Available online at www.ijpab.com

ISSN: 2320 – 7051
Int. J. Pure App. Biosci. **2 (5):** 144-148 (2014)

Review Article

INTERNATIONAL JOURNAL OF PURE & APPLIED BIOSCIENCE

Multifunctional Excipients: The Smart Excipients

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ABSTRACT

The pharmaceutical industry demands innovation in short period of time so as to gain access to new products in market. Formulation is all working with active ingredients and the excipients. The more excipients more are steps involved in manufacturing and higher are the cost incurred on introducing product to market. Excipients having multiple functions help to solve these issues as cost effective paradigm are on top most priorities in the industry. The smart excipients are the multifunctional excipients which are needed for continuous development and for much needed innovation. The existing excipients have been modified, co-processed, modifications are made with existing ones or cross linked in order to improve existing characteristics and impart good compatibility, flowability, dissolution, disintegration, hygroscopicity, palatability to formulate new product with an aim to minimize cost incurred on it. Multifunctional excipients like Ludipress®, F-MELT®, Galen IQ 721, MCC SANAQ® burst etc. have been assigned to be the smart excipients that help in robust formulation development with minimum problem during technological transfer.

Key words*: excipients, multifunctional excipients, co-processed excipient, direct compression.*

INTRODUCTION

The changing landscape of the pharmaceutical industry is increasing the commercial pressure on R&D groups to shorten time so as to market new products. As a result, formulators are demanding more functionality and performance from their pharmaceutical excipients. Formulation development is all about playing with the excipients. [5] Excipients play a significant role in drug formulation processes. They carry out an extensive range of functions to offer desired properties for the finished drug formulation. Also, they offer more effective and safer finished products for patients. They play a critical role in achieving stability, reducing cost, improving manufacturing efficiency and help produce a robust dosage form that is unaffected by variations in process parameters or other ingredients.

Enhancing drug formulation by reducing the investment in number of excipients is the need of the day. There are more than 1,200 pharmaceutical excipients available in the market with various functionalities such as fillers and diluents, binders, coating agents, disintegrants, flavors, colorants, lubricants and glidants, solvents, preservatives, sweeteners, and antiadherents. Increasing number of ingredients increases the steps involved in manufacturing, the complexities in formulation and ultimately the cost incurred. Formulators are now searching on for use of excipients with different functionalities, for example formulations in the development of new drug products contained native corn starch which was used as both a binder and disintegrant. As a binder, the starch was converted to a paste before adding it to the wet granulation. As a disintegrant, it was added dry to the powder blend. Due to flow and compressibility concerns, alternative excipients and excipient combinations were examined similarly Starch 1500 performs multiple functions within a wet granulation formulation, as a binder, disintegrant, filler and lubricant, eliminating the need for a multitude of costly excipients and additional processing steps.

Definitions

Excipients[4,2]: Pharmaceutical excipients are substances other than the pharmacologically active drug or prodrug which are include in the manufacturing process or are contained in a finished pharmaceutical product dosage form. The three U.S. Food and Drug administration (FDA) approval mechanisms are

- Determination by FDA that the substance is "generally recognized as safe" (GRAS) pursuant to Title 21, U.S. Code of federal regulation, parts 182, 184 or 186 (21 CFR182, 184 & 186) ;
- Approval of food additive petition as set forth in 21 CFR 171
- The excipient is referenced in, and part of, an approved new drug application (NDA) for a particular function in that specific drug product

Co-processed excipient[9]: According to International Pharmaceutical Excipient Council (IPEC), co-processed excipient is "a combination of two or more compendial or non-compendial excipients designed to physically modify their properties in a manner not achievable by simple physical mixing, and without significant chemical change".

Synthetic Excipients[10]: Synthetic excipients are those used in the manufacture of tablets to bind the tablet together, reduce die wall friction between the tablet and the tableting press, control pH balance, and to disintegrate the tablet in the stomach once it has been ingested. They're used for about every function of an inactive ingredient except as bulking agents, which are usually natural products. In parenterals, synthetics are used as solubilizing agents.

Multifunctional excipients[1]: These are a class of excipients that includes preprocessed and co processed excipients that provide added functionalities to the formulation (for example, Silicified Micro-Crystalline Cellulose, which is a processed combination of MCC and colloidal silicon dioxide) or the term multifunctional excipients extends to products that play multiple roles in the formulation e.g. Ludipress, which is co-processed product containing lactose, Kollidon and Kollidon-CL, serves the role of directly compressible diluent with binder and disintegrant properties.

Need of novel Excipients[1,6]:

1. Improving efficiency and lowering cost: it helps to reduce the burden on manufacturing processes by making it simpler, faster and affordable. Nowadays co processing of excipients has been preferred to produce product so as to meet the effective ratio of functionality and cost. For example ProSolv® co processed from MCC and silicone dioxide provides better flow, less sensitivity to wet granulation, better tablet hardness.
2. Reduces production time: Direct compression is the technique preferred as it has fewer stability issues, usually two step operation and less excipients required over wet granulation technique. This helps save time and assures arrival of product to market as early as possible. Example Ludiflas consisting of Coprocesed blend of 90% Mannitol, 5% Kollidon ® CL-SF (Crospovidone) 5% Kollicoat SR 30 D (polyvinyl Acetate) used in direct compression technique helps disintegrate a resperidone tablet within 27 sec.
3. Formulating the medicines that provide people with immediate relief: while developing immediate release tablet one can use polymers that provide good tablet hardness at a low concentration, flexibility across multiple manufacturing processes, compatibility with virtually all active and other ingredients, and compliance are needed. METHOCEL™ Cellulose Ethers offer exceptional flexibility can be used as thickeners, binders, film formers, and water-retention agents and they function as suspension aids, surfactants, lubricants, protective colloids, and emulsifiers. In many applications, two, three or even more ingredients may be needed to do the same job performed by one METHOCEL™ product, saving both money and time.
4. Specialized drug delivery systems: The development of novel or specialized drug delivery systems requires the use of special excipients. Metered dose inhalation devices require excipients of a particular size grade and development of mucoadhesive preparations necessitated the utilization of new bio adhesive polymers.

5. **For advancement in formulation**: The use of Novozymes has developed a range of recombinant human albumins (rAlbumins) specifically for the pharmaceutical industry which helps stabilize the drug product by reducing aggregation, oxidation, and surface adsorption. Particularly valuable for liquid formulations, rAlbumin can significantly decrease the attrition rate in formulation development and provides increased freedom to choose the best candidate for further development.
6. **Developing new chemical entities**: The reason for lack of new chemical excipients in market is the relatively high cost involved in excipients discovery and development. However, with the increasing number of new drug moieties with varying physicochemical and stability properties, there is growing pressure on formulators to search for new excipients to achieve the desired set of functionality.
7. **Best to formulate ODT**[5]: Single-bodied multifunctional excipients like F-MELT, Avicel CE-15 are especially developed for ODT formulations. They are tailor-made in order to give binding during compression (to produce a hard tablet at a minimum compression pressure) and show rapid disintegration when brought in contact with a medium.

Multifunctional excipients

An excipient is an inactive substance used as a carrier for the active ingredients of a medication. Now a days the development of new excipients strategy is market driven (i.e. excipients are produced in response to market demands), this leads to least scope for working on new entities as cost involved in these excipients is highest. Hence assessing functionality to the excipients is an important aspect. Functionality has been defined as: a desirable property of a [material] that aids manufacturing & improves the manufacture, quality or performance of the drug product. In the context of the pharmaceutical formulation & products, each formulation will have its own peculiar requirements for functionality.[4] In order to achieve multifunctionality the existing excipients have been modified, co-processing is done with two or more excipients, cross linking of polymers, the existing grades of excipients have been modified so as to achieve improved characteristics and gain multifunctionality.

1. Co-processed excipients[11,8,1]:

TRADE NAMES	COMPONENTS	BENEFITS
Ludipress®	Lactose PVP	Low hygroscopicity Good flow ability, Constant tablet weight, Low hygroscopicity, good disintegrant functionality.
F-MELT®	saccharides, disintegrating agent, and inorganic excipients	pleasant mouth feel, no-complicated route to developing oral disintegrating tablets, good moulding property
Pharmatose® DCL40	ß-lactose Lactitol	Good flowability, high dilution potential, low water uptake at high humidity, high compressibility.
Xylitab® 200	Xylitol Na CMC	Good compressibility with best mouth feel.
PanExcea™	MCC, HPMC and CPVD	Enable Quality by Design (QbD) drug formulation initiatives
Formaxx	Calcium carbonate, Sorbitol	Control particle size distribution

2. Excipients used in Direct Compression technique[7,13,16]**:**

TRADE NAMES	COMPONENTS	BENEFITS
GalenIQ 721	Agglomerated Isomalt	Outstanding compatibility at low compression forces, low hygroscopicity, excellent chemical stability, adds good taste to formulations. Excellent batch to batch uniformity. Cariostatic and low glycemic/insulinemic.
MCC SANAQ® Burst[17]	Microcrystalline cellulose	Good compressibility, used in fast disintegrating tablet
Pharmatose M200	milled lactose monohydrate	Higher compatibility, powder fluidity and disintegrability
Provosolv ODT	**Microcystalline Cellulose, Colloidal Silicon Dioxide, Mannitol, Fructose, Crospovidone**	Fast disintegrating matrix
SSG SANAQ®	Sodium starch glycolate	Disintegrant for tablet and capsule formation
FUJICALIN	anhydrous dibasic **calcium phosphate**	Excellent compression properties, Facilitates mixing/improves flowability, Good disintegrating properties, Low abrasion
StarAc	Maize starch, Acacia gum,	Good flowability, used in direct compression tabletting
Ludiflash	blend of 90% Mannitol, 5% Kollidon ® CL-SF(Crospovidone) 5% Kollicoat SR 30 D (polyvinyl Acetate	good flowability, less water absorption, and no segregation of the active ingredients, pleasant taste

3. Modified cellulose[10]

MODIFIED CELLULOSE	CLASS OF CELLULOSE	BENEFITS
MCC 102	class 1(simplified cellulose)	Provides high bonding strength, used as filler but lack multifunctionality.
UICEL S and UICEL B	Class 3(fully converted cellulose modification)	Rapid dissolving immediate release formulation, used as filler, binder, disintegrant.
UICEL XL	Class 4(cross linked cellulose modification)	Used as filler, binder and good compatible character.

4. Other multifunctional excipients:

TRADE NAME	CHARACTERISTIC	BENEFIT
UNI-PURE WG[15]	Pregelatinized corn starch	Best of Wet granulation binder
Neusilin®[12]	Synthetic Excipient (Magnesium Aluminometasilicate).	Drug protection, improved hardness and improves flow property.
Aerosil ®972	Hydrophobic colloidal silica	Stabilizer for water in oil emulsion, viscosity adjuster.
Syloid® FP[18]	micronized synthetic amorphous silica gels	Capillary wetting agent for better release and disintegration.
Sipernat®22 S	Precipitated silica,aluminium and calcium silicates	High adsorption capacity used as flow and anti-caking agent.
PharmaSmooth™	Second generation multifunctional excipients	Provides excellent flow, compaction and disintegration properties, provide signature mouth feel to formulate chewable tablet.
Polacrilin Potassium	Modified resin	Large swelling capacity.
Orocell 200 & OroCell 400	Modified mannitol	Binder, filler, carrier in formulating ODT
TAP®[17]	Tartaric acid pellet	Used for extended release pellet formulation

CONCLUSION

Cost effective approaches are on priorities in order to boost development in pharmaceutical industry. The formulations are lame without use of excipients. The increasing use of excipients has been leading to more expenditure on development of new entities so introduction of excipients with multiple functions have been boosted up. The smart excipients like Galen IQ, MCC SANAQ Burst, and Neusilin etc have been used because of its additional properties and their superiority over excipients. Compared with existing excipients, the improved physical, mechanical, and chemical properties of such excipients have helped in solving formulation problems such as flowability, compressibility, hygroscopicity, palatability, dissolution, disintegration.

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