ISSN 2582-6441 [Online]
RESEARCH JOURNAL OF PHARMACY AND LIFE SCIENCES
LET OTHERS KNOW YOUR RESEARCH
An International Peer Reviewed Journal
RJPLS

Review Article

Co-Processed Excipients: Unlocking the Potential of Direct Compression in Pharmaceutical Formulation Development

Maddukuri Laxmi Bharani, Arun Kumar Patra, Dipty Rani Nayak, Prasanta Kumar Choudhury*

Royal College of Pharmacy and Health Science, Berhampur, Odisha-760002, India

ARTICLE INFO

Date of submission: 08-02-2024
Date of Revision: 22-02-2024
Date of acceptance: 09-03-2024

Key Words:
Direct compression, Co-processed excipients, Tableting Powder flow, Compressibility, Regulatory considerations

ABSTRACT

Direct compression is a widely preferred tableting method in the pharmaceutical industry due to its simplicity, cost-effectiveness, and suitability for moisture and heat-sensitive drugs. However, achieving desirable powder flow, compressibility, and disintegration properties using conventional excipients can be challenging. Co-processed excipients, obtained by combining two or more excipients using specialized techniques, offer a promising solution to overcome these limitations. This review focuses on the development of co-processed excipients designed specifically for direct compression applications, involving the combination of fillers, binders, and disintegrants in optimized ratios using techniques such as co-fusion, co-grinding, or co-precipitation. The article discusses the advantages, formulation strategies, characterization techniques, and applications of these co-processed excipients, as well as the associated regulatory considerations and challenges.

***Corresponding author:**
Dr. Prasanta Kumar Choudhury
Professor, Department of Pharmaceutics
Royal College of Pharmacy and Health Science, Andhapasara Road, Berhampur, Odisha
E-mail: dr.prasntchoudhury@gmail.com

1. Introduction

Direct compression is a widely used tableting method in the pharmaceutical industry owing to its numerous advantages, including reduced processing steps, lower costs, and minimized exposure of drugs to heat and moisture [1]. However, the successful implementation of direct compression relies heavily on the physicochemical properties of the excipients used, particularly their flow, compressibility, and disintegration characteristics [2].

Conventional excipients often exhibit suboptimal performance in one or more of these critical aspects, necessitating the use of multiple excipients in formulations, which can lead to processing challenges and potential incompatibilities [3]. Co-processed excipients, obtained by combining two or more excipients using specialized techniques, offer a viable solution to address these limitations [4].

2. Advantages of Co-processed Excipients for Direct Compression

Co-processed excipients for direct compression offer several advantages over conventional excipients, including:

i. **Improved Flow Properties:** The combination of excipients with different particle sizes, shapes, and surface properties can enhance the overall flow characteristics of the blend, leading to more uniform die filling and improved content uniformity [5].

ii. **Enhanced Compressibility:** The synergistic interactions between the co-processed excipients can result in improved compressibility, enabling the formation of cohesive compacts with desirable hardness and friability profiles [6].

iii. **Optimized Disintegration:** By incorporating disintegrants into the co-processed system, the disintegration properties of the tablets can be tailored to meet the desired release profiles, ranging from immediate to sustained release [7].

iv. **Reduced Processing Steps:** Co-processed excipients can simplify the formulation process by minimizing the need for multiple excipients, reducing the risk of excipient incompatibilities and streamlining the manufacturing process [8].

v. Improved Stability: The co-processing techniques can enhance the physical and chemical stability of the excipients, potentially improving the shelf-life and robustness of the final formulation [9].

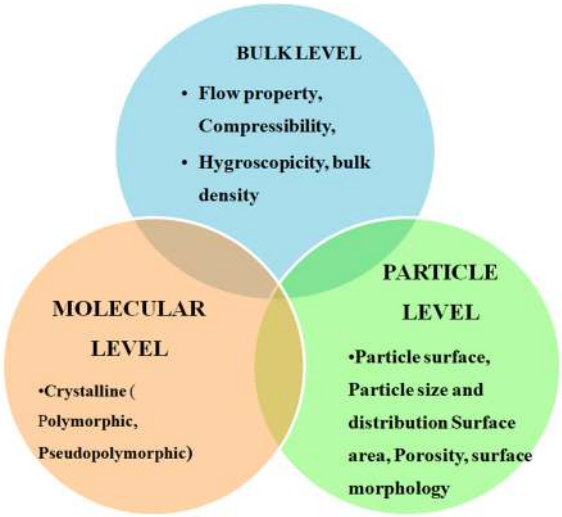

Figure 1: Principle of Co-processing (Particle Engineering)

3. Excipients Selection Criteria in Co-Processing

Selected excipients must be compatible and inert with each other. Co-processing is generally done by one excipient which is plastic in nature and another one is brittle in nature. For optimum tableting performance combination of both excipients are mandatory. It is reported by the researchers that the co-processing done with a large amount of brittle excipient and a small amount of plastic excipient. This particular combination of excipients prevents storage of large amount of elastic energy during compression, which results in a limited amount of stress relaxation and reduced tendency of capping and lamination, e.g., *Cellactose* is composed of Lactose (75%) – a brittle excipient & Cellulose (25%) – a plastic excipient.

4. Formulation Strategies for Directly compressible Co-processed Excipients

The development of co-processed excipients for direct compression typically involves the combination of fillers, binders, and disintegrants in optimized ratios using specialized techniques such as co-fusion, co-grinding, or co-precipitation.

4.1. Co-fusion

Co-fusion involves melting or softening one or more excipients, followed by the incorporation of other excipients and subsequent solidification [10]. This technique is particularly useful for combining hydrophobic and hydrophilic excipients, creating a homogeneous solid dispersion with improved flow and compressibility properties. Examples of co-fused excipients include:

- Ludiflash® (comprised of mannitol, polyethylene glycol, and polyvinyl alcohol) [11]
- Starlac® (composed of lactose and starch) [12]

4.2. Co-grinding

Co-grinding involves the mechanical grinding or milling of two or more excipients together, leading to particle size reduction and increased surface area [13]. This technique can enhance the binding properties of the excipients and improve

their compressibility, while also improving disintegration due to the increased surface area. Examples of co-ground excipients include:

- Ludipress® (consisting of lactose, polyvinylpyrrolidone, and crospovidone) [14]
- Avicel® CE-15 (composed of microcrystalline cellulose and guar gum) [15]

4.3. Co-precipitation

Co-precipitation involves the simultaneous precipitation of two or more excipients from a common solution, resulting in the formation of a co-precipitate [16]. This technique can be used to create intimate mixtures of excipients with improved homogeneity, flow, and compressibility properties. Examples of co-precipitated excipients include:

- Ludiflash® (mannitol and polyvinyl alcohol) [17]
- F-MELT® (composed of mannitol and xylitol) [18]

5. Characterization of Co-processed Excipients

Comprehensive characterization of co-processed excipients is crucial to ensure their suitability for direct compression applications. Key characterization techniques include:

5.1. Particle Size and Surface Area Analysis

Particle size distribution and specific surface area measurements, using techniques like laser diffraction and gas adsorption (BET), provide insights into the flow and compressibility properties of the co-processed excipients [19].

5.2. Powder Flow Characterization

Techniques such as angle of repose, Carr's index, and Hausner ratio are used to evaluate the flow properties of the co-processed excipients, which are essential for uniform die filling during tableting [20].

5.3. Compressibility and Compactibility Evaluation

Compressibility and compactibility are assessed using techniques like Heckel analysis, which provide information on the deformation behavior of the excipients under compression and their ability to form cohesive compacts [21].

5.4. Disintegration and Dissolution Studies

In vitro disintegration and dissolution studies are performed to evaluate the performance of co-processed excipients in facilitating rapid disintegration and drug release from the compressed tablets [22].

5.5. Solid-State Characterization

Techniques like X-ray diffraction (XRD), differential scanning calorimetry (DSC), and Fourier-transform infrared spectroscopy (FTIR) are employed to investigate the solid-state properties and potential interactions between the excipients in the co-processed system [23].

6. Applications of Co-processed Excipients for Direct Compression

Co-processed excipients have found numerous applications in direct compression formulations, offering improved performance and functionality compared to conventional excipients.

6.1. Immediate-Release Tablets

Co-processed excipients with optimized flow, compressibility, and disintegration properties can enhance the manufacturing process and quality of immediate-release tablets, ensuring consistent content uniformity and rapid drug release [24].

6.2. Sustained-Release Tablets

Certain co-processed excipients, particularly those involving hydrophobic polymers or waxes, can be tailored to provide sustained or controlled drug release profiles for extended-release tablet formulations [25].

6.3. Orally Disintegrating Tablets

Co-processed excipients incorporating superdisintegrants and water-soluble diluents can facilitate the development of orally disintegrating tablets with rapid disintegration and improved patient compliance [26].

6.4. Targeted Delivery Systems

Co-processed excipients can be designed to incorporate specialized excipients, such as bioadhesive polymers or site-specific release modifiers, enabling targeted drug delivery to specific regions of the gastrointestinal tract or other sites [27]

Table 1: List of some commercially available co-processed excipients for direct compression

Co-Processed Excipients	Brand Name	Manufacturer	Properties and Potential Applications
cyclodextrin	KLEPROSE DC	Rouquette Pharma, France	Direct compression, Insitu encapsulation of APIs
Agglomerated isomalt	galenI Q 721	Beneo Palatnit, Germany	Direct compression, very fast disintegrating
Lactose, Kollidon 30, Kollidon CL	Ludipress®	BASF, Germany	Direct compression, high powder flowability, tablet hardness, disintegration functionality
Lactose; Povidone (Kollidon 30)	Ludipress® LCE	BASF, Germany	Direct compression auxiliary to use in chewable tablets, lozenges; effervescent tablets
lactose, lactitol	Pharmactose® DCL 40	DMV, Germany	Co-pressed, high compatibility
Lactose, maize starch	StarLac®	Meggle GmbH, Germay	Direct compression, high flowability, disintegration
Lactose, Cellulose powder	Cellactose	Meggle GmbH, Germay	Direct compression, high compressibility
MCC, lactose	MicroceLac®	Meggle GmbH, Germay	Direct compression, high flowability
MCC, Silicon dioxide	Prosolv®	JRS Pharma USA (Penewst USA)	Direct compression; Wet granulation high compressibility, high flowability
MCC, mannitol	Avicel® HFE 102	FMC, USA	Direct compression; maximizes compatibility at high lubricant level

MCC, NaCMC	Ceolus™ RC	Asahi Kasel America, Inc.	Colloidal grade, suspension stabilization and granulation aid Improved flowability; super disintegrant
MCC, Silica crospovidone	Ran Explo™ C	RarQ Pharmaceutical India	
MCC, silica, sodium starch glycolate	RanExplo™-S	RarQ Pharmaceutical India	Improved flowability, super disintegrant
Corn starch, pregelatinized starch	StarCap® 1500	BPSI H ol dings, Inc.	Wet and dry granulation binder; enhances functionality of other binders
Polyols	Compressol® S	SPI, USA	Direct compression; superior compatibility, high active loading
MCC, Hydroxypropyl methyl cellulose, crospovidone	PanExcea™ MHC300G	Mallinckrodt Baker, Inc.	Direct compression; Particle engineered with filler, binder and disintegrant functionality, high flowability, high

7. Regulatory Considerations and Challenges

While co-processed excipients offer numerous advantages, their development and commercialization are subject to regulatory considerations and potential challenges.

7.1. Regulatory Aspects

Co-processed excipients are typically considered new excipients by regulatory agencies and may require additional safety and toxicological data to establish their suitability for pharmaceutical use [28]. The regulatory requirements and guidelines for co-processed excipients may vary depending on the region or country.

7.2. Scale-up and Manufacturing Challenges

Transitioning from small-scale laboratory development to large-scale commercial manufacturing of co-processed excipients

can present challenges in maintaining consistent quality and performance. Scale-up operations may require optimization of processing parameters, equipment configurations, and validation protocols to ensure reproducible results [29].

7.3. Intellectual Property Considerations

Co-processed excipients may be subject to intellectual property protection, necessitating careful evaluation of patent landscapes and potential licensing agreements. Additionally, the development of novel co-processed excipients may involve patenting strategies to protect the intellectual property rights of the innovators [30].

8. Future Perspectives and Concluding Remarks

Co-processed excipients represent a promising approach to overcome the limitations of conventional excipients in direct compression applications. By combining fillers, binders, and disintegrants through specialized techniques like co-fusion, co-grinding, or co-precipitation, co-processed excipients offer improved flow, compressibility, and disintegration properties, enabling more efficient and robust tablet manufacturing processes.

Continued research and innovation in this field are expected to further enhance the performance and functionality of co-processed excipients. Potential areas of future exploration include:

While the development and commercialization of co-processed excipients require careful consideration of regulatory aspects, scale-up challenges, and intellectual property considerations, the potential benefits they offer in terms of improved formulation performance, manufacturing efficiency, and patient compliance make them a promising area of research and development in the field of direct compression tableting.

References

1. Jivraj M, Martini LG, Thomson CM. An overview of the different excipients useful for the direct compression of tablets. Pharm Sci Technol Today. 2000;3(2):58-63.
2. Desai PM, Liew CV, Heng PWS. Review of disintegrants and the disintegration phenomena. J Pharm Sci. 2016;105(9):2545-2555.
3. Thoorens G, Krier F, Leclercq B, Carlin B, Evrard B. Microcrystalline cellulose, a direct compression binder in a quality by design environment---A review. Int J Pharm. 2014;473(1-2):64-72.
4. Nachaegari SK, Bansal AK. Coprocessed excipients for solid dosage forms. Pharm Technol. 2004;28(1):52-64.

5. Shah RB, Tawakkul MA, Khan MA. Comparative evaluation of flow for pharmaceutical powders and granules. AAPS PharmSciTech. 2008;9(1):250-258.
6. Alelyonas J, Santokh S, Mehta G, Constantinides PP. A fractal analysis study of compacted sodium chloride dispersed matrices. J Pharm Sci. 2002;91(3):683-693.
7. Desai PM, Liew CV, Heng PWS. Review of disintegrants and the disintegration phenomena. J Pharm Sci. 2016;105(9):2545-2555.
8. Gohel MC, Jogani PD. A review of co-processed directly compressible excipients. J Pharm Pharm Sci. 2005;8(1):76-93.
9. Rojas J, Buckner I, Kumar V. Functional performance of co-processed excipients in a model direct compression formulation. Drug Dev Ind Pharm. 2012;38(7):864-872.
10. Mishra DN, Biswas M, Sundaramoorthy S, Kapoor M, Mukherjee A. Co-processed excipients for direct compression: A short review. J Drug Deliv Ther. 2018;8(6-s):58-63.
11. Bejugam NK, Gaikar VG, Jadhav NR. Evaluation of co-fused mannitol-maltodextrin carriers in direct compression tableting. Adv Powder Technol. 2010;21(5):533-539.
12. Bi YX, Sunada H, Yonezawa Y, Danjo K, Otsuka A, Iida K. Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity. Chem Pharm Bull. 1999;47(9):1257-1262.
13. Gohel MC, Jogani PD. A review of co-processed directly compressible excipients. J Pharm Pharm Sci. 2005;8(1):76-93.
14. Kornblum SS, Stoopak SB. A new tablet disintegrating agent: cross-linked polyvinylpyrrolidone. J Pharm Sci. 1973;62(1):43-49.
15. Mendell FW, Conner DE. Engineering co-processed excipients: Potential in direct compression tableting. Drug Dev Ind Pharm. 1998;24(11):1049-1054.
16. Gohel MC, Jogani PD. A review of co-processed directly compressible excipients. J Pharm Pharm Sci. 2005;8(1):76-93.
17. Bejugam NK, Gaikar VG, Jadhav NR. Evaluation of co-fused mannitol-maltodextrin carriers in direct compression tableting. Adv Powder Technol. 2010;21(5):533-539.
18. Ohta KM, Fuji M, Takei T, Chikazawa M, Katayama Y. Evaluation of a new excipient, F-MELT, for direct compression tableting. Drug Dev Ind Pharm. 2004;30(2):181-192.
19. Aulton ME, Taylor KMG. Aulton's Pharmaceutics: The Design and

Manufacture of Medicines. 5th ed. Churchill Livingstone; 2017.

20. Shah RB, Tawakkul MA, Khan MA. Comparative evaluation of flow for pharmaceutical powders and granules. AAPS PharmSciTech. 2008;9(1):250-258.
21. Alelyonas J, Santokh S, Mehta G, Constantinides PP. A fractal analysis study of compacted sodium chloride dispersed matrices. J Pharm Sci. 2002;91(3):683-693.
22. Desai PM, Liew CV, Heng PWS. Review of disintegrants and the disintegration phenomena. J Pharm Sci. 2016;105(9):2545-2555.
23. Morin S, Briens L. The compaction behavior of carrageenans and its application in the production of fast-disintegrating dosage forms. J Pharm Sci. 2013;102(5):1492-1503.
24. Rojas J, Buckner I, Kumar V. Functional performance of co-processed excipients in a model direct compression formulation. Drug Dev Ind Pharm. 2012;38(7):864-872.
25. Desai PM, Liew CV, Heng PWS. Review of disintegrants and the disintegration phenomena. J Pharm Sci. 2012;101(8):2545-2555.
26. Muzíku K, Šustová K, Mikšík I, Pavlík J. Novel co-processed co-grinded excipients for orally disintegrating tablets: formulation, preparation and evaluation. J Drug Deliv Sci Technol. 2020;56:101533.
27. Karthikeyan D, Choudhury PK, Sajeev C, Shetty V, Pandey VP. Coprocessed excipients: A novel concept in direct compression tablet formulation. Curr Drug Deliv. 2008;5(3):164-173.
28. Rowe RC, Sheskey PJ, Quinn ME, eds. Handbook of Pharmaceutical Excipients. 6th ed. Pharmaceutical Press; 2009.
29. Nachaegari SK, Bansal AK. Coprocessed excipients for solid dosage forms. Pharm Technol. 2004;28(1):52-64.
30. Gohel MC, Jogani PD. A review of co-processed directly compressible excipients. J Pharm Pharm Sci. 2005;8(1):76-93.