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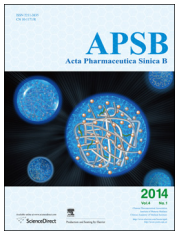

REVIEW

Can formulation and drug delivery reduce attrition during drug discovery and development—review of feasibility, benefits and challenges

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KEY WORDS

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Abstract Drug discovery and development has become longer and costlier process. The fear of failure and stringent regulatory review process is driving pharmaceutical companies towards "me too" drugs and improved generics (505(b) (2)) fillings. The discontinuance of molecules at late stage clinical trials is common these years. The molecules are withdrawn at various stages of discovery and development process for reasons such as poor ADME properties, lack of efficacy and safety reasons. Hence this review focuses on possible applications of formulation and drug delivery to salvage molecules and improve the drugability. The formulation and drug delivery technologies are suitable for addressing various issues contributing to attrition are discussed in detail.

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1. Introduction

The discovery of new drug is a multi-stage complex process, each stage lasting for years. Probability of molecule discovered in early stages making it to market is 1 in 10,000[1]. In addition to complexities in the science of making new safe and efficacious drugs, the political, economic factors coupled with stringent regulatory requirements and review process, the drug discovery has become even more complex and long lasting[2]. As a result, the cost of inventing a new drug has increased to staggering USD 2.6 billion from 100 million during 1979[3–5].

Pharmaceutical industry is being criticized for not bringing more innovative medicine into market for treatment of unmet medical needs. These days, industry is producing too many drugs which are similar to each other and offer marginal advantage over existing treatment. These "me too" drugs although provide alternative treatment options but led to price competition and reduced profit margins before the entry of generic versions in the market[6]. Since regulatory approval process for "me too" drugs is relatively fast and easy as these are structurally similar to approved drugs and hence the pharmaceutical companies tend to focus on analog research rather than real innovative medicine. Hence there has been innovation deficit in pharmaceutical R&D these days[7].

The sharp decline in the number of new drug approvals in the last decade can be attributed to attrition of molecules during discovery and development. The attrition rate is very high in the drug development process, only 15% of molecules entering the clinical trials receive marketing approval[8]. The success rate from phase-III clinical trial to market translation is reported to be 50–70%. The molecules are dropped during preclinical stage and withdrawn from further development during clinical studies for various reasons, such as lack of efficacy, toxicity, poor absorption, distribution, metabolism and elimination (ADME) properties, commercial interest and market competition[9,10]. The survey of molecule in clinical development from 1964–1985 revealed that poor pharmacokinetic profile contributed majorly (39.4%) for attrition of molecules in clinical development[9], however figure dropped to 10% in 2000, thanks to advancement in formulation technologies[10]. Lack of efficacy (30%) and unacceptable clinical safety and toxicity (30%) were found to be major factors for discontinuation of clinical candidates in 2000[10].

There have been several approaches discussed in the literature to reduce attrition of drug candidates in the clinical development[10], identification of right target and strong mechanism of action would reduce the failure with regard efficacy, the attrition due to toxicity and safety can be reduced by eliminating molecules with mechanism based toxicity, the identification of biomarkers, selection of appropriate animal model for efficacy testing, evaluating proof of concept at early clinical studies were suggested for reducing attrition[10].

The failure of drug candidates may not be limited to fore mentioned reasons, there are other several factors contributing to attrition, for example discovery and development of drug candidates for central nervous system (CNS) disorders face additional barriers than those intended for other therapeutic application[11]. The CNS drugs while exerting activity, may also led to unwanted changes in the brain physiology and neurochemical balance, hence the stringent safety requirements for these drugs. In addition, the blood brain barrier (BBB) also poses another barrier for development of drug candidates in CNS category. The several drug candidates reported to be dropped due to their inability to cross BBB. The Gavestinel which had completed phase III clinical trials but was failed to demonstrate clear efficacy due to its poor permeation across BBB[11]. Although there have been significant innovative solutions to address the ADME issues such as absorption by enhancing solubility and permeability of molecules. However issues such as rapid metabolism, especially first pass effects have met with limited success. Good example is resveratrol (RSV), a natural biochemical with diverse biological activity has

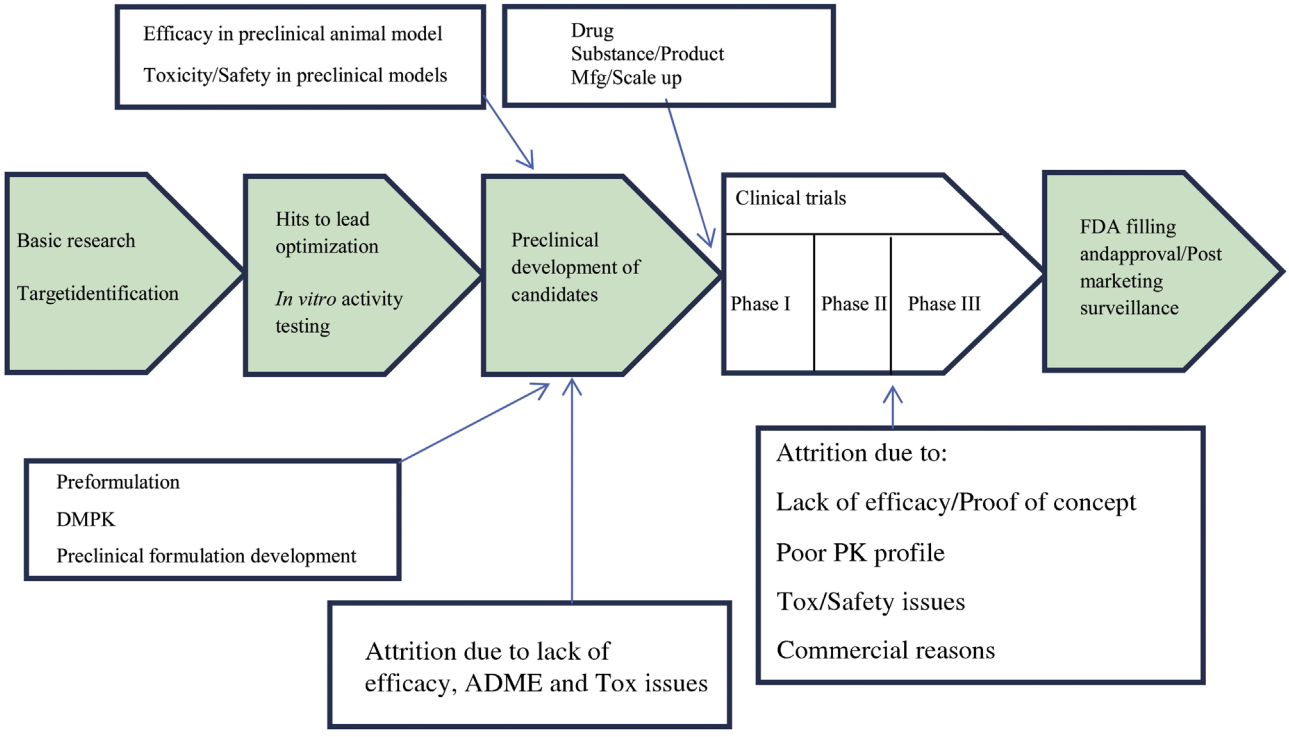

Figure 1 Representative scheme for drug discovery and development with reasons for attrition at each stage.

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