Expert Opinion

Drug delivery for optimised products: from product life-cycle management to first-generation product concepts

Padmanabh P Bhatt
Shire Laboratories, Inc., Rockville, Maryland, USA

Expert Opin. Drug Deliv. (2005) 2(1):1–2

The number of new medical entities gaining FDA approval has declined over the past few years. At the same time the cost of development of each new drug introduced into the market continues to rise, pegged today at > $800 M by some estimates. Built into this estimate is the cost of the multitude of molecules that fail to see the light of commercial development.

The pharmaceutical industry, by and large, continues to follow the approach of screening lead compounds for physicochemical and physiological properties that would allow for facile product development of simple, immediate-release dosage forms such as oral tablets or capsules, and injectable solutions or suspensions. Lead molecules that do not meet certain criteria are sent back to the synthetic chemistry bench for further manipulation; thus starting the development cycle all over again. This approach dates back to the history of the pharmaceutical industry as an offshoot of the chemical industry; times when the fields of physical pharmacy and drug delivery were still in their infancy.

Today, chemical modification of the lead molecule to create a better analogue for use in the dosage form is one option. Another available option is to utilise drug delivery and bioavailability enhancement strategies to overcome the suboptimal physicochemical or physiological properties of a pharmacologically effective drug to create an optimised commercialisable dosage form.

Drug delivery strategies, especially controlled drug delivery, have proven themselves in the form of very successful marketed products. The Duragesic® (Janssen Pharmaceutica) patch, which delivers fentanyl in a controlled-release form via the transdermal route, is one such example. Here is a potent molecule, albeit with a short half-life, that had a small and relatively flat market profile as an injectable product. When this drug was developed into an optimised sustained-release patch the market expanded to generate > $1 B in annual sales revenues. Another example is the short half-life drug nifedipine, which when incorporated into an oral controlled-release dosage form created the successful commercial product: Procardia XL® (Pfizer). There are many more examples of products containing known drugs that when incorporated into drug delivery concepts expanded the market for their use and became franchise products for the marketing companies. Concerta® (Alza Corporation) and Adderall XR® (Shire) are two products that showed that it was not enough to just extend the release of the drug in the gastrointestinal tract. These products were built with a customised release profile – the so-called 'rising dose' profile – that made for a more effective product for the drugs methylphenidate and amphetamine salts, respectively. Both these products are each garnering annual sales revenues in the hundreds of millions of dollars.

The success of these second-generation products established the use of drug delivery for product life-cycle management. Such use of drug delivery concepts is now well accepted in the pharmaceutical industry. The next phase of utilisation, making slow headway in the industry, is where drug delivery strategies and rational dosage form design are considered for, and applied to, new chemical entities as an

alternative to the strategy of continued synthesis of analogues in search of ideal properties.

The rational approach to dosage form development entails the use of diagnostic techniques, screening tools and solution tools to create an optimised dosage form. For a new medical entity, a series of early analogues are tested using cell screening and other *in vitro* techniques to determine their physicochemical and physiological properties. With this data one develops a decision matrix for the 'developability' of each analogue. The definition of 'developability' though is broader and includes the concepts of bioavailability enhancement as well as modified or controlled release. *In vitro* screening techniques are then used to identify 'enhancers' to improve solubility and/or permeability for bioavailability enhancement, if needed. The enhancement concepts are validated in whole body animal and human studies.

Dosage form design is then considered, factoring in the physiological properties of the drug. The desired pharmacodynamic response profile of the drug is translated into a desired pharmacokinetic plasma profile. Such consideration can lead to a determination that modified release of the drug is needed to provide optimum presentation of the drug to the systemic circulation for maximum efficacy and reduced side effects. Given the many different drug delivery technologies available today, consideration is also given to the optimum route of delivery, either to overcome the 'first-pass' effect or for faster onset of action or ease of administration. For developing an oral extended-release dosage form, the issue of region-specific absorption in the different segments of the gastrointestinal tract is also considered.

Using the rational approach to dosage form design is a shift in paradigm for the pharmaceutical industry because, generally, the dosage form development effort is considered to be the less critical phase of product development. The thinking is that if one has synthesised a drug with 'ideal' properties, it can easily be punched into a tablet or filled in a vial. Most of the drug development time, effort and money are expended in the lead generation and clinical testing phases of development. Redistribution of some these resources to dosage form design and development will allow the integration of the drug delivery concepts into the finished product. It will also save many lead molecules with suboptimal properties that today do not see the light of development and commercialisation.

Ultimately though, the rational approach to dosage form design utilising drug delivery will provide a better product for the patient, and such an optimised product will generate better returns for the marketer.

Affiliation

Dr Padmanabh P Bhatt PhD, Vice President, Advanced Drug Delivery
Shire Laboratories, Inc., Rockville, Maryland, USA