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Superdisintegrants in new solid dosage forms – a review

Zastosowanie superdezintegrantów w nowoczesnych stałych postaciach leków

INTRODUCTION

Solid dosage forms like tablets and capsules are the most popular and preferred drug delivery systems. They both have high patient compliance, and they are relatively easy to produce and market in accurate dosing. Such forms present good physical and chemical stability. Tablet dosage forms are mainly composed of the drug and excipients such as a diluent, a binder, a lubricant, a disintegrant and a glidant [11]. The choice of formulation ingredients can have a significant effect on the rate and extent of drug dissolution [3]. Despite increasing interest in controlled-release drug delivery systems, the most common tablets are intended to be swallowed as a whole and to disintegrate and release their medicines rapidly in the gastrointestinal tract [21].

The term superdisintegrant refers to a substance which achieves disintegration faster than the substances conventionally used. A tablet or a capsule content breaks up or disintegrates into smaller particles that dissolve more rapidly than in the case of the absence of such disintegrants [12,23]. Superdisintegrants are generally used at a low level in the solid dosage form, typically from 1 to 10 % of the weight of the total weight of a given dosage unit [15, 3].

The simplest way to achieve quick disintegration is to use the superdisintegrant in connection with suitable diluents. A number of agents have been formerly used as tablet disintegrants, but only a few acceptable disintegrants are currently available for pharmaceutical purposes [4]. Superdisintegrants such as croscarmellose sodium Ac-Di-Sol (ADS), crospovidone (PVP-XL) and sodium starch glycolate (SSG) are frequently used in tablet formulations to improve the rate and extent of tablet disintegration and thereby increase the rate of drug dissolution [7].

M e c h a n i s m o f d i s i n t e g r a t i o n . Despite all theories proposed, the mechanism of disintegration is still not completely understood. The rate of water uptake is of critical importance for a number of tablet disintegrants [21,22]. The three major mechanisms affecting tablet disintegration include water uptake. The combination of swelling, wicking and deformation were found to be the primary action mechanisms for tablets disintegrants [15, 23].

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Swelling. The swelling of disintegrant is the most widely accepted mechanism for tablet disintegration. One of the most significant factors in the disintegration processes of many formulations is water uptake by capillary forces. The contact with water causes swelling which in consequence reduces the adhesiveness of other ingredients in a tablet resulting in a break apart of the tablets constituents.

Two types of swelling are of a particular interest; intrinsic swelling and bulk swelling.

Porosity and Capillary Action (Wicking).

Disintegrants that do not swell, act through porosity and capillary action. The tablet porosity provides pathways for the penetration of fluids into the tablets. The disintegrant particles (with low cohesiveness & compressibility) themselves enhance the porosity and provide pathways into the tablet. The ability to draw water by the pathways created in the particles or by "wicking" trough capillary action results in the break-up of the tablet.

Deformation. Starch grains are "elastic" and once deformed under pressure they return to their original shape when the pressure is removed. With compression forces involved in tableting, these grains deform more permanently and have a higher ability to swell than starch grains which have not been deformed under pressure.

Superdisintegrants applications. In a direct compression process when a drug is mixed with excipients subsequently lubricated and then it compressed into a tablet. A disintegrant used in this type of formulation enables to break the tablet apart and to expose the substance for dissolution.

A disintegrant used in granulated formulation process can both be used extragranulary, and intragranulary or in both phases [7].

A disintegrant used in both phases is claimed to act more effectively. It gradually breaks the tablets into granules enabling disintegration of the granules and further exposure of the drug substance for dissolution. The portion of disintegrant used as intragranulary in the wet granulation process is not as effective as that the process of extragranulary addition. In the wet granulation process the granules are exposed for wetting and drying which reduces the properties of the disintegrant.

Extragranular incorporation produced faster results of the dissolution than in the case of an equal distribution intragranularly and extragranularly. In turns it proved superior to intragranular incorporation. In contrast to crosspovidone and sodium starch glycolate, croscarmelose sodium was relatively unaffected by the wet granulation process with intragranular release profiles similar to extragranular. From the three types of superdisintegrants used in tablet formulations, croscarmellose sodium enabled faster tablet dissolution than sodium starch glycolate or crospovidone [9].

The influence of pH. Fast release tablets are intended to disintegrate in stomach, where the pH is acidic. The influence of swelling capacity of superdisintegrants in different pH media was investigated by Zhao and Augsburger. They used a laser diffraction particle size analyzer for determining the swelling of disintegrant particles in different media. They observed significant reduction of the rate of water uptake and swelling for both anionic croscarmellose sodium (Ac-Di-Sol) and sodium starch glycolate (Primojel) in acid medium (0,1N HCl), whereas crospovidone (Polyplasdone XL 10) that is a nonionic polymer remained unaffected. However, tablets containing croscarmellose sodium where affected less by acid medium than

those formulated with sodium starch glycolate [22]. According to Mohamad and Dashevsky, Ac-Di-Sol as the swelling agent in pulsatile drug delivery system was strongly dependent on the pH of the release medium. Lag times proved longer in the case of 0.1 N HCl than in the case of the phosphate buffer, pH 7,4 [14]. Gordon et al. observed that the superdisintegrants tended to promote faster dissolution in a neutral pH medium than in an acidic medium [9].

The disintegration efficiency. The disintegration efficiency of the three classes of superdisintegrants represented by croscarmellose sodium (Ac-Di-Sol), sodium starch glycolate (Primojel) and crospovidone (Polyplasdone XL 10) was studied by Zhao and Augsburger with the use of a digital video camera. The disintegration process for aspirin tablets as a model formulation, was examined. Superdisintegrants were used at 1%, 2% and 5% concentration in aspirin tablets. The tablets were prepared on an instrumented rotary press. It has been observed that despite close disintegration times (30 seconds when superdisintegrants were used at 2% concentration), the superdisintegrants broke the tablets into particles of different sizes. The appearance of larger total surface areas for drug dissolution affected the drug dissolution itself. The same addition level of Ac-Di-Sol and Polyplasdone XL 10 disintegrated tablets faster than Primojel. However, the dissolution of aspirin from these tablets correlated with the differences in particle size generated in the disintegrated tablets: Ac-Di-Sol> Primojel >Polyplasdone XL [21].

According to Abed et al. fastest in vivo disintegration time of orodispersible tablets of diazepam indicate that crospovidone was stronger superdisinegrant followed by Ac-Di-Sol than sodium starch glycolate [1]. The effect of commonly used superdisintegrants (such as crospovidone Type A, Type B, croscarmellose sodium and sodium starch glycolate) on the dissolution rate of poorly soluble drugs was investigated by Balasubramaniam and Bee. They proved that because of its unique chemistry, particle size and particle morphology crospovidone Type B provided the fastest rate of dissolution for poorly soluble drugs. It simultaneously resulted in a high interfacial activity, which significantly aided the dissolution [3].

Novel superdisintegrants. A novel co-processed superdisintegrant was proposed by Gohel at al. [7,8]. Co-processing is defined as a combination of two or more established excipients by an appropriate process. Co-processing of superdisintegrants can lead to the improvement of the rate and extent of tablet disintegration and the increase of the rate of drug dissolution. In the course of the first investigation croscarmelose sodium and crospovidone were selected. And crospovidone and sodium starch glycolate were selected in the second investigation. These superdisintegrants complement each other and when used together they could accelerate the disintegration process. The water uptake by the tablet is facilitated by wicking action of crospovidone, while the tablet disintegration is facilitated by the swelling force exhibited by croscarmellose sodium or sodium starch glycolate. Moreover, the swelling capacities of crospovidone are not reduced in an acid medium when compared with aqueous medium.

In the first investigation ibuprofen was selected as a model drug and ibuprofen tablets were prepared by the direct compression method. The tablets were prepared using croscarmelose sodium, crospovidone and the physical blend (1:1) of both the superdisintegrants. Co-processing resulted in a number of improvements. The study showed an improvement of the flow due to the size enlargement, a noticeable improvement in the crushing strength and the disintegration time. The results showed more beneficial in the case of the use of the co-processed superdisintegrant rather than in the case of

croscarmellose sodium. The use of the co-processed superdisintegrant in a tablet production proved also to be most efficient in terms of water uptake time.

In the second investigation cefixime and ibuprofen were used as a model drugs. Cefixime tablets were prepared using the wet granulation method. The two independent variables taken into consideration were the mode of addition of superdisintegrant and the type of superdisintegrant. Crosspovidone, the co-processed superdisintegrant and sodium starch glycolate were used extragranularly, intragranularly and in both phases. The tablets were prepared in a single-punch tablet machine. The results reveal that the disintegration time and the percentage of the drug dissolved were influenced by the mode of addition of the superdisintegrant and the type of the superdisintegrant. The order of efficacy of a tablet disintegration (the same mode of superdisintegrant incorporation) was connected with the co-processed superdisintegrant > crospovidone > sodium starch glycolate. The extragranular incorporation resulted in a higher disintegration time.

Ibuprofen tablets were prepared by direct compression. Ibuprofen, the co-processed superdisintegrant, or the physical mixture of superdisintegrant containing 3 parts of crospovidone and 1 part of sodium starch glycolate were blended. The results reveal that there was a noticeable improvement in the dissolution rate when the co-processed superdisintegrant was used.

PEGylated conjugate of microcrystalline cellulose (MCC) was recently synthesized by Bhalekar et al. A recent study evaluated its properties for the water vapour uptake isotherms, the maximum water saturation, the water penetration rate, the disintegration time, the superdisintegration power and the dissolution. When the results of the study were compared with the results of a commercial superdisintegrants MCC-PEG, the examined conjugate proved to be an effective superdisintegrant [4].

SUPERDISINTEGRANT IN NOVEL SOLID DOSAGE FORMS

Orodispersible tablets (Fast disintegrating tablets)

Oral fast-disintegrating dosage forms (tablet, capsule) are a relatively novel dosage technology that involves the rapid disintegration or dissolution of the dosage form into a solution or suspension in the mouth without the need of water [1]. Orally disintegrating tablets combine hardness, dosage uniformity, stability and other parameters, with an extremely easy way of administration [6]. Mouth dissolving tablets are very beneficial for patients with difficulties in swallowing (children younger than 5 years and the elderly have a great difficulty, or are unable to swallow a solid dosage form) or with a restricted access to water [10,12,18]. These tablets display a fast and spontaneous disintegration, soon after the contact with saliva that is within 30-50 seconds after their administration. The active agent can rapidly dissolve in the saliva and the solution is then swallowed enabling the active agent to be absorbed through the gastrointestinal epithelium reaching the target and producing the desired effect. Orodispersible tablets can be formulated with the use of a number of methods [11, 12]. Some of them involve the increase of the porosity of the tablet and the decrease of the disintegration time. Superdisintegrants are used to disintegrate the tablet by swelling or by rapid water absorption.

Researchers studied recently the design and evaluation of the orodispersible formulations using superdisintegrants (such as indomethacin -Polyplasdone XL, ibuprofen -Kollidon CL-K, tramadol - crospovidone, diazepam - crospovidone was the strongest superdisintegrant followed by croscarmellose sodium then sodium starch glycolate, and Granisteron hydrochloride novel formulation using β-cyclodextrin as a diluent and croscarmellose sodium as a disintegrant) [1,6,11,12,18].

Solid dispersion fast disintegrating tablets

The incorporation of a superdisintegrant in the solid dispersion tablets can strongly enhance the dissolution rate of the highly lipophilic drug - fenofibrate [19]. The dissolution rate enhancement depends on the type of the superdisintegrantsand increased in the following order: Polyplasdone XL-10<Polyplasdone XL< < Ac-Di-Sol and Primojel. An larger increase was observed in the case of a superdisintegrant incorporated in the drug containing solid dispersion than the case of when it was physically mixed with the solid dispersion. Sodium starch glycolate has a positive impact on the disintegration time of the solid dispersion of risperidone (low soluble drug) increasing its dissolution rate [17]. The solid dispersion along with the use of the superdisintegrants also increase the dissolution rate of a poorly soluble drug e.g. Valdecoxib [13].

Fast disintegrating tablets with cyclodextrins

A composition of 60% β-cyclodextrin, 6% croscarmellose sodium and 30% of spray-dried lactose was an optimal formulation of novel fast disintegrating tablets using β-cyclodextrin as a diluent. Granisteron hydrochloride was selected as a drug candidate for the novel fast disintegrating tablet formulation. These tablets were prepared by the direct compression method on rotary tablet press using plain-face punches. Disintegration time was affected by quadratic terms of β-cyclodextrin, croscarmellose sodium and spray-dried lactose. β-cylodextrin was found to improve the hardness of the tablets without increasing the disintegration time [10]. Croscarmellose sodium was also used in the tablet formulations of nimesulide - β-cyclodextrin and meloxicam - γ-cyclodextrin binary systems [16].

Pulsatile drug delivery systems

Pulsatile drug delivery systems are characterized by a rapid drug release after a defined lag time. These systems especially desirable in case of drugs acting locally, which present an extensive first pass metabolism (e.g. β-blocker, for drugs developing biological tolerance or a drug acting in a specific site in the intestinal tract e.g. colon) [5, 14, 20]. Most of pulsatile drug delivery systems contain a drug reservoir, surrounded by a diffusional barrier. This barrier erodes, dissolves or ruptures after a specified lag time. The lag time is controlled by the thickness and the viscosity grade of the hydroxypropylmethylcelulose (HPMC) layer (Chronotopic erosion system) [5].

Crosscarmelose sodium (Ac-Di-Sol) was proposed by Dashevsky and Mohamad as preferable superdisintegrant in the swelling layer of the pulsatile drug delivery systems. The recommended pulsatile drug delivery systems contain: drugs containing hard gelatin capsules, core tablets or the pellets layered with the swelling layer (superdisintegrant and a binder) coated with a water insoluble ethylcellulose coating. Crosscarmelose sodium was a more preferable superdisintegrant as the swelling layer when compared to low substituted hydroxypropylcelulose (L-HPC) and sodium starch glycolate. The pH dependency of Ac-Di-Sol could be eliminated by the addition of fumaric acid to the swelling layer [5, 14].

Vaginal tablets

A superdisintegrant (Ac-Di-Sol) along with the effervescent mixture (citric acid and sodium bicarbonate) was used to enhance the swellability of the vaginal bio-adhesive tablet of clotrimazole and metronidazole [2].

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SUMMARY

Despite increasing interest in controlled-release drug delivery systems, the most common tablets are intended to be swallowed whole and to disintegrate and release their medicaments rapidly in the gastrointestinal tract. The therm superdesintegrant refers to a substance which achieves disintegration faster than the disintegrants conventionally used. Tablets or capsules content breakup or disintegrate into smaller particles that dissolve more rapidly than in the absence of disintegrant and increase the rate of drug dissolution. The present study describes mechanisms of disintegrants action, influence of pH, disintegration efficiency and application of commonly used superdisintegrant: crospovidone, croscarmellose sodium and sodium starch glycolate in novel solid dosage forms.

Keywords: superdisintegrants, disintegration, dissolution, novel solid dosage forms.

STRESZCZENIE

Niezależnie od wzrostu zainteresowania systemami o kontrolowanym uwalnianiu leku, wiele uwagi w najnowszych opracowaniach naukowych poświęcono tabletkom przeznaczonym do połykania w całości, szybkiego rozpadu i uwalniania substancji leczniczej w przewodzie pokarmowym. Szybki rozpad tabletek możliwy jest dzięki zastosowaniu substancji przyspieszających rozpad. Termin „superdezintegrant" odnosi się do substancji, która umożliwia rozpad formy leku szybciej niż pod wpływem zwykłych substancji przyspieszających rozpad. Tabletka lub kapsułka rozpada się na małe cząstki, które rozpuszczaja się szybciej w obecności „superdezintegrantu" zwiększając rozpuszczalność leku. Przedstawiona praca opisuje mechanizmy działania, wpływ pH, efektywność i zastosowanie w nowoczesnych postaciach leków najczęściej stosowanych „superdezintegrantów": poprzecznie usieciowanego poliwinylopirolidonu, poprzecznie usieciowanej karmelozy sodu oraz skrobi glikolanu sodu.

Słowa kluczowe: superdezintegranty, rozpad, dezintegracja, rozpuszczanie, nowe stałe formy leku.