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MINI REVIEW

MULTIFUNCTIONAL EXCIPIENTS FOR SOLUBILITY ENHANCEMENT AND BEYOND

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Excipients are integral part of pharmaceutical dosage forms and manufacturing processes. Multifunctional excipients are a class of products that includes pre-processed and co-processed excipients for providing added functionalities to the formulation. Excipient development is seen as a large global market and is projected to reach USD 11.9 billion in 2026. Various multifunctional excipients have contributed not only to ease and accelerate the manufacturing processes, but also provided with beneficial pharmaceutical and biopharmaceutical properties to the formulations in terms of improved tableting properties, increased solubility and stability, reduced toxicities, achieving desired release profiles, lowering surfactant concentration, reducing parenteral toxicities and many more. The present mini review briefly outlines the role and scope of multifunctional excipients in pharmaceutical manufacturing along with few representative examples that are being used for various applications.

Keywords: Excipients, Multifunctional excipients, Co-processing, Functional excipients

Introduction

The global pharmaceutical excipients market was valued USD 6.6 billion in 2017 and USD 6.9 billion in 2019, is projected to reach USD 9.7 billion by 2025 at a CAGR of 5.8%[1] expected to reach USD 11.9 billion in 2026 at a CAGR of 6.87% from 2018 to 2026[2]. The reasons behind this acceleration are attributed to various factors such as growing pharmaceuticals market with advancements in functional excipients, increased acceptance of orphan drugs, and enhanced uptake of biopharmaceuticals. With the advent of multifunctional excipients, the focus of pharmaceutical manufacturing has been shifted to emerging markets. The growing biosimilars industry is also contributing consequential growth opportunities for market players in the pharmaceutical excipients sector[1].

Organic chemical excipients had the largest share of the pharma excipients market because of their increased efficacy in oral delivery and increased compressibility and flowability properties. Based on functionality, fillers and diluents dominated the market in 2017 because of their ability to improve taste and ease administration. Additionally, binders experienced growth as they be can co-processed to help overcome formulation obstacles and reduce development costs[2]. In this annual Drug Development & Delivery report, some of the industry's key players discuss the role excipients are playing in continuous manufacturing, biopharma formulation, and controlled- and immediate-release delivery.

Multifunctional Excipients

Excipients are integral part of pharmaceutical dosage form and manufacturing. Multifunctional excipients are a class of excipients that includes pre-processed and co-processed excipients for providing added functionalities to the formulation.

For instance, silicified microcrystalline cellulose, which is a processed combination of MCC and colloidal silicon dioxide. These functionalities add flowability, compressibility, particle size distribution, shape, porosity, etc. in the new polymer as compared to their basic excipient ingredient. The term multifunctional excipient also includes those excipient products which perform multiple tasks in a formulation.

For instance, Ludipress, which is co-processed product containing lactose, Kollidon and Kollidon-CL, serves the role of directly compressible diluent with binder and disintegrant properties)[3].

Multifunctionality Strategy

Multifunctional excipients can be obtained by developing a new excipient from the known established excipients. The strategies to achieve multifunctional excipients are: (i) cross-linking the polymer, (ii) developing new grades of existing excipients, (iii) co-processing excipients. Modifications in the original excipients leads to changes in the particle size distribution, particle shape and morphology and porosity. Developing a new excipient by any of these strategies presents problems in getting regulatory approvals. Usually, mere blending of two or more excipients do not results in significant improvement in their physical or functional properties. However, changing the manufacturing process of an excipient along with addition of minor amount of another known excipient results in a new excipient product that has enhanced physical characteristics leading to added functionality. The modified properties usually get improved include enhanced surface area, increased porosity, enhanced compressibility, good flowability, etc.

Many co-processed excipients developed by spray-drying or other suitable techniques are also suitable for direct compression and thus aid in simplifying the tablet manufacturing. The reason for enhanced compressibility can be drawn from the fact that most of the co-processed excipients principally consists of a large amount of brittle material and a smaller amount of plastic material. Thus, a co-processed material displays the property, which is a combination of plasticity as well as brittleness[2]. The general co-processing steps to achieve multifunctional excipient is depicted in **Figure 1**.

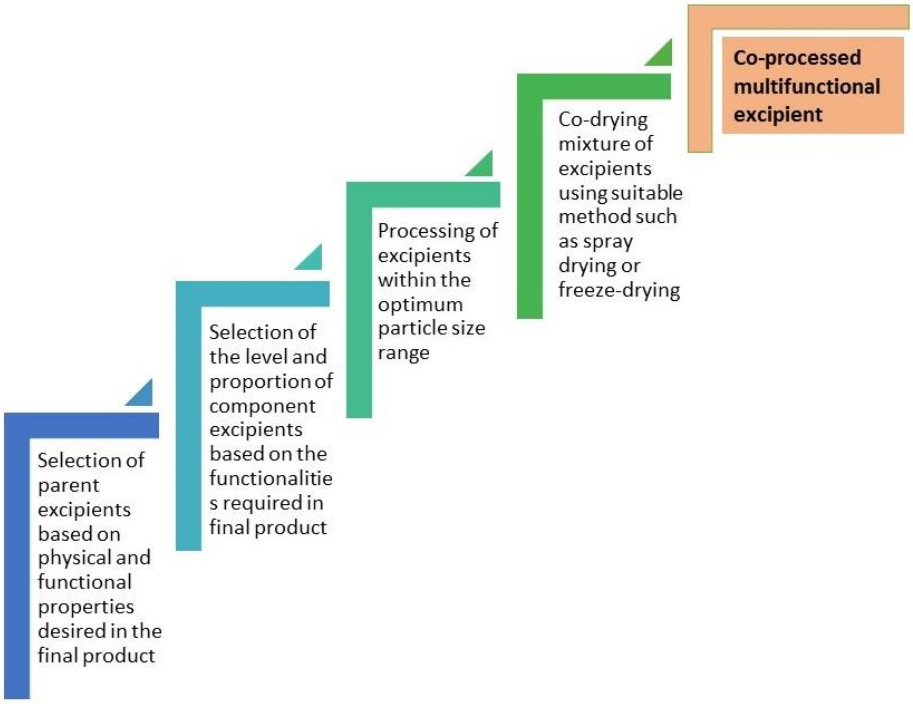

Fig. 1. General steps in development of multifunctional excipient

Scope of Multifunctional Excipients

Since their emergence, multifunctional excipients have been developed with an intent to achieve directly compressible excipients with improved tableting properties. Pharmaceutical developers are now focusing on development of excipients that provide targeted functionality for a specific manufacturing process4. Co-processed excipients offer the possibility of simplifying drug product formulations while meeting functional and technical requirements enabling formulation and manufacturing simplification[4]. A common feature of all co-processed excipients is capability of reducing total number of excipients used in formulation.

Despite many benefits, the co-processed excipients do not find place in pharmacopoeia. However, with recent

recommendations from the International Pharmaceutical Excipients Council, we expect large number of these products will find their way into official monographs in near future[5]. The role of world's leading market players in the development of multifunctional excipients is enormous and several grades are available for specific manufacturing applications. Some representative excipients and their functional applications are summarized in **Table 1**.

Table 1. Novel multifunctional excipients and their applications

Developer Company	Multifunctional Excipient(s) Examples	Composition	Applications/Functions/Benefits
JRS Pharma	PROSOLV®	Microcrystalline cellulose + (MCC) colloidal silicon dioxide (CSD)	Excellent compactibility, High intrinsic flow, Enhanced lubrication efficiency, Improved blending properties, Superior binding properties, Increased production capacity
Ligand	CAPTISOL®	Uniquely modified β-cyclodextrin, known as Sulfobutylether-β-cyclodextrin	Solubilizer, Increased bioavailability, Stabilizer
BASF	SOLUPLUS®	polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (PCL-PVAc-PEG)	Increase solubility and bioavailability, Ideal for hot melt extrusion (HME)
	LUDIPRESS®	Lactose monohydrate, Povidone K30 (Kollidon® 30) and Crospovidone (Kollidon CL)	Dry binders, pore formers for tailoring dissolution profiles, and ready-to-use formulations for tablets for orally disintegrating tablets
	LUDIFLASH®	Mannitol+Crospovidone+PVA	
	KOLLICOAT®	A graft copolymer comprised of polyethylene glycol and polyvinyl alcohol (PEG: PVA, 1:3)	Instant release coating of tablets and pellets
Roquette	KLEPTOSE®	Modified β-cyclodextrin and HP-β-cyclodextrin	Replacing polysorbates as surfactants while also providing a mechanism for protein stabilization, parenteral grade enhances solubility, stability and reduced irritation at injection site and low toxicity
Colorcon	STARCH 1500®	Partially pregelatinized starch	Functions as both a binder and distintegrant, suited for moisture-sensitive formulations, acting as a moisture scavenger while producing a mix of tablet hardness and rapid disintegration
Evonik	EUDRAGIT®	Polymethyl methacrylates	EUDRAGIT® portfolio, such as EUDRAGIT L 100-55 and EUDRAGIT L 100, have solid dispersion forming and recrystallization inhibition characteristics.
Gattefosse	Geluicre® 48/16	Polyoxylglycerides	Excellent candidates for low-temperature melt

Geluicre® 44/14		granulation and melt extrusion to obtain granules or multiparticulate systems. Help solubilize the API in the gastric media, trigger fed vs. fasted state environment that is amenable to absorption, enhance lymphatic transport that is desirable for drugs that are subject to hepatic elimination
Compritol®	Glyceryl behenate	Helps disperse the drug in a lipid matrix, providing protection against hydrolysis or oxidation for sensitive APIs, and taste masking or sustained-release profile depending on the percentage used.

Conclusion

Development in pharmaceutical multifunctional excipients to meet specific manufacturing requirement is a field of growing interest in recent times. With increasing market potential, this area is growing than ever before thanks to the efforts of global market players. With advancements in this field, role of excipients has not been only remained limited as inert formulation ingredients, but is expanded to achieve enhanced desirable biopharmaceutical properties including increased solubility, desired release profiles, taste masking and patient compliance, aid in API absorption and reduction of API toxicities and many more. However, issues such as increased development cost, time investment and problems with regulatory approval must be taken into consideration while undertaking development of multifunctional excipient.

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