release profiles



Source: Pharmavision.co.uk

- **Sustained-release** (solid black line) can enhance drug safety and efficacy by minimising peaks and troughs in blood levels, and improve patient compliance by reducing the number of doses taken by a patient.
- **Modified-release** (dotted black line) can optimise treatment in cases where different drug levels are required at different times, providing rapid onset of action and sustained-release benefits within a single dose.
- **Chrono-release profile** (solid blue line) enables a drug to be released in time with natural biorhythms of the human body e.g. hormonal release and gastric pH.
- **Pulsatile-release** (dotted blue line) can provide variable treatment dependent on expression or severity with a circadian rhythm e.g. acid reflux, insomnia or excessive sleepiness.

For example, Eli Lilly's Zyprexa, an antipsychotic, is one of the most widely prescribed drugs to have been adapted to oral disintegrating tablet (ODT) delivery, Zyprexa Zydis. More recently, GSK's Lamictal ODT product was approved by the FDA in this class of products; it uses Eurand's technology, and is the first antiepileptic treatment available in an orally disintegrating formulation.

2.1.5 Targeted delivery technologies

Although targeted drug delivery is mainly associated with parenteral delivery systems, there are special circumstances in which targeting can be achieved with oral delivery. These include the targeting of drugs directly to the colon and also the stomach.

Colonic drug delivery has attracted interest primarily for local delivery in diseases of the colon such as Crohn's disease, ulcerative colitis and colorectal cancer. Furthermore, it has been proposed that the colon is a better site than the small intestine to promote oral macromolecule uptake.

The colon is also typically a site of drug absorption from extended-release preparations where a substantial portion of the drug is delivered to the colon. Approaches being investigated include Alizyme's Colal delivery system and Cosmo's MMX technology. Research continues in the area of gastro-retentive delivery, where dosage forms are retained in the stomach to achieve a prolonged and predictable drug delivery profile in the GI tract. Depomed's AcuForm is a multi-hour, gastroretentive, controlled-release drug delivery system which allows for the targeted, controlled delivery of pharmaceuticals to the upper GI tract.

2.1.6 Orally Disintegrating Tablets (ODTs)

These dosage formulations, also known as melts, are useful in a variety of circumstances, for example when immediate or at least prompt action is required. Fast-dissolving drug delivery systems have rapidly gained acceptance as an important new way of administering drugs. There are many fast-dissolving OTC and prescription products on the market worldwide, most of them launched in the past 3 to 4 years. There have also been significant increases in the number of new chemical entities under development using a fast-dissolving drug delivery technology.

ODTs disintegrate and/or dissolve rapidly in the saliva without the need for water. Some tablets are designed to dissolve in saliva remarkably quickly, within a few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely disintegrate. When put on the tongue, this kind of tablet disintegrates instantaneously, releasing its drug, which dissolves or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of the drugs is significantly greater than those observed from conventional tablet dosage form.

The advantages of ODTs are increasingly being recognised in both industry and academia. Their growing importance was underlined when the European Pharmacopoeia adopted the term "Orodispersible Tablet" as a tablet to be placed in the oral cavity where it disperses rapidly before swallowing.

The main benefits of ODTs are that they:

- Allow high drug loading;
- Are easily administered for patients who are mentally ill, disabled and uncooperative;
- Are adaptable and amenable to existing processing and packaging machinery;
- Are cost-effective;
- Can be designed to leave minimal or no residue in the mouth after administration and also to provide a pleasant mouth feel;
- Can provide advantages of liquid medication in the form of solid preparation;
- Overcome unacceptable taste of the drugs;
- Quickly disintegrate and/or dissolve; and
- Require no water.

The fast-dissolving property of the tablet is attributable to a quick ingress of water into the tablet matrix resulting in its rapid disintegration. Hence, the basic approaches to developing fast-dissolving tablets include maximising the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent, and using highly water-soluble excipients in the formulation.

Various technologies used in the manufacture of fast-dissolving tablets include freeze-drying or lyophilisation; tablet moulding, direct compression, spray drying, sublimation and taste masking. Several proprietary technologies have been developed by companies active in this field, and some are summarised in Table 2.1.1.

During 2008, the company signed two feasibility studies using the Medusa and Micropump platforms and received milestone payments from Wyeth regarding the delivery for a Medusa formulation of a marketed protein.

In February 2009, Merck Serono exercised the option to develop an extended-release formulation of a therapeutic protein. In July 2009, Flamel signed an agreement with Baxter Healthcare for controlled-release preparations of blood clotting factor replacement therapies; Flamel will receive technology access fees totaling €2.5 million and Baxter will cover all development costs.

4.2.22 KV Pharmaceuticals, Inc

Overview

KV Pharmaceuticals is a fully-integrated speciality pharmaceutical company which began as a contract researcher and manufacturer for major pharmaceutical companies. The company now develops, manufactures, and markets products through three distinct businesses: Ther-Rx Corporation (established 1999, branded prescription), ETHEX (established 1990, generic and non-branded) and Particle Dynamics (acquired in 1972, value-added, specialty ingredient products). The company has 14 technological approaches in four principal areas: site release (bioadhesive), taste-masking, quick-dissolving tablets and oral extended/delayed release.

Oral Delivery Technologies

Oral Extended/Delayed Release: The company's oral extended/delayed release technologies can be tailored to the desired release profile for a given drug. The release profile is dependent on parameters such as drug solubility, protein-binding and site of absorption. Oral extended/delayed release technologies include KV/24 (for once-daily dosing) and Meter Release (for twice-daily dosing).

Commercialised Products

KV's oral-delivery products are mainly marketed by its ETHEX business segment. The range includes 45 cardiovascular products as well as products for women's health and pain management; many are identified as leading products in their respective generic categories. ETHEX contributed 61% of KV revenues in fiscal 2008.

Deals, Alliances, M&A

KV has established partnership agreements with a number of companies including: Altana Pharma, Gedeon Richter, Glenmark Pharmaceuticals, ISDIN (an affiliate of Esteve), OM Pharma, Pan Malayan Pharmaceuticals, Sigma Pharma, Schering/Merck KGaA, Schwarz Pharma and Technilab.

In September 2010, KV announced that it had entered into an agreement with U.S. Healthcare I, LLC and U.S. Healthcare II, LLC for a US$20 million loan secured by assets of the company. KV will utilise the proceeds of the loan for working capital and general operating purposes.

4.2.23 Labopharm

Overview

Labopharm is an international pharmaceutical company specialising in the development of drugs using advanced controlled-release technology. The company's core technology, Contramid, can be applied to a wide variety of drugs in solid oral dosage form, to improve their oral administration and performance.

Oral Delivery Technology

Contramid: is a patented controlled-release drug-delivery system, based on high amylose starch, for the oral administration of solid dosage forms. When used as an excipient and compressed with an active drug substance into a solid dosage form, Contramid allows for the controlled release of the active drug over an adjustable period of time. The company claims Contramid is different from conventional hydrophilic matrix systems and can be applied to a wide range of medications to improve oral administration and performance.

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