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Overview of Multicomponent Solid Forms

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ABSTRACT

Multi-drug therapy involves the simultaneous or sequential administration of two or more drugs with similar or different mechanisms of action and is efficient in combating various ailments such as cancer, diabetes, and rheumatoid arthritis. It has emerged advantageous due to larger therapeutic benefits, an increase in patient compliance, lower administrative costs, and reduced number of prescriptions. In the recent past, the clinical success of the Novartis product Entresto (sacubitril, disodium valsartan and water) and Esteve product E-58425 (tramadol and celecoxib) has boosted the development of multi-drug . The present article is hence designed to provide an overview of different multicomponent addicts which provide option of combining the drugs at a supramolecular level (nano-sized level). Key features of multi-drug cocrystal, co-amorphous system and eutectics are described with major emphasis on screening tools, preparation methods, characterization techniques, biopharmaceutical aspects and scale up.

KEYWORDS

Clinical Concerns, Multicomponent Adducts, Multi-Drug Therapy, Pharmacological Concerns, Regulatory Guidelines

INTRODUCTION

Concurrent administration of two or more therapeutic agents which have similar or different mechanisms of action are termed as multi drug therapy and can be used to combat various ailments (Shin et al., 2009). In comparison to single drug therapy, this approach helps in targeting different key signal transduction pathways which can be more efficacious in management of diseases, since they can evade cellular resistance mechanisms. The advantages offered by multi-drug therapy are schematically depicted in Figure 1. To date, this approach has been successfully implemented for management of diseases such as HIV/AIDS, cancer, multiple sclerosis, malaria, infectious diseases, cardiovascular and metabolic diseases, hypertension, auto immune disorders and many psychiatric maladies (Conway et al., 2010; Thipparaboina et al., 2015). Multi-drug therapy when administered in fixed dose combinations (FDC) are cost-effective which help in reducing pill load without any additional risk of adverse events or drug resistance and hence improve the patient compliance. FDC also facilitate the reduction of managerial and manufacturing costs by reducing the outflow related to packaging and drug prescriptions. FDC products contain simple drug–drug combinations or drug–device combinations, such as drug-eluting stents or drug-biological products for use in cancer therapy. The benefits offered by FDC are often overshadowed because of its severe disadvantages such as stability issues, and solubility differences and incompatibility between the parent drugs (Thipparaboina et al., 2015). Hence, there is a need to develop alternative approach which will facilitate the development of therapeutic hybrids to counter such problems. Multicomponent solids such as

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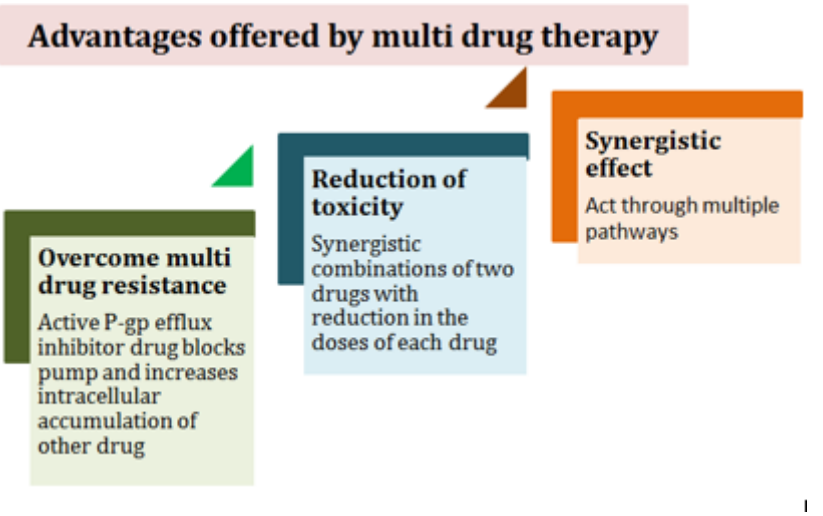
Figure 1. Advantages offered by multi drug therapy: MDR multi-drug resistance



cocrystals, co amorphous system (CAM) and eutectics may provide solution required for delivering the drug-drug combinations with improved benefits in terms of stability, improved solubility and dissolution when compared to FDC.

Clinical success of Novartis product Entresto a multi drug cocrystal which was approved in 2015 for effective management of chronic heart pain, is comprised of monosodium sacubitril, disodium valsartan and water, and has given a boost to pharmaceutical industry to improve the pharmaceutical attributes using multi component systems. However, developments of such multi component solid system need careful attention as it requires supportive evidence on its pharmacological action and safety such as synergistic or additive effect of two drugs in addition to stability and formulation related attributes. This review article aims to provide a brief overview on multi component solid forms (cocrystals, CAM and eutectics) and furnish information ranging from preparation, characterization, scale up and regulatory concerns related to these systems.

MULTI-DRUG COCRYSTALS

Multi drug cocrystals (MDC) are a subset of pharmaceutical cocrystals wherein the conformer is a bioactive molecule which possess independent drug activity instead of being an inert coformer. As per FDA, co-crystals are dissociable multicomponent solid crystalline supramolecular complexes which contain two or more components within the same crystal lattice where in the components are in neutral state and interact via nonionic interactions' (Aitipamula et al., 2012). MDC offer numerous advantages from enhanced bioavailability to reduction of multidrug resistance, synergistic and/or additive effects, enhanced solubility and dissolution of at least one component, possible stabilization of unstable components through intermolecular interactions, lifecycle management of existing products, and finally combination therapies (Thipparaboina et al., 2016). Our research group was the first one to propose the definition of co-crystals to MDC systems, and defined it as 'dissociable solid crystalline supramolecular complexes comprising two or more therapeutically effective components in a stoichiometric ratio within the same crystal lattice, wherein the components may predominantly interact via nonionic interactions and rarely through hybrid interactions (a combination of ionic and nonionic interactions involving partial proton transfer and hydrogen bonding) with or without the presence of solvate molecules' (Thipparaboina et al., 2016). Approval of Entresto a MDC appeared just