

Pharmaceutical Issues when Crushing, Opening or Splitting Oral Dosage Forms

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Introduction

It is important to recognise the potential consequences of manipulating a medicinal product. Changing the way in which a dosage form is presented can alter its absorption characteristics, result in medicines instability, produce local irritant effects, cause failure to reach the site of action, may produce occupational health and safety issues, and could result in a preparation with an unacceptable taste. Most of these considerations apply equally to Specials (see Footnote), as well as to splitting and crushing of tablets and opening of capsules; there are risks and benefits associated with both. In most circumstances in which no appropriate licensed medicine is available, the prime objective should be to provide patients with a ready-to-use unlicensed medicine. There may, however be circumstances in which this is not the preferred choice.

A recent study¹ found that a tablet splitting device (Pilomat) was able to split a range of tablets more accurately than splitting by hand (for scored tablets), cutting with scissors (for unscored tablets), or using a kitchen knife. Accuracy of splitting is critical if the objective is to give less than a whole tablet dose to a patient but less so if the aim is simply to give the full dose to a patient who cannot swallow the tablet whole. If a situation arises where an oral dosage form has to be split, crushed, opened or manipulated in any other way for the benefit of a patient, the resulting preparation should be taken by the patient as soon as possible to reduce the likelihood of degradation and minimise any risks.

There are certain types of dosage form that should never be split or crushed and this document aims to highlight these dosage forms, the science behind why they should remain intact, and the possible consequences of splitting or crushing various dosage forms. This document does not cover the decision making process for deciding whether it is more appropriate to crush, split or open an oral dosage forms, or to use a Special; this can be found in RPS Guidance on Specials (<http://www.rpharms.com/best-practice/specials.asp>).

When describing the types of dosage forms that should not be crushed, split or opened, and the potential consequences of manipulating a dosage form, a selection of medicines has been listed to illustrate the types of product that have the effect or action under discussion. The medicines included are intended to act as examples and must not be viewed as an exhaustive list. If a pharmacist has any concerns about whether a medicine is suitable for crushing, splitting or opening, advice from the manufacturer of the product should be sought.

Footnote: a Special may be, a) a medicine manufactured by a specials manufacturer holding a Manufacturer's Specials Licence (MS) in multiple quantities with end product analytical testing, b) a special medicine produced by a specials manufacturer holding an MS as a bespoke medicine without end product analytical testing, or, c) an extemporaneously prepared medicine, which is an unlicensed medicine made in a pharmacy under a pharmacist's direct supervision

As with the preparation of Specials, the crushing or splitting of dosage forms will be an unlicensed use of the medicine (unless this form of manipulation is covered by the product's Marketing Authorisation). This will mean that the pharmacist supplying the medicine may assume additional responsibility and liability for the decision to crush or split the dosage form. Some tablets can also be dispersed in liquids, and, as this is done immediately prior to administration to patients, drug stability is not usually a major issue. However, if only part of the liquid containing the dispersed tablet is to be administered to a patient, problems can arise with drugs that are insoluble in aqueous vehicles.² Aggregation, sedimentation and precipitation of insoluble drugs can result in poor accuracy of the dose administered. Powders or some other dosage forms can be added to beverages and foods although data to support this are lacking, and no single food or beverage will be suitable for all drug substances.

Potential Consequences of Splitting, Crushing and Opening

Risks to Healthcare Workers and Carers

Crushing products with carcinogenic (e.g. tamoxifen; methotrexate) or teratogenic (e.g. valganciclovir) potential may expose carers or healthcare professionals to health risks through powder aerosolisation and as such should not be undertaken. Similarly, preparations containing hormones (oral contraceptives; hormonal replacement therapy), corticosteroids (such as dexamethasone) and some other drugs (finasteride; mycophenolate) should not be crushed due to the risks associated with powder aerosolisation.³⁻⁶ It should be noted that the effects of many other drugs when inhaled are largely unknown.

In addition several drug substances may also cause irritation if the powder is aerosolised and inhaled or comes into contact with the eyes, skin, or other mucous membranes e.g. alendronate, diflunisal, isotretinoin, piroxicam. Ganciclovir is known to be a skin irritant, and exposing the skin to hydroxycarbamide powder can cause serious skin toxicity.

Drug Instability

Crushing an oral solid dosage form may have a negative impact on the stability of the drug substance.

If an enteric coating, which protects a drug from the acidic environment in the stomach, is removed by crushing the tablet, the *in vivo* drug degradation will increase, with less drug available to produce the desired clinical effect.

Coatings are also added to oral solid dosage forms to protect the drug from the effects of light. Nifedipine is an example of a drug that is highly light sensitive after tablets have been crushed.

Changes in Pharmacokinetics and Bioavailability

Splitting or crushing oral dosage forms may produce changes in the drug pharmacokinetics and bioavailability resulting in underdosing or adverse effects. Such changes may be particularly important for drugs that have narrow therapeutic windows e.g. phenytoin, digoxin, carbamazepine, theophylline, or sodium valproate.⁴

Drug Irritation

Many drugs have irritant actions and are formulated or coated to minimise the risk to patients. Some medications may cause oesophageal or stomach irritation or ulceration if tablets are crushed or capsules opened (e.g. nitrofurantoin, potassium chloride, alendronate, diclofenac).

Bitter Tasting Drugs

For drugs which have a particularly bitter taste, a coating (sugar/film) is often used to help mask the taste of the active substance. A sugar coating provides a thick hard coat to a tablet and is traditionally used to mask the taste of particularly unpleasant tasting drugs such as ibuprofen or quinine. Film coating produces a much thinner layer on tablets but this is still capable of masking the unpleasant taste of drugs. Other examples of bitter or unpleasant tasting drugs include cefuroxime axetil, ciprofloxacin, docusate, pseudoephedrine and praziquantel. Crushing tablets containing bitter or unpleasant tasting drug substances may produce a preparation which is unpleasant to taste and which a patient may refuse to take unless the taste can be masked using a suitable food or liquid.

Other Effects

Sertraline is known to have an anaesthetic effect on the tongue; patients may become aware of this effect if a formulation of sertraline is given in a powdered form.⁷

Requirement for Patient Monitoring

Patient monitoring should be undertaken when some products are crushed. Blood pressure monitoring has been advised when crushed preparations of alfuzosin, carvedilol, nifedipine, or ramipril are administered due to the risk of hypotensive effects.⁷ If oral dosage forms of glibenclamide, gliclazide, or metformin are crushed or opened, monitoring of blood glucose levels has been suggested.⁷

Dosage Form Effects

Extended Release Preparations

Extended-release products are formulated to release the drug over an extended period of time, generally over 12 to 24 hours. The aim of an extended-release preparation is to produce a constant plasma drug concentration, although in practice there are small rises and falls in drug concentration over the period that the drug is released. Extended-release formulations often have one of the following abbreviations after the product name CR, ER, LA, SR, XL or XR.

Several different methods can be used to modify the rate of release of a drug from an oral dosage form including the following:-

- Modifying the pharmaceutical form - by increasing the drug particle size or forming insoluble crystals leads to a reduced rate of drug release e.g. Tegretol Retard, Adalat Retard.
- Coating pellets – coating drug pellets with a slowly dissolving polymer of varying thickness can vary the drug release rate. The pellets can either be compressed into a tablet or put in gelatin capsules e.g. Slo-Phyllin, Inderal-LA.
- Insoluble matrix – drug is dispersed within an insoluble matrix and as fluid enters the matrix, the drug is dissolved and slowly diffuses out e.g. Slow-K, Imdur Durules.
- Eroding matrix – the drug is dispersed within a soluble matrix and as the matrix is slowly eroded the drug is released e.g. MST Continus, Phyllocontin Continus.
- Osmotic pump – the drug and an osmotic agent are enclosed in a semi-permeable membrane; water is drawn into the matrix and the dissolved drug is released in a controlled manner through a laser drilled hole e.g. Adalat LA.

Crushing an extended-release preparation may change the drug release characteristics, with the potential for an unintended large bolus dose being delivered rather than controlled release over the intended timescale. The consequence of this would be for a potentially toxic dose of medication to be delivered following administration with an increased risk of adverse effects. While there is the risk of initial overdosing of drug, there will be under dosing at later times which could result in a lack of clinical efficacy.^{8,9}

A case has been reported in which a crushed extended-release nifedipine tablet contributed to a patient fatality;¹⁰ the administration of a crushed nifedipine XL tablet resulted in severe hypotension and the concurrent administration of labetalol prevented a compensatory heart rate increase in the patient.

Crushing sustained-release isosorbide mononitrate tablets and administration through a percutaneous endogastric tube to a 78 year old patient produced recurring chest pain and nausea, with an ECG confirming ischaemic changes;¹¹ symptoms resolved when therapy was changed to a short acting nitrate administered three times daily.

With some capsule formulations where the controlled release properties are built into individual pellets contained in the capsule, it may be possible to open the capsule and use the contents provided the pellets are not crushed.¹²

Enteric Coated Preparations

Enteric coatings on tablets are produced by coating the tablet with polymers that remain intact in the stomach but dissolve and release the drug from the dosage form in the more alkaline pH of the small intestine. Enteric coatings are applied to tablets to delay the release of drugs that are inactivated by the stomach contents (pancreatin; erythromycin; omeprazole), to prevent stomach irritation (aspirin; diclofenac; naproxen; corticosteroids), or to delay the onset of action to a specific site within the gastrointestinal tract (sulphasalazine in the treatment of Crohn's disease).

Crushing enteric coated tablets may result in the drug being released too early, destroyed by stomach acid, or irritating the stomach lining.

In general, manipulation of enteric coated and extended-release formulations is not, therefore, recommended. However, it is accepted a few extended-release preparations may be manipulated, but this should only be done on the recommendation of the product manufacturer.

Other Types of Dosage Forms

Sublingual and buccal tablets allow a drug substance to be directly absorbed across the mucosal membrane leading to rapid rises in the drug concentration in the blood; this method of delivery also avoids first pass metabolism in the liver. Lozenges are large tablets that are intended to stay in the mouth for periods of 10 to 15 minutes while they dissolve and have a local action in the mouth.

If these types of dosage form are crushed, the pharmacokinetics and bioavailability of buccal and sublingual products will be altered, and the local action of lozenges will be affected. However, in practice, there is unlikely to be any circumstance where it will be necessary to crush these types of dosage form.

An indication of which oral dosage forms should not be crushed and the reasons for this can be found at the following sites which list American products (<http://www.ismp.org/tools/donotcrush.pdf>; <http://www.rphworld.com/viewlink-23475.html>), and the ways in which pharmacists can help optimise the treatment of patients, and in particular children, who have swallowing difficulties has recently been described.¹³

When May it be Appropriate to Consider Crushing, Opening or Splitting?

If a decision is taken that the most appropriate way to address an individual patient's needs is to manipulate a preparation, it may be possible to crush, open, or split uncoated tablets, film coated tablets, sugar coated tablets or immediate-release capsules provided that consideration is given to any cytotoxic, teratogenic, stability, irritancy and bitterness issues associated with the dosage form. If a tablet is sugar- or film-coated, the reason for the coating should be determined before the tablet is crushed.

If crushing of tablets or the opening of capsules is to be considered, useful information on whether this form of manipulation is appropriate for a drug product can be found in the Handbook of Drug Administration via Enteral Feeding Tubes,¹⁴ and at the website created by Colchester Medicines Information at Colchester Hospital University NHS Foundation Trust.⁷ While these sources provide guidance on whether a dosage form can be manipulated, there is an absence of data to indicate how this manipulation may affect the bioavailability of the product, or if the manipulated product remains bioequivalent with the original dosage form. Methods that have been used to crush tablets include using a mortar and pestle, one of the commercially available devices designed to crush tablets, or a tablet crushing syringe. It should be recognised that there is the possibility of powder loss in using some of these methods; about 25% of aspirin was lost when a mortar and pestle was used to crush tablets prior to suspending the powder in water.¹⁵

It has been reported that crushing film coated telithromycin tablets and administering them with a nutritional supplement drink was found to be bioequivalent to ingesting whole tablets.¹⁶ When splitting tablets, either by hand or using a splitting device, it is not uncommon to obtain two tablet pieces that are not the same size, and whose weight can vary by 15% to 20% of the theoretical weight i.e. half the weight of the intact tablet.¹⁷⁻¹⁹ This may be highly significant if only a part of the tablet dose is to be administered, but may be insignificant if the aim is simply to help a patient who can't swallow a tablet whole. Dose variation is greater for non-scored tablets than scored tablets.²⁰

It should be borne in mind that there is the possibility of a reduced or absent clinical effect when the smaller portion of a split tablet is administered. When unscored cyclobenzaprine 10 mg tablets were split using a kitchen knife and a tablet splitter, it was found that the variation in weight of the two tablet pieces obtained was less with the tablet splitter than the kitchen knife; variations of up to about 30% of the theoretical weight were obtained with the tablet splitter while variations of up to 50% were noted with the kitchen knife. Interestingly, the smaller of the two tablets pieces could contain as little as 2.49 mg cyclobenzaprine when tablets were split with a kitchen knife; the authors noted that the efficacy of cyclobenzaprine 2.5 mg has been shown to be no different from placebo.²¹

There is relatively little published information on the clinical effects resulting from the administration of split tablets to patients. Two studies have investigated the effect of splitting tablets containing statins on *in vivo* markers; in one study, splitting tablets had no significant effect on total cholesterol and LDL cholesterol,²² while the other study reported that tablet splitting produced no difference in total cholesterol and triglycerides.²³

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