

Babe 2014- Design of drug delivery system for poorly water soluble drugs with enhanced bioavailability- Jim Jingjun Huang- CEO Ascendia Pharmaceuticals

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Poor water solubility of more than 60% of new chemical entity present a major hurdles in the design of suitable drug delivery systems for the market dosage form. Current controlled-release drug technologies for water insoluble drug are summarized. The key considerations in design of controlled release dosage forms, such as drug physico-chemical and biopharmaceutical properties, in-vitro and in-vivo correlation, and key material and process attributes for the robust manufacturing and reproducible performance of the product are presented. The multidisciplinary collaboration between CMC, biopharm, clinical, M&S, and marketing teams were found critical for the successful development of controlled release dosage forms with enhanced bioavailability.

Introduction: For poorly soluble compounds, an honest bioavailability is usually needed to assess the therapeutic index and therefore the suitability of the compound for technical development. In industry, the selection of the delivery technology is not only driven by technical targets, but also by constraints, such as production costs, time required for development and the intellectual property situation.

Areas covered: This review covers developments in oral and parenteral delivery system and products for poorly water-soluble compounds, like solid dispersions, liposomes and nano-suspensions. In addition, the use of biorelevant dissolution media to assess dissolution and solubility properties is described. Suggestions also are included to systematically address development hurdles typical of poorly water-soluble compounds

intended for parenteral or oral administration. Expert opinion: A holistic assessment is suggested to pick the acceptable delivery technology by taking under consideration intellectual property as well as technical considerations. Therefore, complete physico-chemical characterization of poorly water-soluble compounds can provide a successful selection and development result. In this context, the identified physical sort of the compound within the formulation is employed as a guide for a risk-benefit assessment of the chosen oral delivery technology. The prospect of nano-suspensions for intravenous administration is obscure. In the case of oral administration, nano-suspensions are mainly wont to improve the oral absorption characteristics of micronized formulations. The development of an in situ instantaneous solubilization method, based on stable, standardized liposomes with low toxicity, opens new avenues to solubilize poorly water-soluble compounds.

Drug Delivery approach for Poorly Water-Soluble Drugs provides a complete overview of currently used formulation strategies for hydrophobic drugs, including liposome formulation, cyclodextrin drug carriers, solid lipid nanoparticles, nanocrystals, hydrosol colloidal dispersions, polymeric drug encapsulation delivery systems, self-microemulsifying drug delivery systems, microemulsions, solid dispersions, cosolvent use, polymeric micelles, dendrimers, polymer-drug conjugates and mesoporous silica nanoparticles. For each approach the book discusses the main instrumentation, operation principles and theoretical background, with a focus on critical formulation features and

clinical studies. In current years, with the extensive application of high-throughput screening technologies in drug development, an rising number of latest chemical entities with extremely poor aqueous solubility are generated. Their poor solubility represents a serious challenge for formulation of those compounds for both oral and parenteral administration. Formulations for intravenous (i.v.) application are of serious importance because they're frequently utilized in several key therapeutic areas, like oncology and anesthesia. Furthermore, i.v. formulations of latest compounds are often needed to work out basic biopharmaceutical parameters and to get proof of concept leads to the first phase of development. This review provides an summary of the recent advances in formulation approaches and drug delivery technologies for poorly water-soluble compounds applicable to i.v. administration. The advantages and disadvantages of different strategies are highlighted and an expert opinion on each technical field is presented. The oral route is the most commonly used for drug administration due to significant inherent advantages compared to other routes, such as safety, non-invasive nature, convenience and comfort to the patient. Among all types of oral dosage forms, the solid ones, such as tablets and capsules, are the most used in therapy, because they offer many benefits, such as simplicity and low cost of production, high stability, convenience of the presentation in unit doses, portability, simple administration and masking the unpleasant taste of the many drugs. A major obstacle to the event and large-scale production of oral solid dosage forms is that the low solubility of the many drugs, given the negative effect that this property has on drug absorption and bioavailability. Concern about drug solubility in the pharmaceutical industry has intensified from the 90s, when the use of techniques, such as combinatorial chemistry

and high throughput screening (HTS), increased the achievement of latest chemical entities with high relative molecular mass and high lipophilicity. Recognizing that drug dissolution and gastrointestinal permeability are the fundamental parameters controlling the rate and the extent of drug absorption grounded the proposition of the Biopharmaceutical Classification System (BCS) for correlating drug product in vitro dissolution and in vivo bioavailability, during which classes II and IV encompass drugs with low solubility.

The need for effective formulations for BCS-classes II and IV drugs led to the progress of data within the area of drug delivery systems for oral administration, over the years, and to the development of various technological strategies to remedy unsatisfactory biopharmaceutical properties, for example, micronization, formation of complexes with cyclodextrins, self-emulsifying drug delivery systems (SEDDS), liquisolid systems and solid dispersions.

Large investments in research and development of solid dispersions brought good results for the pharmaceutical industry, with the emergence of products based on this technology on the market. Nevertheless, there is still plenty of room for improvement, aiming to overcome some limitations of the solid dispersion technology. Additional studies for development and improvement are still needed regarding the assembly processes, carrier materials and stabilization strategies, in order that the complete potential of solid dispersions is explored, thus resulting in increased number of commercially available products. This review presents an overall approach to the factors affecting the dissolution and oral bioavailability of BCS-classes II and IV drugs and a brief review of the state-of-the-art of solid dispersion technology.

2.Oral Administration Of Poorly Water-Soluble Drugs

For producing the specified pharmacological response after oral administration, as shown in Figure 1, a dosage form must release the drug within the alimentary canal to be absorbed, reach the systemic circulation, and be distributed in the site of action in the body at sufficient rate and extent. The term bioavailability refers to the rate and extent at which the active drug reaches the systemic circulation. Many factors may influence the bioavailability of medicine, which can be associated with the dosage form, the manufacturing process and therefore the drug itself.

Biography

Jim Jingjun Huang received his PhD in Pharmaceutics from the University of the Sciences in Philadelphia (formerly Philadelphia College of Pharmacy and Sciences). He has 15 years of experience in preclinical and clinical formulation development of a variety of oral and parenteral dosage forms through his industrial experience

with Wyeth, Baxter, Astra Zeneca, and Hoffmann-La Roche. His research interests are centered on solubilization and delivery of poorly water-soluble drugs. His publications include studies on drug solubilization and controlled delivery in polymeric solid dispersion systems, amorphous drug delivery systems, etc. He credits several publications in peer-reviewed international journals, presentations at international pharmaceutical conferences, and patent publication. He has been invited to serve as a reviewer for Journal of Pharmaceutical Sciences, International Journal of Pharmaceutics, Journal of Controlled Release, Drug development and Industrial Pharmacy, Molecular Pharmaceutics, Pharmaceutical Research, and PDA Journal of Pharmaceutical Science and Technology. Currently, he is a member of American Association of Pharmaceutical Scientists (AAPS) and American Chemical Society (ACS).

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