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REVIEW OF THE FRACTIONATION OF MEDICINES AVAILABLE IN SOLID FORMULATIONS (TABLETS)

Dr. Olga Baudrit*, Eleaneth Baltodano and Luis Jiménez

INIFAR Institute of Pharmaceutical Research, Faculty of Pharmacy, University of Costa Rica, San José, Costa Rica.

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***Corresponding Author**
Dr. Olga Baudrit
INIFAR Institute of Pharmaceutical Research, Faculty of Pharmacy, University of Costa Rica, San José, Costa Rica

ABSTRACT

Not always people receive the just dose of active ingredient required for his health problem. To obtain success in pharmacology treatment, sometimes the physicians prescribe drugs in a dose that is impossible obtain in the market because this specific strength does not exist in the pharmaceutical form that they proposed. This is the case of some tablets, which need to be divided to achieve this objective. Several reasons are to justify the need to split pills, since there exist some consequences of this act in different contexts. Laboratories produce pharmaceutical forms with Good Manufacturing Practices, but not all medications are designed to be split. Dividing a scored tablet into two parts, it is no guarantee to find accurately the half dose in each fraction. More research is required in Costa Rica, Central America to know the magnitude of the actual situation in this topic.

KEYWORDS: split tablets, fractionation, drugs, dosage forms, pharmaceutical.

INTRODUCTION

The fractionation of drugs can be observed in clinical practice, especially tablets or others solid dosage forms, because the desired dose is lower than the declared in the intact tablets, which are available of the pharmaceutical market.[1-2]

This may have advantages or also unfavorable consequences for medicines users and the pharmaceutical sector.[3]

The health risk caused by the drug's fractionating is an issue that arouses different opinions and controversy, especially because there is no established standard that allows people carry

out this practice with accurately[4] although there are some general advices as proposed by the FDA.[5]

THE FRACTIONATION OF MEDICINES AVAILABLE IN SOLID FORMULATIONS (TABLETS)

To make the decision of prescribing fractions of tablets, it must take in account aspects related with: availability of a big therapeutic arsenal, the patient characteristics (age, weight, sex, pathological condition and evolution, genetics, easily to swallowing and others).[6]

Also aspects of the tablet (standards of quality, dimensions, shape, hardness, presence of score, uniformity of active ingredient, stability, packing materials, etc.) and finally the techniques recommended for fractionation.[2]

The importance of this phenomenon focuses on the extent that can affect health and disease of the people involved, who act under the knowledge of everyone involved in the health care of people.

Then, the development of this issue is divided into three sections: reasons for fractionating of tablets, the advantages and disadvantages of splitting and the alternatives for fractionation.

REASONS FOR FRACTIONATING OF TABLETS

The main justifications for fractionation are

1) The flexibility and individualization of drug therapy to achieve the effectiveness of treatment, adherence, protect security and to find appropriate costs low especially when it comes to chronic diseases such as hypertension, diabetes and dyslipidemia.[7-10]

2) Titration of active ingredients with narrow therapeutic index such as anticoagulants, cardiovascular agents or products for thyroid disorders.[9, 11-13]

3) Have the exact dose when this is not available it is marketed, especially to meet the needs of elderly, children, people with disorders that cause delay in metabolism and to aid swallowing.[14-17]

4) Aspects of economic savings when splitting the tablets at twice causes a decrease in spending.[18-20]

5) Consumption without a prescription of some medicines used to combat pain, anxiety or depression.[21-22]

6) The limitation on the strength or potency of the dosage forms that are released from the hospital for outpatient use.[2, 23]

THE ADVANTAGES AND DISADVANTAGES OF SPLITTING

Proponents argue tablets cutting advantages as adjusting the dose according to need or convenience of treatment facilitate and save money intake.[24]

Although there is strong resistance to this, there are studies that promote successfully training for professionals in general medicine prescribed fractions tablet, so the case study conducted with prescribed statins to American veterans mentioned [9] and one with risperidone in schizophrenic patients.[25]

There are studies in which the problems associated with crushing or cutting tablets and capsules are mentioned. It is known that altering modified release formulations may increase the risk of side effects or toxic levels that increase the release rate of the active ingredient. The breaking of a tablet can cause inactivation of enteric-coated drug was intended to get the gastric level and therefore could be presented therapeutic failure. In addition, the same result occurs with sublingual tablets crushing. The mask the bitter taste not fulfill its function, the texture would be irregular, they could stain the teeth, anesthetic effect that would irritation in the lining of the esophagus and stomach would be lost. The skin contact with carcinogens and teratogens would endanger the health of those who administer the medicine.[26]

It is further added that fractions tablet can make confusion in the pharmacy, because if the letter of the prescriber is not clear, the words "½ tab" may be confused by "1-2 tab". Another complication occurs if the patient consumes more doses of prescribed with a consequent toxicity box, or if in doubt, it is demotivating and stop therapy. Poor hygiene management to cut the tablets would cause health problems for microbial contamination or cross contamination to cut several drugs with the same device for failing to care cleaning.[18]

The lack of low-dose formulations that meet the needs of patients with custom requirements represents a major challenge for the pharmaceutical industry. Permission marketing of medicines is required and the manufacturer ensures the quality, safety and efficacy of the medicines produced. Such permission is granted within limitations including directions, precautions, contraindications, warnings along with recommended doses and routes of administration. Thus, the use of medication for the patient is protected by the manufacturer

within the prescribed limits and authorized and yet the safety of the drug is not entirely reliable.[27-28] Hence drugs like thalidomide remember cases of insecurity caused by phocomelia and heart attacks in people that consumed Vioxx®.[29]

With these considerations, it is understood that the manufacturer must ensure the safety and efficacy of the product during use of the same but within the parameters he says. If the drug is broken down without precise indication of the manufacturer, the legal liability is the prescriber, dispenser and who makes the partition and not the manufacturer. Hence, it warranted more information about the fragmentation of solid formulations such as tablets, particularly by prescribers.[30]

In the UK health professionals, managers and suppliers know their responsibility in the fact crush the drug without this indication given by the manufacturer.[30] In any case, for purposes of legal defense, the patient should be informed of the situation and preference should sign a document such as an informed consent.[31]

The powdering tablets and subdividing the crushed is a common practice in pediatrics and it is know that the child population is highly susceptible to the occurrence of adverse effects result of medication errors.[32]

One difficulty occurs when failing to obtain the suitable formulation to achieve the required dosage, however, crushing the partition or no evidence of a significant loss in the pharmacological effect of some drugs.[33-37]

In order to address these specific needs, the hospital pharmacy prepares unit doses (or single-dose in a non-reusable container) and other particular formulations to each pediatric patient but this practice is rare in community pharmacies respect to outpatients.[38-39]

In view of this, the pharmaceutical industry cares about innovation and offer appropriate solutions[40-41] and for some years it has in the market mini-tablets that disintegrate in the mouth and prevent aspiration of children;[42-44] pellets for flexible dosing;[45] a lubricant spray to facilitate swallowing tablets and capsules in children, adolescents and older adults with dysphagia.[46]

Also the advent of dispersible tablets[47] and the use of alternative routes of administration that the skin by applying transdermal patches.[48-49]

Older adults who have difficulty taking medicines or also have other problems that can cause aspiration as well as those who lie in bed are the subject of special attention regarding the administration of drugs.[50-55]

As age increases can augment the number of drugs to be used, for example, there are those who use 5 or 10 different medications and this polypharmacy can lead to errors worth asking how many of these drugs are fractionating.[56-59]

Another difficulty to fractionation is related with people who split medicines. In 2007, a research in the United States studied a partition program of statin tablets with elderly. Some findings show how 15% of participants reported having difficulties fractionation, while others indicate their displeasure by not getting upset symmetrical parts perceive as rough edges and a bitter taste after ingestion of drug fractions.[20]

Despite the low percentage of dissatisfied, these facts cannot be ignored given the nature of the complaints. Other problems have to do with aspects of geometry [60] and generally can show changes in the characteristics of the product intact that inducing serious health risks and influence the increase in adverse events and of course the limitation on the efficacy of treatments.[61]

In this regard, in 2006 a report of adverse events writing by Sales and Cunningham showed some errors in splitting tablets. They included among the most popular: receiving more than the prescribed dose, fractionation despite the existence of lower doses available in the market, the split tablets included in the watch list of the Institute for Safe Medication Practices ISMP and finally, in a few cases, the cause devastating damage in patients.[62]

ISMP alert list of great importance because it is a collection of medication errors reported in the United States and reviewed by specialists in pharmacovigilance. In the list of the liquid solution as the most controversial mentioned dosage form; however, some cause difficulties cited solid formulations.[63]

In comments made about this alert recommendations they include avoiding from enteric-coated tablets, special cover or modified release are provided; not fractionate very small, asymmetrical tablets -such as bosentan- teratogenic tablets; not from drug tablets very precise dosage requirements and ultimately not cut capsules.[64]

There is a risk of reaching toxic states or suffer significant adverse effects and in this sense, chronic treatment with three drugs with a narrow therapeutic margin exemplify various drug-related problems: Lactic acidosis due to excessive consumption of metformin,[65] seizures and other nervous system disorders overdose of levofloxacin[66] and finally myoclonus, confusional states and seizures produced by imipenem.[67]

In therapeutics, medicinal products as digoxin and sodium warfarin with narrow therapeutic range have special consideration in critical pathologies.[68] Other group of medicines has great therapeutic relevance and they are administrated in chronic diseases. Among the main ones are metoprolol succinate, metoprolol tartrate, simvastatin, citalopram, lisinopril,[69] diltiazem, amlodipine, atenolol, propranolol, sotalol, amiodarone, nifedipine, enalapril, pimobendan, spironolactone.[70] All of the principles actives cited have tablet formulations and they are affected by splitting in dose adjustment.

To assess the accuracy of the partition of the tablets, the physical characteristics mentioned above and others play a key role: shape (cylindrical, oval, irregular, flat, convex), three-dimensional dimensional, flat or beveled edge, degree of fragility, groove (absent, one or more, on the one hand or both)[71-76] also include special conditions such as filing a polymeric shell or an enteric coating, have hard gelatin capsules, be formulated for administration of modified release, among others.[77-78]

Other variables relating to the personal skills of users such as physical limitations fine motor, visual acuity care, concentration or mental fatigue,[78-81], pathological conditions, hereditary factors are also added, changes themselves the age of the elderly population affecting the different variations of pharmacokinetic parameters.[16]

Another contribution constitutes different fractionation maneuvers by applying pressure with your hands, with knives or commercial cutters.[82-85]

There is widespread concern about this issue and is expressed in different releases trade organizations like the American Medical Association and American Pharmacists Association. Meanwhile, organizations such as WHO[8, 86-87] and Food and Drug Administration FDA issued guidelines warning of the potential risk of this practice.[88]

There are intermediate positions state that the split tablets is considered a voluntary practice based on the patient's ability to divide tablets and appropriateness of medication and also

encourages pharmacists to disclose the division of specific tablets, promote accuracy of dosage and patient safety through counseling. To justify or not the fractionating of tablets and the consequences in the variability of doses in each half of tablet, there are numerous studies related with the accuracy of splitting.

Some authors considered the variations in terms of weight and content uniformity of active ingredient in tablet fractions. Some of these studies show mixed results. One of the controversial aspects is to use the same content uniformity test of entire dosage forms to assay the halves. Because of these inaccuracies in the European Pharmacopoeia 2002 introduced a trial of different content (Uniformity of multi-unit tablets) and also includes standards for content uniformity, weight variation and mass loss for halve.[9]

In 2009 the USP Forum pharmacopoeia comments in order to contemplate trials for half tablets given the practice of partition and try to include the policies of the European Pharmacopoeia were issued.[89] In the United States between 2009 and 2010, the Supervisory Board of drug safety (CDER's Drug Safety Oversight Board) considered appropriate division of tablets.[90]

Nevertheless, the externalized concern is respect to variations in the content, weight, disintegration, dissolution and stability as is mentioned in Na Zhao *et al*. and Rakhi Shah *et al*.[91-92]

In March 2013, the FDA issued recommendations to the pharmaceutical industry to ensure the quality of tablets with slots.[88]

A bibliographic revision published in March 2013 about split tablets exhibited 94 articles related with this subject, [93] and in 2016 the situation is no still resolved.

Finally, in September 2013, a *Stimuli* to the Revision Process article in *Pharmacopeial Forum* gives further insights into the rationale for the new general chapter and its contents: <705> “Quality Attributes of tablets labeled as having a functional score”. It is why this chapter is introduced at the end of 2014 into Second Supplement of the USP 37th.[94]

ALTERNATIVES DRUG FRACTIONATION

To overcome differences concerning the partition of the tablets have been proposed some alternatives that are viable in some mediated. Three references are cited the following:

1. Fractionate the tablets one by one so that successive doses fluctuations are compensated and that the stability of the fractions are not significantly affected.[40]

2. Starting with high precision cutting machines, develop tablets with multiple slots -of 1 to 8-, make extemporaneous preparations, administer medications by alternate routes for oral administration, for example dermal.[49]

3. Use online resources to consult on measures to take in case of elderly patients and improve medication administration.[92]

CONCLUSIONS

Although, that many drugs are available in the pharmaceutical market, they do not meet the particular needs in all cases and for all people. Many people are not informed about the risk posed by the fractionation of their particular medicines. Elderly, mentally ill or those without assistance from a person who care for them, may be at increased risk if their medicines fractionate improperly. The technique (instrument, force or vision of the person) used to fractionate drugs could provide a consideration to ensure the safety of the drug to be used after its partition. Among the alternatives available to fractionate medicines, there are devices that can help at least with the partition of the tablet.

Despite the importance of this issue, no studies were found in Costa Rica, so research on this is needed.

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