To crush or not to crush: A brief review of novel tablets and capsules prepared from nanocrystal and amorphous solid dispersion technologies

Elizabeth Uttaro (PharmD student), Wegmans School of Pharmacy, St. John Fisher College, Rochester, NY, USA

Madhu Pudipeddi, PhD, Parakam Pharma LLC, Plano, TX, USA

Anne Schweighardt, PharmD, BCPS, Wegmans School of Pharmacy, St. John Fisher College, Rochester, NY, USA, and University of Rochester Medical Center, Rochester, NY, USA

Fang Zhao, PhD, Wegmans School of Pharmacy, St. John Fisher College, Rochester, NY, USA

Purpose. To educate healthcare professionals regarding the risks of manipulating drug products formulated via nanocrystal or amorphous solid dispersion technologies.

Summary. Recent pharmaceutics innovations such as nanocrystals and amorphous solid dispersions have been used successfully to improve oral bioavailability of drugs. Over 30 drug products based on these technologies have been approved by the Food and Drug Administration, and more are in the development pipeline. While these products are similar in appearance to traditional tablets or capsules, they should not be crushed or suspended in liquid vehicles. Such manipulations can compromise the integrity of the formulation and subsequently alter the oral bioavailability. It is alarming that the majority of these products are not included in the Institute for Safe Medication Practices (ISMP) "Do Not Crush" list. A summary drug table is presented in this article to provide accurate information for pharmacists and other healthcare providers.

Conclusion. Novel formulations of tablets and capsules are being used to increase the oral bioavailability of certain drugs. Crushing these products can significantly alter product performance and clinical outcomes. We encourage ISMP to add these drug products to the Do Not Crush list due to wide use of this list throughout healthcare. In the meantime, pharmacists should be mindful of the new formulation technologies and advocate for the proper use of these drug products.

Keywords: amorphous, bioavailability, compounding, formulation, nanocrystal, stability

Am J Health-Syst Pharm. 2021;78:389-394

Oral medications are often manipulated by healthcare providers to overcome administration challenges in certain patient populations. Common practices include crushing and grinding, followed by direct administration or mixing with food and other suspending media. The Institution for Safe Medication Practices (ISMP) "Do Not Crush" list is widely used by healthcare professionals to determine if a medication can be safely crushed and administered to a patient.[1] Unfortunately, this list includes mostly modified-release dosage forms and is not updated on a set schedule (N. Shah, PharmD, ISMP, email, November 26, 2019). This article is intended to raise awareness among pharmacists of a new generation of oral drug products that should be on the list but currently are not.

Over the last few decades, pharmaceutical scientists have explored a multitude of novel formulation and drug delivery approaches to improve the oral bioavailability of challenging drug candidates.[2-4] Several new technology platforms have emerged in recent years and their effectiveness has been demonstrated in proof-of-concept studies, resulting in product approvals by the US Food and Drug Administration (FDA) and other regulatory authorities. Two notable advancements are nanocrystals and amorphous solid dispersions.[5] Over 30 drug products based on these

Address correspondence to Dr. Zhao (fzhao@sjfc.edu).

DOI 10.1093/ajhp/zxaa412

technologies have been approved by FDA, as shown in Table 1, and more are in the development pipeline.[5-9] Interestingly, the drug products prepared from these technologies are similar in appearance to traditional tablets or capsules. There is also little to no discussion regarding these products' unique formulation in the respective product labeling documents,[8] probably due to the proprietary nature of the technologies used. As such, it is not evident to pharmacists or other healthcare providers that these products are prepared from unique drug materials, functional excipients, and highly sophisticated processes. Unfortunately, manipulation of these products by common methods will compromise the intended drug release properties in the gastrointestinal (GI) tract and may lead to potential treatment failures.[5]

To assist pharmacists with recognition and proper utilization of these new drug products, this article will provide a brief review of the scientific principles of the new technologies and present a summary drug table (Table 1) cross-referenced with the ISMP Do Not Crush list and alternative dosage form options.

KEY POINTS

- The Institute for Safe Medication Practices "Do Not Crush" list does not include tablets and capsules prepared from novel technologies of nanocrystals and amorphous solid dispersions.
- Crushing of these drug products may lead to reduced oral bioavailability and subtherapeutic drug levels in patients.
- A reference table is provided to assist pharmacists in recognizing these products and making prescribing recommendations.

How nanocrystals and amorphous solid dispersions work

After a tablet or capsule is administered orally, the drug has to dissolve in the GI fluid before it can cross the biological barriers to enter the systemic circulation. The term *oral bioavailability* refers to the percentage of the dose that enters the systemic circulation. One of the main challenges in achieving adequate oral bioavailability for many drug candidates is the poor aqueous solubility and slow dissolution rate. The nanocrystal and amorphous solid dispersion technology platforms were developed to address this specific issue.[4,5] Both of these approaches enhance the drug dissolution rate in the GI tract, but they accomplish this via different mechanisms.

The nanocrystal approach uses size reduction milling processes to produce nano-sized crystalline drug particles.[11] According to the Noyes-Whiteney equation, drug dissolution rate is directly proportional to the total surface area of the solid drug particles. In theory, for every 10-fold decrease in particle size, the dissolution rate increases 10-fold. The reduction in particle size to the nano scale offers a tremendous increase in total surface area, which allows faster drug dissolution in the GI tract. The downside, driven by thermodynamic principles, is that the extremely small particles have a tendency to grow back to larger sizes when they come close to each other and when they are exposed to moisture for prolonged periods of time (relative to the GI transit time).[4,5] Suitable excipients, packaging, and storage conditions are carefully selected to maintain the physical stability of this type of drug product. However, crushing these dosage forms will compromise the formulation integrity and lead to increased exposure to ambient moisture. Suspending the crushed powder in aqueous media, such as beverages or compounding vehicles, will further accelerate the crystal growth, as illustrated in Figure 1.

The amorphous solid dispersion approach is another way to engineer the raw drug material to enhance the dissolution rate.[12,13] It involves the conversion of a crystalline drug form to an amorphous form, typically by continuous hot melt extrusion or spray drying processes. The dissolution rate of a crystalline drug material is generally slow, because the drug molecules in the tightly packed crystal lattice need to overcome the intermolecular bonding among themselves before they can freely interact with the surrounding water molecules. In contrast, the drug molecules in the amorphous form are not packed in any crystal lattice with long-range order, and this is usually reflected by the lack of a clear melting point. When exposed to the GI fluid, the drug molecules in the amorphous form can easily dissociate from each other and interact with the surrounding water molecules. In fact, the use of amorphous material typically leads to the formation of a supersaturated solution, which can also drive the drug absorption process across the intestinal epithelium. As shown in Table 1, there have been more successful commercial products based on the amorphous approach as opposed to the nanocrystal approach, mostly due to the continuous process technology and the benefit of supersaturation with the former. Despite these advantages, the amorphous form is also a metastable phase that readily converts back to the crystalline form, which is favored by thermodynamics.[4,5,14] To minimize this conversion, the formulations typically require some carefully selected polymers to trap the amorphous drug material in a dispersion state, and hence the term *amorphous solid dispersion*. Unfortunately, when these formulations are exposed to moisture for an extended period of time, the amorphous form will eventually convert to the crystalline form through the solution phase and lose the desired properties of rapid dissolution and increased bioavailability (Figure 1).

Why these formulations should not be crushed

Manipulation of the nanocrystal and amorphous solid dispersion formulations by crushing or similar

Table 1. Summary of FDA-Approved Oral Tablets and Capsules Based on Nanocrystal or Amorphous Solid Dispersion Technology[a]

Brand (Generic) Name and Manufacturer	Technology	On ISMP Do Not Crush List?[1]	Alternative Dosage Forms Available[8,10]
Emend (aprepitant) Merck	Nanocrystal	No	Powder for oral suspension, IV emulsion
Rapamune (sirolimus) Pfizer	Nanocrystal	Yes	Oral solution
TriCor (fenofibrate) AbbVie	Nanocrystal	No	Other oral capsules/tablets
Triglide (fenofibrate) Sciele Pharma	Nanocrystal	No	Other oral capsules/tablets
Afinitor (everolimus) Novartis	Amorphous solid dispersion	Yes	Tablet for oral suspension
Astagraf XL (tacrolimus) Astella Pharma	Amorphous solid dispersion	No	IV solution, granule for oral suspension
Belsomra (suvorexant) Merck	Amorphous solid dispersion	No	No
Cesamet (nabilone) Meda Pharmaceuticals	Amorphous solid dispersion	No	No (discontinued in US)
Epclusa (sofosbuvir/velpatasvir) Gilead Sciences	Amorphous solid dispersion	No	No
Harvoni (ledipasvir/sofosbuvir) Gilead Sciences	Amorphous solid dispersion	No	No
Incivek (telaprevir) Vertex	Amorphous solid dispersion	No	No (discontinued in US)
Intelence (etravirine) Janssen	Amorphous solid dispersion	Yes	No
Isoptin SR (verapamil) Ranbaxy Laboratories	Amorphous solid dispersion	Yes	IV solution
Kaletra (lopinavir/ritonavir) AbbVie	Amorphous solid dispersion	Yes	Oral solution
Kalydeco (ivacaftor) Vertex	Amorphous solid dispersion	No	Oral granules
Lynparza (olaparib) AstraZeneca	Amorphous solid dispersion	Yes	No
Mavyret (glecaprevir/pibrentasvir) AbbVie	Amorphous solid dispersion	No	No
Norvir tablet (ritonavir) AbbVie	Amorphous solid dispersion	Yes	Oral solution, oral powder
Noxafil DR tablet (posaconazole) Merck	Amorphous solid dispersion	Yes	Oral suspension, IV solution
Onmel (itraconazole) Merz Pharma	Amorphous solid dispersion	No	Oral solution, other oral capsules
Orkambi (lumacaftor/ivacaftor) Vertex	Amorphous solid dispersion	No	Oral granules
Prograf (tacrolimus) Astrellas Pharma	Amorphous solid dispersion	No	Granule for oral suspension
Sporanox (itraconazole) Janssen	Amorphous solid dispersion	No	Oral solution

Continued on next page

Continued from previous page

Table 1. Summary of FDA-Approved Oral Tablets and Capsules Based on Nanocrystal or Amorphous Solid Dispersion Technology[a]

Brand (Generic) Name and Manufacturer	Technology	On ISMP Do Not Crush List?[1]	Alternative Dosage Forms Available[8,10]
Stivarga (regorafenib) Bayer	Amorphous solid dispersion	Yes	No
Symdeko (tezacaftor/ivacaftor) Vertex	Amorphous solid dispersion	No	No
Tibsovo (ivosedinib) Agios Pharmaceuticals	Amorphous solid dispersion	No	No
Trikafata (elexacaftor/tezacaftor/ivacaftor) Vertex	Amorphous solid dispersion	No	No
Venclexta (venetoclax) AbbVie	Amorphous solid dispersion	Yes	No
Viekira XR (dasabuvir/ombitasvir/paritaprevir/ritonavir) AbbVie	Amorphous solid dispersion	Yes	No
Zelboraf (vemurafenib) Roche	Amorphous solid dispersion	No	No
Zepatier (elbasvir/grazoprevir) Merck	Amorphous solid dispersion	No	No
Zortress (everolimus) Novartis	Amorphous solid dispersion	Yes	Tablet for oral suspension

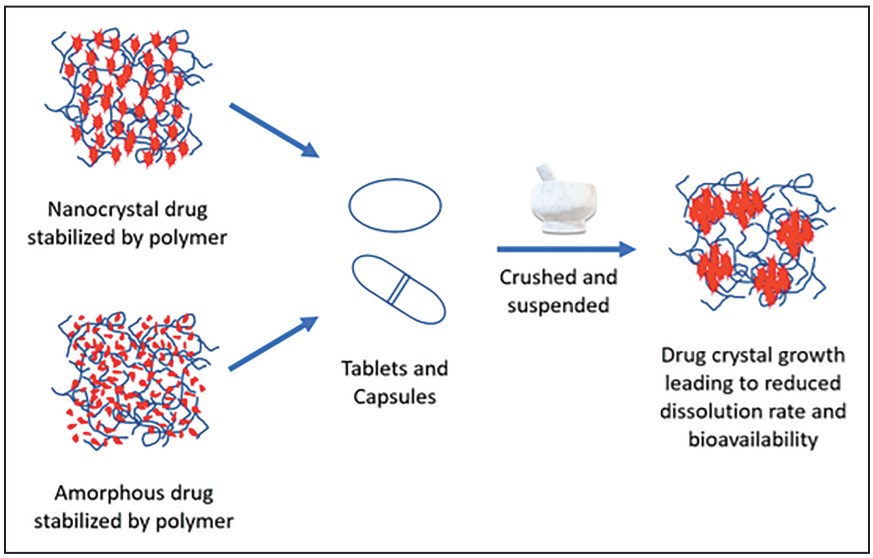
Abbreviations: DR, delayed release; FDA, Food and Drug Administration; ISMP, Institute for Safe Medication Practices; IV, intravenous; SR, sustained release; XL, extended release.
[a]This summary list was compiled from literature published as of December 31, 2019. Two review articles[5,6] served as the primary source for identifying nanocrystal and amorphous solid dispersion products. Additionally, all FDA approvals from 2017 through 2019 were reviewed and screened using a 3-step process. First, the oral tablet and capsule products were identified from the annual approval list.[7] Next, the FDA-approved labels of identified products were reviewed carefully, with a focus on drug solubility, formulation, and bioavailability.[8] Lastly, formulation patents listed in the Orange Book[9] were analyzed for confirmation. Due to the proprietary nature of formulation technologies, some relevant products might have been inadvertently omitted from this list.

techniques can have significant impact on oral bioavailability and clinical consequences. As mentioned above, nanocrystals and amorphous solid dispersions offer an improved dissolution rate to achieve adequate oral bioavailability for poorly water soluble drugs. However, they are both metastable forms that tend to convert to the stable crystal forms of large particle size and lose the benefit of rapid dissolution. This conversion is accelerated when the dosage form is crushed into powder, exposed to moisture, or, worse yet, suspended in aqueous media. The subsequent decrease in oral bioavailability will result in reduced drug exposure, which may lead to treatment failure and other complications.

A 2011 publication provided an example to illustrate the potential issues when these special products are manipulated.[15] A clinical study was conducted to compare the pharmacokinetics of intact and crushed Kaletra (lopinavir/ritonavir [200 mg/50 mg]) tablets (AbbVie) in pediatric patients. Kaletra tablets were manufactured through amorphous solid dispersion technology. The crushed tablets were mixed with pudding for administration. The data revealed decreases in area under the curve (AUC) of 45% and 47% for lopinavir and ritonavir, respectively. This reduced drug exposure can increase the risks of treatment failure and development of viral resistance.

A recent article evaluated the in vitro drug release of 4 products based on amorphous solid dispersion technology, namely Sporanox (Janssen Pharmaceuticals), Intelence (Janssen Therapeutics), Noxafil (Merck Sharpe & Dohme), and Norvir (AbbVie).[16] Significant differences were observed between intact and crushed products, especially for Noxafil and Norvir. Interestingly not all trends from this laboratory evaluation were consistent with the expectations, highlighting the challenges of predicting the performance of these metastable formulations when used outside the manufacturers' recommendations. Based on these data, the researchers urged users not to crush any type of amorphous

Figure 1. Crushing tablets or capsules prepared from nanocrystal or amorphous solid dispersion formulations can lead to undesirable changes in drug dissolution or bioavailability.[4,5]



formulation to avoid unpredictable clinical outcomes. They also emphasized that the in vitro observations should be supported by additional bioequivalence clinical studies.

Due to the lack of funding and commercial interest in this particular area, it is unlikely that bioequivalence studies will be conducted to compare the intact vs crushed forms of all these special formulations in the near future. Furthermore, it is nearly impossible to study all possible ways in which dosage forms are manipulated and mixed with foods and fluids. In the absence of bioequivalence data, it is imperative that pharmacists are aware of the science behind these special dosage forms and advocate the proper use of them.

Summary list of drug products based on the new technologies

Table 1 provides a summary list of drug products based on nanocrystal or amorphous solid dispersion technologies that were approved by FDA as of December 31, 2019.[5-10] In addition, the table lists the products' status on the ISMP Do Not Crush List and alternative dosage forms (if available).[1,8,10] It is alarming that more than two-thirds of these medications are not currently listed on the ISMP Do Not Crush list. Similarly, warnings against crushing these products are often lacking in tertiary drug references[10]; this leads to the misconception that these products may be manipulated by crushing or similar techniques.

It should be noted that for some of these products, statements advising against crushing are included in the FDA-approved labeling. However, many traditional products carry similar statements to indicate that there are no data to directly support the use of crushed tablets or capsule contents. As a result, healthcare providers often disregard these statements in the product labeling and rely instead on the ISMP Do Not Crush List.

Fortunately, most of the drug products listed in Table 1 are available in other dosage forms, such as oral solutions and/or suspensions, oral powders and/or granules, intravenous solutions, and traditional tablets and/or capsules, which can be crushed. Pharmacists are encouraged to recommend use these alternative dosage forms to treat patients who cannot swallow whole tablets or capsules. For medications without alternative dosage forms, the prescribers should consider different drug options.

Conclusion

Nanocrystals and amorphous solid dispersions are two recent formulation innovations that have enabled the development and launch of many new oral drug products. Medications produced using these new technology platforms are similar in appearance to traditional tablets and capsules. This can be misleading to pharmacists and other healthcare workers trying to manipulate the products for patients who are unable to swallow whole tablets or capsules. Crushing or grinding of these products will comprise the integrity of the formulation and may lead to treatment failure; alternative dosage forms or drugs should be considered. It is essential that these medications be properly represented on the ISMP Do Not Crush list to ensure that oral bioavailability is not compromised and patients are receiving the best treatment possible.

Disclosures

The authors have declared no potential conflicts of interest.

References

1. Institute for Safe Medication Practices. Oral dosage forms that should not be crushed. https://www.ismp.org/

recommendations/do-not-crush. Published February 21, 2020. Accessed January 26, 2020.
2. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques, *ISRN Pharm*. 2012;2012:195727.
3. Hughey JR, Huang S, Williams RO. Solid-state techniques for improving solubility. In: Williams RO, Watts AB, Miller DA, eds. *Formulating Poorly Water Soluble Drugs*. 2nd ed. *AAPS Advances in the Pharmaceutical Sciences Series*; vol 22. Springer; 2016:121-164.
4. Fong SY, Bauer-Brandl A, Brandl M. Oral bioavailability enhancement through supersaturation: an update and meta-analysis. *Expert Opin Drug Deliv*. 2017;14(3):403-426.
5. Jermain SV, Brough C, Williams RO 3rd. Amorphous solid dispersions and nanocrystal technologies for poorly water-soluble drug delivery – an update. *Int J Pharm*. 2018;535(1-2):379-392.
6. Gala UH, Miller DA, Williams RO 3rd. Harnessing the therapeutic potential of anticancer drugs through amorphous solid dispersions. *Biochim Biophys Acta Rev Cancer*. 2020;1873(1):188319.
7. US Food and Drug Administration. New drugs at FDA: CDER's new molecular entities and new therapeutic biological products. https://www.fda.gov/drugs/development-approval-process-drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products. Accessed January 26, 2020.
8. Drugs@FDA: FDA-Approved Drugs search engine. US Food and Drug Administration. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. Accessed January 26, 2020.
9. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. US Food and Drug Administration. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm. Accessed January 26, 2020.
10. Lexi-Drugs. In: Lexicomp Online [proprietary data]. UpToDate, Inc.; 2020. Accessed February 4, 2020.
11. Merisko-Liversidge E, Liversidge GG. Nanosizing for oral and parenteral drug delivery: a perspective on formulating poorly-water soluble compounds using wet media milling technology. *Adv Drug Deliv Rev*. 2011;63(6):427-440.
12. Sandhu H, Shah N, Chokshi H, Malick A. Overview of amorphous solid dispersion technologies. In: Shah N, Sandhu H, Choi D, Chokshi H, Malick A, eds. *Amorphous Solid Dispersions. Advances in Delivery Science and Technology*. Springer; 2014:91-122.
13. Schittny A, Huwyler J, Puchkov M. Mechanisms of increased bioavailability through amorphous solid dispersions: a review. *Drug Deliv*. 2020;27(1):110-127.
14. Kou X, Zhou L. Stability of amorphous solid dispersion. In: Shah N, Sandhu H, Choi D, Chokshi H, Malick A, eds. *Amorphous Solid Dispersions. Advances in Delivery Science and Technology*. Springer; 2014:515-544.
15. Best BM, Capparelli EV, Diep H, et al. Pharmacokinetics of lopinavir/ritonavir crushed versus whole tablets in children. *J Acquir Immune Defic Syndr*. 2011;58(4):385-391.
16. Pas T, Verbert S, Appeltans B, Van den Mooter G. The influence of crushing amorphous solid dispersion dosage forms on the in-vitro dissolution kinetics. *Int J Pharm*. 2020;573:118884.