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Review

Review of Disintegrants and the Disintegration Phenomena

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ABSTRACT

Disintegrant is one of the most important components in a typical tablet dosage form. It is responsible for ensuring the break-up of the tablet matrix upon ingestion. Disintegrants act by different mechanisms, and a number of factors may affect their performance. It is important for formulators to understand how disintegrants function so as to be able to judiciously use disintegrants to develop optimized formulations. If the formulator is required to implement the quality by design paradigm while developing a tablet formulation, it would be important to determine the impact of component ranges and process variations on tablet performance and of particular importance, tablet disintegration. Thus, a better understanding of the mechanisms of disintegrants and the tablet disintegration processes can be critical to product design success. This review aims to provide an overview of tablet disintegrants and the disintegration processes with particular focus on the factors affecting the functionalities of disintegrants. An updated compendium of different techniques employed to evaluate disintegrant action and measure disintegration time is also provided. The objective of this review is to assemble the knowledge about disintegrants and the measurement of tablet disintegratability so that the information provided could be of help to tablet formulation development.

Introduction

The orally administered compacted tablet is the most common and preferred solid unit dosage form for delivering medicaments to patients.[1] Advantages of tablets include the ability for accurate dosing, long shelf life, and cost-effective production.[2,3] Most tablets manufactured are for oral administration although some tablets may be prepared for other uses. Oral tablets may be designed as immediate or modified release dosage forms by the use of appropriate ingredients and manufacturing techniques. Tablet formulations generally consist of active pharmaceutical ingredients (APIs) together with a mix of other ingredients, collectively referred to as additives or excipients. Upon ingestion, the tablet should be capable of releasing the API in the manner it is designed for. Some tablets may also contain 2 or more APIs. Excipients play a vital role in the design of the tablet dosage form by determining its functionality and performance. Excipients are generally regarded as pharmaceutically "inactive" ingredients added with APIs during formulation but they often have important specific functions and should possess some important requisite features for their functionality. However, substances selected to be pharmaceutical excipients must be physiologically inert or inactive and when incorporated into the dosage form remain physically and chemically stable throughout the required shelf life of the dosage form. Excipients must not introduce microbiological contamination, be commercially available, and can be manufactured or processed according to the required pharmaceutical standards.[4]

Excipient types used in tablet formulations include disintegrants, fillers, binders, glidants, lubricants, antioxidants, ultraviolet absorbers, dissolution modifiers, absorbents, flavoring agents, colorants, wetting agents, and preservatives.[1,3] Not all the excipient types may be included in a formulation except when expressly needed. A good tablet formulation should not be the result of a random combination of excipients with API but by a systematic approach with rational excipient selection to provide the optimally balanced combination in the formulation design space aimed at providing the desired product performance, cost consideration, manufacturability, and patient acceptability.[3] A newer class of excipients called "co-processed" excipients is now increasingly being introduced. Co-processed excipients are made by combining 2 or more excipients in an optimized ratio or method to provide superior synergistic properties.[5] In formulation development, they

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can reduce the number of ingredients needed and can improve production consistency.[1]

Despite being considered as physiologically inactive, excipients may have significant impact on the biopharmaceutical performance of the dosage form. Among the tablet excipients, disintegrants are often considered as the most important as they ensure the break-up of the dosage form into smaller fragments upon ingestion, to allow the onset of drug dissolution and eventual absorption.[6] Disintegrants are often associated with promoting moisture penetration into the tablet matrix to initiate the disintegration process (Fig. 1). The bioactive fraction in a tablet only becomes bioavailable after disintegration.[7] The disintegration process can mechanistically be subdivided into 2 stages—breakdown into coarse aggregates and subsequent deaggregation into fine primary particles. Some non-disintegrating tablets may also be produced for highly soluble APIs with excipients that would rapidly dissolve upon ingestion.[1,2]

A comprehensive understanding of the functionality of disintegrants and their mechanisms of action would be very important in the selection of disintegrants. Thus, the aim of this review is to provide the required overview of the disintegrant types and their mechanisms of action with an updated compendium of relevant studies undertaken.

Disintegrants

Disintegrants bring about tablet matrix break-up in an aqueous medium and are commonly classified further in literature as disintegrants and superdisintegrants.[6] "Normal" disintegrants include starch- and cellulose-based excipients such as corn starch, partially pregelatinized starch, microcrystalline cellulose, and low-substituted hydroxypropyl cellulose. Some clays (e.g., Veegum HV), gums (e.g., agar, guar, tragacanth, alginate), resins (e.g., polacrilin potassium), and finely divided solids (e.g., colloidal silicon dioxide, magnesium aluminum silicate) have also been employed as disintegrants. Chemical modification of starch, cellulose, and povidone brought about the development of more efficient disintegrants, capable of good disintegration action at much lower concentrations in the tablet formulations and are referred to as superdisintegrants. Superdisintegrants include sodium starch glycolate, croscarmellose sodium, and crospovidone.[8,9] In general, disintegrants are hydrophilic but insoluble in water or gastrointestinal juices.[6] Nonetheless, effervescent additives could also be considered as disintegrants even though they are soluble, thus an exception to the insolubility general rule. Effervescents are formed by combining a soluble organic acid with inorganic carbonate or bicarbonate and the volumetric air expansion helps in disintegration of the effervescent tablets when wetted. Another material class, inorganic carbonates, may also be considered as secondary disintegrants as they can facilitate tablet disintegration by reacting with the acidic juices in the stomach to generate carbon dioxide.

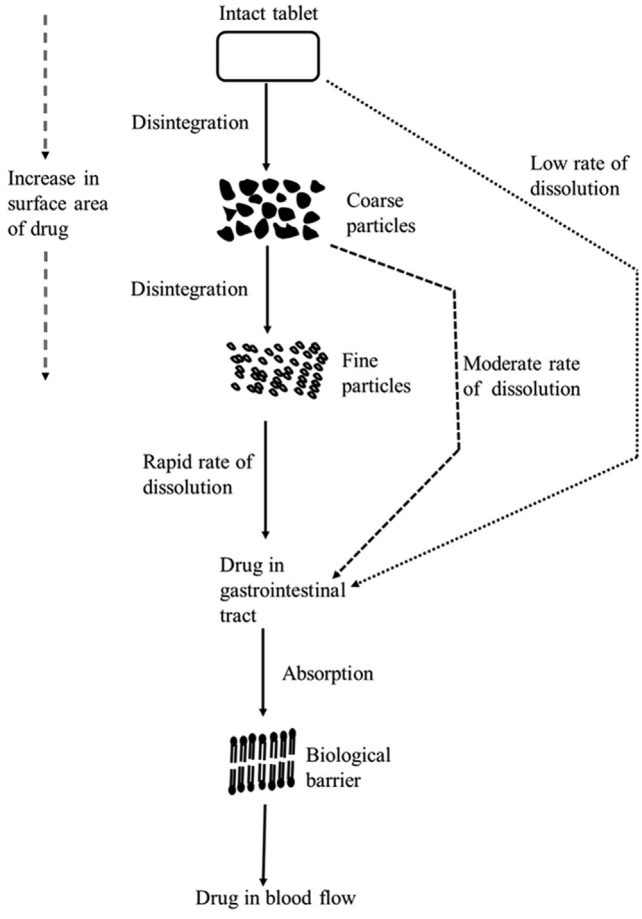

Figure 1. Fate of a disintegrating tablet upon wetting. Adapted from Alderborn[2] and Kottke and Rudnic.[1]

Different theories have been proposed for mechanisms of disintegrant action but a complete understanding of how all disintegrants act may still be deficient.[8,10] Disintegrant actions proposed include swelling, wicking (capillary action), strain recovery, interruption of particle-particle bonds, and heat of interaction.[6] Attempts had been made to propose a universal disintegration mechanism but it was later realized that the different types of disintegrants may function differently. In many cases, it was realized that a synergistic combination of mechanisms had acted together.[9,11]

Mechanisms of Disintegrant Action

Swelling

The most accepted mechanism for tablet disintegration is by disintegrant swelling.[8,12] Swelling is associated with dimensional amplification where particles enlarge omni-directionally to push apart the adjoining components, thereby initiating the break-up of the tablet matrix (Fig. 2a).[13] Most popular disintegrants swell to some extent and swelling phenomena have been well reported.[1] The swelling ability of a disintegrant depends on several factors and some of the most commonly cited factors are chemical structure and degree of crosslinking.[6] Porosity of the compact is also a very important contributor to the performance of swelling disintegrants. A porous tablet matrix with large void spaces could muffle the swelling action of disintegrants and impede their efficiency in tablet disintegration. Conversely, low porosity compacts prepared by using very high compression forces could hinder liquid entry and prolong the disintegration time or result in failure to disintegrate. Thus, tablets should be prepared at the optimal porosity to provide adequate mechanical integrity without compromising disintegratability.

A correlation was found between the rate of disintegration force development and the disintegration time but not between the extent of disintegrant swelling and the maximum disintegration force. Thus, the rate of disintegration force development is important for rapid matrix disintegration.[14,15] The concentration of disintegrant in a formulation is also important. Clearly, not all swelling materials can be disintegrants. A swelling substance that becomes gelatinized after swelling will form a gel plug and not bring about tablet disintegration. Hence, strongly swelling gums such as agar, karaya, and tragacanth are not effective disintegrants.[1] Ferrero