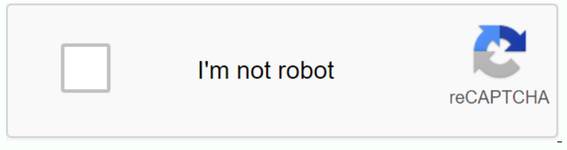

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Formulation development of parenteral dosage forms pdf

Many of the intravenously administered drug compounds are formulated as frozen dose forms due to a lack of sufficient chemical stability at comfortable or cooling temperatures. The product is stored in a freezer in a hospital pharmacy and thawed before use. These products therefore require a long-term frozen shelf life plus short-term room temperature and/or temperature coolers. The formulation is optimized for overall stability in the frozen state, as well as in the thawed state. This paper reviews the importance of phase changes in frozen state and the influence of various formulation factors such as drug concentration, diligence, buffer concentration, pH and purity of raw materials on the stability of the drug in a frozen state. An overview of analytical and production considerations unique to frozen products is also presented. An injection of ® (Vaprisol) for the treatment of hyponatremia has been developed to treat hyponatremia. Since the drug is very mildly soluble in water, pH and cosolventity control techniques were used to achieve the optimal concentration required for the material for clinical trials. Stability studies of retained samples of clinical trial materials for early stage studies showed white visible particles mainly in the headspace of the glass ampoule long after the end of the study. The mechanism for the formation of particulate matter was the formation of a free base of conivaptian hydrochloride due to an increase in pH. Ph formulations for late-stage clinical trials, primary stability and commercial production trials were fine-tuned to prevent particulate matter formation. The formulation contains propylene glycol and ethanol. Given the nature of the cosolvent used in the formulation, the estimated amount of di(2-ethylhexyl)phthalate (DEHP) was delivered from the infusion system, and we confirmed that the DEHP level is less than the level specified in the guidelines. During the commercialization study, the formulation failed the filter integrity test after filtering the compound solution. Dimethyliloxan extracted from the silicone tube used to transfer the solvent coated the surface of the filter, resulting in a suppression of the value of the bubble point. The formulation and production process enabled the approval and initiation of conivaptian hydrochloride on the market as a parenteral formulation. Lay abstract: Formulation scientists have recognized the trend that promising new chemical entities at the drug discovery stage often do not have ideal physicschemical properties for formulation. In particular, poor solubility is one of the challenges for the development of parenteral doses. Here we describe the case of such a new chemical entity, a very mildly soluous hydrochloric salt, which has been handed over from a drug discovery research laboratory to a pharmaceutical laboratory. pH control and co-insolvency techniques were used to achieve optimal concentration of for the product. However, several questions arose; During development, we performed affirmative studies, and the results of these studies were used to devise the formulation and production process. The most prominent problems were the formation of particulate matter on the inner surface of the main ampoule space and the failure of the filter integrity test. In addition, we discuss the root causes and mechanisms of the above issues and the measures taken to prevent them. Part of them is crucial, and the information obtained from this study is important for the development of new chemical subjects as injections in the future. Keywords: Alkali rinse; Conivaptan hydrochloride; Cosolvent, Cosolvent, Cosolvent, Cosol DEHP; Esterification; Ethanol; Filter Integrity Test; Free base; Hydrolysis; Lactic acid; Particles; Propylene glycol; Silicon. As the number of poorly soluble and complex molecules, such as biological, entering drug development increases, the industry is also witnessing a positive impact within the parenteral formulation market. The benefits of non-oral application techniques for these complex and poorly soluble molecules, where the absorption of the active ingredient is simplified and avoids the first passage, are well documented. Parenteral formulations are dose forms administered non-oral, subcutaneous, intravenous, intraososal or intramuscular. According to market research, rising approval rates for new parenteral drugs worldwide should drive significant revenue growth in the home drug market in the near future (1). In particular, looking at the global sterile injecting drug market, for example, transparency market research predicts that the compound annual growth rate will exceed 11% between 2017 and 2020. However, compared to oral-solid dose forms, parenteral formulations require very specific and important considerations and raise certain challenges and limitations, such as drug stability issues. Primarily, solutions, suspensions or emulsions that are developed for injection or implantation are directly entered into the systemic system of human circulation and thus must be sterile and safe for use. Furthermore, sterile parenteral formulations must be pirogen-free and clean from visible and visible particles, to list several criteria specified for the compendia. To learn more about the intricacies of parenteral formulation, Pharmaceutical Technology spoke with Fabio Stevanon, director of the Global Injection Platform at CordenPharma International. Important considerations for parenteralsPharmTech: What are some of the most important considerations for the formulation of parenteral drugs? Stevanon (CordenPharma): All considerations regarding parenteral formulation begin by ensuring successful, targeted delivery of the API for effective treatment of the targeted condition. The formulation must support the desired therapeutic effects of the API after administration. So much of any day the therapeutic value of the drug is associated with its specific formulation of the API in solution or suspension. Bioanimibility and other desired pharmacokinetic effects depend on the eventual, commercial formulation of the finished drug. Parenteral formulations go to places they have never been before, where we see many sterile injections increasingly paired with new delivery technologies to ensure practical and timely, prescribed dosing of drugs over time. For combination products with medicines, formulations must be adapted to achieve specific attributes associated with both the device and the medicine, such as stability during the target shelf life, compatibility with primary packaging, viscosity and similar parameters, plus other aspects of drug use in relation to a particular medical device. Only proven expertise gained through testing and effective development of analytical methods, as well as experience in combining device and drug products, will deliver a successful formulation in this space. In addition, parenteral formulation chemistry must serve commercial and manufacturing interests as best as possible. The formulation has a direct impact on scale-up and the process of variability, stability and other processing, and production-oriented aspects related to the successful commercial development of the drug. PharmTech: Can you clarify the importance of excipients in the formulation of parenteral drugs? Stevanon (CordenPharma): Two things are important about auxiliary substances. First, regardless of the API, excipients must be selected based on their performance and usefulness in the service of the particular formulation and therapeutic function in question. The earlier this selection is established in the development phase, the better. Another priority is to assess assistance for certain attributes that help maintain the commercial production of the drug, including compliance, sterility profiles, availability, reliability of supply, stability in the process and more. ParenteralsPharmTech-specific benefits and challenges: In your opinion, what are the main advantages of parenteral drug formulation in other forms? Stevanon (CordenPharma): Parenteral drugs provide faster therapeutic action compared to slower-acting dose forms such as oral-firm dose (OSD). Parenteral drug formations also allow for higher dose levels in circumstances where critical therapies must immediately enter the bloodstream, such as emergency surgery, heart attack or infections, and so on. There are other benefits related to dosing accuracy such as how properly, strictly validated injection formulation will, in most cases, give better bio-viability at the desired dose level. PharmTech: And the biggest challenges in the formulation of parenteral drugs? Stevanon (CordenPharma): Confirming parenteral formulation is much more challenging compared to OSD. The quick-hearted nature of this administrative path means that parenteral formulations are subject to stricter regulations to ensure patient safety and must remain within specific and usually very narrow parameters for obtaining approval from regulatory authorities. Processing and production of sterile parenteral dosing forms therefore requires a comprehensive approach, including mastering sterile containment, filling/finishing and data-driven processes. As this is a challenge that not all pharmaceutical companies can or are willing to address, many are turning to strategic partners who outsource full service to support their business models and drug development strategies as a result. Small compared to large moleculesPharmTech: Can you discuss the main differences to consider when formulating a small molecule or biological drug as a parenteral drug? Stevanon (CordenPharma): There is an additional level of expertise, technology and skill that is required to formulate a biological drug as a parenteral drug. Small molecule parenteresses can be produced and produced by traditional analytical methods that are standard practice throughout the industry. However, biologics require a different approach to analytical testing and manufacturing processes, which older, less technologically advanced facilities may not be able to handle. In addition, biological parenteral production requires a najmodamo-in-the-art facility in which in most cases one-time/disposable technology is given, and sometimes a dedicated biological plant is required. Regulatory considerationsPharmTech: What are the main regulatory challenges facing parenteral drug formulators? Stevanon (CordenPharma): Due to difficulties in maintaining supply for high demand for injectable drugs, while keeping pace with production quality and safety at large volumes, we have seen increasing pressure from regulators on drug manufacturers to control processes more efficiently and remove the potential for process variation and contamination. Regulators are also closely monitoring developments in the combined device and drug products space. Many new pharmacy development projects and lifecycle management capabilities explore the integration of medical devices with drug products and invest in the development of these technologies due to their therapeutic effectiveness and potential value to patients. For many combined device-drug developers, guidelines and applicable production standards have and are evolving rapidly. Such strong growth in this pharmaceutical industry sector has increased significant development, formulation, clinical supply, transmission and control of design, risk management and commercial supply of these combined products, which makes their engineering and compliance very challenging. Future Trends: Optimization of developmentPharmTech: Over the next decade, what trends do you anticipate will affect the space of parenteral drug formulation? Stevanon (CordenPharma): For many pharmaceutical companies everything greater need to invest in facilities, equipment and controls related to the production of parenteral medicines and combination products from medicinal products and devices. Optimal development strategies will require extensive, as well as broader expertise, often found by hiring established, competent CDMO providers [contract development and manufacturing organization] - this trend will continue to gain momentum over the next decade. The industry is also witnessing the adoption of advanced technologies to ensure quality and reliability in manufacturing. For example, the emergence of single-use/disposable injection technologies provides alternatives to traditional complex filling in stainless steel or glass-coated containers. Options for one-month compound filling packages will therefore be increasingly needed to handle oxidation-prone compounds that are incompatible with traditional stainless steel mixing and transfer vessels. References 1. Fact.MR, Parenteral Drug Market Forecast, Trend Analysis and Competition Tracking-Global Market Insights 2018 to 2028, fact.mr.com, Market Report, accessed on July 8, 2019. Transparency Market Research, Sterile Injectable Drug Market-Global Industry Analysis, Size, Share, Growth, Trends, and Forecast 2017-2027, transparencymarketresearch.com, January 2018. Article detailsPharmaceutical Technology Vol. 43, No. 8 August 2019 Pages: 24–25 24-25