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The pharmacological perspective on tablet splitting or crushing

Abstract

Purpose: It is a common practice to use drugs in tablet form by splitting or crushing. Especially in geriatric and pediatric clinics, it offers important advantages such as providing appropriate dosing, saving costs, and increasing compliance in patients who have difficulty swallowing tablets. The purpose of this review is to evaluate the efficacy and safety of splitting or crushing tablets.

Method: Literature was retrieved by a PubMed search, using different combinations of pertinent keywords (e.g., tablet splitting, tablet crushing) without any limitations in terms of publication date and language. Papers, which assessed the efficacy and safety of tablet crushing or splitting, were selected for inclusion according to their relevance for the topic, as judged by the authors.

Results: This method, which is based on splitting and breaking the tablets by hand, with the help of scissors, a knife, or a tablet splitter, is often used by both patients and their relatives to facilitate the swallowing of tablets in pediatric patients or patients with swallowing difficulties and/or due to economic reasons. It is reported that almost a quarter of all drugs used in treatments are used by splitting or crushing. It is also known that more than half of the patients (57%) use the drugs in tablet form by splitting them. It states that uncoated, sugar-coated or film-coated tablets can be used by splitting or crushing, considering the patient compliance and pharmacoeconomic benefits of splitting the drugs in tablet form. Active ingredient-containing tablets with a broad therapeutic index and long half-life are suitable candidates for the splitting-crushing process. Clinical studies report that the use of uncoated, sugar-coated, or film-coated tablets with the same dose of crushed forms and their use as a whole tablet has the same efficacy and safety data.

Conclusion: In the light of a patient's needs and in order to increase the patient's compliance with the treatment, uncoated tablets, film-coated tablets, sugar-coated tablets are suitable for use in terms of drug efficacy and patient safety by breaking, crushing, splitting, or opening immediate-release capsules. Physical manipulations on drugs with these coating properties do not cause any change in bioavailability and pharmacokinetic data.

The use of uncoated tablets, film-coated tablets, sugar-coated tablets, or immediate-release capsules by splitting or crushing tablets is an effective and safe application that increases patient compliance. For example, propiverine, ibuprofen, cefuroxime axetil, ciprofloxacin, pseudoephedrine, and praziquantel or quinine are coated with sugar or film to facilitate the swallowing of the drug in terms of taste. Medicines of this nature can be used by splitting or crushing into small pieces to facilitate swallowing in terms of size. In terms of bioavailability and pharmacokinetics, there is no harm in consuming drugs with this structure by breaking and splitting.

With tablet breaking, the cost of treatment can be reduced, and it can also increase patients' compliance with their drug regimens. As a result, unnecessary emergency room visits or hospitalizations can be reduced by preventing non-compliance with the treatment that may develop due to the inability to swallow the drug.

Sustained-release drug products, enteric-coated tablets, tablets that are small in size, easily fall apart, or cannot be split in proportion due to having a brittle form, tablets with a narrow therapeutic window and short half-life are not suitable for splitting use. From a pharmacokinetic point of view, the split use of such tablets may increase the risk of side effects or change their effectiveness.

Keywords: tablet breaking, tablet crushing, tablet splitting, manipulation of tablets

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Introduction

Patients in all age groups can use tablets in tablet form by splitting or crushing them when necessary. This method, which is generally performed by hand, with the help of scissors, a knife, or a tablet splitter, can be preferred by both patients and their relatives, due to economic reasons and to facilitate the easy swallowing of large tablets in pediatric patients or patients with swallowing difficulties.[1-5]

Physicians may recommend splitting or crushing tablets in order to prescribe the lowest drug dose that will be effective in the treatment and thus minimize the frequency of side effects due to drugs. However, it is also possible to experience undesirable situations such as breaking and/or splitting the drugs in tablet form into unequal pieces, and the patient feeling a possible bad taste while swallowing the drug due to the loss of the tablet's coating. However, this method may cause some disadvantages, such as the ability to monitor bioavailability and pharmacokinetic data changes depending on the coating properties of the tablet form of the drug in which this method is applied.[6–8]

The form in which a drug is presented (e.g., tablet, capsule, solution for injection, cream, etc.) is called the pharmaceutical form.[9] The variety of these forms allows the physician to choose the pharmaceutical form of drugs according to the patient, the disease or the person administering it. Tablets, capsules, ampoules, vials, syrups, ointments, creams, drops, sprays, etc. are some of the pharmaceutical forms of drugs.[10] Tablets are obtained by mixing powdered drugs with various binders and compressing them in special machines. It can be cylindrical, disc or lentil shaped. They take up water in the gastrointestinal tract, swell and disperse (disintegrate). There are also forms such as foaming (effervescent) tablets and chewable tablets.[10]

Drug theraphy of pediatric patients are generally planned in light of body mass index. However, since pediatric patients show great variability in terms of this parameter, these drugs can be used by splitting or crushing, especially in order to ensure appropriate dosing of drugs in tablet form. In addition, splitting or crushing the tablets is a frequently preferred method in order to facilitate the swallowing of tablets in these patient groups.[11]

Studies show that when compared to drugs in the form of powder, suspension, and syrup, drugs in tablet form can be preferred by physicians and parents even in children younger than 6 months, infants, and newborns.[12–14]

Use of tablets by breaking or splitting in terms of pharmacoeconomics and patient compliance

Splitting or crushing tablets is a method that arises from the need to change or optimize drug doses, as well as facilitating the swallowing of tablets in tablet form. It has been reported in the publications that almost one-fourth of all drugs administered in primary care are used by splitting.[6] When 882 patients were evaluated in a cross-sectional study in Germany, it was reported that 24.1% (762 drugs) of 3158 drugs used in primary health care were used by splitting or breaking.[6]

Taking tablets by splitting or crushing can be preferred because of the advantages such as ease of swallowing, providing appropriate dosing, as well as economic benefits.[15] Physicians may also recommend the drugs in tablet form that they prescribe in their treatment planning to be split or crushed. With this approach, it is aimed to facilitate the swallowing of tablets in especially pediatric and geriatric patient groups and/or to protect these special patient groups against side effects with lower drug dosing.[16] In a survey conducted in 2016, it was shown that more than half of the patients (57%) used drugs in tablet form by splitting.[17]

It has been reported that the most important reason for patients to use tablets in tablet form by splitting or crushing is dysphagia developed due to forced swallowing of large tablets by patients.[18] Splitting or crushing the tablet facilitates swallowing, thus increasing patient compliance.[19,20] In addition, it is possible to prescribe the lowest effective dose to reduce side effects with this method. However, tablet splitting is a cost-saving application.[6,15] It is reported that uncoated, sugar-coated or film-coated tablets can be used by splitting or crushing, considering the patient compliance and pharmacoeconomic benefits of splitting the drugs in tablet form.[15,21,23–25]

As a result, unnecessary emergency room visits or hospitalizations can be reduced by preventing non-compliance with the treatment that may develop due to the inability to swallow the drug.[22] In addition, in the survey studies conducted to determine the opinions of the patients about the use of tablets by splitting and crushing, it was shown that the patients responded positively to the idea of using drugs in this way and that these patients were not adversely affected clinically and were satisfied with this form of treatment.[2,15,26]

Suitability of taking tablets by splitting-crushing in terms of pharmacokinetics and bioavailability

Tablet splitting is safe and easy when drug and patient-specific criteria are met. In the splitting of tablets, tools such as breaking by hand, cutting with a sharp tool such as a knife or scissors, or tools developed for this process such as tablet splitters can be used. Although the tablet splitter seems to be the most practical and safe method on the subject, some physical factors such as the size, shape, hardness, structure, and components of the tablet or the presence and depth of the score line and the individual characteristics of the patient are also important in the method preference.[27,28]

There are also studies in the literature claiming that it is a better choice for splitting drugs by hand, a knife, or scissors compared to an inadequate and inappropriate tablet splitter device.[29,30] On the other hand, the shape and size of the score, in addition to the presence of a score, can make the splitting process healthier.[31] Active ingredient-containing tablets with a broad therapeutic index and long half-life are suitable candidates for the splitting-crushing process.[32]

In contrast, caution should be exercised when splitting drugs with a narrow therapeutic index, such as digoxin. Because small changes in the daily dose of drugs with a narrow therapeutic index such as digoxin or fluctuations in blood levels can result in significant adverse effects. Again, drugs with short half-lives should not be split or crushed, as disproportionate splitting may cause fluctuations in plasma concentrations and adverse pharmacological consequences.[33,34]

Additionally, sustained-release drug products, enteric-coated tablets, tablets that are small in size, easily fall apart, or cannot be split in proportion due to having a brittle form, tablets with a narrow therapeutic window and short half-life are not suitable for splitting use. From a pharmacokinetic point of view, the split use of such tablets may increase the risk of side effects or change their effectiveness.[32] The use of tablets that do not have these properties by breaking and splitting is suitable in terms of pharmacokinetic and provides a number of pharmacoeconomic advantages such as cost savings, patient compliance with treatment, and optimal dose adjustment.

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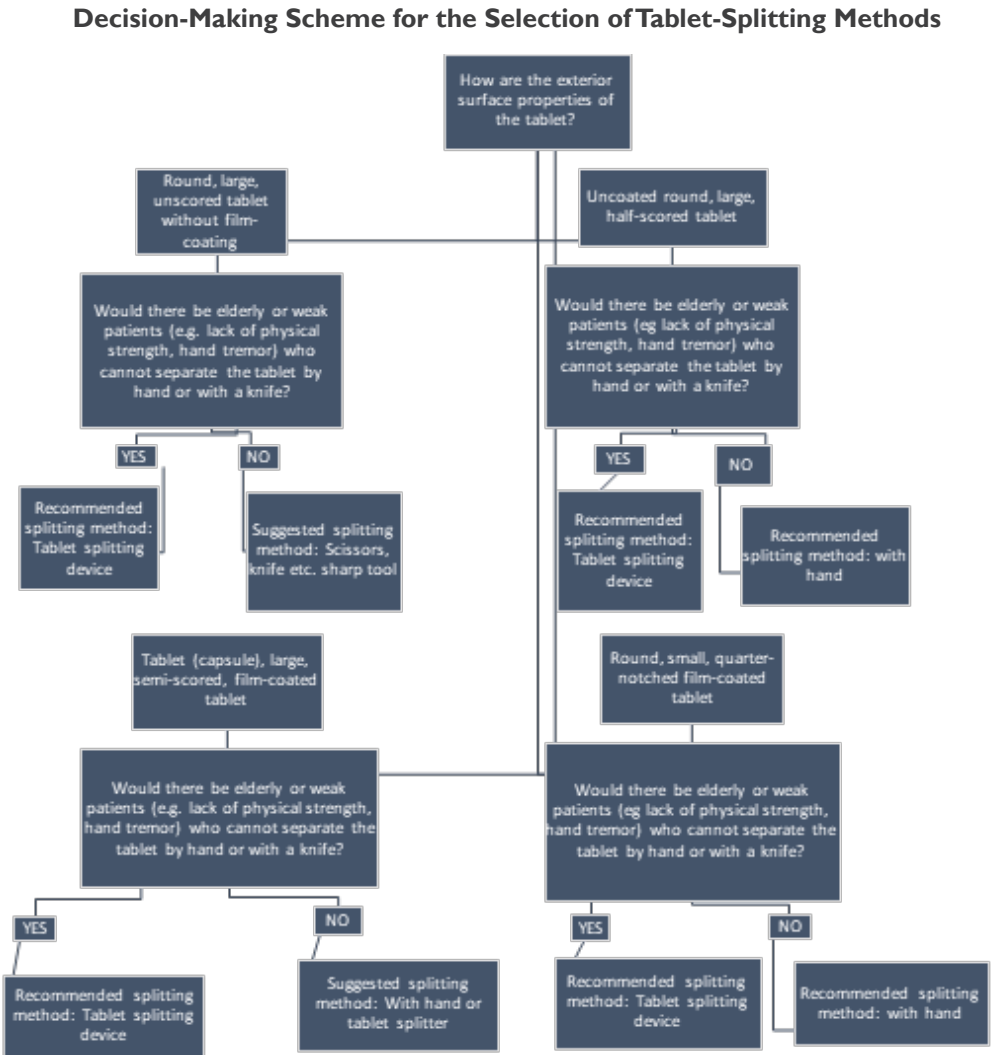

The scheme is adapted from reference no.[35]

Clinical results of taking split-crushed tablets

Although clinical research on tablet splitting is limited, most of the available data relate to cholesterol-lowering drugs, antihypertensives, and psychotropic drugs. In the retrospective study of Duncan et al., in 109 patients using simvastatin and atorvastatin, it was investigated whether the use of these drugs by splitting had an effect on low-density lipoprotein (LDL) and total cholesterol values. According to the laboratory results of the patients, it has been reported that the use of tablets in split form does not have a negative effect on blood parameters and that the same dose of crushed tablet or whole tablet intake has the same efficacy and safety.[2] Additionally, there are studies reporting that splitting-crushing tablets do not make any difference in total cholesterol and triglyceride levels.[15]

In a study conducted in 2002, taking simvastatin, lovastatin, and atorvastatin after splitting them were evaluated in terms of blood parameters, and when the laboratory values before and after taking these drugs after splitting or crushing the tablets were examined, it was shown that the use of tablets in split or crushed forms did not cause a significant change on the lipid values and blood parameters of the patients.[15] In another study involving 3787 patients, it was also demonstrated that splitting-crushing simvastatin tablets did not make a significant difference in low-density lipoprotein cholesterol levels or the incidence of increased transaminases compared to the outset.[36] The clinical effects of splitting-crushing tablets were evaluated in a study conducted on 29 patients using antihypertensive lisinopril. It has been shown that the use of splitting-crushing tablets did not cause any significant changes in the systolic and diastolic blood pressure values of the patients.[37]

Discussion

In a recent study, it is reported that using a tablet splitter is more successful than splitting by hand, cutting with a cutting tool such as scissors or a knife. If the main purpose of breaking-splitting the tablets is to treat the patient with a lower dose, the accuracy of breaking-splitting is very important. However, if the aim is to break-split the tablet to a patient who cannot swallow the tablet whole, and if the tablet does not exhibit sustained-release properties and/or is not enteric-coated, the patient's compliance and the continuation of the treatment should be considered rather than the accuracy of breaking-splitting. In this respect, there is no harm in using uncoated or film/sugar-coated tablets, which do not have pharmacokinetic

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effectiveness, by breaking-splitting them in patient groups who have difficulty swallowing the tablet as a whole.[38]

Breaking-splitting of drug products with carcinogenic (e.g. tamoxifen; methotrexate) or teratogenic (e.g. valganciclovir) potential; hormones (oral contraceptives; hormonal replacement therapy), corticosteroids (such as dexamethasone), and certain other drugs (finasteride; mycophenolate) will pose a risk to patients, patient relatives or health professionals with their powder aerosolization, and therefore, the use of such drug products by breaking-splitting should be avoided. Additionally, splitting-crushing drugs with known skin irritating properties such as diflunisal, isotretinoin, piroxicam, and ganciclovir is not recommended.[39–42]

Splitting-crushing use of drugs in tablet form may also cause adverse effects on the stability of the active substance. For example, if an enteric-coating that protects the active substance from the acidic environment is removed by breaking-splitting the tablet or crushing it, the drug efficacy will be reduced due to active substance being affected from stomach acidity. For this reason, it is very important for the success of the treatment that enteric-coated tablets are not used by breaking, splitting or crushing. In addition, drugs that are sensitive to light such as Nifedipine should not be used by breaking, splitting or crushing. However, there are case reports of severe hypotension associated with the use of crushed extended-release nifedipine tablets.[41]

Drugs with narrow therapeutic windows, such as phenytoin, digoxin, carbamazepine, theophylline, or sodium valproate, should not be used by breaking or splitting because of the risk of side effects.[40,43] Some drugs are covered with special coatings due to their irritating effects on the gastrointestinal tract. For example, drugs such as nitrofurantoin, potassium chloride, alendronate, diclofenac should not be used by breaking or crushing, as they may cause irritation or ulceration of the esophagus or stomach.[41]

For drugs with a bitter taste, a coating (sugar/film) is often used to help mask the taste of the active ingredient. For example, drugs such as propiverine, ibuprofen, cefuroxime axetil, ciprofloxacin, pseudoephedrine, and praziquantel or quinine are coated with a thin film of sugar to mask their bitter taste or unpleasantness to facilitate swallowing. The drugs in this group can be used by splitting and crushing into smaller pieces in order to facilitate swallowing in terms of size. In terms of bioavailability and pharmacokinetics, there is no harm in consuming drugs with this structure by breaking and splitting.[41]

Sertraline is known to have an anesthetic effect on the tongue; it should be noted that patients may be aware of this effect if the sertraline formulation is given in crushed form or in powder form.[44] If the active ingredient tablets of alfuzosin, carvedilol, nifedipine, or ramipril are crushed, patients are recommended to monitor blood pressure because of the risk of hypotensive effects. Monitoring of patients' blood glucose levels is also recommended if oral dosage forms of tablets containing glibenclamide, gliclazide, or metformin are also crushed or opened.[44]

Extended-release products, usually symbolized by abbreviations such as CR, ER, LA, SR, XL, or XR, developed to produce a constant plasma drug concentration despite small increases or decreases in drug concentration throughout the time the drug is released, are usually formulated in a way to release the active substance within 12 to 24 hours. The use of extended-release tablets or tablet forms with coatings applied to change the release rate of the drug by splitting-crushing is not recommended as it may cause changes in release rates.[41,45,46] In addition, a case report of recurrent chest pain and nausea along with ECG findings showing the presence of ischemic changes due to the use of crushed isosorbide mononitrate tablets with sustained-release properties has also entered the literature.[47]

Enteric-coatings on tablets are used to ensure that the tablets remain intact in the stomach while exhibiting effectiveness at a more alkaline pH of the small intestine compared to the stomach. Enteric-coatings can be applied to tablets to delay the release of drugs (pancreatin; erythromycin; omeprazole) caused by acidic stomach contents, to prevent irritation of the gastric mucosa (Acetylsalicylic acid; diclofenac; naproxen; corticosteroids), or to delay the onset of drug effectiveness. The use of enteric-coated tablets by breaking, splitting, or crushing may cause too early release of the active substance, destruction by gastric acid, or damage to the gastric mucosa. For this reason, the use of tablet forms with enteric-coated and extended-release formulations by breaking-splitting or crushing is not recommended.[41]

Sublingual and buccal tablets allow a drug substance to be absorbed directly across the mucosal membrane, resulting in rapid increases in drug concentration in the blood. This method of drug distribution also prevents first-pass metabolism in the liver. Since the use of such tablet forms by breaking, splitting or crushing may change the pharmacokinetics and bioavailability of the drugs in this form, any manipulation is not recommended in these tablet forms.[48]

In the light of a patient's needs and in order to increase the patient's compliance with the treatment, it is appropriate in terms of drug efficacy and patient safety to break, crush, open, or split uncoated tablets, film-coated tablets, sugar-coated tablets, or immediate-release capsules. Since physical manipulations on these tablet forms will not cause a change in bioavailability and pharmacokinetic data, they can be taken safely.[44,49] For example, crushing and co-administration of film-coated telithromycin tablets with a nutritional supplement beverage have been found to be bioequivalent.[50]

When splitting or breaking uncoated tablets, film-coated tablets, sugar-coated tablets, or immediate-release capsules by hand or by means of a device, it can often be observed that more than one tablet piece is not the same size and can vary in weight is obtained. This can be very important if only a portion of the drug dose is to be administered, but does not pose a risk to treatment efficacy and safety if the goal is only to assist a patient who cannot swallow a tablet whole.[51–54]

Conclusion

In the light of a patient's needs and in order to increase the patient's compliance with the treatment, uncoated tablets, film-coated tablets, sugar-coated tablets are suitable for use in terms of drug efficacy and patient safety by breaking, crushing, splitting, or opening immediate-release capsules. Physical manipulations on drugs with these coating properties do not cause any change in bioavailability and pharmacokinetic data.

The use of uncoated tablets, film-coated tablets, sugar-coated tablets, or immediate-release capsules by splitting or crushing the tablets is an effective and safe application that increases patient compliance. For example, propiverine, ibuprofen, cefuroxime axetil, ciprofloxacin, pseudoephedrine, and praziquantel or quinine are coated with sugar or film to facilitate the swallowing of the drug in

terms of taste. Medicines of this nature can be used by splitting or crushing into small pieces to facilitate swallowing in terms of size. In terms of bioavailability and pharmacokinetics, there is no harm in consuming drugs with this structure by breaking-splitting.

With tablet splitting, the cost of treatment can be reduced, and it can also increase patient's compliance with their drug regimens. As a result, unnecessary emergency room visits or hospitalizations can be reduced by preventing non-compliance with the treatment that may develop due to the inability to swallow the drug. Sustained-release drug products, enteric-coated tablets, tablets that are small in size, easily fall apart, or cannot be split in proportion due to having a brittle form, tablets with a narrow therapeutic window and short half-life are not suitable for splitting use. From a pharmacokinetic point of view, the split use of such tablets may increase the risk of side effects or change their effectiveness.

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Conflicts of interest

Gokhan Faikoglu, Kubra Saygisever-Faikoglu and Fatmanur Otmar Ozcan are medical advisors of Recordati.

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