Summary

This report lists 94 publications on clinical and pharmaceutical aspects of the splitting or breaking of tablets and similar dose forms. It does not address tablet splitting purely as a cost-saving measure, or issues related to the crushing of tablets.

The bibliography is based on searches of the National Electronic Library for Medicines (NeLM), Medline, Embase, CINAHL and Google Scholar, and references cited in retrieved papers, without restrictions of language, and lists retrieved papers in alphabetical order by author, with a summary and a link to the original publication in each case.

A synopsis attempts to provide a general overview of the main themes which emerge. It may be concluded that the uniformity of tablet segments depends on a wide range of variables, involving the composition, manufacture and scoring of the tablet, the means used to divide it and the ability of the person carrying out the division. For drugs with a wide therapeutic range and long half-life, lack of uniformity may not be a problem, but in other cases it may become critical.

Assessment of the safety of tablet splitting should be assessed on a case-by-case basis. It cannot be assumed that versions of a particular tablet from different manufacturers will behave identically when broken, or that scored tablets are necessarily suitable for splitting.
Synopsis

Rationale for tablet splitting
In some countries – the United States, Canada and Germany, for example – it is a common practice to divide tablets as a cost-saving measure. The pricing structure, patient co-payment arrangements and drug dispensing and packaging practices which make tablet splitting economically attractive in those countries differ from those in the United Kingdom, and so this bibliography does not consider tablet splitting purely as a cost-saving measure. However, there may be other reasons for dividing tablets. For example, when adjusting the dose of an oral medicine according to the patient’s weight or some other characteristic, dosage forms of the appropriate strength may not be available on the market, and in such cases it may be appropriate to subdivide a standard tablet. This occurs frequently with medicines for children (and for small animals in veterinary practice). This is sometimes done unnecessarily; a study of prescriptions for tablet formulations in Sweden showed that 10% would require tablets to be split, but in more than 80% of these, it would have been possible to avoid splitting by combining existing licensed strengths of tablet. It has been suggested that in some instances it may be more appropriate to use another dosage form, such as a liquid formulation. Also, a study in the Netherlands found a substantial amount of tablet division by patients on their own initiative, because they wanted to take a lower dose or found smaller fragments easier to swallow.

Effect on outcomes
Although there are theoretical dangers arising from non-uniform division of tablets, the limited evidence available suggests that these are not important in practice, at least for drugs with a wide therapeutic range and long half-life being taken long-term. A study of 3787 patients on uniform simvastatin doses in the US Veterans Administration system showed that conversion to tablet splitting did not have any adverse impact on LDL cholesterol levels or patient compliance, supporting earlier results with simvastatin. Using split lisinopril tablets had no effect on blood pressure.

Effect on adherence
Reviews on this topic concluded that there was no evidence that tablet splitting adversely affected adherence, although evidence was limited as regards quantity and methodology.
A survey of splitting statin tablets in the US Veterans Administration found no adverse effect on patient satisfaction or adherence (as determined by patient questionnaire). Introduction of tablet splitting with individuals with schizophrenia or schizoaffective disorder, also in the US Veterans Administration, showed no apparent impact on adherence; an increase in unscheduled outpatient visits in the first 60 days after the implementation of splitting suggests that patients may have experienced minor difficulties early on. On the other hand, another study in the USA investigated the use of financial incentives to persuade members of a health plan to split their tablets and found that a reduction in their co-payment of at least half would be needed.

Occurrence
A previously cited study in Sweden showed that 10% of the prescriptions examined required tablets to be split. In a survey in general practice in Germany, about 24% of prescriptions required tablets to be split, and about one-eighth of these involved tablets that should not be split. An analysis of prescriptions for statins in British Columbia, Canada, from 1996 to 2006 found that an average of 2.6% involved splitting tablets. The percentage increased over time, reaching 4.6% in 2006, and there were also differences...
between individual statins, and between prescriptions by GPs and by specialists. Tablet splitting is said to be a frequent practice in elderly care homes in Canada\textsuperscript{23}.

**Methods of splitting**

Tablets can be split by hand or using scissors, a knife or razor blade\textsuperscript{76} or a splitting device\textsuperscript{10}. There are many designs of device on the market, and numerous patents have been filed in this area. One important design consideration is that the tablet is held firmly in position during cutting. Results comparing the different methods are mixed, although in some tests a table knife\textsuperscript{5,75} or even hands\textsuperscript{20} have proved more effective than a purpose-designed tablet splitter. Scissors seem to be least satisfactory. Probably, the splitting method interacts with the various tablet-related factors which may affect splitting behaviour – size, shape, presence and type of scoring, hardness and composition. A few studies have used sophisticated techniques to investigate tablet microstructure with a view to predicting breaking properties\textsuperscript{70,71,80,81}.

One study\textsuperscript{38} found that some split tablets were less stable than complete tablets, and it is suggested that tablets should not be split until they are to be used. However, no stability problems were found in an investigation of broken levothyroxine tablets\textsuperscript{67}.

**Patients’ problems in performing splitting**

Dividing tablets using any of the above methods will require some combination of manual strength and dexterity and good eyesight. Elderly patients have been found to be much less able to break tablets than younger patients\textsuperscript{5} and caution is advised with such patients\textsuperscript{27,49}. Patients in the Netherlands were found to experience a number of problems with breaking tablets\textsuperscript{60}.

**Information provision**

A survey showed that for a substantial proportion of scored tablets the official medicines information sources did not indicate whether splitting was safe. A proportion of scored tablets were not suitable to be split, on the basis of either the SPC/package insert or replies to enquiries to the manufacturer\textsuperscript{5}.

At a hospital in Germany, a computerised decision support system was found to reduce the incidence of inappropriate tablet splitting (tablets with no score lines or those with enteric or modified-release coatings)\textsuperscript{57}.

**Some regulatory considerations**

The European Pharmacopeia (EP) currently applies accuracy of subdivision standards for scored tablets, and has at various times also included standards for content uniformity, weight variation and loss of mass, while the United States Pharmacopeia (USP) proposed criteria for loss of mass and accuracy of subdivision for split tablets in 2009. The US Food and Drug Administration has regarded splitting tablets as an atypical practice which is outside the scope of regulation, but in the light of complaints and confusion from patients and pharmacists, it has moved towards regulation and in March 2013 published guidance for industry\textsuperscript{94}. It is intended to define “functional scoring“ of tablets\textsuperscript{77}. The FDA has also ruled that the production of split tablets by a company on a large scale is a manufacturing operation which is required to comply with the relevant quality standards. However, the FDA ‘generally would not object to tablet splitting if it is performed by a pharmacist pursuant to a valid prescription for an individually identified patient’\textsuperscript{77}.

**Uniformity of segments**

Considerable research has been conducted over the last 30 years in this area\textsuperscript{14,22,24,28,30,31,33,41,44,72,73,74}, albeit with rather variable results. One study\textsuperscript{36} found variation to be so great that the authors advised against splitting tablets of drugs with a narrow therapeutic range.
A study in Belgium showed a loss of weight and inequality of the two halves when tablets were split using scissors or a kitchen knife, rather less when a purpose designed splitting device (Pilomat) was used.\textsuperscript{83,84}

A study in the USA showed that nearly a quarter of tablets split by 4th-year pharmacy students using a tablet splitter had drug contents that would have been outside USP limits.\textsuperscript{32}

However, another study showed that although four out of twelve products split by a pharmacy student using a tablet splitter failed the weight-uniformity test, weights were generally within 20% of target, which might not present problems in practice.\textsuperscript{51}

Some features of proprietary tablet cutters probably make for greater accuracy (claimed for the Tru-Cut Multi-Tablet Cutter, Links Medical Products, Irvine, CA, USA, for example),\textsuperscript{45} compared with other devices.\textsuperscript{44}

In the case of metoprolol succinate extended release tablets examined by the FDA using near infrared imaging, the controlled release pellets were found not to be uniformly distributed through the tablet, explaining the observed large variation in split tablet weights and content uniformity.\textsuperscript{93} These results contrast with those at the university of Sarajevo, where it appears that adequately designed score lines permit CR metoprolol tablets to be split.\textsuperscript{85}

For captopril/hydrochlorothiazide tablets, those from one manufacturer yielded uniform segments while another manufacturer's product did not.\textsuperscript{37} It has been suggested that such differences between producers are likely to cause problems in the case of German insurance companies mandating generic substitution with a particular company's products.\textsuperscript{53}

An earlier study found that even unscored tablets could be cut accurately, whether with a splitting device or by hand,\textsuperscript{8} although this differed from other results at about the same time.\textsuperscript{14}

The type of scoring appears to be important.\textsuperscript{18}

Some research has also investigated not just whether the segments are of equal weight but whether they contain equal amounts of the active ingredient (i.e. whether this is evenly distributed throughout the tablet).\textsuperscript{32,67,86,92} The AccuBreak tablet\textsuperscript{28} has a drug-free zone around the division in an attempt to avoid this problem.

The importance of educating patients to divide tablets accurately has been emphasised\textsuperscript{50,64} and scored tablets are seen as less potentially problematic,\textsuperscript{68} although not all sources agree.\textsuperscript{73}

Even split tablets dispensed by pharmacists have been found to have an unacceptably high variability.\textsuperscript{62}

A number of in vivo or in vitro tests have been proposed to assess whether specific tablets can be broken into uniform parts.\textsuperscript{5,6}

**Dosage forms that should not be divided**

An experimental study of capsule splitting found about 75% of the dose in the base of the capsule and 25% in the top, and the authors advise against splitting capsules.\textsuperscript{9}

Theophylline sustained-release tablets were found to exhibit substantially increased release rates after division into halves\textsuperscript{35,52} and modified-release formulations in general should not be split. Enteric-coated\textsuperscript{46} and bilayer tablets should also be regarded with caution as regards splitting.

**Guidance**

Recommendations were made in 2004 by the American Pharmacists’ Association and in 2003 by the (US) Institute for Safe Medication Practices.\textsuperscript{34} In the past, the US Food and Drug Administration has advised consumers against splitting tablets where possible (FDA Consumer Health Information, July 2009). This concludes that tablet splitting may not have adverse clinical consequences and can reduce costs, but using a whole tablet is the safest way to ensure accurate dosing, and splitting tablets is not appropriate for all patients or all drugs.
References

1. Tablet splitting: evaluating appropriateness for patients. Tool for pharmacists from the 2003-2004 APhA Strategic Directions Committee
American Pharmacists Association
The idea of splitting tablets has centred on patients using a device to halve their drug costs. Health insurers in the USA are increasingly urging patients to buy higher-strength tablets and taking half at a time. In fact, some are offering free tablet splitters to anyone who accepts to do this voluntarily. But for some patients tablet splitting is not easy or voluntary. Cutting dosage forms into even doses can be tricky, particularly for those who are elderly. Further, promoting half tablets could tempt some patients to split other drugs that should always be taken whole. The American Medical Association and APhA formally oppose mandatory tablet splitting. Done correctly, splitting prescription tablets can save money. Done incorrectly, the practice can endanger patient health. The Strategic Directions Committee (SDC) reviewed the available literature and input from practitioners regarding the impact of the splitting of tablets on patient care. The SDC developed questions for pharmacists and decision makers to consider when evaluating the appropriateness of tablet-splitting for individual patients and products. The guidelines appear in this paper. The Committee also recommends that the US Food and Drug Administration and the United States Pharmacopeia study the splitting of tablets to provide data on the appropriateness of tablet splitting from a scientific basis.

2. Misleading score-lines on tablets: facilitated intake or fractional dosing?
Arnet, I, Hersberger, KE
Swiss Medical Weekly 2010;140(7-8):105-110
Question under study/principles: Scored tablets are often split to facilitate swallowing or to fractionate the dose. In the latter case, the fragments of the tablet should comply with the content or mass uniformity requirements of the European Pharmacopoeia. For health professionals the splitting information is expected to be in the Summary of Product Characteristics (SPCs), the package leaflets (PLs) or Hospital Drug Formularies. We investigated the accuracy of splitting statements in these three sources of drug information.
Methods: We selected the tablets mentioned as 'scored' in the Swiss Compendium Online and in the Drug Formulary of Basel University Hospital, and screened the corresponding SPCs and PLs for information on divisibility and fractional dosing. Missing information was obtained from the drug marketing licence holder.
Results: The Swiss Compendium Online contained 698 different scored tablets whose SPCs mentioned fractional dosing for 43.8% and explicitly forbade it for 2.7%. The Hospital Drug Formulary indexed 188 items as scored tablets. The corresponding SPCs mentioned fractional dosing for 107 (59.4%) and a sentence forbidding it for 5 (2.8%). The manufacturers' answers permitted fractional dosing for 49 (27.2%) of the remaining tablets and forbade it for 19 (10.5%). Lack of dosage uniformity or presence of 'historic decorative' score-lines were the reasons given.
Conclusions: For the majority of scored tablets the official sources of drug information contained no explicit indication on fractional dosing. Improvement of splitting information is necessary to avoid potential medication errors.
http://www.smw.ch/docs/PdfContent/smw-12953.pdf
3. **Evaluation of the content of atenolol tablets divided with a domestic knife and a cutting device** (Avaliação do teor de atenolol em comprimidos divididos com faca caseira e aparelho cortador)

Auricchio, MT, Yano, HM, Santos, AP, Bugno, A


Objective: To evaluate whether the content of atenolol in fragments of 100mg, 50mg and 25mg tablets available on the Brazilian market, broken into four parts with the aid of a kitchen knife and a pill cutter is different, depending on how the division is performed.

Methods: The intact tablets were divided with a knife and with a pill cutter device, and the concentrations of atenolol were determined in all fragments.

Results: No significant difference existed between the levels of atenolol obtained after splitting the tablets with the domestic knife or the pill cutter device, although the division led to severe levels of dispersal among fragments. When divided in half, the dispersion of results was between 7% and 12.1%, and when divided into four parts, it was between 9.2% and 21.1%, indicating the possibility of compromising the effectiveness of treating patients regardless of how the division was made.

Conclusions: The results indicated a greater dispersion than would be acceptable to guarantee a uniform dose received at each drug administration, regardless of the way the division was performed, either by knife or pill cutter.


4. **The practice of splitting tablets: cost and therapeutic aspects**

Bachynsky, J, Wiens, C, Melnychuk, K


Background: Tablet splitting is used in pharmacy practice to adjust the dose to be administered. It is also being advocated as a method of reducing prescription drug costs.

Methods: The potential for using this practice as a cost-saving method was examined. The top 200 prescription products in Canada were evaluated for their potential for tablet splitting to reduce costs. The assessment was based on the dosage form (only tablets could be split), availability of dosages in multiples, whether the drug was used for long-term therapy, whether the product was packaged suitably (e.g. oral contraceptives in a therapeutic package), whether pricing structure would allow substantial saving, and the physical nature of the tablets (e.g. whether there were special dose-release characteristics). The products most commonly split in three Canadian pharmacies were compared with the products that had a substantial savings potential. Costs for splitting tablets in the pharmacy and costs of instructing patients to split tablets were calculated.

Results: Savings could be generated from tablet splitting for only 15 of the 200 products. There was little overlap between these 15 products and the products that were most frequently split in the three pharmacies. The costs associated with tablet splitting in the pharmacy were approximately Can$ 0.1 per tablet. The cost of instructing a patient to split the tablets was approximately Can$1.

Conclusions: Tablet splitting appears to have limited usefulness as a cost-reduction strategy. Only a small proportion of products are suitable for splitting and have the potential for savings. There are also costs arising from splitting tablets in the pharmacy, or instructing patients to do so, and from wastage of product. There are also issues such as patient compliance and the risk of an incorrect dose being taken that should be considered.

5. Development of an in vivo test procedure for the ease of breaking of scored tablets
Barends, DM, Groot, DW, Frijlink, HW, Rodenhuis, N, van der Steen, JC
An in vivo test for ease of breaking of scored tablets was developed. Scored tablets covering a wide range of dimensions, type of break-mark and ease of breaking were used as training set. Test panels of healthy volunteers (25-61 years old), and panels of elderly (mean age 75 years or older) were used. Five different test procedures were investigated. Subjective assessment of ease of breaking appeared more cumbersome than objective scaling in 'breakable' and 'not breakable'. Elderly were far less able to break the tablets than healthy volunteers. So, healthy volunteer panels are not a good substitute for the 'worst case' patients situation. A test procedure is proposed specifying that not less than 80% of a panel of elderly (mean age 75 years or older and none younger than 65 years old) must be able to break the scored tablet, with a confidence of not less than 90%.

6. Results of a market surveillance study in the Netherlands on break-mark tablets
Barends, DM, Groot, DW., van der Steen, JC, de Kaste, D, Frijlink, HW
Pharmeuropa Scientific Notes 2006;(2):1-7
A representative market surveillance study on break-mark tablets for human use, having a marketing authorisation (MA) in The Netherlands (NL), was carried out. The uniformity of mass of subdivided break-mark tablets into halves was assessed according to Ph.Eur.5.5, now current; and for comparison also according to Ph.Eur.4.1 (no longer in force) and Pharmeuropa 16.2. The compliance was 24%, 14% and 45%, respectively. The compliance with a criterion for loss of mass by subdivision of break-mark tablets (1.0% or less of the total mass) was 86%. The compliance with a criterion for ease of subdivision of break-mark tablets (80% or more of a panel of elderly able to break, 90% or higher probability) was 34%. Of the 29 tablets studied, 5 complied with all criteria, amongst which were all three oblong tablets that were included in the study. The Summary of Product Characteristics (SmPC) of the tablets was independently evaluated by experts to assess whether their break-mark was needed for the posology. The experts came to a uniform conclusion for only 66% of the tablets. It is concluded that the proposed test procedures for ease of subdivision and loss of mass by subdivision are workable, that the proposed criteria are reasonable and that their inclusion in Ph.Eur. can be considered. From a pharmaceutical-technological point of view, the requirements of Ph.Eur. 5.5 Subdivision of tablets for uniformity of mass of subdivided tablets, and the proposed criteria for ease of subdivision and loss of mass, are all simultaneously attainable. It is also concluded that the majority of the break-mark tablets with a MA in NL do not meet the requirements of Ph.Eur.5.5 Subdivision of tablets, and that they do not fulfill the proposed criterion for ease of subdivision. This is expected to also be the case in other countries. It is proposed that the test Ph.Eur. 5.5 Subdivision of tablets should give instructions on how to handle tablets that cannot be broken, or that crumble upon subdivision. It is also proposed that the criteria Ph.Eur. 5.5 Subdivision of tablets should not be restricted to break-marks needed for the posology, as dosing instructions in SmPCs are open to different interpretations, and that this restriction should be deleted.

7. Dosages involving splitting tablets: common but unnecessary?
Berg, C, Ekedahl, A
Objectives: Prescribing of treatments with dosages involving split tablets is common. Many patients report they have difficulties in dividing the tablets and in following the prescribed treatment. The objective of this study was to examine to what extent dosages involving split tablets are prescribed in Sweden.

Methods: The dosage text strings were analysed on prescriptions dispensed during 1 month at Swedish pharmacies on all tablet formulations for beta-blockers, calcium blockers, ACE inhibitors, angiotensin receptor blockers (ARBs), lipid-lowering agents, levothyroxine, neuroleptics, anxiolytics, hypnotics/sedatives and selective serotonin reuptake inhibitors (SSRIs). Numbers and percentages of prescriptions with split tablets were compared with all dispensed prescriptions.

Key Findings: 600,000 prescriptions on tablet formulations for the investigated drugs were dispensed. 10% of the prescriptions had a dosage where tablets have to be split. Hypnotics and SSRIs had the highest proportions, accounting for 22 and 19% of prescriptions involving split tablets. SSRIs constituted 30% of the prescriptions with split tablets. Dosages with split tablets varied with drug across patient age but not across gender. In 45% of the cases with levothyroxine and SSRIs, a tablet strength fitting the prescribed dosage was licensed and available. Furthermore, it would have been possible to avoid splitting tablets by adjusting and combining existing licensed strengths for more than 80% of the prescriptions.

Conclusions: Prescribing of dosages involving the splitting of tablets was common and constituted 10% of the prescriptions for tablet formulations. Many prescriptions on dosages with split tablets can be avoided if physicians adjust prescribing to licensed and available strengths fitting the prescribed dosages.


8. **Accuracy of splitting unscored valdecoxib tablets**
Boggie, DT, DeLatre, ML, Schaefer, MG, Morreale, AP, Plowman, BK
*American Journal of Health-System Pharmacy* 2004;61(14):1482-1483

Splitting unscored valdecoxib tablets by hand or with a tablet splitter (model 70028, Apex Medical Corp., South Dakota, USA) resulted in consistent half-tablet weights, with the tablet splitter giving slightly fewer half tablets outside USP limits, compared with hand splitting. The authors comment that valdecoxib has a long half-life and high therapeutic index. They advise caution when splitting tablets for agents with short half-lives or low therapeutic indexes, because even slight variability may affect clinical outcomes. Also, different drugs, and different brands of a drug, may vary in relevant pharmaceutical characteristics, and consistent splittability across products should not be assumed. (7 refs.)

http://www.ajhp.org/content/61/14.toc

9. **Oral medication administration: implications caused by capsule splitting**
Caldwell, SM, Raitt, JR
*Journal of the American Pharmacists Association* 2010;50(4):532-533

Objective: To demonstrate that capsule splitting does not result in an equal quantity of drug in both parts of the capsule, affecting the dosage of the drug.

Design: Descriptive non-experimental study.


Intervention: At varying times, three student pharmacists (two from the University of Maryland and one from Creighton University) filled and packed 62 capsules ranging in size from No 4 to No 000 using bulk powder. Each capsule was weighed and then split. The capsule split was also weighed, as well as the amount of powder found in each portion of the capsule. Statistical analyses were performed, including t-test, standard error and relative error.
Main Outcome Measure: Whether after splitting a capsule the top of the capsule supplies less of the drug and the base of the capsule more of the drug, leading to non-weight uniformity of splitting capsules.

Results: The weight of the base of the capsule powder was always more than the weight of the top portion of the capsule. Capsule size No 1 showed the most deviation and capsule size No 4 the least deviation between the top and bottom of the capsule.

Conclusions: Capsules should not be ordered to be split because the base of the capsule holds more of the drug powder than that of the top of the capsule. This study infers that the patient would receive approximately 75% of the dose when given the base of the capsule and about 25% of the dose when given the top of the capsule.


10. The tablet splitter: barrier to compliance or cost-saving instrument?
Carr-Lopez, SM, Mallett, MS, Morse, T
American Journal of Health-System Pharmacy 1995;52(23):2707-2708
Brief report on this topic. Commercially available tablet cutters should increase the accuracy of tablet splitting, but these devices require a degree of manual dexterity in loading the tablet.
http://www.ajhp.org/content/52/23.toc

11. Using a data warehouse to monitor clinical outcomes associated with simvastatin tablet splitting
Coblio, NA, Mowrey, KA, Ford, V
Hospital Pharmacy 2004;39(8):758-764
The results of this initiative showed that tablet splitting is an effective mechanism for cost saving. A data warehouse is a useful tool for ensuring that therapeutic outcomes are not sacrificed to save money. It appears that concern about tablet splitting is most warranted during initial stages of converting patients from whole to half tablets. (19 refs.)
http://thomasland.metapress.com/content/121650/?sortorder=asc

12. Impact of patient financial incentives on participation and outcomes in a statin pill-splitting program
Choe, HM, Stevenson, JG, Streetman, DS, Heisler, M, Standiford, CJ, Piette, JD
American Journal of Managed Care 2007;13(6-Part 1):298-304
Objectives: To examine willingness to participate in a pill-splitting programme and the impact of pill splitting on patients’ adherence and lipid control.
Study Design: Nested randomised trial.
Methods: A total of 200 patients who used statins and were candidates for a pill-splitting regimen were identified from a large university-based health plan in the USA. 63% of study participants were female, 41% were nonwhite, and 94% had at least some college education. Patients were surveyed regarding their willingness to split pills, and 111 consented to participate in a 6-month trial in which half were randomised to receive a financial incentive to split pills: a 50% reduction in their per-refill copayment. Data on patients’ statin refills and lipid control were obtained from billing and medical records.
Results: Compared with patients unwilling to participate in the programme, those agreeing to split pills were more likely to be female and white. After 6 months, most patients in the trial (89%) were willing to continue pill splitting for a 50% copayment reduction. Patients reported few problems with pill splitting and had no noticeable change in their adherence. The financial-incentive group and the control group did
not differ significantly with respect to their low-density lipoprotein cholesterol levels after pill splitting: -2.0 mg/dL and -1.2 mg/dL, respectively.

Conclusions: Most patients indicated that at least a 50% copayment reduction would be required to enroll in a pill-splitting programme after the study ended. However, in this relatively educated population, financial incentives did not influence patients’ adherence, satisfaction or health outcomes.

13. **Tablet splitting: imperfect perhaps, but better than excessive dosing**
Cohen, JS
A viewpoint article reviewing the practice of tablet splitting. (15 refs.)

14. **Variability in tablet fragment weights when splitting unscored cyclobenzaprine 10 mg tablets**
Unscored cyclobenzaprine hydrochloride 10mg tablets from one generic manufacturer were split with a tablet splitter or a kitchen knife by a pharmacist and 2 doctor of pharmacy students (n = 15 tablets for each method per participant).
Concludes that splitting cyclobenzaprine 10mg tablets to achieve 5mg doses could result in unpredictable dosing and therapeutic response.
http://japha.org/data/Journals/JAPhA/20411/10.1331_1544-3191.44.5.583.Cook.pdf

15. **The paradox of scored tablets: a cost saving risk**
De Spiegeleer, B, Van Hoorebeke, L, De Spiegeleer, A, Castelein, B, van Bortel, L
*Pharmazie* 2009;**64**(8):550-552
One of the cornerstones of pharmacotherapy is the proper dose of medicine, which should ideally be tailored to the individual patient. However, even if clinically possible, this is economically not feasible as an excessive number of different dosage strengths would be required. Therefore, a balance is required between the patient's benefit/risk and the cost to the individual and society on the other hand. Scored or split tablets were, and still are, strategies that are often used to achieve these opposing aims, enabling more dose flexibility, but also at the same time increasing dose variability as a consequence of the breaking process. The question of how to deal with this paradox was investigated by exploring the prevalence and classification of scored tablets as well as the cost-benefits. A strategy for clinical pharmacologists is presented to improve the outcome of this paradox.
http://pharmazie.govi.de/contents_0809.htm

16. **Splitting antidepressant medications: more studies are needed to confirm clinical outcomes and potential savings**
Donoghue, J
*CNS Drugs* 2002;**16**(5):359-360
Editorial commenting on a paper in this issue by Cohen and Cohen.

17. **Frequency and predictors of tablet splitting in statin prescriptions: a population-based analysis**
*Open Medicine* 2008;**2**(3):e74-e82
Background: The price per milligram for most statin medications decreases at higher strengths, which provides an economic incentive to split tablets. We sought to determine the frequency with which statin tablets are split, and to evaluate factors associated with this practice.

Methods: We obtained prescription claims data for statins from the British Columbia (Canada) Ministry of Health for the period 1 Jan 1996 to 31 Dec 2006. We estimated the number of tablets per day, based on the ratio of the number of tablets to days-supply in each prescription, to estimate the frequency with which splitting occurred with each statin. We used multivariable logistic regression to assess patient and physician characteristics and the level of public drug plan coverage associated with tablet splitting. To estimate related cost savings, we used information on drug costs and quantities of dispensed statins reported by pharmacies.

Results: During the 11-year study period, we estimated that tablet splitting occurred in 2.6% of 7.2 million statin prescriptions. There was an increasing trend in the practice over time, to 4.5% of prescriptions in 2006. Lovastatin was the only scored tablet and was the most likely to be split, followed by rosuvastatin and atorvastatin. 50% of the prescriptions in which tablet splitting occurred were prescribed by only 7.9% of the routine statin prescribers (i.e. more than 10 statin prescriptions over the study period). Specialists were less likely than general practitioners to prescribe statins that were subsequently split (odds ratio (OR), 0.43; 95% CI, 0.40 to 0.46). Statin prescriptions that were fully covered by the public drug plan were half as likely as those with no such coverage to involve tablet splitting (OR, 0.48; 95% CI, 0.44 to 0.92). Having no public drug coverage, having a low annual household income and being female were patient factors found to be positively associated with tablet splitting. In 2006, the cost savings associated with tablet splitting was $2.3 million.

Interpretation: The frequency of tablet splitting in statin prescriptions in British Columbia was low but increased over time. It varied between patients, physicians and different levels of insurance coverage. In the final study year, 94.5% of the statin prescriptions were dispensed at strengths for which a tablet of twice the strength was available and could have been split, which suggests a potentially enormous cost saving.


18. Effect of scoring design on the uniformity of extended release matrix tablet halves
Duman, E, Yuksel, N, Olin, B, Sakr, A
Pharmazeutische Industrie 2000;62(7):547-550

API030611 is an anti-anxiety agent that needs to be titrated/adjusted relative to patients' responses and tolerances. The research objective was to evaluate the effect of scoring design on weight and content uniformity and dissolution of the extended release matrix tablet halves. Various scoring designs of capsule shaped tablets were evaluated. Ten subjects varying in age, weight and gender broke the scored tablets in the same way as in normal life. Certain scoring designs produced qualitatively more uniform tablet halves; there were no statistical differences due to scoring design, age, weight and gender. The most reproducible tablet halves were produced using the design of top and bottom scoring, independent of the type (deep or shallow) of scoring.

19. Effect of tablet splitting on serum cholesterol concentrations
Duncan, MC, Castle, SS, Streetman, DS

Retrospective chart review of total cholesterol and LDL cholesterol values of 109 patients (mean age 64.7yr) instructed to split simvastatin or atorvastatin tablets at a
US Veterans Affairs medical centre. Half-tablet dosing appeared to be at least as effective as whole-tablet dosing. (13 refs.)

http://www.theannals.com/content/36/2/205.abstract

20. Evaluation of split tablets of cardiovascular medicines
El-Baseir, M, Bsir, HEL

Introduction: The ability to adjust doses to individual patient depends on the availability of multiple dose sizes and adequate dose response information. These are not always provided, so splitting of tablets is sometimes necessary. Tablet splitting is an accepted practice in dispensing medications to obtain appropriately-sized dosage units, however, the advantages, problems and performance of this method is still controversial. The aim of this work was to study tablet weight variability, deviation and loss after splitting with three commonly used methods.

Methods: Four volunteers with no previous experience in splitting were asked to split five tablets each of lisinopril 10mg, warfarin 5mg and three brands of captopril 25mg into halves and quarters using scissors, hands and a tablet splitter device. Intact tablets, halves and quarters were individually weighed on a precision mass balance and variation in weight was calculated using United States Pharmacopoeia (USP) criteria for tablets. Deviation in weight was calculated by subtracting the weight of each half and quarter from their theoretical weight. The weight loss was estimated by subtracting the weight of the two tablet halves or four quarters from the weight of the intact tablet. Statistical analysis was performed using the t-test with P values less than 0.05 considered significant for the difference in weight between tablet halves and using ANOVA one way to compare the differences in weight among quarters. Ethics committee approval was not required.

Results: The variation in the sample weight was high for halves and quarters as compared with the intact tablets for all the studied medicines. Relative standard deviation was less than 2% (1.5, 1.4 and 1.6) for intact tablets, more than 6% (21.2, 8.6 and 14.4) for halves and more than 15% (30.4, 17.2 and 21.2) for quarters using scissors, hands and a tablet splitter device. The percentages of tablet fragments deviating by more than 15% from the theoretical weight using scissors, hands and a tablet splitter device were 53% (108/200), 8% (16/200) and 28% (56/200) for halves and 58% (232/400), 37% (147/400) and 44% (176/400) for quarters. The associated tablet weight loss ranges after halving were 1-4%, 0-2% and 1-3% using scissors, hands and a tablet splitter device, which was doubled after splitting of tablets into quarters. Significant difference (P value of less than 0.05) in weight between tablet halves and among quarters was observed after splitting using scissors and the splitter device. However, no significant difference in the weight of tablet halves for two medicines and among quarters of one medicine was detected using the hands method.

Discussion: The results showed a wide weight variability among tablet halves and quarters compared to whole tablets with the three splitting methods. Deviation from the theoretical weight for tablet halves and quarters and the tablet weight loss after splitting were in the descending order of splitting methods as scissors > splitter device > hands. Although the hands method gave the best results, values obtained with this method were beyond the USP adopted criteria for tablets. Tablet splitting procedures could result in fluctuations in the administered dose that can be clinically significant especially for medicines with narrow therapeutic indices.

21. **Relationship between tablet splitting and compliance, drug acquisition cost, and patient acceptance**

Fawell, NG, Cookson, TL, Scranton, SS

*American Journal of Health-System Pharmacy* 1999; **56**(24):2542-2545

As managed care pharmacy continues to grow and medication costs increase, pharmacy managers are continually looking for ways to reengineer distributive services to provide the most cost-effective care. In an effort to save money, the San Diego US Veterans Affairs Healthcare System (SDVAHS) and other health systems have implemented tablet-splitting programmes targeted at high-cost and widely prescribed medications. Despite this growing practice, published research examining the effects on compliance rates, patient acceptance and actual cost savings is lacking. A recent computer-assisted literature search revealed only one study of tablet splitting that addressed patient compliance and acceptance. In that study, patients taking lovastatin and using a tablet splitter were mailed a questionnaire to assess their impressions of tablet splitting. A majority of the patients found tablet splitters easy to use and reported that compliance was not hindered. However, compliance was subjectively evaluated through patients' responses to questions; actual tablet counts were not performed. Furthermore, actual cost savings (if any) were not determined.

http://www.ajhp.org/content/56/24/2542.abstract

22. **Influence of splitting of furosemide tablets on dose uniformity** (Avaliacao do efeito da particao de comprimidos de furosemida sobre a uniformidade da dose)

Ferreira, AAA, Prates, EC, Fernandes, JPS, Ferrarini, M


In order to assess the uniformity of the dose of active ingredient in the halves of tablets subjected to splitting, the hardness, friability, weight variability and uniformity of content were studied in four samples of 40mg tablets of furosemide obtained on the Brazilian market, both whole and split into two parts. All the tablets complied with the official specifications before splitting, but, after this procedure, the drug content in the halves showed excessive variation, indicating that this procedure is inadvisable.

http://serv-bib.fcfar.unesp.br/seer/index.php/Cien_Farm/article/view/1220/1046

23. **Pill-splitting in a long-term care facility**

Fischbach, MS, Gold, JL, Lee, M, Dergal, JM, Litner, GM, Rochon, PA

*Canadian Medical Association Journal* 2001; **164**(6):785-786

Prospective study of 370 nursing home residents (Canada). Pill-splitting occurs frequently in long-term care facilities but also has implications for older adults still living in the community. Health professionals should be aware that pill-splitting may limit the efficacy of the medication prescribed. (8 refs.)

http://www.cmaj.ca/content/164/6/785.full.pdf+html

24. **Tablet splitting: a review of weight and content uniformity: Part 1 of a 2-part series**

Freeman, MK, White, W, Iranikah, M

*Consultant Pharmacist* 2012; **27**(5):341-352

Objective: To describe the product integrity and ethical/ legal issues associated with tablet splitting.

Data Sources: PubMed (1966-Jun 2011), International Pharmaceutical Abstracts (1975-Jun 2011) and bibliographic searches were conducted.

Study Selection: All studies that evaluated the weight/dose variations (N = 13) of split tablets were included.
Data Extraction: The American Pharmacists Association guidelines, recommendations from the Food and Drug Administration and clinical studies evaluating product integrity of split tablets were used to provide an overview of issues related to this practice. Legal considerations from various sources were also included.

Data Synthesis: The practice of tablet splitting is increasing and is associated with variations in drug distributions related to the tablet-splitting technique and other causes. The first part of this two-part series will evaluate the product integrity and practice-related issues associated with tablet splitting.

Conclusions: The majority of the studies associated with tablet splitting reveal large fluctuations in weight/dosage, but few studies evaluate variability with narrow therapeutic index medications. Therefore, the clinical impact of these variations is not globally applicable across medication classes. Although tablet splitting has the potential to save patients and health care organisations a significant amount of money, appropriateness of tablet splitting should be determined for individual medications and individual patients. Assessments should include an evaluation of patient understanding and physical abilities for tablet splitting.

http://ascp.metapress.com/content/q37854711354168m/?p=766037baf8124f749d94baeafc

25. Tablet splitting: a review of the clinical and economic outcomes and patient acceptance. Second of a 2-part series
Freeman, MK, White, W, Iranikhah, M
Consultant Pharmacist 2012;27(6):421-430

Objective: To describe the clinical outcomes, patient acceptance and economic effect associated with tablet splitting.

Data Sources: PubMed (1966 to Jun 2011) and International Pharmaceutical Abstract (1975 to Jun 2011) searches were conducted using tablet splitting as the search terms.

Study Selection: All studies that evaluated the clinical outcome (n = 4), patient acceptance (n = 5) and economic effects (n = 8) of tablet splitting were included.

Data Extraction: American Pharmacists’ Association guidelines, recommendations from the US Food and Drug Administration and clinical trial data were evaluated.

Data Synthesis: The majority of trials conducted to evaluate clinical outcomes associated with tablet splitting were in patients receiving statins and antihypertensives. Clinical outcomes associated with risperidone were also assessed. No adverse clinical outcomes were observed with therapy. Most studies evaluating the economic effects of tablet splitting have revealed cost savings associated with this process; however, many studies were subject to limitations. The first part of this two-part series reviewed the weight and content uniformity in tablet splitting.

Conclusions: Tablet splitting does not seem to affect clinical outcomes related to management of hypertension, cholesterol or psychiatric disorders significantly, nor influence overall patient adherence.

http://ascp.metapress.com/content/03667827730k88g4/?p=e20f149a74674258a9989da9b2d4cdc0&amp;pi=3

26. Effects of a tablet-splitting program in patients taking HMG-CoA reductase inhibitors: analysis of clinical effects, patient satisfaction, compliance, and cost avoidance
Gee, M, Hasson, NK, Hahn, T, Ryono, R
Journal of Managed Care Pharmacy 2002;8(6):453-458

Objective: The primary objective was to determine the effect of a hydroxymethylglutaryl-CoA reductase inhibitor (HMG) tablet-splitting programme on laboratory outcomes (lipid panel and liver enzyme tests). Other objectives were to
assess patient compliance and satisfaction with splitting tablets and to measure the reduction in drug acquisition costs.

Methods: Patients at a US Veterans Affairs Health Care System facility were included in this study if they participated in the HMG tablet-splitting programme between April and September 2000. Patients taking the same drug and dosage before and after implementation of the programme were asked to complete a mailed questionnaire designed to measure satisfaction and compliance with the programme. Data collected through electronic charts included patient demographics, prescribed medication and the values for lipid panel and liver function tests.

Results: A total of 2019 patients were included in the study. The total cost avoidance achieved over 1 year for atorvastatin, lovastatin and simvastatin was US$ 138,108 (N = 2019). The majority of patients who responded to the questionnaire were satisfied and compliant with tablet splitting. In the laboratory analysis (N = 512), there was no difference between pre-values and post-values for total cholesterol and triglycerides. There was a statistically, but not clinically, significant decrease in LDL (102 vs 97, P less than 0.001) and increase in HDL (46 vs 48, P less than 0.001), AST (26 vs 28, P less than 0.001) and ALT (24 vs 26, P = 0.006) after the initiation of tablet splitting.

Conclusions: Tablet splitting of HMGs had no short-term negative effects on laboratory outcomes and favourable effects on humanistic outcomes as measured by patient satisfaction and compliance. Tablet splitting of HMGs is an effective way to reduce costs and nearly double the number of patients who can be treated for the same expense.

http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=6686

27. **Crushing or splitting medications: unrecognized hazards**
Gill, D, Spain, M, Edlund, BJ
Journal of Gerontological Nursing 2012;38(1):8-12
Given the high use and the cost of medications in the current economy, one way older adults may save money on prescription costs is to split some of their medications in half. However, not all oral medications can be split. Splitting inappropriate medications such as extended-release tablets can be harmful and in some instances very dangerous. In addition to splitting medications, older adults who have difficulty swallowing pills may resort to crushing the medication for ease of administration. This option is also problematic and potentially harmful if the medication is not intended to be crushed. Clinicians managing the care of older adults need to discuss medication administration, clarify the dosing schedule, and clearly indicate the route of administration. Patients should be cautioned not to split or crush a medication without checking with the health care provider or pharmacist.

http://www.healio.com/Nursing/journals/JGN/{3C13C551-8FB5-4127-96CD-3AB8320DC24A}/Crushing-or-Splitting-Medications-Unrecognized-Hazards

28. **Pharmacopeial standards for the subdivision characteristics of scored tablets**
Green, G, Berg, C, Polli, JE, Barends, DM
USP Pharmacopeial Forum 2009;35(6):1598-1611
The practice of tablet splitting as a way to reduce prescription medication costs has become increasingly prevalent. The United States Pharmacopeial Convention (USPC) has no standards for the subdivision characteristics of scored tablets. Literature results show that many tablets on the US market exhibit unacceptable subdivision characteristics. The European Pharmacopoeia (EP) provides requirements for subdivision accuracy of scored tablets, if subdivision is indicated in order to comply with the product label. This Stimuli article provides a rationale for why standards should be included in USP to address the accuracy of subdivision, as well as to
account for loss of mass upon subdivision. We propose that for accuracy of subdivision current EP standards be adopted, applicable only to any tablet that bears a score mark. For loss of mass, we propose an average of 3% of the intact tablet mass. From data reported in the literature we estimate that as many as half of the scored tablets on the US market would be in compliance with these standards. Generally, we do not advocate such standards be tested on a batch-to-batch basis but rather that the testing should be conducted as part of the development process before marketing approval. We also discuss a third, related, quality attribute: ease of subdivision. Although future research and discussion in this area are warranted, we believe that not only should scored tablets break into accurate partial doses with minimal loss of mass, but also that the tablets should be breakable by a representative sample of the population, including the elderly.

http://www.usppf.com/pf/pub/data/v356/GEN_STIMULI_356_s200020.xml

29. **Accuracy and ease of splitting scored Coumadin, Lanoxin and Toprol XL Tablets**

Green, GA, Berg, C, Valdez, N, Kaplan, A
American Association of Pharmaceutical Scientists (AAPS) Annual Meeting, Los Angeles, 8-12 Nov 2009. Poster T2390

Purpose: To determine the ease and accuracy of manually splitting scored Coumadin (warfarin) (C), Lanoxin (digoxin) (L) and Toprol XL (metoprolol XL) (T) tablets by elderly patients.

Methods: 18 volunteers from an outpatient cardiology clinic attempted to manually split 5 scored tablets each of C, L and T. Each whole tablet (WT) was weighed on a precision mass balance and, after splitting, the 2 largest tablet fragments (TFs) were selected and similarly weighed. The TF weights were compared to the ideal half tablet weight to assess splitting accuracy. Patients were instructed to break each WT through the score mark without a 'practice split', and had a 30-60 second rest between groups of 5 tablets. Tablets of each brand were split in succession; however the order of the brands was random for each patient. Each splitting attempt was assessed as 'breakable' or 'unbreakable' and undesirable descriptive characteristics (UDCs) were recorded: 'uneven breaking', 'breaking into more than two pieces' and/or 'crumbling or powdering'.

Results: 12 females and 6 males between the ages of 62 and 85 completed the study. 15 patients (83%) experienced at least one unbreakable T tablet, compared to 5 patients (28%) for C tablets and 2 patients (11%) for L tablets. Of the breakable tablets, 39% of L TFs, 38% of C TFs and 9% of T TFs deviated by more than 15% from the ideal half tablet weight. The percentage that broke into uneven pieces, more than two pieces and/or with significant crumbling or powdering was 80%, 72% and 74% for L, C and T, respectively.

Conclusions: Split tablet accuracy results were relatively poor for C and L. T tablets split more accurately but nearly all patients experienced difficulty splitting. Although L was the easiest to break, it had the most UDCs upon breaking. The notion that the presence of a score mark facilitates easy and accurate breaking is invalid for C, L and T tablets. Caution should be exercised when instructing elderly patients to split medications due to the potential for unpredictable dosing, and regulatory standards relative to splitting accuracy should be considered for scored dosage forms. NB: The authors are from Accu-Break Pharmaceuticals, Inc. and note that 'new tablet technologies, known as Accu-Break, hves been developed that address this specific medical need. Accu-Break tablets have a drug-free layer within each tablet that is used as a break zone in the event a partial dose is desired.'

30. **Influence of tablet characteristics on weight variability and weight loss in split tablets**
Gupta, A, Hunt, RL, Khan, MA
*American Journal of Health-System Pharmacy* 2008;65(24):2326,2328

Experimental study to determine the effect of filler, binder, disintegrating agent, tablet hardness and presence of a score line on the splitting properties of verapamil HCl tablets prepared under otherwise identical conditions. Tablets were split using a safety shield tablet cutter (Apothecary Products, Inc., Burnsville, Minnesota, USA). Scored tablets exhibited a significantly lower mean weight variation and weight loss than unscored tablets. The filler and disintegrating agent also had a significant effect.

http://www.ajhp.org/content/65/24.toc

31. **Broken tablets: does the sum of the parts equal the whole?**
Gupta, P, Gupta, K
*American Journal of Health-System Pharmacy* 1988;45(7):1498

http://www.ajhp.org/content/45/7.toc

32. **Analysis of drug content and weight uniformity for half-tablets of 6 commonly split medications**
Hill, SW, Varker, AS, Karlage, K, Myrdal, PB
*Journal of Managed Care Pharmacy* 2009;15(3):253-261

Background: Cost savings can be achieved with the practice of tablet splitting. Previous research has shown weight nonuniformity within tablet halves. However, limited research to date has found that the potential dose inaccuracy resulting from splitting tablets does not significantly affect clinical outcomes.

Objective: To determine the drug content and weight in split half-tablets of 6 commonly split medications using drug assay analysis.

Methods: This study was performed by 2 fourth-year students at a US school of pharmacy using 30 randomly selected tablets of each of the following 6 medications: warfarin sodium 5 milligrams (mg), simvastatin 80 mg, metoprolol succinate 200 mg, metoprolol tartrate 25 mg, citalopram 40 mg, and lisinopril 40 mg. A randomly selected half of the tablets were split by a single pharmacy student using a Locking Tablet Cutter (Apothecary Products, Inc.), and the remaining tablets were kept whole. Drug content was analysed for 15 whole tablets and 30 half-tablets for each of the 6 drugs using HPLC. Drug content uniformity was assessed by comparing drug content within half tablets with one-half of the drug content mean found for all whole tablets in the sample. Weight uniformity was assessed by comparing half-tablet weights, as determined by a Mettler analytical balance, with one-half of the mean weight for whole tablets in the sample. The percentages by which each whole tablet's or half-tablet's drug content and weight differed from sample mean values were compared with proxy United States Pharmacopeia (USP) specification ranges for drug content (95%-105% for warfarin sodium and 90%-110% for the other 5 drugs). Additionally, these outcomes were compared for nonscored versus scored tablets. The percentage relative standard deviation (%RSD, ratio of the standard deviation to the mean), a commonly used measure of the repeatability and precision of assays used to analyse drug content, was also calculated in order to determine whether the drugs met proxy USP specification for %RSD (less than 6% for all drugs studied).

Results: A total of 43 of 180 half-tablets (23.9%) differed from sample mean values by a percentage that fell outside of proxy USP specification for drug content; warfarin sodium (11 of 30 half-tablets, 36.7%), simvastatin (3 of 30 half-tablets, 10.0%) metoprolol succinate (10 of 30 half-tablets, 33.3%), metoprolol tartrate (4 of 30 half-tablets, 13.3%), citalopram (5 of 30 half-tablets, 16.7%), and lisinopril
Half-tablets outside of proxy USP specification for weight included warfarin sodium (10 of 30 half-tablets, 33.3%), metoprolol succinate (6 of 30 half-tablets, 20%), and lisinopril (7 of 30 half-tablets, 23.3%). The %RSDs for drug content and weight fell outside of the proxy USP specification for %RSD for metoprolol succinate (drug content = 8.98%, weight = 7.70%) and lisinopril (drug content = 10.41%, weight = 8.13%). Mean percent weight loss after splitting was less than 1% for all drugs except lisinopril, which had an average weight loss of 1.25%. The total numbers of scored (nonscored) tablet halves that fell outside of proxy USP specification were 20 (23) for drug content and 10 (13) for weight. When measuring drug content, the numbers of out-of-range half-tablets for scored (nonscored) drugs were 36 (44) at 95%-105%, 9 (23) at 90%-110%, 0 (10) at 85%-115%, and 0 (1) at 75%-125%. When measuring weight, the numbers of out-of-range half tablets for scored (nonscored) drugs were 28 (38) at 95%-105%, 0 (14) at 90%-110%, 0 (3) at 85%-115%, and 0 (0) at 75%-125%.

Conclusions: Dose variation exceeded a proxy USP specification for more than one-third of sampled half-tablets of warfarin sodium, metoprolol succinate, and lisinopril and appeared to be greater for nonscored tablets as compared with scored tablets. Drug content variation in half-tablets appeared to be attributable primarily to weight variation occurring when tablets powder or fragment during the splitting process. Therefore, equal daily doses will be determined by the ability of patients to split tablets perfectly in half.

http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=8124

33. Evaluation of the reproducibility of tablet splitting to provide accurate doses for the pediatric population
Horn, LW, Kuhn, RJ, Kanga, JF
Study noting amongst other findings that dividing a tablet into quarters is even more difficult than into halves and is likely to incur a greater rate of tablet wastage and inaccuracy in final dosage.

http://www.jppt.org/loi/jppt

34. Tablet splitting: do it only if you 'half' to, then do it safely
Institute for Safe Medication Practices
ISMP Medication Safety Alert 2003;11(1-2):10
Recommends that healthcare providers should make every effort to use commercially available oral tablets when available in both inpatient and outpatient settings. However, tablet splitting may still be necessary if the drug is not commercially available in the patient-specific dose, or if the patient’s inability to afford the medication as an outpatient outweighs the risks involved with tablet splitting. Under these circumstances, consider the following suggestions: verify suitability; select patients carefully; dispense split tablets for inpatients; keep it clean; prescribe by weight; counsel patients; provide the right tools; provide discharge education.

http://www.ismp.org/newsletters/acute-care/articles/20060518.asp

35. Change in the drug release behavior of theophylline sustained-release tablets after division into two halves
Ishitsuka, K, Onuki, Y, Takayama, K
Yakugaku Zasshi 2012;132(2):225-230
Dividing a tablet into two halves and providing them to patients is a routine approach in clinical practice. Obviously, the drug release behaviour of tablets should be constant, regardless of the dividing process. Here, we investigated the change in
drug release behaviour after dividing tablets into two halves. Five commercial theophylline sustained-release tablets designed to be taken once a day were used as test tablets (two original products and three generic products). A 24-hour dissolution test was performed for each tablet, and changes in drug release behaviour were evaluated using similarity factors, f2, calculated from the drug release profiles. The drug release rates were substantially increased by dividing the tablets into two halves. Analysis of variance (ANOVA) revealed that the effect of the dividing process on drug release behaviour was more significant than that of changing the products. We further observed the feature of cross-sectioning of the surface of the tablets using a scanning electron microscope (SEM) and a laser-scanning microscope (LSM). The microscopic observations confirmed that the surface became rough and developed many cavities with the prolongation of the duration of the dissolution test. This study clarified that the division of tablets into two halves exerts significant effects on their drug release behaviour, and may offer a profound insight into the proper use of pharmaceutical products.

36. Accuracy research on divided dose of five narrow therapeutic-window tablets
Liu, Y-J, Miao, J-W, Chen, J-Y
Chinese Journal of Clinical Rational Drug Use 2011;8:002
Objective: To explore the accuracy of divided doses of 5 narrow therapeutic-window tablets, in order to provide a reference for clinical drug use. Methods: 5 tablets were split in half or quarters by 3 different methods: a splitting device, scissors and a surgical knife. Results: Of the 5 tablets, the hardest and least hard were aminophylline and digoxin, respectively. The drugs with the largest and smallest diameters were carbamazepine and digoxin, respectively, which also had the greatest and smallest thickness respectively. There was statistical significance between FW1/2, FW1/4 and TW1/2, TW1/4 of digoxin (splitting) and phenytoin (splitting), respectively (P less than 0.05). There was statistical significance between FW1/4 and TW1/4 of digoxin (scissors), aminophylline (scissors), warfarin sodium (scissors) and phenytoin (scissors), respectively (P less than 0.05, P less than 0.01). There was statistical significance between FW1/2, FW1/4 and TW1/2, TW1/4 of warfarin sodium (knife) respectively (P less than 0.01). Of 5 tablets, at least 5 tablets of the divided dose were above 15% of the quality variety, which did not conform to EDQM. When divided into half, the number of tablets divided by scissors 15% above average quality was more than when using the other 2 methods. When divided into quarters, the number of tablets divided by the 3 above methods 15% above the average quality, were respectively more than when dividing into half. Conclusions: Dose accuracy when dividing 5 narrow therapeutic-window tablets is so poor that it warrants attention. When dose adjustment is needed, a liquid preparation may be a good choice.

37. Evaluation on splitting captopril/hydrochlorothiazide tablets produced by different manufacturers
Liu, Y-J, Miao, J-W, Deng, X
Pharmacy Today 2012;1:008
Objective: To evaluate the rationality of splitting captopril/hydrochlorothiazide tablets produced by different manufacturers (two groups, A and B) to provide a reference for clinical use. Methods: The whole tablets were split into halves. Then tablets of A and B were compared with respect to the following: accuracy of subdivision, percentage weight loss, friability of half tablets, weight uniformity and dissolution.
Results: Group A met the requirements except for content uniformity. For group B, the weight loss passed the test while other items failed to meet requirements.
Conclusions: Tablets from different manufacturers (A and B) are not suitable for dividing into halves in the clinic.


38. Analysis of weight uniformity, content uniformity and 30-day stability in halves and quarters of routinely prescribed cardiovascular medications
Margiocco, ML, Warren, J, Borgarelli, M, Kukanich, B
Journal of Veterinary Cardiology 2009;11(1):31-39
Objectives: Congenital and acquired cardiac disorders are frequently diagnosed in small breed dogs and cats. In order to appropriately dose cardiovascular drugs for small patients, fractions of commercially available tablets must be prescribed. The aims of this study were to evaluate weight and content uniformity and 30-day chemical stability in halves and quarters of 11 drug formulations commonly prescribed to treat cardiovascular disorders in small breed dogs and cats.
Animals, Materials and Methods: 15 tablets from 11 drug formulations were obtained within the same lot. Tablets were split by a single operator using a commercially available pill splitter. Whole tablets, halves and quarters were weighed and stored in plastic containers. High-pressure liquid chromatography or liquid chromatography with mass spectrometry were utilised to determine drug content and repeated 30 days later to estimate chemical stability.
Results: Statistically significant weight variability, content non-uniformity and chemical degradation were found for some formulations. Digoxin showed a significant degradation that should be considered in clinical practice.
Conclusions: It appears that pill splitting is overall a relatively reliable practice; however tablets should not be split ahead of time but only immediately prior to intended usage.


39. Splitting tablets
Marriott, JL, Nation, RL
Australian Prescriber 2002;25(6):133-135
Patients split tablets for a variety of reasons, however there are problems associated with this process. Tablet-related factors include inaccuracy in splitting tablets and the resultant dose fluctuations, increased degradation of drug as a result of exposure to air and alterations in the dissolution rate of some formulations. Even when commercial tablet cutters are used the accuracy of splitting may be variable. Patients may experience difficulty in splitting tablets especially if their dexterity, eyesight or cognition is impaired. Compliance is likely to be decreased if the regimen requires tablets to be split. Although splitting tablets may potentially save the patient money the possible impact on the quality of medication use must be considered. (7 refs.)


40. Mean dose after splitting sertraline tablets
Matuschka, PR, Graves, JB
Journal of Clinical Psychiatry 2001;62(10):826
Letter.

http://article.psychiatrist.com/dao_1-login.asp?ID=10001723&RSID=67668947346822

41. Accuracy of tablet splitting
McDevitt, JT, Gurst, AH, Chen, Y
We attempted to determine the accuracy of manually splitting hydrochlorothiazide tablets. 94 healthy volunteers each split ten 25mg hydrochlorothiazide tablets, which were then weighed using an analytical balance. Demographics, grip and pinch strength, digit circumference and tablet-splitting experience were documented. Subjects were also surveyed regarding their willingness to pay a premium for commercially available, lower-dose tablets. Of 1752 manually split tablet portions, 41.3% deviated from ideal weight by more than 10% and 12.4% deviated by more than 20%. Gender, age, education and tablet-splitting experience were not predictive of variability. Most subjects (96.8%) stated a preference for commercially produced, lower-dose tablets, and 77.2% were willing to pay more for them. For drugs with steep dose-response curves or narrow therapeutic windows, the differences we recorded could be clinically relevant.


42. **The appropriateness and risks of tablet splitting**
Mosena, MS, van der Merwe, E
*South African Pharmaceutical Journal* 2009;76(7):30-36

Tablet division is applied where tablets of higher strength are split in half, or quarters, to provide the patient with a lower dose. The exercise is considered compounding by the pharmacist and is mostly used to make the titration of the required dose possible, as well as to save cost where tablets in a product range are flat-priced. Studies showed that medication cost can be reduced substantially by implementing tablet splitting. Cost of tablet splitters and additional dispensing fees may however reduce savings somewhat, as may possible additional outpatient facility visits, especially in the initial few weeks after introducing tablet division to a medical scheme population. Splitting scored tablets is approved by the FDA as efficacious and safe, but studies show that the half tablet weights of divided scored tablets often do not pass the dose content uniformity tests. Furthermore, in a recent study the drug content of half tablets, as determined by chemical assay, was not within the USP specifications for nearly 25% of products tested. In these studies, the physical characteristics like scoring and shape did not seem to predict which products would pass the uniformity test. Certain types of tablets are generally not suitable for splitting, for example extended-release formulations and film or enteric-coated tablets, but there may be exceptions. Tablet size and shape may also play a role in the decision to split a tablet or not. Tablets containing drugs with a wide therapeutic index and long half-life may be more suitable candidates for division. Therefore, some tablets used for depression, hypertension and hyperlipidaemia may be considered for splitting, provided that product and patient characteristics are taken into account. Elderly patients, or those with impaired eyesight, cognition and/or dexterity may find it difficult to split tablets and take them correctly. Tablet splitting carries a risk of errors due to misinterpretation of the prescription or label instructions by the pharmacist or patient, respectively. Nevertheless, where implemented carefully and with the appropriate counselling, tablet splitting does not compromise patient adherence and satisfaction or clinical outcomes negatively, and this was especially proven for statins.


43. **Tablet splitting: much ado about nothing?**
Navarro, RP
*Journal of Managed Care Pharmacy* 2009;15(3):272-274

Commentary referring to a paper by Hill et al. (*JMCP* 2009;15(3):253-261) which gives an analysis of the accuracy and precision of tablet splitting by measuring the active drug component in tablet halves. The methods and results are discussed, with
particular reference to those for warfarin. Concludes that ‘tablet splitting may be an effective method to individualise dosages and/or reduce costs when performed under the guidance of pharmacists, for informed and competent patients, and for appropriate drugs.’

http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=8109

44. **Weight variability of scored and unscored split psychotropic drug tablets**  
Nolly, RJ, Rashed, SM, Robinson, L, Thoma, L  
*Hospital Pharmacy* 2003;**38**(10):930-934  
The object of this study was to determine the weight variation of half tablets obtained by splitting scored and unscored tablets using a commercially available tablet-splitting device. The authors concluded that tablet splitting does not generally produce uniform and equal half tablet doses. (8 refs.)

http://thomasland.metapress.com/content/121650/?sortorder=asc

45. **Weight variability of scored and unscored psychotropic drug tablets split by a uniquely designed tablet splitting device**  
Nolly, RJ, Rodrigues, P, Thoma, L  
*Hospital Pharmacy* 2005;**40**(4):321-325  
The objective of this study was to determine the weight variation of half-tablets obtained from splitting scored and unscored tablets of paroxetine, risperidone and setraline, utilising a commercially available tablet splitting device (Tru-Cut Multi-Tablet Cutter, Links Medical Products, Irvine, CA, USA) that minimised tablet movement during splitting. (19 refs.)


46. **Which medications can be split without compromising efficacy and safety?**  
Noviasky, JA, Lo, V, Luft, DD  
*Journal of Family Practice* 2006;**55**(8):707-708  
Clinical inquiries feature. Split tablets of lisinopril are as effective as whole tablets of the same dose for hypertension (SOR: B, based on small randomised crossover study). Similarly, split tablets of atorvastatin, lovastatin and simvastatin are no less effective for lowering cholesterol (SOR: B, based on retrospective cohort studies). Extended-release, enteric-coated or tablets that cannot be split accurately are not appropriate for splitting (SOR: C, based on observational studies); the accuracy of splitting also depends on device used and user skill (SOR: C, based on observational study).


47. **Identified safety risks with splitting and crushing oral medications**  
Paparella, S  
*Journal of Emergency Nursing* 2010;**36**(2):156-158  
http://www.jenonline.org/article/S0099-1767(09)00545-5/abstract

48. **Effect of splitting simvastatin tablets for control of low-density lipoprotein cholesterol**  
Parra, D, Beckey, NP, Raval, HS, Schnacky, KR, Calabrese, V, Coakley, RW, Goodhope, RC  
*American Journal of Cardiology* 2005;**95**(12):1481-1483  
The efficacy, safety and economics of a voluntary conversion from whole simvastatin tablets to split tablets in 6 US Veterans Affairs medical centres were retrospectively evaluated in 3787 patients who received a consistent daily dose (5 to 40 mg) of simvastatin in 1999. Baseline and final low-density lipoprotein cholesterol levels and average change from baseline were not significantly different between groups (p
greater than 0.05), nor were the incidence of transaminase increases (p greater than 0.05) or measurements of patient compliance (p = 0.07). Widespread implementation of this initiative resulted in a cost avoidance of more than US$1.2 million in the 6 medical centres and $10.3 million across the Veterans Affairs medical system in 1999, with more than $46 million avoided in 2003.

http://www.ajconline.org/article/S0002-9149(05)00479-0/abstract

49. **Accuracy of tablet splitting by elderly patients**
Peek, BT, Al-Achi, A, Coombs, SJ
*Journal of the American Medical Association* 2002;**288**(4):451-452
Letter discussing this topic.

50. **Tablet splitting: a little bit risky?** (Tablettenteilung: Stückchenweise riskant?)
Picksak, G, Stichtenoth, D
*Medizinische Monatsschrift fur Pharmazeuten* 2007;**30**(9):340-342
For economic reasons, doctors are increasingly prescribing tablets with a relatively high content of the active ingredient, which must then be divided by the patient to give individual doses. However, accurate dosing can only be ensured by skilful division. For this, patients need reliable instructions for splitting tablets.

51. **Weight uniformity of split tablets required by a Veterans Affairs policy**
Polli, JE, Kim, S, Martin, BR
*Journal of Managed Care Pharmacy* 2003;**9**(5):401-407
Study to split several tablet products relevant to the Veterans Affairs (VA) Maryland Healthcare System and assess whether the resulting half tablets provide equal doses. From a VA list of products that are required to be split, 7 products were evaluated, along with 5 other commonly split tablet products. A trained pharmacy student split tablets using a tablet splitter provided by the VA. Half tablets were assessed for weight uniformity. Of the 12 products subjected to splitting, 8 products (atorvastatin, citalopram, furosemide, glipizide, metoprolol, paroxetine, sertraline and warfarin) yielded half tablets that passed the weight-uniformity test. The 4 failing products were lisinopril, lovastatin, rofecoxib and simvastatin. Unusual tablet shape and high tablet hardness predisposed products to failing the weight-uniformity test. The 4 failing products resulted in half tablets that were generally within 20% of their target weight range, suggesting that splitting these specific products would not result in adverse therapeutic effects due to dose variation created by tablet-splitting. Concludes that split-tablet results were relatively favourable and generally support a VA practice to split specific tablets. Public quality standards for half tablets, including their content uniformity, are needed to better delineate the policies for acceptable tablet splitting. (27 refs.)
http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=6860

52. **Alteration of pharmacokinetics after halving a slow-release theophylline tablet**
Primrose, WR, Clee, MD, Moody, JP, Hockings, N
*Pharmatherapeutica* 1983;**3**(6):429-432
A study was carried out in 10 healthy volunteers to determine the effects on the bioavailability of theophylline from a biconvex-shaped, slow-release 400 mg theophylline tablet formulation when the tablet was taken whole or as two separate halves in a single dose. The subjects took one or other dosage regimen on different occasions separated by a 7-day washout period. The results showed that absorption
was faster and plasma levels were higher when the 400 mg tablet was taken as 2 halves.

53. **Splitting tablets: what is the effect of discount contracts on the quality of prescribing?** (Teilung von Tabletten: welchen Einfluss haben die Rabattverträge auf die Verordnungsqualität?)

Quinzler, R, Bertsche, T, Szecsenyi, J, Haefeli, WE

*Medizinische Klinik* 2008; **103**(8):569-574

Background: In Germany, about one fourth of all tablets are split before ingestion. Since Apr 2007, by German law, pharmacists are legally obligated to substitute a prescribed drug with a generic drug, provided the patient's health insurance company has made corresponding contracts with pharmaceutical companies (discount contracts). However, generic drugs may differ substantially in their splitting properties. Until now it is not known how generic substitutions due to discount contracts will influence the prescribing quality with regard to tablet splitting.

Methods: The prescription data of 425 ambulatory patients with polymedication insured at the Allgemeine Ortskrankenkasse (AOK) were analysed and their drugs switched according to current discount contracts. Results: Altogether 24% of all tablets were split before ingestion. For 54% of these split tablets (182 of 335) existing discount contracts mandated generic substitution. In about 10% of the substitutions there was a chance of substituting a scored tablet for a dosage form not suitable for splitting (unscored tablet or capsule). Conclusions: The authors consider that current legislation should not only aim at reducing medication cost but also safeguard both effectiveness of the drugs and handling by the patients.


54. **The frequency of inappropriate tablet splitting in primary care**

Quinzler, R, Gasse, C, Schneider, A, Kaufmann-Kolle, P, Szecsenyi, J, Haefeli, WE

*European Journal of Clinical Pharmacology* 2006; **62**(12):1065-1073

A cross-sectional questionnaire survey was conducted of patients of 59 general practitioners in Saxony-Anhalt, Germany, in 2005 to collect detailed information on all drugs of patients maintained on more than 3 drugs. The response rate was 82.1% (n = 905) and 3158 drugs (tablets and dragees) were included in the analyses. Of all drugs, 24.1% were split (762 of 3158): 8.7% of all split tablets were unscored (66 of 762) and 3.8% of all split tablets were not allowed to be split (29 of 762). Tablets of higher price categories and higher strengths were twice as likely to be split. Only 22.5% of the SPCs (9 of 40) of the split unscored tablet brands contained explicit information on divisibility and only 36.4% of the package inserts (8 of 22) of the split brands that were not allowed to be split stated that splitting was not appropriate. Concludes that the splitting of tablets in primary care is a frequent practice, most likely driven by medical and economic considerations. Almost 1% of all tablets are split that must not be fragmented. However, the SPC and package insert provide only limited information on divisibility stressing the need to improve this information promptly to avoid medication errors. (21 refs.)


55. **Dividing tablets: why it can be dangerous and what to look out for in practice**

(Zerkleinern von Tabletten: warum es gefährlich sein kann und was in der Praxis zu beachten ist)

Quinzler, R, Haefeli, WE

*TMJ (The Medical Journal)* 2008; (2):44-47

Dividing tablets can be sensible, but involves some risks and in the worst case can result in serious adverse effects or in loss of effectiveness. In order to judge whether
it is possible to divide a tablet without problems, it is necessary to consider both the
properties of the active ingredient and the galenic form of the preparation. Dividing
tablets is particularly problematic with delayed action preparations and enteric-
coated formulations. In addition, the doctor should consider before prescribing
whether the patient is in fact willing and able to split his or her tablets, so that
adherence is not compromised.

http://www.rosenfluh.ch/images/stories/publikationen/tmj/2008-
02/15_Zerkleinern_2.08.pdf

56. **Tablet splitting** (Tabletten teilen)
Quinzler, R, Haefeli, WE
Therapeutische Umschau 2006;63(6):441-447

The splitting of scored tablets provides many advantages. One benefit is to achieve
dose flexibility to account for the huge inter-individual differences in dose
requirements for instance in paediatric and geriatric patients, which are often not
covered by the available strengths in the market. Moreover, large-sized tablets can
be swallowed more easily if broken before swallowing and medication costs can often
be reduced by splitting brands with higher strength. But not all tablets, mostly
unscored tablets, are suitable for splitting. Splitting of extended release formulations
can result in an overdose by uncontrolled release of the active component and
degradation of the compound can occur if an enteric coating is destroyed by the
splitting process. Whether tablets are suitable for splitting depends on the properties
of the active component (e.g. light sensitivity), the galenics, the shape of the tablet,
and the shape of the scoreline. Moreover, not all patients are informed, able or
willing to split tablets and the majority of the elderly population is not capable of
breaking tablets. When split tablets are prescribed it is therefore important to view
the shape of the tablet, to assess the patient's ability and willingness to break
tablets, to properly inform the patient about the appropriate way of splitting, and if
necessary to suggest (and instruct) the use of a tablet splitting device.

http://www.verlag-
hanshuber.com/zeitschriften/journal.php?abbrev=TUM&abstract=18082&show=abstract

57. **Substantial reduction of inappropriate tablet splitting with computerised
decision support: a prospective intervention study assessing potential benefit and
harm**
Quinzler, R, Schmitt, SPW, Pritsch, M, Kaltschmidt, J, Haefeli, WE
BMC Medical Informatics and Decision Making 2009;9:30

Background: Currently ambulatory patients in Germany break 1 in 4 tablets before
ingestion. Roughly 10% of them are not suitable for splitting because they lack score
lines or because enteric or modified release coating is destroyed impairing safety and
effectiveness of the medication. We assessed impact and safety of computerised
decision support on the inappropriate prescription of split tablets.
Methods: We performed a prospective intervention study in a 1680-bed university
hospital in Germany. Over a 15-week period we evaluated all electronically
composed medication regimens and determined the fraction of tablets and capsules
that demanded inappropriate splitting. In a subsequent intervention phase of 15
weeks duration for 10553 oral drugs divisibility characteristics were indicated in the
system. In addition, an alert was generated and displayed during the prescription
process whenever the entered dosage regimen demanded inappropriate splitting
(splitting of capsules, unscored tablets, or scored tablets unsuitable for the intended
fragmentation).
Results: During the baseline period 12.5% of all drugs required splitting and 2.7% of
all drugs (257/9545) required inappropriate splitting. During the intervention period
the frequency of inappropriate splitting was significantly reduced (1.4% of all drugs (146/10486); p = 0.0008). In response to half of the alerts (69/136) physicians adjusted the medication regimen. In the other half (67/136) no corrections were made although a switch to more suitable drugs (scored tablets, tablets with lower strength, liquid formulation) was possible in 82% (55/67).

Conclusions: This study revealed that computerised decision support can immediately reduce the frequency of inappropriate splitting without introducing new safety hazards.


58. Tablet splitting: patients and physicians need better support
Quinzler, R, Szecsenyi, J, Haefeli, WE
European Journal of Clinical Pharmacology 2007;63(12):1203-1204
Letter, suggesting that errors involving splitting tablets where this is not appropriate are mainly initiated by physicians during the prescribing process.

59. Evaluation of tablet-splitting in patients taking lisinopril for hypertension
Rindone, JP
In hypertensive patients taking lisinopril, splitting tablets did not result in a significant change in blood pressure. Most patients were willing to split tablets if doing so would result in a cost saving.

60. Patient experiences with the performance of tablet score lines needed for dosing
Rodenhuis, N, De Smet, PAGM, Barends, DM
Objective: The aim of this study was to measure the experience of patients with score line tablets where breaking was necessary for dosing.
Method: In three community pharmacies in the Netherlands, patients were asked about their experiences with the functioning of the score line. The survey was restricted to scored tablets that had to be broken to obtain the prescribed dose. It was also asked what actions were taken by the patient when breaking problems were encountered.
Results: Of all the score line prescriptions included in the study, 36% received a negative evaluation by the patient. The main negative experiences were related to loss of mass after breaking the tablets and difficulty in breaking, reported in 32% and 15%, respectively, of the prescriptions included in the study. In only 28% of the negative experiences had this been reported back to the pharmacy.
Conclusions: Many patients experience an unsatisfactory performance of tablets with score lines. Improvement will need a combination of technically better score lines and the alertness of the dispensing pharmacy for breaking problems.

61. The rationale of scored tablets as dosage form
Rodenhuis, N, De Smet, PAGM, Barends, DM
The aim of the study was to get insight into the rationale of scored tablets. This was pursued by studying patient’s reasons for subdividing (‘breaking’) scored and unscored tablets. Patients who picked up their prescriptions in 5 community pharmacies in the Netherlands were questioned. 275 prescriptions were studied.
31% of the tablets dispensed were subdivided, mostly because a dose that needed subdivision was prescribed. However, 30% were subdivided on the initiative of the patient himself: 13% for ease of swallowing and 17% because the patient chose to take a lower dose. Even unscored tablets were subdivided: because the dose prescribed was half the tablet dose (6%), for ease of swallowing (1%) and the wish of the patient to take a lower dose (3%). It was also inquired about the patient’s perception of the ease of subdivision of scored tablets. Problematic subdivision of scored tablets was reported in 55% of the cases, 42% of which was attributed to a disfunctioning score line. We also studied the possibility to prescribe and dispense other medicinal products as alternatives for tablets that needed to be subdivided. For 46% a dosage form with a lower dose was on the market, for 54% it was not. We conclude that scored tablets still fulfil an important role. Even when lower dosed tablets would become available, there remains a substantial wish of patients to subdivide tablets for ease of swallowing and adapting the dose. Improving the functioning of score lines may be a more practical approach than banning this dosage form.


62. **Weight variability of pharmacist-dispensed split tablets**  
Rosenberg, JM, Nathan, J, Plakogiannis, F  
*Journal of the American Pharmaceutical Association* 2002;42(2):200-205  
22 dispensed prescriptions containing 560 split tablets were collected and fragments weights were determined. Theoretical weights were determined mathematically. Concludes that tablet splitting resulted in an unacceptably high incidence of weight variation.


63. **Tablet splitting**  
Sales, MM, Cunningham, FE  
*Topics in Patient Safety* 2006;6(3):1  
Limited literature suggests that manually or mechanically splitting tablets does not always produce equal portions. The current evaluation of tablet splitting events within the US Veterans Administration revealed no problems regarding accuracy in splitting tablets to produce equal halves. However, a potential source for problems was found in a number of areas: ordering, verifying, filling, and administering medications that require splitting. Although tablet splitting remains a common practice in many settings, common elements of the cases reviewed demonstrate the need for increased awareness for both patients and providers.

http://www.patientsafety.gov/TIPS/Docs/TIPS_MayJune06.pdf

64. **Development and implementation of a tablet splitting education program in a Veterans Affairs Medical Center**  
Schellhase, EM, Hardin, AK  
*Hospital Pharmacy* 2003;38(5):453-457  
The authors discuss a tablet splitting pilot programme, which provided complete patient education, assessed potential cost savings and demonstrated the importance of pharmacy clerkship students. Patients receiving simvastatin, sertraline or sildenafil were eligible for the programme. (23 refs.)

http://www.factsandcomparisons.com/assets/hospitalpharm/may2003_peer2.pdf

65. **General practitioners' awareness towards patients suffering from problems with swallowing solid oral dosage forms**  
Schiele, JT, Quinzler, R, Haefeli, WE
Introduction: General practice patients often (37.4%) suffer from problems with swallowing solid oral drugs. To facilitate swallowing they tend to modify their medicines leading to destruction of pharmaceutical formulations by splitting or crushing tablets and opening capsules. This can have serious consequences, such as overdosage (dose dumping) and reduction or loss of efficacy.

Materials and Methods: After ethical approval a questionnaire survey was conducted at 11 general practices enrolling consecutive adult patients taking at least one long-term solid oral drug for 4 weeks or longer. In addition, the responsible general practitioners documented patients' individual ability to swallow oral drugs in a short questionnaire.

Results: The majority of patients (70.4%) who expressed swallowing difficulties (389 of 1051) were not identified by their GPs. Physicians did not diagnose the majority of patients (59.1%) who always, daily, or often suffered from such problems and missed even 74.0% who experienced these difficulties only sometimes or rarely. Only 6.7% of all patients (71/1051) had ever been asked about such problems by their doctor. Conversely, only a few of the affected patients (13.7%) informed their doctor about these problems.

Conclusions: These results show that general practitioners grossly underestimate their patients' difficulties in swallowing drugs. Given the prevalence of the problem, physicians should regularly rule out swallowing difficulties to avoid non-adherence and inappropriate modification of dosage forms by the patients, prescribe alternative dosage forms, and give suitable administration advice to facilitate swallowing.


66. Splitting tablets in half
Sedrati, M, Arnaud, P, Fontan, JE, Brion, F
American Journal of Hospital Pharmacy 1994;51(4):548,550

Letter from a hospital in Paris. Authors identified several tablet products that, when split using a tablet splitting device (The Pill Splitter, LGS Health Products, Ohio, USA), resulted in half tablets with doses outside a 85% to 115% range of the target half-tablet dose. Best results were obtained with the larger tablets, and those that were coated, were oblong but not pointed, and had flat edges. Aluminium hydroxide tablets were friable, and were found to break into more than two parts on several occasions.

http://www.ajhp.org/content/51/4.toc

67. Tablet splitting of a narrow therapeutic index drug: a case with levothyroxine sodium
Shah, RB, Collier, JS, Sayeed, VA, Bryant, A, Habib, MJ, Khan, MA
AAPS PharmSciTech 2010;11(3):1359-1367

Levothyroxine is a narrow therapeutic index, and to avoid adverse effect associated with under or excessive dosage, the dose response is carefully titrated. The tablets are marketed with a score providing an option to split. However, there are no systematic studies evaluating the effect of splitting on dose accuracy, and current study was undertaken to evaluate effects of splitting and potential causes for uniformity failures by measuring assay and content uniformity in whole and split tablets. Stability was evaluated by assaying drug for a period of 8 weeks. Effect of formulation factors on splittability was evaluated by a systematic investigation of formulation factors by preparing levothyroxine tablets in house by varying the type of excipients (binder, diluent, disintegrant, glidant) or by varying the processing
factors (granulating liquid, mixing type, compression pressure). The tablets were analyzed using novel analytical tool such as near infrared chemical imaging to visualize the distribution of levothyroxine. Assay was not significantly different for whole versus split tablets irrespective of method of splitting (hand or splitter), and splitting also had no measurable impact on the stability. Split tablets either by hand or splitter showed higher rate of content uniformity failures as compared to whole tablets. Tablet splitter produced more fragmentation and, hence, more content uniformity and friability failures. Chemical imaging data revealed that the distribution of levothyroxine was heterogeneous and was dependent on type of binder and the process used in the manufacture of tablets. Splitting such tablets could prove detrimental if sub- or super-potency becomes an issue.


68. **Scored tablets make pill splitting easier**
Solomon, L
*American Journal of Managed Care* 2007;13(11):e4

Comment on an article by Choe et al. (*Am J Manag Care* Jun 2007;13:293-304). Writer believes that the underlying problem is that the pricing of statins is generally not proportional to the dose. He suggests that scored tablets would not only benefit patients and prescribers, but insurers too, as they would not have to evaluate flat-priced medications and/or educate patients of varying ages and different levels of competence to split unscored tablets.


69. **Comparison of the halving of tablets prepared with eccentric and rotary tablet presses**
Sovany, T, Kasa, P, Pintye-Hodi, K
*AAPS PharmSciTech* 2009;10(2):430-436

The aim of this study was to compare the densification of powder mixtures on eccentric and rotary tablet presses and to establish relationships with the halving properties of the resulting scored tablets. This is an important problem because the recent guidelines of EU require verification of the equal masses of tablet halves. The models of Walker, Heckel, and Kawakita were used to describe the powder densification on the two machines. The calculated parameters revealed that the shorter compression cycle of rotary machines results in poorer densification and lower tablet hardness at a given compression force. This is manifested in poorer halving properties, which are influenced mainly by the hardness. Better densification improves the halving even at lower tablet hardness. This demonstrates that these parameters can be good predictors of tablet halving properties.


70. **Modeling of subdivision of scored tablets with the application of artificial neural networks**
Sovany, T, Kasa, P, Pintye-Hodi, K
*Journal of Pharmaceutical Sciences* 2010;99(2):905-915

The subdivision of scored tablets is an important problem for the exact individual therapy of patients. The recent guidelines of the EU require verification of the equal mass of the tablet halves, but this problem has previously never been investigated in papers published on the production technological aspects. Our aim was therefore to study the effects of the physicochemical properties of the raw materials and the effects of the compression process on the breaking parameters of the tablets. Artificial neural networks (ANNs) were applied for data analysis and modelling, which are very useful optimising systems. The abilities of four different types of ANNs to
predict the parameters of the compression process and the tablets were compared. The radial basis function and multilayer perceptron ANNs furnished statistically significant better results than linear or generalised regression neural networks. These ANN models revealed that the subdivision of scored tablets is strongly influenced by the production parameters and the compositions of the powder mixtures.


71. **X-ray computed microtomography for determination of relationships between structure and breaking of scored tablets**
Sovany, T, Kasa, P, Vakli, K, Pintye-Hodi, K
*X-Ray Spectrometry* 2009;**38**(6):505-509

This paper reports on the relationship between the structure and halving properties of scored tablets. The results of the density measurements and structure determination by X-ray computed microtomography revealed that this analytical technique is very suitable for the investigation of porous structures and aggregates thanks to its noninvasive character. The results of the analyses show that besides various porosities also big differences exist in the arrangement of the particles inside the comprimates. These basic qualitative differences in the structure of tablets prepared with different tablet presses greatly influence their breaking, and must be taken into consideration during the production of dosage forms.


72. **Breaking tablets in half**
Stimpel, M, Kuffer, B, Groth, H, Vetter, W
*Lancet* 1984;**I**(8389):1299

Letter from the Zurich university hospital, Switzerland describing the results of a study to find out if scored tablets really break evenly. 100 tablets of each of 14 brands of antihypertensive drug were broken in half along the dividing line and each half weighed. Only 2 brands divided well. Most others tested broke easily but deviations in half-tablet weights of up to 10% were frequent. Some brands were unsuitable for breaking. This potential source of inaccuracy could be significant in the clinical situation and the industry should either improve divisibility or market a wider range of unscored tablets.


73. **The scored tablet - a source of error in drug dosing?**
Stimpel, M, Vetter, H, Kuffer, B, Groth, H, Greminger, P, Vetter, W
*Journal of Hypertension* 1985;**3**(1-Suppl.):S97-S99

To determine the weight deviation of scored tablets after breaking we took 100 tablets of each of 34 brands of commercially available antihypertensive drugs and broke them into two, using the scored line. We graded the weights of the tablet halves according to their deviation from the expected weight (1 = less than or equal to +/- 5%, 11 = +/- 6-10%, 111 = greater than or equal to +/- 10%). The brands were ranked by the proportion of tablet halves (n = 200) in each category. Only seven brands divided very accurately and 11 brands divided reasonably accurately. Despite the scored line the remainder were either moderately (n = 10) or absolutely (n = 6) unsuitable for breaking, by hand or otherwise. A high proportion of these tablet halves showed weight deviations of 6-10% or more than 10% when compared to the expected weight. These findings show that a great number of antihypertensive drugs do not break evenly despite a scored line. This leads to inaccuracy of dosage.

74. **Tablet splitting and weight uniformity of half-tablets of four medications in pharmacy practice**
Tahaineh, LM, Gharaibeh, SF

**Background:** Tablet splitting is a common practice for multiple reasons including cost savings; however, it does not necessarily result in weight-uniform half-tablets.

**Objectives:** To determine weight uniformity of half-tablets resulting from splitting 4 products available in the Jordanian market and investigate the effect of tablet characteristics on weight uniformity of half-tablets.

**Methods:** Ten random tablets each of warfarin 5mg, digoxin 0.25mg, phenobarbital 30mg and prednisolone 5 mg were weighed and split by 6 PharmD students using a knife. The resulting half-tablets were weighed and evaluated for weight uniformity. Other relevant physical characteristics of the 4 products were measured.

**Results:** The average tablet hardness of the sampled tablets ranged from 40.3 N to 68.9 N. Digoxin, phenobarbital and prednisolone half-tablets failed the weight uniformity test; however, warfarin half-tablets passed. Digoxin, warfarin and phenobarbital tablets had a score line and warfarin tablets had the deepest score line of 0.81 mm.

**Conclusions:** Splitting warfarin tablets produces weight-uniform half-tablets that may possibly be attributed to the hardness and the presence of a deep score line. Digoxin, phenobarbital and prednisolone tablet splitting produces highly weight variable half-tablets. This can be of clinical significance in the case of the narrow therapeutic index medication digoxin.

http://jpp.sagepub.com/content/25/4/471.abstract

75. **Splitting tablets: the knife is not in fact as bad as it is supposed to be** (Tabletten teilen: Messer doch nicht so schlecht wie ihr ruf)
Tawab, M, Luhr, G, Bohnet, J, Schubert-Zsilavecz, M, Klamb, R
*Pharmazeutische Zeitung* 2011; **43**:156

30 each of 10 tablets (with and without scoring) were divided using 6 different tablet splitting devices, with a table knife and by hand. Accuracy of division was assessed by determining whether one half of the tablet differed in weight by more than 15% from half the weight of the original tablet. Contrary to expectations, the results obtained with a table knife compared favourably with those using the tablet splitting devices. Unscored tablets could not be reliably divided, but even where scoring was provided, it was not always associated with more accurate splitting. The authors advise that tablets should not be split unless it is explicitly stated in the product literature, even if the tablets are scored.

http://www.pharmazeutische-zeitung.de/index.php?id=39800&type=0

76. **Lack of medication dose uniformity in commonly split tablets**
Teng, J, Song, CK, Williams, RL, Polli, JE

A trained individual split tablets of 11 products using a single-edged razor blade and 3 products by hand alone. All the hand-split tablets and 8 of the 11 razor-split products failed a liberal adaptation of the United States Pharmacopeia uniformity test. No visible tablet features such as scoring, predisposed a product's split tablet to pass or fail the uniformity test.


77. **New term will distinguish tablets known to split in half**
Thompson, CA
*American Journal of Health-System Pharmacy* 2012; **69**(19):1619-1621
Describes work in progress by the US Food and Drug Administration (FDA) and the United States Pharmacopeia to produce guidelines for tablets intended to be divided. Tablets will be described as 'functionally scored' if the scoring permits the tablet to be divided into halves which individually meet requirements for properties such as uniformity. The FDA has also ruled that the production of split tablets by a company on a large scale is a manufacturing operation which is required to comply with the relevant quality standards. However, the FDA 'generally would not object to tablet splitting if it is performed by a pharmacist pursuant to a valid prescription for an individually identified patient'.

http://www.ajhp.org/content/69/19/1619.full

78. The breaking of scored tablets prior to the Ph Eur test
Vaes, LPJ, Frijlink, HW, Barends, DM
Pharmeuropa Scientific Notes 2002;14(2):302-304

79. The Ph Eur requirement for scored tablets: sampling procedure and test
van der Steen, JC, Frijlink, HW, Rodenhuis, N, Barends, DM
Pharmeuropa Scientific Notes 2004;16(1):51-55

80. Prediction of the ease of subdivision of scored tablets from their physical parameters
van der Steen, JC, Frijlink, HW, Schipper, MA, Barends, DM
AAPS PharmSciTech 2010;11(1):126-132
At present, the ease of subdivision of scored tablets is estimated in vivo. In order to replace such in vivo testing and to develop a surrogate test which uses in vitro techniques, the association between physical parameters of scored tablets and their ease of subdivision was studied. The physical properties of 23 brands of scored tablets of which their ease of subdivision in vivo was known were established. Statistical modeling using a logistic regression model was used to fit the data and estimate the contribution of each physical parameter to the goodness of the fit. For scored oblong tablets, the critical parameters for their ease of subdivision are: diameter; diameter/width ratio; depth of score line and resistance to crushing.
Criteria for each of these parameters were derived. All criteria need to be complied with to guarantee sufficient ease of subdivision of scored oblong tablets. For scored round tablets the critical parameters, in decreasing order of importance, for their ease of subdivision, are: resistance to crushing, diameter, score mark (1- or 2-sided), and shape (flat or biconvex). A 5-parameter predictive model was developed, showing excellent discrimination. For development, the proposed surrogate tests are sufficiently reliable. For release testing and stability studies, resistance to crushing of a scored tablet is a reliable predictor of its ease of subdivision.

81. Breaking of scored tablets: a review
van Santen, E, Barends, DM, Frijlink, HW
European Journal of Pharmaceutics and Biopharmaceutics 2002;53(2):139-145
The literature was reviewed regarding advantages, problems and performance indicators of score lines. Scored tablets provide dose flexibility, ease of swallowing and may reduce the costs of medication. However, many patients are confronted with scored tablets that are broken unequally and with difficulty, reducing compliance and reliance on the drug. Possibilities to reduce breaking difficulties are breaking instructions, tablet-splitters and breaking in advance. Factors influencing
the performance of score lines are shape, size, curvature and thickness of the tablet and the form and deepness of the score line. Performance of score lines can be defined by breaking ease, uniformity of mass of subdivided tablets and loss of mass by the subdivision. An in-vivo reference test and a routinely applicable in-vitro test need to be established for ease of breaking. For the uniformity of mass of subdivided tablets a requirement has recently been set by the European Pharmacopoeia. Loss of mass upon breaking can be limited to not more than 1%.


82. Statistical analysis of tablet breakability methods
Van Vooren, L, De Spiegeleer, B, Thonissen, T, Joye, P, Van Durme, J, Slegers, G

Purpose: Using a model tablet, the influence of breakability methodology on mass uniformity of half- and quarter-tablets as well as the comparison of different data acquisition and evaluation approaches were investigated. Moreover, different breakability evaluation criteria were compared based upon distribution as well as distribution-free models. Methods: A cross-scored tablet, i.e. having two break-marks, was broken by different methods by different persons, and the masses determined for the whole (unbroken) tablets, the half-tablets and quarter-tablets. Results: Beside the possible interaction between the methodology and the person breaking the tablets, the major factor significantly influencing the mass uniformity of broken tablets is the breakability methodology. The best results, i.e. smallest loss and smallest variability, are obtained when the breaking force applied by the thumbs is directed towards the score side of the tablet, i.e. by "opening" the score. Using our model tablet, significant differences between the different evaluation criteria are observed, with the USP/NF approach being best in line with the detailed analysis of all broken tablets. Conclusions: Assuming that for this model tablet the variance is a linear function of the break-line length, the standard deviation of quarter-tablets is theoretically calculated to be 0.87 times the standard deviation of the half-tablets. As the absolute standard deviation, expressed in mass units, will thus remain approximately identical, the relative standard deviation will nearly double as the mean mass of the quarter-tablets will be half of the mean mass of the half-tablets. This was experimentally confirmed.

http://www.ualberta.ca/~csps/JPPS5(2)/L.Vooren/tablet.pdf

83. Tablet-splitting: a common yet not so innocent practice
Verrue, C, Mehuys, E, Boussery, K, Remon, J-P, Petrovic, M

Aim: This paper is a report of a study conducted to quantify (i) the mean deviation from theoretical weight and (ii) the mean weight loss, after tablet-splitting with three different, commonly used splitting methods. Background: Tablet-splitting is a widespread practice among all sectors of health care for different reasons: it increases dose flexibility, makes tablet parts easier to swallow and allows cost savings for both patients and healthcare providers. However, the tablet parts obtained are often not equal in size, and a substantial amount of tablet can be lost during splitting. Method: Five volunteers were asked to mimic the situation in nursing homes in Belgium, and to split 8 tablets of different sizes and shapes using three different routine methods: (i) with a splitting device (Pilomat (R)), (ii) with scissors for unscored tablets or manual splitting for scored tablets and (iii) with a kitchen knife. Before and after splitting, tablets and tablet parts were weighed using an analytical balance. The data were collected in 2007. Results: For all tablets, method 1 gave a statistically significantly lower mean deviation from theoretical weight. The difference between method 2 and method 3 was not statistically
significant. When pooling the different products, method 1 also induced significantly less weight loss than the two other methods. Conclusions: Large dose deviations or weight losses can occur while splitting tablets. This could have serious clinical consequences for medications with a narrow therapeutic-toxic range. On the basis of the results in this report, we recommend use of a splitting device when splitting cannot be avoided.


84. **Is splitting tablets dangerous?**
Verrue, C, Mehuys, E, Boussery, K, Remon, J-P, Petrovic, M
*Nursing Times* 2011; **107**(8):23
This study examined the different methods of tablet splitting to establish which one was likely to be most accurate.
http://www.nursingtimes.net/nursing-practice/clinical-zones/prescribing/is-splitting-tablets-dangerous/5026305.article

85. **Influence of splitting on dissolution properties of metoprolol tablets**
Vranic, E, Uzunovic, A
*Bosnian Journal of Basic Medical Sciences* 2009; **9**(3):245-249
The objective of this work was to compare several profiles of dissolution data for metoprolol controlled release tablet formulations in order to identify possible changes in dissolution profiles of whole and scored tablets. Adequate design of score lines (on one or both sides) as well as the technology of preparation of tablet mixtures ensure forming a score line of adequate thickness, shape, size and curvature. According to the results obtained, this type of extended release formulation is eligible for splitting and use in therapy either as a whole or scored tablets.

86. **Multiple-scored tablets. Weight and content uniformity of subdivisions and the distribution of active constituent within and between tablets**
*Journal of Pharmacy and Pharmacology* 1978; **30**(1):401-406
Using three brands of multiple-scored levodopa tablets BP (500 mg) and one brand of sulphamethoxypyridazine tablets BP (500 mg) the weight and content uniformity of the subdivisions has been examined. It is shown that quartering of such tablets can result in sub-units which do not conform to recognized standards of weight uniformity, and in some instances content uniformity may be questionable. The homogeneity of distribution of active constituent between tablets has been determined and compared with that within tablets (between quarters of individual tablets). Statistical evaluation of the results is presented.

87. **Impact of splitting risperidone tablets on medication adherence and on clinical outcomes for patients with schizophrenia**
Weissman, EM, Dellenbaugh, C
*Psychiatric Services* 2007; **58**(2):201-206
Study to determine whether risperidone tablet splitting is associated with changes in medication adherence, service utilisation or clinical outcomes, by a retrospective analysis of administrative data from the New York-New Jersey region of the US Veterans Health Administration for 2436 individuals with schizophrenia or schizoaffective disorder who were prescribed risperidone from Jan 2001 to Mar 2003. Antipsychotic medication adherence was measured by medication possession ratio (MPR). Clinical outcomes included attendance at scheduled and unscheduled
outpatient appointments and psychiatric and medical admission rates. The MPR increased from 0.83 to 0.90 (p less than 0.001) after initiating tablet splitting. The rate of unscheduled mental health appointments increased significantly, particularly in the first 60 days after initiating splitting; attendance at scheduled outpatient mental health appointments was unchanged. Psychiatric admission and general medical admission rates were unchanged. Concludes that the results provide some assurance that prescribing tablet splitting for patients with schizophrenia does not result in poor outcomes as measured by psychiatric and medical inpatient admissions. Increased MPRs and unscheduled appointments suggest that some patients may have experienced minor difficulty, especially early on (crumbled tablets or misunderstood splitting instructions). Patients should be instructed carefully when tablet splitting is prescribed. Future studies should address longer-term clinical outcomes and system-wide costs.


88. **Tablet-breaking ability of older persons with Type 2 diabetes mellitus**
Wilson, M-MG, Kaiser, FE, Morley, JE
*Diabetes Educator* 2001;**27**(4):530-540

**Purpose:** The purpose of this study was to assess the ability of older persons with type 2 diabetes to accurately break in half 2 different formulations of micronized glyburide tablets.

**Methods:** 30 persons with type 2 diabetes, over age 70, were recruited from the St Louis University (USA) geriatric clinics. Participants were randomly assigned to 2 groups. Group A broke 30 Glynase Prestabs and 30 generic tablets using 2 different manual tablet-breaking methods. Group B broke 15 Glynase Prestabs and 15 generic tablets without instructions. Visual analogue scales were used to assess pain and difficulty of tablet breaking.

**Results:** A higher percentage of successful tablet breaking was reported with Glynase Prestabs (80%) compared with the generic tablets (33%). Mean pain scores for breaking Glynase Prestabs were 0.1 (Group A) and 0.9 (Group B). Higher pain scores were obtained for the generic tablets (2.1 for Group A, 3.2 for Group B). Glynase Prestabs were easier to break in both groups, and the resultant half tablets showed less variance from the expected theoretical weight (50% of whole parent tablet weight).

**Conclusions:** Older adults broke Glynase Prestabs more accurately and with less difficulty than generic micronised glyburide tablets. This variation in ease of tablet breaking and accuracy between different tablet formulations affects bioavailability and patient compliance.

http://tde.sagepub.com/content/27/4/530.abstract

89. **Compliance of scored tablet halves produced by Palestinian pharmaceutical companies with the new European Pharmacopoeia requirements**
Zaid, AN, Abu Ghosh, A
*Archives of Pharmacal Research* 2011;**34**(7):1183-1189

The aim of this study was to evaluate the weight uniformity of commonly divided tablets produced by Palestinian pharmaceutical companies and to evaluate the importance of both patient- and formulation-related variables on the splitting results. 84 volunteers were enrolled in this study; their age, gender and occupation were documented in order, and the effect of these variables on the tablet splitting results was evaluated. Each volunteer was asked to divide six scored tablets of each product tested and was given clear instructions on how to conduct the splitting process. The split units were individually weighed and the RSD for each product was calculated as instructed in the European Pharmacopoeia (Ph. Eur. 5.5). Only one scored tablet
product passed the Ph. Eur. test of mass uniformity, while the remaining 13 products failed; this indicates that the splitting of these tablet products is not a reliable means for the provision of accurate doses to patients. Age, gender and occupation of volunteers were not found to be predictive of any variability noted in the splitting results. The only factors that were suspected to be linked to passing the splitting test, as per the European Pharmacopoeia, were the shape, friability and hardness of the tablets. As a result of this study, the authors believe that the practice of dividing tablets, which should provide therapeutic and economic benefits for the patient, may potentially cause significant problems, especially in drugs with low therapeutic indices. Tablets produced by Palestinian pharmaceutical companies should comply with the new Ph. Eur. splitting regulations to reduce this potential for complications.


90. **Evaluation of the discrepancy between the European Pharmacopoeia test and an adopted United States Pharmacopoeia test regarding the weight uniformity of scored tablet halves: is harmonization required?**
Zaid, AN, Abu Ghosh, A, Al-Ramahi, R, Are'r, M


The aim of this study was to evaluate whether there is any discrepancy between the European Pharmacopoeia (Ph. Eur.) and adopted United States Pharmacopeia (USP) tests concerning the weight uniformity measurements of tablet halves after splitting. The USP method does not contain provisions to evaluate split tablets, so here we adopt their whole tablet weight uniformity method. 29 different commercial scored tablets (local to Palestine and imported) were divided. The split units were individually weighed and the relative standard deviation (RSD) for each product was calculated and then evaluated according to both the adopted USP and the Ph. Eur. tests of weight uniformity. 20 out of the 29 products tested failed the USP test, while 14 of them failed the Ph. Eur. test. 9 products passed both the USP and Ph. Eur. tests. 6 products passed the Ph. Eur. test but failed the USP test, with all of these products having an RSD greater than 6%. The correlation coefficient between the weight and content of split halves for three randomly selected products - corotenol 100mg, corotenol 50mg and lorazepam 2.5mg - was found to be 0.986, 0.998 and 0.72, respectively. A clear difference can be seen between outcomes obtained by the two compendial tablet splitting methods with regard to weight uniformity. Results from the USP test showed that tighter measures are needed to pass the test. Our results argue that the Ph. Eur. should revise the existing weight uniformity test on scored tablets to include the RSD parameter in it. The USP should include this adopted test as a specific test for scored tablet halves, not just whole tablets. Manufacturers in some cases will need to improve the quality of the produced scored tablets in order to pass the USP test, especially those with low therapeutic indices. Finally, harmonisation between the pharmacopoeias regarding the weight uniformity testing of split tablets is warranted.

http://journal.pda.org/content/66/1/20.short

91. **Weight uniformity of scored tablet halves manufactured by Palestinian pharmaceutical companies**
Zaid, AN, Abu Ghosh, A, Kittana, N


The purpose of this study was to evaluate the weight uniformity of some commonly divided tablets produced by Palestinian pharmaceutical companies. Volunteers were asked to divide scored tablets. The split units were individually weighed and the relative standard deviation for each product was calculated. Five scored tablet products failed the United States Pharmacopoeia test of mass uniformity; this
indicates that the splitting of these tablet products is not reliable for the provision of accurate doses. The practice of dividing tablets to achieve therapeutic and economic benefits for the patient may cause significant problems, especially in drugs with low therapeutic indices. Pharmacists may resolve this inconvenience by reformulating the tablet into a new dosage form, such as capsules, which should contain the exact amount of the medication.

http://www.ijpc.com/Abstracts/Abstract.cfm?ABS=3144

92. **Weight and content uniformity of lorazepam half-tablets: a study of correlation of a low drug content product**
Zaid, AN, Al-Ramahi, RJ, Ghoush, AA, Qaddumi, A, Zaaror, YA
*Saudi Pharmaceutical Journal* 2013;21(1):71-75

The aim of this study was to investigate the degree of correlation between the weight and the content of split-halves of lorazepam 2.5mg tablets. Weight variation and drug content (using HPLC) of lorazepam half-tablets were evaluated according to the European Pharmacopoeia tests. Only one individual mass of the 30 half tablets was outside the limits of 85-115% of the average mass, but since it was within 75-125% of the average mass, the product passed the test. Each individual content was between 85% and 115% of the average content (99.8% expressed as a percentage of label claim) and within the limits of 75-125%, so the product passed the uniformity of content test. The correlation coefficient (r) between the weight and the content of split halves was found to be 0.994. The weights of split tablet halves appear to be directly correlated with their drug content even for a medication with a low drug content, thus it is recommended that pharmacists who split tablets into two halves, assure the weight uniformity of the resultant halves. Manufacturers should develop formulation and manufacturing procedures that ensure high degree of correlation between weight and content not only among the whole tablet but also among the obtained tablet halves. NB: The paper does not specify the method used to divide the tablets.


93. **Tablet splitting: product quality assessment of metoprolol succinate extended release tablets**
Zhao, N, Zidan, A, Tawakkul, M, Sayeed, VA, Khan, M

Metoprolol succinate extended release tablets comprise a multiple unit system containing metoprolol succinate in a multitude of controlled release pellets. Each pellet acts as a separate drug delivery unit and is designed to deliver metoprolol continuously over the dosage interval. Despite the flexibility that controlled release pellets may offer, segregation is one of the challenges that commonly occur during tableting for such drug delivery system. Since all commercial metoprolol succinate extended release tablets are scored, they are deemed suitable for splitting. The present study was aimed at utilizing an innovative technology to determine the dose uniformity for split tablets. Four marketed drug products consisting of innovator and generics were evaluated for effect of splitting on weight, assay and content uniformity. Novel analytical tool such as near infrared (NIR) chemical imaging was used to visualize the distribution of metoprolol succinate and functional excipients on the surfaces of the marketed tablets. The non-homogeneous distribution of directly compressed metoprolol succinate beads on the surface of the tablets as well as the split intersection explained the large variation in the split tablets’ weight and content uniformity results. The results obtained indicated the usefulness of NIR chemical imaging to determine the need for content uniformity studies for certain split tablets.

94. Guidance for industry. Tablet scoring: nomenclature, labeling, and data for evaluation

Silver Spring, MD, USA, US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Mar 2013, 5pp.

This guidance provides recommendations to sponsors of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) regarding what criteria should be met when evaluating and labelling tablets that have been scored. Specifically, this guidance recommends: (i) guidelines to follow, data to provide, and criteria to meet and detail in an application to support approval of a scored tablet, and (ii) Nomenclature and labelling for approved scored tablets. This guidance does not address specific finished-product release testing, where additional requirements may apply to scored tablets. This guidance does not describe the medical practice conditions under which tablet splitting is considered or recommended.