CROSS-INDUSTRY Organizations

AAPS FDD: 2014 Annual Meeting features a session on combination products

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On behalf of the AAPS Formulation Design and Development (FDD) Section

During the 2014 AAPS Annual Meeting and Exposition in San Diego, CA, US, a mini-symposium on Combination Products and Innovation in Drug Delivery Systems was organized under the auspices of the Formulation Design and Development (FDD) Section led by Dr. Panayiotis P. Constantinides. The proposed title stemmed from the consideration that drug delivery systems, at least in the perception of the scientific community, play a pioneering role in the field of combination products. They typically combine active pharmaceutical ingredients (APIs), excipients, polymers and devices in a scientific and innovative or inventive manner so as to best exploit their functionality and therapeutic benefit.

Indeed, the term "combination product" has broad meaning. The most recognized usage is in "fixed-dose combination products" (formulations including two or more active pharmaceutical ingredients combined in certain respective fixed-doses in a single dosage form), and "drug/device combination products." Both are complex products that have already gained regulatory status and wide market share. The aim of the mini-symposium was to discuss the therapeutic/technological advantages of both categories of combination products. The workshop also provided the occasion to highlight the regulatory hurdles that may arise in formulation development and evaluation procedures for such products. Finally, in the interest of time, the scope of the meeting was restricted to oral and inhalation administration as the most common routes that take advantage of fixed-dose combination products and drug/device combination products, respectively.

Chaired by Dr. Carla M. Caramella and Dr. Paolo Colombo, the mini-symposium featured three lectures. Dr. Douwe Breimer from Leiden University discussed "Current and future uses of medicinal combinations;" Dr. Colombo, from the University of Parma, Italy gave a lecture entitled "Fixed-dose combination for the oral route: Assembling modules for complex release kinetics requirements;" and Dr. Hugh Smyth from University of Texas, Austin discussed "Drug/device combination products for the inhalation route."

Current and future uses of medicinal combinations

Dr. Breimer gave an illuminating lecture focusing on the new paradigm of drug discovery/utilization, based on the concept of System Biology, which aims to understand the behavior of a complex biological system as a whole, as opposed to the behavior of its individual constituents. Applying this concept to the interplay between disease, drug and drug PK and PD, (System Pharmacology), it is possible to explain the resilience of biological systems to existing drugs and to identify novel pathways of disease, novel drug targets and novel therapeutic interventions, thereby fulfilling the scope of System Therapeutics. If applied to drug combinations, the new paradigm will allow the flexibility needed to identify new combinations of targets and molecules, to predict combined drug effects and to evaluate the therapeutic potential of innovative combination therapies. At this time, System Therapeutics needs pharmaceutical formulators to develop appropriate drug delivery systems to cope with differences in required drug delivery rate and intersubject variability inherent in oral drug delivery.

Fixed-dose combination for the oral route

In his presentation, Dr. Colombo noted that emphasis should be put on drug delivery, after the recent FDA statement, according to which, fixed-dose combinations have become increasingly prevalent in certain therapeutic areas and play an important role in ameliorating adherence to therapy and patient compliance. Drug delivery represents a very important feature of any medicinal products, but in particular of fixed-dose combinations because, in addition to compatibility problems, different drugs administered simultaneously may require different release sites, duration and kinetics. Therefore, there is an urgent need for new and innovative delivery platforms based on novel technologies, especially in the case of complex therapies and/or heavy administration schedule. Dr. Colombo described a novel, patented delivery system, called the Dome Matrix, composed of two or more modules adhered to form a one-piece assembly. The Dome Matrix provides variable release duration and kinetics and interacts with different sites depending on module composition and assembly. Examples of practical realizations including *in vitro* release and, in humans, PK data were presented on a gabapentin/flurbiprofen combination.

Drug/device combination products for the inhalation route

In the third presentation, Dr. Smyth addressed the topic of drug/device

combination products for the inhalation route. He began by explaining that a marriage between drug and device is necessary. Since the dispersion pattern of the formulation strongly influences the product performance (as linked to its quality target product profile), to get such a marriage, the device should be designed so as to improve product performance via an exact knowledge of the dispersion mechanism involved. Then Dr. Smyth presented interesting data on the mechanisms of dispersion of different powders and the complex interplay between particle/powders properties (size, surface energetics, etc.), flow rate and device geometry in balancing detachment and adhesion forces, and ultimately determining particle dispersion and delivery efficiency. His conclusion was that the formulation and the device are largely dependent on each other and that very few formulations and particle engineering technologies allow optimum performance in an "off-the-shelf" device. In contrast, he showed how device technology can be improved to free the performance of the inhalation system from the subtle differences in powder formulation. This can be achieved, for example, by adding the use of a patented Axial Oscillating Sphere (AOS) powder deaggregator to the device. Therefore, it can be stated that a perfect marriage of drug and device can be obtained only if a certain degree of independence between the two is assured.

Topics of discussion

The mini-symposium was attended by more than 200 people who attentively and actively participated at the session. During the final discussion, questions were addressed to Dr. Breimer relating to both specific examples of drug combination and the generalities of the System Therapeutics approach proposed. Questions on Dr. Colombo's presentation mainly concerned manufacturing aspects and procedures and machinery for assembling individual Dome Matrix modules. The data presented by Dr. Smyth raised specific questions on the functionality features of the proposed device as well as more general questions on the impact of device functionality on the adherence to therapy. During the panel discussion, many attendees also expressed appreciation for the topic choice of combination products.

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