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EFFECT OF SUPERDISINTEGRANT TYPE ON DISINTEGRATION TIME OF ORALLY DISINTEGRATING TABLETS

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Abstract

Orally disintegrating tablets are designed to break down in the mouth within seconds, and the choice of superdisintegrant is the formulation decision that most obviously governs how quickly they do so. This short narrative review summarises published work on how crospovidone, sodium starch glycolate, croscarmellose sodium and related materials influence disintegration time, and it reports no new experimental data. It covers the mechanisms involved, the interaction with concentration, mode of incorporation, diluents, lubricants and compression, and the tests used to measure disintegration in vitro and in the mouth. Studies agree that no single class is best in all formulations, and that compendial tests tend to be faster than disintegration in the mouth.

1. INTRODUCTION

Swallowing a tablet is not easy for everyone. Surveys of the general population and of patient groups show that a considerable minority of adults report difficulty swallowing solid dosage forms, and that the difficulty is much more common in older people, in children and in people with neurological disease or dysphagia [1, 2, 3]. Some patients delay or skip doses as a result, which defeats the purpose of treatment. Orally disintegrating tablets (ODTs) were developed partly to meet this need. They are placed on the tongue, break down in saliva within seconds and are swallowed as a suspension or solution without water [4, 5].

Disintegration time is the most visible quality attribute of an ODT. A patient notices at once whether the tablet melts in a few seconds or

lingers as a gritty lump, and that experience influences acceptance and adherence. The formulator controls it mainly through the choice and level of a superdisintegrant, a class of excipients that promote rapid breakup at low concentration, together with the compression conditions and the matrix of diluents that surround them [6, 7, 8]. A large literature compares individual superdisintegrants, though the conclusions are not always easy to reconcile.

This short review summarises that literature on the effect of superdisintegrant type on the disintegration time of ODTs and reports no new data. It describes the requirements and technologies for ODTs, the main classes of superdisintegrant and the mechanisms by which they act, the formulation and process variables that modify their performance, and the methods used to measure disintegration. The final section deals with limitations of the evidence. Throughout, the focus is on directly compressed tablets, and published studies of conventional tablets are used where they explain mechanisms that apply equally to ODTs [9, 10, 11].

2. ODT REQUIREMENTS AND TECHNOLOGY

Regulatory definitions give a target. The United States guidance on ODTs describes a solid dosage form containing medicinal substance that disintegrates rapidly, usually within a matter of seconds, when placed on the tongue, and it suggests an in vitro disintegration time of about 30 seconds or less by the pharmacopoeial method, with a tablet weight ideally not above 500 mg [12]. The British Pharmacopoeia, reproducing the European monograph, defines orodispersible tablets as those that disperse in the mouth before swallowing and specifies disintegration in less than three minutes in its standard apparatus [13]. The two definitions differ by a factor of six, a gap that matters when results from different papers are compared.

Several manufacturing routes are in use, and each places different demands on the formulation. Freeze drying produces highly porous wafers that dissolve almost instantly but are fragile and costly to make. Moulding of moistened powders gives soluble tablets that need little disintegrant, and sublimation of a volatile ingredient leaves pores in a compressed tablet [4, 14, 15]. Direct compression has the lowest cost and the widest use, and it is also the route that depends most on the performance of the superdisintegrant, since there is no special structure to rely on [15, 16]. For that reason most formulation research on ODT disintegration concentrates on directly compressed systems.

Meeting this target means balancing two properties that pull in opposite directions. A tablet must be hard enough to survive manufacture, blister packing and handling, yet porous or soft enough to break down at once when wet. Early ODT technologies solved the problem by making a very porous, fragile structure that needed special packaging, but direct compression products aim for an ordinary tablet that can be handled normally [14, 16, 17]. Hardness, friability, disintegration time, wetting time and taste are all traded against one another, and the superdisintegrant sits at the centre of the compromise [15, 18].

The matrix around the superdisintegrant matters as much as the disintegrant itself. Water-soluble diluents such as mannitol, lactose and other saccharides dissolve in saliva and give a smooth mouthfeel, while microcrystalline cellulose adds compressibility and also helps to wick water into the tablet [16, 19, 20]. Mannitol has become particularly popular because it is non-hygroscopic and gives a cooling sensation [20]. A formulation is thus a system of diluent, binder, disintegrant, lubricant, sweetener and flavour, and changing one component changes the others, so conclusions about a superdisintegrant need to be tied to the matrix in which it was tested [16, 19, 21].

Taste and mouthfeel add more constraints. A bitter drug dissolving in the mouth is unpleasant, so ODTs often contain taste-masked granules or coated particles, and these need to stay intact through compression. Particles that are too coarse leave a gritty feeling on the tongue, whereas very fine particles can feel pasty. Studies of granule size and palatability found that rough

mouthfeel depends on the size and hardness of particles that remain after the tablet has disintegrated, and the properties of the superdisintegrant itself contribute, since some swell into a viscous gel and others do not [8, 22, 23].

3. SUPERDISINTEGRANTS

Three chemical classes dominate. Crospovidone is a cross-linked homopolymer of N-vinyl-2-pyrrolidone, introduced as a tablet disintegrant in the early 1970s, and it is insoluble and does not form a gel [24]. Sodium starch glycolate is a cross-linked, carboxymethylated starch that swells rapidly in water to form a gel. Croscarmellose sodium is cross-linked sodium carboxymethylcellulose, which swells and also draws water in by capillary action [7, 19]. Low-substituted hydroxypropylcellulose and a few other materials are used as well, but these three account for the large majority of the published work on ODTs [8, 25].

Physical properties that go beyond disintegration influence the choice. Crospovidone compresses well and tolerates moisture, which makes it a convenient workhorse for directly compressed tablets, although it can be poorly flowing in fine grades. Sodium starch glycolate has high swelling but its performance falls when it is exposed to excess lubricant or when the tablet is very hard. Croscarmellose sodium is effective at low levels and highly sensitive to the pH and ionic strength of the medium, as noted above [7, 9, 19]. Cost, supplier reliability and regulatory acceptance enter the decision as well, and published comparisons seldom address them [8, 19].

The mechanisms of disintegration have been debated for decades. Water penetrates the tablet through its pores by capillary action, which is wicking. Particles of disintegrant swell and push against the surrounding matrix, or, if elastic, recover their shape after compression and break bonds. Some workers have proposed that the heat of wetting or repulsion between particles contributes [26, 27]. Measurements of water uptake rate and disintegrating force led to the view that the two properties together describe a disintegrant better than swelling alone [27, 28]. In practice more than one mechanism usually operates, and the dominant one depends on the disintegrant and the matrix [11, 25].

Comparisons of the three classes, summarised with other findings in table 1, rarely give a clear winner. In aspirin tablets, Zhao and Augsburger compared representatives of the three classes and found that the performance of each depended on concentration, tablet hardness and the dissolution medium, so no fixed ranking applied to every condition [10]. A study using a poorly soluble drug found that superdisintegrants were not interchangeable and that the choice affected dissolution as well as disintegration [29]. Swelling capacity in different media also varied: the swelling of some grades was reduced in acidic fluids, which bears on performance in the mouth, where saliva is close to neutral [9].

Table 1: Selected published findings on superdisintegrants and disintegration of ODTs

Material, variable or method	Reported finding	Ref.
Crospovidone Cross-linked PVP	Insoluble, non-gelling; water uptake by wicking; fine grades work faster; supplier sources differ	[23, 24, 29]
Sodium starch glycolate Cross-linked starch	Rapid swelling and gel formation; efficiency depends on cross-linking and substitution	[9, 30]
Croscarmellose sodium Cross-linked cellulose	Swelling plus wicking; swelling capacity varied with pH of the medium	[9, 10]
Saccharide matrix Granulated mannitol and maltose	Hard tablets at low pressure with rapid disintegration were obtained	[16]
Intragranular and extragranular use Disintegrant placement	Mode of incorporation changed debris size and dissolution in wet-granulated tablets	[26, 31]
Lubricant and moisture treatment Process variables	Both affected hardness and disintegration time; brief moisture treatment strengthened tablets	[21]
Compendial basket-rack test Pharmacopoeial method	Fast, standardised, but generally shorter than disintegration in the mouth	[12, 13, 32]
Texture analyser or probe methods In vitro	Penetration-based times correlated with times measured by volunteers	[32, 33]

Material, variable or method	Reported finding	Ref.
Magnetic resonance imaging Real-time	Showed water ingress, swelling and breakup and distinguished disintegrants	[34]
Particle size and grittiness Mouthfeel	Residual particle size and hardness affected rough mouthfeel and palatability	[22]
Swallowing difficulty Patient need	Considerable minority report difficulty swallowing tablets, more in older people and in dysphagia	[1, 2, 3]

Disintegration is not the same thing as drug release, although the two are related. A disintegrant that breaks a tablet into fine particles increases the surface area available for dissolution, so for poorly soluble drugs the choice of superdisintegrant may influence dissolution as much as disintegration time [10, 29]. For a bitter drug in an ODT, the opposite concern applies, since rapid release in the mouth increases the exposure of taste receptors, and a formulator may prefer a disintegrant that breaks the tablet quickly into coated particles that do not dissolve before swallowing [4, 22]. The ideal disintegrant therefore depends on the purpose of the product as well as on the numbers.

Within a class, grade and source matter. Crospovidone is supplied in grades of different particle size, and coarse grades work mainly by wicking and recovery, whereas fine grades give faster and more uniform disintegration at the same weight fraction because they provide more particles and a larger surface area [23, 29]. Crospovidone from different suppliers has been found to differ in particle size, surface area and bulk properties, so labels such as crospovidone NF do not guarantee equivalent behaviour [23]. For sodium starch glycolate, the degree of cross-linking and substitution changes the swelling and gel-forming behaviour, with disintegration efficiency falling when the polymer is too soluble or too highly cross-linked [30].

The distribution of these findings by theme is shown in fig. 1, and they suggest a practical approach. Candidates from at least two classes should be screened at the same level in the actual matrix, using a fixed compression force and a method that discriminates between fast formulations, and the best candidate then optimised for level. Reports that compare disintegrants at unequal levels, or in different matrices, say little about the materials themselves. Where wetting is slow, a wicking agent such as crospovidone often has an advantage; where the matrix is soluble, a swelling agent may be adequate [8, 10, 29].

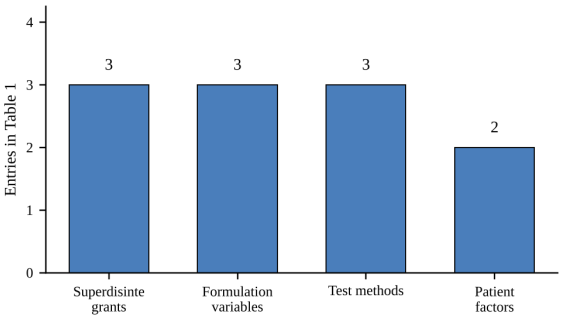


Fig. 1: Number of entries in table 1 by theme

4. FORMULATION AND PROCESS VARIABLES

Concentration is the first variable. Superdisintegrants in conventional tablets are used at around 2 to 5 percent of tablet weight, and ODTs often use more, from about 5 up to 10 percent or higher, to achieve the very short times required [7, 19, 21]. The relationship is not linear. Disintegration time generally falls as the level rises and then reaches a plateau, after which further additions bring little advantage and may slow disintegration by forming a viscous gel or by increasing the strength of the compact. The optimum differs between classes, so comparisons at a single level may favour one material by accident [8, 10].

The mode of incorporation also matters. A disintegrant added before granulation, within the granules, is exposed to wet massing and drying and may lose some of its capacity, while an extragranular disintegrant remains intact and swells on contact with water; many workers use both [26, 31]. Early work showed that the particle size of the debris formed on disintegration depended on whether the disintegrant was inside or outside the granule [26]. In wet-granulated tablets, the mode of incorporation changed dissolution, and the effects varied between the disintegrants studied [31]. For direct compression the issue

is moot, which is one attraction of that route.

Lubricants and moisture can undermine a good disintegrant. Magnesium stearate coats particles with a hydrophobic film that slows wetting, and prolonged blending makes the effect worse, so low levels, short blending times and sometimes alternative lubricants are recommended for ODTs [19, 21]. Late and colleagues optimised fast-disintegrating tablets by varying the disintegration-promoting agent, lubricant and moisture treatment, and found that each affected hardness and disintegration time [21]. Moisture treatment, a brief exposure to humidity followed by drying, strengthened tablets without a large penalty in disintegration. Storage humidity matters too, since hygroscopic disintegrants take up water and can lose function over time [8, 21].

Compression force sets porosity, and porosity governs how quickly water enters. Higher force gives harder tablets with smaller pores, which may slow wetting, and also compacts disintegrant particles more tightly so that they have less room to expand [11, 25]. An approach designed by Mizumoto and colleagues combined a low-moldability saccharide such as mannitol with a high-moldability saccharide such as maltose, granulated to give particles that formed hard tablets at low pressure while keeping rapid disintegration [16]. Such matrix engineering shows that the disintegrant is only one lever, and that a modest compression force with a well-chosen diluent often does more than a higher level of disintegrant [16, 25].

Co-processed excipients have become a popular answer to these formulation problems. Commercial mixtures combine a soluble diluent such as mannitol with a superdisintegrant and sometimes a binder, processed together by spray drying or granulation so that the components are intimately mixed, and they can be compressed directly to give hard tablets that disintegrate quickly [4, 8, 25]. Such products reduce the number of variables for the formulator, though they restrict the choice of disintegrant and make it harder to attribute an effect to a single material. They are best seen as a practical option alongside, and not a replacement for, studies of individual excipients [16, 19, 25].

5. MEASURING DISINTEGRATION

The compendial disintegration test uses a basket-rack assembly that moves a tablet up and down in water at 37 °C, with the end point defined as the time at which no residue remains on the mesh. It is robust, standardised and used in specifications [12, 13]. For ODTs the test has two weaknesses. The volume of water is large compared with the few millilitres of saliva available in the mouth, and the mechanical agitation is far stronger than the gentle pressure of the tongue, so times are typically much shorter than those experienced by patients [32, 33, 35].

Several alternative in vitro methods have been devised. The wetting time test places a tablet on tissue paper soaked with a dye solution and records the time for the dye to reach the upper surface, giving a simple index of water penetration [17, 18]. Texture analysers can drive a probe into the tablet under a small constant load and follow its penetration as the tablet softens and breaks apart, and times from such methods correlated with times measured in volunteers [32, 33]. These tests can discriminate between fast formulations that the compendial test would report as equal, which is more useful in development [15, 18].

In vivo measurement uses healthy volunteers who hold the tablet on the tongue and record the time until it has dispersed, with the mouth rinsed between trials. A study of commercial famotidine ODTs combined a simple in vitro method with a human sensory test and found that the in vitro result reflected the order seen in the mouth, although the compendial times were shorter than the sensory times [35]. Human panels bring cost, ethical approval and variability between subjects, so they are usually reserved for final selection or for validating an in vitro method, with development relying on the cheaper tests [32, 35].

Disintegration time is also used to set specifications, and the limit chosen has practical consequences. A requirement of 30 seconds or less demands a discriminating method and a formulation with a safety margin, because batch-to-batch variation in

hardness, moisture and excipient properties can move times by several seconds [12, 15]. A three-minute limit, as in the pharmacopoeial monograph, accommodates almost any tablet that dissolves in the mouth, although patients would find a three-minute tablet unacceptable [13]. Manufacturers therefore often set tighter internal limits than the regulatory ones, and the test used for release is then validated against the performance in the mouth [12, 18, 32].

Imaging has begun to clarify what happens inside a tablet. Real-time magnetic resonance imaging of tablets in contact with water showed the progress of water penetration, swelling and breakup, and allowed different disintegrants to be distinguished by the way they acted, for instance by rapid water ingress and wicking in some tablets and by swelling-driven expansion in others [34]. Such techniques are not routine in industry, but they provide direct evidence for mechanisms that earlier workers inferred from indirect measurements of water uptake and force [27, 28, 34]. They also show that disintegration is not a single event, but a sequence of wetting, swelling and erosion.

6. LIMITATIONS AND FUTURE DIRECTIONS

The evidence on superdisintegrants has several weaknesses. Most studies use one model drug, one diluent system and one tablet press, so results cannot be assumed to transfer, and comparison between papers is hampered by different levels, grades, compression conditions and test methods [8, 10, 11]. Few papers include human disintegration data, and those that do use small panels [32, 35]. Information on the grade and supplier of excipients is often missing, even though differences between sources are known to matter [23]. Taste and mouthfeel, which determine whether patients accept a product, receive less attention than speed [22].

Scale-up deserves more attention than it receives. Laboratory work is commonly done on single-station presses at low speed, whereas production rotary presses give much shorter dwell times, and the same formulation can produce tablets of different hardness and disintegration behaviour when compressed faster [11, 25]. Fine superdisintegrant grades that perform well in small batches may segregate or flow poorly in a large blender, and moisture uptake during long runs can change the properties of hygroscopic materials [8, 21]. Studies that carry a formulation through at least a pilot-scale run would make the conclusions about superdisintegrant type much more useful to those who must manufacture the product.

Better practice would be straightforward to define. Comparisons should test several superdisintegrants at equal and at optimised levels in the same matrix, report grade and supplier, use more than one disintegration method including a discriminating in vitro test, and relate times to hardness and friability. Quality-by-design approaches, with factorial or response-surface designs, are well suited to the problem because they reveal interactions between disintegrant level, lubricant and compression force that one-factor studies miss [11, 21]. Linking in vitro times to a small volunteer panel would add credibility without much expense [32, 35].

7. CONCLUSION

The published work indicates that the type of superdisintegrant strongly influences the disintegration time of ODTs, but it does not identify a universal best choice. Crospovidone, sodium starch glycolate and croscarmellose sodium act through different mixtures of wicking, swelling and recovery, and their ranking changes with level, grade, diluent, drug, lubricant and compression conditions [9, 10, 29, 30]. Within a class, source and particle size also matter, so naming a material is not enough to specify its behaviour [23].

Measurement is the second lesson. Compendial tests give times that are shorter than those in the mouth, so discriminating in vitro methods, and where possible small human panels, give a more reliable picture [32, 33, 35]. Studies that compare several disintegrants at matched levels in one matrix, with full reporting of grades and test conditions, would add more to the field than further single-material reports [8, 11, 21].

8. ABBREVIATIONS

ODT-Orally disintegrating tablet, PVP-Polyvinylpyrrolidone, USP-United States Pharmacopeia, NF-National Formulary

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10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

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