MAÍRA TELES TEIXEIRA

AVALIAÇÃO DA INFLUÊNCIA DE MÚLTIPLOS FATORES ENVOLVIDOS NA PARTIÇÃO DE COMPRIMIDOS

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UNIVERSIDADE DE BRASÍLIA
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PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE

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Dissertação apresentada como requisito parcial para a obtenção do Título de Mestre em Ciências da Saúde pelo Programa de Pós-Graduação em Ciências da Saúde da Universidade de Brasília.

Orientador: Marcílio Sérgio Soares da Cunha Filho
Coorientadora: Dayde Lane Mendonça da Silva

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RESUMO

Introdução e objetivo: A partição de comprimidos é uma prática corriqueira, amplamente utilizada no tratamento de idosos e crianças. Entre os problemas relacionados a essa atividade estão a possível variação da dose e a diminuição da estabilidade do fármaco após a partição. No caso de medicamentos de baixo índice terapêutico, o fracionamento de comprimidos adquire contornos críticos, uma vez que pequenas alterações na sua dose podem trazer graves repercussões na saúde do paciente. Esse trabalho teve como objetivo analisar a problemática da partição no que se refere aos aspectos regulatórios, técnicos e experimentais. Método: A primeira parte do estudo foi dedicada a realizar uma análise das legislações sanitárias no mundo sobre a regulamentação da partição de comprimidos. Na segunda parte do trabalho, foi realizado um amplo levantamento na literatura científica acerca do tema. Na terceira parte da dissertação foi realizado um estudo experimental para avaliar o impacto da partição de comprimidos em suas propriedades físicas e mecânicas. Resultados: Na maioria dos países, incluindo parte da América do Sul, a partição de medicamentos ainda não é regulamentada pelos órgãos sanitários. Estados Unidos e Europa possuem especificações ainda rudimentares e testes adaptados para avaliar o desempenho dos comprimidos ante o fracionamento. Os estudos científicos sobre o tema são controversos e inconclusivos sobre a segurança dessa prática e a melhor forma de realizá-la. De maneira geral, comprimidos oblongos, revestidos, planos e com sulco profundo favorecem a uma partição mais precisa. Observa-se maior prevalência de resultados vantajosos na partição manual e com partidor de comprimidos, comparados ao fracionamento com faca. O estudo experimental conduzido revelou resultados similares aos da literatura, mostrando que o partidor de comprimidos consegue uma melhor performance na partição que a faca. Comparados aos comprimidos íntegros, os comprimidos fracionados apresentaram uma redução de aproximadamente 50% na dureza, aumento de 0,65% na friabilidade e desintegração em torno de 20% mais rápida. A perda de peso, relacionada à fragmentação e esfarelamento dos comprimidos, foi de até 2% e a variação de peso oscilou entre 0 e 50%, com valor médio de 9.9% ± 10.0. A variação média da área superficial dos comprimidos foi de 15.2%, apresentando correlação com teste de variação de peso (r=0,169, p=0,001).

Comprimidos redondos exibiram perda de peso (2,59% ± 0,23) e variação de área (17,57% ± 0,95) maiores que os obtidos pelos comprimidos oblongos (0,66% ± 0,78, e 5,47% ± 0,52; p=0,000 para ambos). Comprimidos revestidos apresentaram menores perdas de peso (p=0,000), variações de dureza (p=0,022) e área (p=0,009), com valores de 1,4% ± 0,2, 51,5% ± 1,2 e 13,0% ± 1,2, comparados com comprimidos não revestidos que apresentaram 2,8% ± 0,3, 54,4% ± 1,3, e 16,6% ± 1,1. Finalmente, comprimidos sulcados obtiveram menor perda de peso (p=0,000) e variação de área (p=0,000; 8,63% ± 0,7 e 13,44% ± 1,01) comparados aos comprimidos não sulcados (12,63% ± 0,72 e 18,57% ± 1,32). Conclusão: Há a necessidade de mais estudos e de uma regulamentação sanitária mais consistente que possam nortear os pacientes e os profissionais de saúde acerca da partição de comprimidos.

Palavras-chave: partição de comprimidos; regulação sanitária; método de partição; ensaios mecânicos e físicos.

ABSTRACT

Introduction and objective: Tablet splitting is a common practice, widely used in treatments of the elderly and children. Among the problems related to this activity are the possible dosage variation and the decrease of drug stability after split. Subdividing tablets acquires critical contours in the case of low therapeutic index drugs, since small changes in dosage can lead to serious repercussions on patient's health. This study aimed to analyze the splitting problem in regulatory, technical and experimental aspects. Method: The first part of the study was dedicated to conduct an analysis of world's health legislation concerned to regulation of tablets split. In second part, a study of the subject in scientific literature was conducted. In the third part, an experimental study to evaluate the impact of tablets subdivision on their physical and mechanical properties was done. Results: In most countries, including part of South America, drug subdivision is not regulated by health authorities. United States and Europe have rudimentary specifications and tests adapted to assess the performance of the tablets after split. Scientific studies on the subject are controversial and inconclusive about the safety of this practice and the best way to do it. In general, oblong, coated, flat surface and deep groove favor a more accurate subdivision. There is greater prevalence of advantageous results in manual breaking and tablet splitter device, compared to knife split. The experimental study conducted revealed results similar to the literature's results, showing superiority in split with tablet splitter device compared with knife. Split tablets showed a decrease of approximately 50% in hardness, 0.65% increase in friability and disintegration around 20% faster compared to intact tablets. Weight loss related to fragmentation and crumbling of the tablets was up to 2% and weight variation varied between 0 and 50%, with an average of 10.0 ± 9.9%. The average of surface area variation of the tablets was 15.2%, showing a correlation with weight variation test ($r = 0.169$, $p = 0.001$). Round tablets exhibited weight loss (2.59% ± 0.23) and area change (17.57% ± 0.95) higher than those obtained by oblong ones (0.66 ± 0.78% and 5, 47% ± 0.52; $p = 0.000$ for both). Coated tablets had lower weight loss ($p = 0.000$), hardness ($p = 0.022$) and area ($p = 0.009$) variations, with values of 1.4% ± 0.2, and 51.5 ± 1.2% 13.0% ± 1.2 compared to uncoated tablets that had 2.8% ± 0.3% 54.4 ± 1.3, and 16.6 ± 1.1%. Finally, scored tablets had lower weight loss ($p = 0.000$) and area change (p

= 0.000; 8.63% ± 0.7 and 13.44% ± 1.01) compared to nonscored tablets (12.63 % ± 0.72 and 18.57 ± 1.32%). Conclusion: There is a necessity of more researches and consistent health regulations to guide patients and healthcare professionals in tablets split.

Keywords: tablets subdivision; sanitary regulation; split method; physical and mechanical tests.

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1.1 INTRODUÇÃO

A partição de comprimidos consiste no fracionamento da unidade farmacêutica realizada sob recomendação médica ou por iniciativa do próprio paciente ou cuidador. Essa prática é realizada por diversas razões, principalmente para ajustar dose, facilitar a ingestão pelo paciente e reduzir os custos da terapia (1).

Vários estudos relacionados ao tema mostram que a divisão de comprimidos em cuidados primários de saúde é um hábito frequente, o que contrasta com os riscos associados a este procedimento, que muitas vezes estão subestimados e podem trazer graves consequências à saúde dos usuários (2–4). No cuidado geriátrico, a partição de comprimidos é bastante comum, devido à necessidade de obtenção de doses menores ou intermediarias às encontradas no mercado e à necessidade de viabilizar a administração do medicamento, no caso de idosos que apresentam algum tipo de demência ou dificuldade de deglutição (5).

Existe uma preocupação crescente dos profissionais de saúde de que a qualidade dos comprimidos após a partição pode ser afetada de forma difícil de prever. Estudos têm identificado uma série de potenciais problemas relacionados à prática, como variações no peso fracionado esperado do medicamento e perda da estabilidade decorrentes do processo de fratura dos comprimidos. As mudanças nas características do comprimido com a partição assumem caráter alarmante no caso de medicamentos com baixo índice terapêutico (4,6–11)

Os estudos técnicos publicados sobre o tema apontam que há vários fatores de produção que podem influenciar no sucesso da partição de um comprimido, como seu tamanho, formato, espessura, dureza, composição e presença de sulco. Contudo, a literatura disponível não é suficiente para esclarecer completamente como esses fatores afetam o processo de partição e que condições de fabricação são mais apropriadas para habilitar um comprimido a ser submetido a esta prática. Alguns estudos apresentam inclusive conclusões contraditórias em relação a

algumas dessas variáveis, o que evidencia a complexidade do tema e a necessidade de mais estudos e de uma revisão bibliográfica apurada que leve em consideração as diferentes nuances tecnológicas de cada trabalho experimental (8,12–15).

Apesar de existirem indícios sobre a correlação entre o sulco e uma maior facilidade na divisão, é comumente difundida a falsa premissa de que comprimidos sulcados podem ser fracionados, o que não possui sustentação legal, e na maioria dos casos, não há respaldo do fabricante. A simples presença do sulco pode induzir pacientes e até mesmo profissionais de saúde a enganos com repercussão clínica desastrosa (6–9,11,15,16).

No caso de comprimidos que possuam tecnologia de liberação modificada, o seu fracionamento estaria vedado para aqueles casos em que o mecanismo de liberação possa ser comprometido pelo processo de partição. Comprimidos com revestimentos gastro-resistentes, por exemplo, não poderiam ser submetidos à partição, enquanto que sistemas matriciais multiparticulados, em tese, poderiam ser fracionados. Contudo, a dificuldade de informação acerca da tecnologia envolvida na concepção da forma farmacêutica, bem como o desconhecimento técnico do prescritor nesse tema, torna o processo decisório bastante delicado (8,12–14,16,17)

A forma de execução do procedimento de partição é igualmente uma questão que envolve múltiplas variáveis. A partição, comumente, é realizada com o auxílio de uma faca ou de um partidor de comprimidos, este último vendido em farmácias comerciais, mas também pode ser feita manualmente, dependendo da dureza do comprimido em questão. Há estudos relacionando a forma de partir com a precisão da partição, porém não há consenso quanto ao melhor procedimento a ser adotado (7,9,11,17–21).

O armazenamento dos fragmentos de comprimidos pelo paciente também é uma questão importante, uma vez que a divisão do comprimido expõe o seu núcleo às intempéries ambientais. Comprimidos que sofrem partição e são devolvidos ao frasco podem ter sua friabilidade aumentada, sofrer alteração na dissolução e apresentar uma maior degradação química (22).

Os dados técnicos disponíveis sobre o procedimento de partição de comprimidos são contraditórios e estão distantes de confirmar se esta prática é correta ou de qual maneira seria mais adequada de executar. Soma-se a isso a negligência das agências sanitárias no Brasil e na América Latina acerca do tema, que não apresenta qualquer tipo de regulação. Este panorama expõe de forma

alarmante a necessidade de se desenvolver um estudo amplo, multidisciplinar e sob bases teóricas e experimentais que esclareçam o impacto que a partição de comprimidos pode trazer para a eficácia e segurança do tratamento medicamentoso (7,9,11,17–21).

1.2 OBJETIVO

1.2.1 OBJETIVO GERAL

Analisar a partição de coprimidos através de estudo com bases regulatórias, teóricas e experimentais, que permitam um maior entendimento dos fatores que afetam esta prática clínica.

1.2.2 OBJETIVOS ESPECÍFICOS

- Realizar pesquisa bibliográfica na literatura científica acerca da partição de comprimidos, compilando o resultado em um artigo científico;
- Analisar as legislações sanitárias do Brasil e de alguns países do mundo, com enfoque na América do Sul, no que versa sobre a partição de comprimidos;
- Avaliar experimentalmente o impacto físico e mecânico da partição de comprimidos.

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CAPÍTULO 2

PANORAMA DOS ASPECTOS REGULATÓRIOS QUE NORTEIAM A PARTIÇÃO DE COMPRIMIDOS

RESUMO

A partição de comprimidos é uma prática que, apesar de gerar controvérsia no meio de saúde, é amplamente difundida, principalmente em tratamentos envolvendo crianças e idosos. Os riscos dessa prática estão relacionados principalmente à imprecisão na dosagem das frações e a problemas de estabilidade do medicamento partido. O objetivo desse trabalho foi traçar um panorama sobre as bases sanitárias que norteiam esse tema com enfoque na América do Sul, Estados Unidos e Europa. Foi constatado que as agências regulatórias de saúde dos países da América do Sul pesquisados não possuem qualquer norma publicada que trate de partição de comprimidos. Entre todas as agências sanitárias analisadas, a FDA dos EUA é a única a apresentar normas que abrangem desde instruções para orientar a realização desse fracionamento, até possíveis testes de desempenho do sulco na partição, introduzindo o conceito de sulco funcional, queestabelece algumas garantias quanto à capacidade do comprimido de ser fracionado. Pode-se concluir que ainda faltam bases técnicas e científicas para direcionar as normas sanitárias, tornando a decisão sobre a partição de comprimido, em determinadas situações, aleatória e de alto risco para a saúde pública. A necessidade de regulação mais pormenorizada é patente e a julgar pela importância do tema, espera-se que em um curto espaço de tempo essa enorme lacuna técnica possa ser finalmente preenchida, para o bem dos usuários de medicamentos.

Palavras-chaves: partição de comprimidos, regulação sanitária, sulco funcional

2.1 INTRODUÇÃO

A partição de comprimidos consiste em submetê-los a uma divisão física originando duas ou mais frações, sendo realizada para ajuste de dose, facilitar a ingestão do medicamento, ou redução do custo do tratamento medicamentoso (1). Até a existência de normativa sanitária específica sobre o tema com instruções de produção e realização do procedimento, o que só ocorreu em 2012, as agências reguladoras preferiam assumir que a partição de comprimidos era uma prática atípica. Contudo estudos mostram que fracionar um comprimido é algo mais corriqueiro que os órgãos sanitários gostariam (3-5).

Os comprimidos são a forma farmacêutica mais comercializada no mundo devido, principalmente à sua facilidade de administração, ao seu baixo custo e a sua maior estabilidade quando comparado a outras formas farmacêuticas, o que implica em um enorme universo de usuários (2). Na Alemanha, estima-se que 49% dos pacientes da atenção primária realizam partição de comprimidos (3). Um estudo realizado em farmácias comunitárias na Suíça com pacientes adultos em uso de polifarmácia mostrou que 12% dos pacientes afirmam ter dificuldades para engolir os comprimidos, sendo que 23% deles não aderem intencionalmente à farmacoterapia devido a essas dificuldades (6). No Reino Unido, uma pesquisa realizada em lares para idosos mostrou que esmagar comprimidos ou abrir cápsulas ocorre em mais de 80% dos cuidados da enfermagem (4). Outra pesquisa realizada na Austrália mostrou que, dos medicamentos utilizados em unidades de cuidados de idosos, 34% tinham sua forma farmacêutica original alterada antes da administração (5).

A preocupação dos profissionais de saúde com essa prática se justifica quando se analisam os seus riscos potenciais, o que leva os mais radicais a condenar a partição de comprimidos em qualquer hipótese. O principal risco apontado diz respeito à imprecisão na dosagem das frações obtidas pela partição - não há como garantir que um comprimido partido em dois originará fragmentos com exatamente a metade da dose original. De fato, segundo evidências científicas recentes, é quase certo que existirá variação na dose pretendida que, a depender do medicamento e do protocolo de tratamento, pode provocar desde dosagens subterapêuticas, até sobredosagens com graves consequências ao paciente (7).

A exposição ambiental do conteúdo interno do comprimido, ora revestido,

pode provocar problemas de estabilidade no medicamento. Há também a possibilidade de intoxicação decorrente do manuseio do comprimido durante o processo de partição, no caso de fármacos tóxicos (como antineoplásicos, por exemplo), e de dano ao trato gástrico com fármacos irritantes. É preciso mencionar ainda o risco de danificar os mecanismos de liberação modificada que sejam dependentes da integridade dos comprimidos (8).

Ressalta-se ainda que a partição de comprimidos é realizada especialmente no caso de crianças e idosos - populações mais vulneráveis às consequências clínicas negativas desse procedimento. Diante da magnitude do problema exposto, esse trabalho tem como objetivo apresentar um panorama sobre as bases sanitárias existentes acerca desse tema em diferentes países.

2.2 BASES REGULATÓRIAS

A Organização Mundial de Saúde reconhece a divisão de comprimidos como uma prática comum em farmácias, hospitais, e no ambiente doméstico e alerta para os riscos associados que podem levar a falhas no tratamento terapêutico ou mesmo toxicidade, contudo não estabelece nenhuma diretriz sobre o tema (9).

A agência sanitária europeia - *European Medicines Agency* (EMEA) - aborda o tema em um documento voltado para formulações pediátricas elaborado em 2006 (10). Nessa publicação, há também um alerta dos riscos da partição que são acentuados para comprimidos de menor tamanho, de baixa dosagem e não sulcados. Um novo guia contendo informações para o desenvolvimento de medicamentos para uso pediátrico foi finalizado em 2013 (11). Antes disso, em 1997, a Farmacopeia Europeia incluiu testes de acurácia para a divisão de medicamentos sulcados, sendo a primeira no mundo a propor algum tipo de controle de qualidade nos comprimidos destinados à partição (12, 13).

As agências regulatórias de saúde dos principais países da América do Sul, incluindo a ANVISA do Brasil, a ANMAT da Argentina, o ISP do Chile e a UNIMED da Bolívia, não possuem qualquer norma publicada que trate de partição de comprimidos. A ANVISA divulga apenas algumas recomendações superficiais sobre

o tema em seu *site* (14). Ao ignorar a existência da partição não há, consequentemente, políticas públicas voltadas para mitigar o problema. Medidas como a concessão de incentivo às indústrias farmacêuticas para disponibilizarem medicamentos em faixas de dosagens mais amplas e em formas farmacêuticas alternativas, poderiam reduzir consideravelmente a demanda do fracionamento dos comprimidos.

Entre todas as agências sanitárias pesquisadas, a *Food and Drug Administration* (FDA) dos EUA é a única a apresentar normas mais detalhadas acerca da partição de comprimidos. A FDA, além de fornecer avisos e instruções para orientar a realização da prática, também estabelece normas para regular o processo de fabricação e seus controles de qualidade específicos (13,15,16). A seguir, destacam-se alguns dos principais pontos abordados pela agência norte-americana.

2.2.1 Informação técnica para realizar a partição

A FDA delega ao profissional de saúde a responsabilidade de decidir sobre a partição em determinadas situações específicas, inclusive quando não há recomendação do fabricante, contudo estabelece algumas instruções para nortear esses profissionais e os pacientes acerca da melhor maneira de realizar o fracionamento de comprimidos (13).

Uma recomendação importante versa sobre o armazenamento das frações partidas. Instrui-se evitar locais úmidos, como o armário do banheiro. Outra advertência simples e valiosa diz respeito à realização da partição de um comprimido por vez. Os riscos de problemas de estabilidade e de imprecisão na dosagem aumentam muito quando há vários comprimidos na caixa, uma vez que o atrito mecânico entre as frações seccionadas pode aumentar o seu grau de esfarelamento, levando a perda de massa e consequentemente, redução da dosagem (16).

Diante da falta de estudos sobre as melhores condições de armazenamento e considerando as alternativas disponíveis, a *pill box* aparece como a opção mais

indicada, porém está longe de ser ideal. Esse dispositivo de armazenamento deixa seu conteúdo exposto à umidade ambiental e à luz, e não é capaz de imobilizar as frações do comprimido, favorecendo o atrito mecânico com outras frações ou mesmo com as paredes da caixa. Os problemas relatados poderiam ser minimizados com uma vedação hermética, a adição de um componente dessecante aos casulos, e o emprego de materiais impermeáveis e opacos na constituição da *pill box*. O desgaste das frações poderia ser minimizado com a colocação de algodão para preencher o espaço de cada casulo, evitando o movimento das frações de comprimidos durante o transporte.

Quanto à forma de partir os comprimidos, a FDA recomenda avaliar as características de tamanho e formato de cada comprimido, e reconhece que o uso de partidor de comprimidos é uma forma frequente de realizar esse fracionamento. O referido utensílio, encontrado em qualquer farmácia comercial, é provido de uma forquilha capaz de centralizar o comprimido e de uma lâmina para cortá-lo, contudo seu uso ainda está longe de ser uma unanimidade. Estudos conduzidos por Shah e colaboradores verificaram que, no caso da partição de comprimidos de levotiroxina, que apresenta índice terapêutico estreito, o uso de partidor provoca maior fragmentação e piora as características de friabilidade e uniformidade de conteúdo das frações (7). A farmacopeia adota a partição manual dos comprimidos nos testes de controle de qualidade (17).

A agência norte-americana estabelece também os casos em que a partição é vetada: quando o fracionamento origine doses fora da faixa de uso; quando envolva um fármaco que não seja seguro para o manipulador; ou quando o comprimido apresente mecanismo de liberação modificada que possa ser comprometido pelo processo de partição.

No caso de comprimidos de liberação modificada, a decisão deve basear-se no mecanismo de liberação envolvido. Comprimidos com revestimentos gastro-resistentes, por exemplo, não poderiam ser submetidos à partição, enquanto que sistemas matriciais multiparticulados devem ser estudados caso a caso. Há dificuldades em identificar a tecnologia envolvida em cada medicamento, pois essa informação não consta na bula e dificilmente é revelada pelo serviço de atendimento ao consumidor devido ao segredo industrial de produção. Os médicos, prescritores do medicamento, não possuem formação farmacotécnica para decidir nesses casos, o que evidencia a complexidade e o caráter multiprofissional da decisão sobre a

partição de um comprimido.

2.2.2 Especificações de fabricação

A FDA estabelece que a dosagem de cada fração do comprimido obtido após a partição não pode estar abaixo da dose mínima terapêutica indicada no registro do medicamento. Os comprimidos fabricados para esse fim devem ser submetidos a testes mecânicos de laboratório. Os fragmentos de comprimidos que se pretendam armazenar devem ainda cumprir outros requisitos mais específicos, como provar que possuem estabilidade por, pelo menos, 90 dias em temperatura ambiente (13).

De forma coordenada com as normas estabelecidas pela FDA, as principais farmacopeias do mundo – Farmacopeia Americana USP e Farmacopeia Europeia – estabelecem monografias que especificam critérios de qualidade a serem atendidos pelos comprimidos submetidos ao processo de partição (12, 17). Contudo, as monografias recorrem a adaptações dos ensaios preexistentes para avaliação de comprimidos inteiros, não havendo, portanto, ensaios que tenham sido desenvolvidos de forma específica para avaliar a partição de comprimidos.

Os ensaios ainda não são capazes de garantir que o comprimido de fato pode ser fracionado com segurança. A farmacopeia estabelece como aceitável um intervalo de variação de massa para as frações de comprimidos de 75 a 125% (17). Esses limites parecem ser arbitrários e certamente são uma generalização perigosa para fármacos que possuem janela terapêutica estreita, como por exemplo, a Varfarina, que apresenta vasta utilização em pacientes idosos, e é amplamente fracionada na rotina médica para ajuste de dose (18).

2.3 O SULCO FUNCIONAL

Originalmente, a presença de sulcos em comprimidos tinha razões estéticas, além de servir para aumentar a sua resistência mecânica. A ideia de que a existência de sulco em um comprimido o habilitava a sofrer divisão mecânica não passava de um mito e ainda o é em países sem regulação específica.

Pôde-se comprovar através de pesquisas que vários são os laboratórios no Brasil que fabricam comprimidos sulcados sem fornecer qualquer garantia sobre sua partição, muitos inclusive desaconselham o procedimento, alegando que a presença de sulco em seus comprimidos deve-se as configurações das máquinas de fabricação e que apenas são realizados estudos de estabilidade com os comprimidos íntegros, não havendo como assegurar a viabilidade e segurança do processo de partição (dados não publicados).

Alguns estudos mostram que a presença de sulco minimiza variações importantes na uniformidade da massa dos comprimidos partidos, contudo isso não é observado para todos os medicamentos sulcados (19).

Provavelmente a contribuição mais inovadora da regulação estabelecida pela FDA seja a instituição do sulco funcional. A denominação - sulco funcional - é uma espécie de selo de qualidade que mostra que o fabricante testou a capacidade de seu comprimido de originar subdivisões uniformes aceitáveis, segundo critérios de qualidade previamente estabelecidos (13).

Atualmente nos EUA, apenas os laboratórios farmacêuticos que atendam às recomendações dessa norma e aos ensaios farmacopeicos poderão produzir comprimidos sulcados. Comprimidos que não atendam a esses critérios não poderão apresentar sulcos, como o caso de comprimidos com tecnologia de liberação modificada que dependam da integridade do comprimido para o seu correto funcionamento. De momento, essa exigência não é necessária para o registro de comprimidos sulcados em países da América do Sul.

2.4 A INTERCAMBIALIDADE DOS MEDICAMENTOS GENÉRICOS ESTÁ EM CHEQUE

A regulação brasileira, que especifica os requisitos técnicos que os medicamentos genéricos e similares devem cumprir para se tornarem bioequivalentes ao medicamento referência, desconsidera a partição e a presença de sulco nos comprimidos, o que na prática pode levar a divergências entre genéricos e referências neste quesito (20).

A FDA reconhece a necessidade de que o sulco existente no medicamento referência deve ser reproduzido no medicamento genérico com a mesma funcionalidade (13, 21).

2.5 AS BASES CIENTÍFICAS

Os estudos científicos publicados até a data apontam que fatores como formato do comprimido, espessura, dureza, tipo de sulco podem ser decisivos na obtenção de frações de comprimidos com uniformidade de dose, porém ainda não há certezas estabelecidas (22). É possível que haja uma idiossincrasia entre esses fatores, contudo sua magnitude ainda é desconhecida.

Apesar da importância do problema relacionado e de sua extensa prática, há poucos artigos publicados até a data com foco no estudo do processo de partição de comprimidos e suas implicações. Em busca realizada nas bases de dados *scifinder scholar e pubmed* utilizando as principais palavras-chave do tema (*spitting tablets, tablet breakability, tablet functional score* e *tablet break line*), 45 artigos foram encontrados, sendo que apenas 12 deles foram publicados nos últimos cinco anos.

CONCLUSÕES

Não restam dúvidas de que a existência de normas regulatórias é a única maneira de tornar a partição de comprimidos uma prática controlada, fornecendo um mínimo de garantias para os usuários de medicamentos. Contudo, a legislação sanitária atual sobre o tema ainda se mostra rudimentar. Faltam subsídios científicos para nortear a prática de partição de comprimidos, o que explica o caráter insipiente das especificações sanitárias sobre o tema.

A legislação norte-americana, mesmo que ainda de maneira superficial, estabelece critérios mínimos de produção e controle para os comprimidos comercializados que podem ser partidos. O estabelecimento do sulco funcional representa também um avanço significativo para tornar mais segura a prática, ainda que não elimine completamente seus riscos.

O problema apontado possui grande alcance sanitário e é demasiadamente abrangente para continuar sendo ignorado pelas agências regulatórias da América do Sul. Torna-se imperativo estabelecer normas mínimas para regular a correta utilização e fabricação de comprimidos que serão submetidos à divisão.

A recomendação geral dos laboratórios farmacêuticos de deixar a decisão nas mãos dos prescritores parece temerária, haja vista a falta de informação técnica sobre a prática, que somada ao desconhecimento desse profissional acerca da composição do medicamento e dos processos de produção envolvidos, torna a decisão sobre a partição completamente aleatória e de extremo risco para a saúde da população.

A massificação desse procedimento evidencia a necessidade de mais estudos científicos que embasem novas regras e especificações sobre o tema. Muitos trabalhos recentes têm sido conduzidos nesse sentido, porém as determinações técnicas ainda caminham em terreno instável. Novos estudos devem aparecer nos próximos anos que permitam aprimorar as normas sanitárias existentes até o momento. Até lá, cautela parece ser a palavra de ordem a ser adotada pelos profissionais de saúde.

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CAPÍTULO 3

UPDATED TECHNICAL ASPECTS TO GUIDE TABLETS SPLITTING

ABSTRACT

Splitting tablets is a common practice in hospitals and day care, especially used by elderly and children for dose adjustment, facilitate swallowing and to reduce treatment costs. Splitting tablets involves different aspects, such as pharmaceutical manufacturing and possible therapeutically outcomes. The most important concern is about inaccurate dose, notably critical for drugs with narrow therapeutic window, correlated with poor split, resulting in high weight variation and weight loss. Splitting modified-release medicines are also a complex matter, potentially leading to toxicity or ineffectiveness of the drug. The objective of this review was to compile publications and group them into topics, covering subjects as the risks of splitting, the procedures, patient profile, tablets characteristics, the role of breakmark, laboratory assays and clinical trials, in order to draw a clearer picture about this practice, and to identify the technical gaps that may guide future works in this area.

Keywords: dose accuracy; quality control tests; score; splitting procedures; stability; tablet splitting; weight variation.

3.1 INTRODUCTION

Splitting tablet refers to the subdivision of this unit dosage form in two or more parts. This procedure is commonly done following physician prescriptions, recommended by health insurance or on the initiative of patients. A study in Germany showed that about two-thirds of patients split tablets and almost forty percent of them believe that all tablets could be split (1,2).

The segmentation of tablets is performed for various reasons, mainly to dose adjustment, dosage titration, to facilitate swallowing and to reduce treatment costs (3–7). Scored tablets with higher price and higher doses are especially chosen to be split in routine (8).

Despite the high frequency of splitting tablets in clinics and its consequent health importance, there is no consensus about this subject in the medical field, causing recurring doubts in prescribers, health professionals and patients (1,2). There are no clear health guidelines, which still causes more uncertainty regarding the security of this practice. Pharmaceutical companies, in general, disclaim any responsibility, leaving to prescribers and health professionals the responsibility about the subdivision of tablets.

One of the most important problem with this practice is the wide dosage variation between the two halves (inaccurate dose), which can compromise medication therapy, especially for elderly and children that are commonly the target group of such procedure (5,9–13). Another important issue is about drugs with narrow therapeutic window (or low therapeutic index), since every dosage difference could result in a very distinct physiological response for this class of drug (14–16).

From this background, the objective of this review is to conduct a compilation of studies on the subject of splitting tablets, identifying tendencies, what is consistent in this practice and what needs to be further studied. The assembly of this puzzle will draw more clear recommendations that will guide health professionals in the light of what has been discovered so far.

3.2 RISKS OF SPLITTING

Weight variation is the most critical parameter in splitting because it can lead to variation in drug therapy dosage. Many researches have shown a large variation in half tablets weight, do not reaching satisfactory results according to The International Phamacopoeia and European Pharmacopoeia (Ph. Eur.), which establish a range of values that should be within 85%-115% and no more than one tablet could be outside the range of 75%-125% (5,9,10,16–29). Some studies reports that 16% to 41% of tested medications are out of this first limit (9,10,17,19-20). Weight variations out of the range 75%-125% are described for approximately 12% of the tested tablets in two of these studies (9,10).

Some researches pointed out that weight variation is associated with weight loss during the splitting process, due tablet fragmentation and crumbling (5,17,19). Studies pointed out an average weight loss extends from 0.2 to 3.75% (9,13,17,18,30), with some high individual weight loss, as 23.5% (13) and 19.4% (9).

Though it causes fewer splurges than weight and dose variations, the impact on the stability of tablet fragments after split is a matter which can compromise relevantly drug therapy and endanger patient's health (16). In theory, the new surface created with tablet division, increases exposure to environmental moisture and oxygen. In many cases, tablet is removed from primary packaging to store the halves after fractionation process in containers for days, weeks and even months (31). In the case of coated tablets, the splitting process eliminates this protective barrier, exposing the central core of the tablet to environmental weathering.

Despite the latent risk of chemical decomposition due subdivision process that can shorten the drug expiration time, few studies have been dedicated to this topic. Margiocco and col. tested cardiovascular tablets split in quarters after 30 days of storage and found significant decrease in some of the tested drugs, especially in digoxin, which had a decrease from 105% to 68% of expected content, specially critic because of its low therapeutic index (16). On the other hand, gabapentin tablets tested in long-term and intermediate conditions (30^{o}C/60% relative humidity and 25^{o}C/60% relative humidity, respectively) for nine weeks did not show difference in drug content comparing to whole tablets (32). Valdecoxib tablets stored for two

weeks at 10°C – 21°C and 50-80% of relative humidity found no weight variation during this period of time (33).

These few studies highlight the clear conclusion that split tablet stability depends heavily on the drug and its sensitivity to challenging storage conditions and that this aspect should be considered in the decision of storage a tablet after split.

3.3 SPLITTING PROCEDURES

There is no agreement about the best way to split tablets. The most commons procedures use table knife, tablet splitting device or break the tablet by hand. Although some studies conclude that one of splitting methods have better performance than others, those conclusions are still quite contradictory (Figure 1) (5,14,22,23,26,34–37).

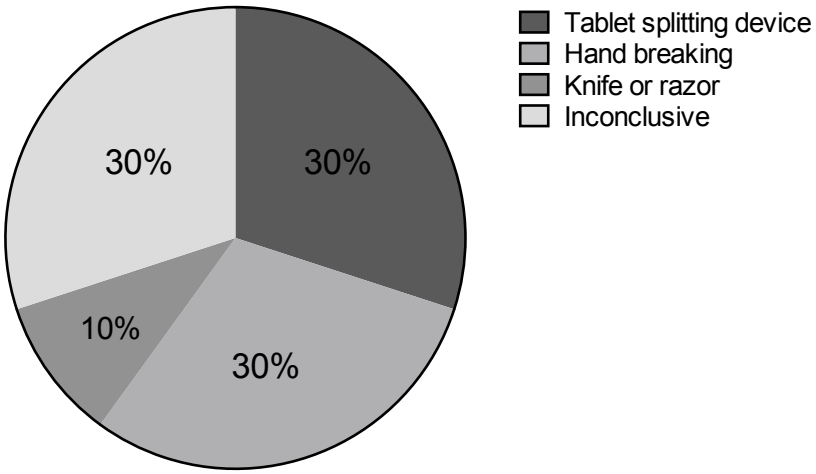

Figure 1. Best methods to tablet splitting according to literature.

A couple of studies has shown best results with a tablet splitter rather a kitchen knife (23) or hand breaking (5). Verrue and col. have found superiority in tablet splitter considering weight variability and weight loss compared with manual

splitting or using knife or scissor (35). A study comparing tablets split by hand and tablets split using a knife has shown better results with knife (22).

Van-Riet Nales and col., after testing six different tablet splitter, kitchen knife and hand breaking, have concluded that hand broken tablets had better accuracy and precision than the others splitting methods (17). Similar results were found by Shah and col., who have found less fragmentation in tablets split manually, comparing to tablet splitter (14). Another study has established that the presence of score facilitate the tablet division by hands (18). However it is easy to see that small size tablets have difficulty to be broken by this method.

It was noticed by researches that irregularities in tablets fractures are accentuated in hand splitting comparing to splitter device or razor split which provide a "cleaner" split (5,22). The way in which the hand splitting is executed also plays an important role in the success of the operation. Less weight loss and weight variability were obtained when the breaking force applied by the thumbs is directed towards the score side of the tablets, as by “opening” the score (37).

Against that, three studies did not found any difference between a splitting device or a kitchen knife or between a splitting device or a splitting by hand (26,34,36).

3.4 INFLUENCE OF PATIENT PROFILE ON SPLITTING

McDevitt and col. conducted a study with 94 volunteers splitting hydrochlorothiazide tablets by hand and found no predictive factor between age, gender, education and tablet-splitting experience (9). Similar conclusions were found by other authors, shown no correlation in age and gender with capacity of split tablets (38,39). Peek and col. found that in elderly patients the reference of the tablet splitter, training for that practice and patient experience are decisive factors for tablet-splitting accuracy (40). Other study pointed out that the patients acceptance and their interest in splitting tablets are affected by education level and therapeutic regimen (41).

Polli and col. research has showed that economic incentive and appropriate orientation improve the splittability of tablets (42). Surveyed patients show a high

level of satisfaction with splitting practice, and more than 90% found easy using tablet splitter (41,43–45).

A study performed in the Netherlands to measure the experience of patients with splitting tablets showing 36% of negative experiences, with complains about uneven split and difficulties in breaking (38). Also, Hixson-Wallace and col. found better compliance in whole tablet treatment compared with split treatment using warfarin tablets (46).

3.5 INFLUENCE OF TABLETS CHARACTERISTICS ON SPLITTING

Shape, diameter, thickness and width are important factors to predict ease of breakability. Large tablet thickness, a deep score line and a flat face are desirable (10,18,20). Also, it was shown that oblong tablets are split easier than round ones, and unusual tablet shape such as trapezoid, shield-like, and spherical, seems to hinder splitting when a tablet splitter is used (10,18,20,42).

Spiegeleer and col. found a linear function between variability of split tablets and score length, which could help explains best results of oblong tablets compared with round tablets, once oblong have proportional smaller length of score (47). Helmy listed as convenient characteristics for tablets that will be split:, scored, flat, oblong or oval and large size (20).

Another study classify the breakability factors in decreasing importance order as crushing strength, diameter, score mark and shape (flat or biconvex) (18). Sovány and col. have showed that tablet hardness and properties of the materials that composes it are related to breaking quality and had superior results with higher tensile strength (2). Although these findings shown hardness as an important factor for tablet splitting prediction, a discordant study found high tablet hardness a bad factor that predisposes non-uniformity, but this study did not measure this factor directly, just used the tester's perception (42). Other studies also showed friability as a more decisive aspect than hardness (21,48).

Van der Steen and col. defined some acceptance criteria for tablets critical physical parameters for an easy tablet splitting, which are diameter not less than 10

mm, the ratio diameter/width not less than 2.0, depth of score line not less than 0.5mm, resistance to crushing not more than 100N (18).

Concerning the tablet with an aesthetic coating, most of the studies reveal that this component increase tablet splittability (9,36,49). Pimple and col. found no difference in weight loss and content uniformity for coated and uncoated split tablets (36).

Gupta and col. tested different excipients and found better results in weight variability and weight loss using dibasic calcium phosphate as filler instead of lactose monohydrate, and microcrystalline cellulose as disintegrating agent instead of sodium carboxymethyl cellulose (32).

3.6 SCORE OR BREAKMARK

It is generally thought that tablets with score lines (or breakmarks) allow the dosage form to be subdivided into half doses (5,36). This misunderstanding lead patients and even health care providers to think that score tablets can always be split, what is not true. A proof of it is shown in a study that reveals that more than two thirds of nurses answered “yes” to a question asking if it is allowed split every tablet with a score-line (50).

Score lines seem to improve tablets breakability in most of the studies focus on this subject. Scored tablets show less weight and content uniformity variations after subdivision than nonscored tablets (10,19,21,32,51). Gupta and col. evidenced the benefit of score for splitting in tablets prepared with equal formulation and in same conditions (32).

Despite of this, two studies in which no difference were found between scored and nonscored tablets for the content uniformity test (16,22). Controversially, a recent study conducted by Helmy and col. found more variability in drug content and weight in scored medications than in nonscored ones. The authors explain their findings suggesting that other characteristics are influencing in results, such as hardness, size, thickness and shape of the tablets (20).

The splitting of cross-scored tablets has also been studied, since clinical practice in some cases performs the tablet subdivision up to four fragments. Spiegeleer and col. showed that the relative standard deviation of quarters tablets weights was about the double than halves tablets (47). Similarly, Van Vooren study shows the weight variation of quarters are almost twice than in halves (37). Margiocco and col. found high variability in content uniformity for quarters than halves (16). Although there are not many studies related to cross-scored tablets, the results published to date indicate a wide variation in dose and weight suggesting that the risks of quadruple splitting tablets outweigh the benefits that the procedure can bring.

Although most findings shown better marks for scored tablets splitting, it does not mean they are allowed to be split. Even scored tablets did not reach acceptable uniformity for their halves in many studies (4,7,12). Also, it seems that the depth of the score line is critical for the splitting (10,18,20,52). Van der Steen an col. found the minimum value for score depth as 0.5mm and that two sided score marks made easier tablet's split (18) .

FDA established a new concept of functional scores, which drug tablet have to present safety for hand manipulation, halves should not have less than the minimum therapeutic dose indicated for that drug and need to achieve the same finished-product testing requirements as for a whole-tablet with same strength. Also, halves should exhibit stability for a minimum period of storage of 90 days at 25ºC/60% of relative humidity. Tablets which split could compromises delivery technology should not have score (53).

3.7 WHEN RESORTING TO SPLITTING?

Many experts maintain that the splitting tablets should only be performed when no other option is available, as in the case of patients who are unable to swallow the whole tablet or in the case of the lack of other doses available in the market. However, it cannot disregard the usefulness of this practice for purely economic reasons, especially for economically vulnerable populations.

The capability of reducing treatments costs for patient and health system is one important factor taken into account in the decision of splitting tablets in many countries. According to Choe and col., patients show a good acceptance in splitting tablets for save money (88%) (41). Many studies showed economic advantages in that practice (43,54–59). Gee et al. showed an annual saving of US$ 138.108,00 splitting simvastatin, atorvastatin and lovastatin tablets (54). Cohen found a possible annual saving of U$1.45 billion in splitting twelve psychotropic medications, and U$1.5 billion with splitting three antidepressants (55,56). Dormuth and col. found an economy of $2.3 million associated to statin split in British Columbia (59).

Another aspect to consider is regard to the type of tablet object of splitting. Currently, it is increasingly frequent the insertion into the market of tablets containing modified release technology designed to modulate the drug release (60). Modified release preparations, when fragmented, may undergo changes in their properties releasing a high dose of active ingredient, resulting toxicity and lives risk to the users (61). The US health agency seals the splitting tablets that have modified release mechanisms that can be compromised by the division process (62).

In the case of modified release tablets, the decision on splitting should be based on the release mechanism involved. Tablets containing gastro-resistant coatings, for example, could not be subjected to subdivision since the drug control release depends on the coating integrity, however matrix systems require further studies that measure the impact of splitting in its release kinetics (20,26,42,50,63).

A study with methylphenidate extended-release tablets found no difference in dissolution between split and whole tablets, concluding that split methylphenidate tablets could be clinically acceptable (64). In an opposite way, halves tablets of aspirin sustained-release formulations showed a consistently higher release profile over time, with a 50% higher release at 6 h compared with whole tablets (65).

Shah and col. shown a fast dissolution profile of halves theophylline controlled-release tablets comparing with whole tablets (66). Zhao found more weight variation after split metoprolol extended release tablets compared with intact one because of the uneven distribution of metoprolol beads in tablet surface (67). Despite it, Vranic and Uzunovic seen no difference in dissolution rates of metoprolol extended release tablets after and before split concluding that this tablet is eligible for splitting (68). Clinical studies conducted with dosage forms containing such technology have also shown conflicting results (see section - splittability tablet: clinical trials).

Splitting drugs with narrow therapeutic range is controversial because drug content variation could lead to serious clinical consequences, and the possibility of segregation in the compaction step of manufacture of the tablet cannot be ignored (3,5). The International Pharmacopoeia advises that tablets of drugs with narrow therapeutic window, as warfarin and digoxin, shound not have scores for subdivision (30).

3.8 TABLET SPLITABILITY: LABORATORY ASSAYS

Laboratory quality control tests routinely recommended to evaluate tablets splittability are the same used for whole tablets described in pharmacopoeias: average weight, friability, content uniformity, disintegration time, assay and dissolution. American Pharmacopoeia establishes the range of 85 to 115% the acceptable weight variation for halves tablets (69). However, these limits can be a dangerous generalization to drugs that have a narrow therapeutic window.

Some articles propose new analytical methods that may be useful to assess specific aspects involved in splitting tablets. Scanning electron microscopy evaluations were used to measure the surface topography of halves tablets identifying irregularities in the break point (5). Raman spectroscopy is able to identify the drug distribution in tablets halves, which can be very useful in low dosage drug tablets (3). Sovány and col. studied tablet's structure by X-ray computed microtomography (micro CT), seen particle structure and density distribution of tablets (70).

3.9 TABLET SPLITABILITY: CLINICAL TRIALS

A fairly valid way of assessing the impact of splitting tablets can be carried out through clinical studies evaluating biochemical and or clinical responses of patients (54,71–74).

Patients using whole or half lisinopril tablets for hypertension control shown no significant differences in blood pressures levels between both groups (71). Some of studies are performed with HMG Co-A reductase inhibitors, which monitored lipid panels and also liver enzyme levels (41,54,72–74). Most of than found no differences between halves and whole tablet therapy, probable due the wide therapeutic index of drugs used (42). However, in Coblio and col. research, almost 20% of patients presented LDL increased using split tablets and returned to whole tablets treatment (75).

Concerning to modified-release tablets, studies using verapamil sustained-release tablets did not find statistics differences in bioavailability between split and whole tablets (76,77). A study using theophylline slow-release tablet showed faster absorption and higher plasma levels when volunteers took the halves instead whole (78). However, pharmacokinetics studies using this same dosage form affirms that the difference in serum curves of whole and split theophylline tablets are negligible and the splitting for dose convenience is recommended (79,80).

FINAL CONSIDERATIONS

The majority of the studies conducted on this subject focus in measure the weight variation cause by tablet splitting. Drug instability after this procedure is a patent possibility and should be evaluated on an individual basis following stability protocols. While there are no studies of this type available, the recommendation that tablets should be split only immediately prior to intended use is the option to follow.

The most appropriate procedure to split a tablet is also far from being an established certainty. Among the options used, there is a tendency to identify tablet splitter as the best way to execute it and hand broken are indicated for scored tablets.

It was not possible establish any clear relationship between the efficiency in the splitting and individual characteristics of the operator, such as gender and age. However it is suggested that instruct the patient on the practice by a health professional can make a difference in the success of the operation.

Studies so far show that the tablets characteristics influence relevantly its splittability. While there is not absolute agreement, score coated tablets, with oblong shape and high hardness appear to be more suitable for splitting process. Although the presence of score is no guarantee for a satisfactory splitting, its existence is a relevant factor in the efficacy of this procedure. There is a need to study the technological aspects involved in this component in order to optimize its benefits. Some studies dedicated to split cross-scored tablets show a linear increase in weight variation in the tablet subdivision into 4 fragments, suggesting that the risks outweigh the benefits in this case.

The splitting of modified-release matrix tablets is still quite contradictory. The studies published to date often come to opposite conclusions for the same commercial preparation. It seems important to identify the mechanical and physical aspects of the process and the impact that the splitting of each matrix can bring in the drug release kinetics.

Beyond the simple adaptation of pharmacopoeial tests recommended for tablets, it is clear the need to develop specific laboratory tests to assess splittability tablet. Analytical techniques such as microscopy, Raman spectroscopy, X-ray microtomography have been identified as alternatives.

Clinical studies show different conclusions from laboratory tests. Clinical trials seen to present a less critical relationship between splitting and fluctuations in therapeutic responses of patients, which is closely related to the drug therapeutic index.

Although many studies shown the inaccuracy of tablet splitting, that practice is still important for patient dosage adjustment, especially when are taken into account that dose-related adverse effects of medications are the extensive problem in current medical practice.

Finally, it is necessary to consider splitting tablets as a necessary and inevitable evil in clinical practice. From this premise, it is required to establish a greater methodological rigor in the evaluation of formulations intended for this purpose. The information brought in this review has to answer several important issues and point the way to future studies on this subject in order to increase the safety of splitting.

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CAPÍTULO 4

INFLUENCE OF TECHNOLOGICAL AND METHODOLOGICAL ASPECTS INVOLVED IN TABLET SPLITTING

ABSTRACT

Splitting tablets is a common practice used for many reasons, such as dose adjustment, dosage titration, swallowing facilitation and reducing of treatment costs, especially for therapies with elderly and children patients. The aim of this study was to investigate how technological aspects of production as well as methodological procedures influence accuracy of tablets splitting. Five drugs used in medications commonly split by elderly patients were selected. Mechanical and physical tests and image analysis were performed comparing scored and nonscored generics tablets with scored reference tablets, before and after splitting. It was also compared the method of split, and others tablets technological aspects, such as shape, presence of coating and types of diluents. Image analysis based on surface areas proves to be a useful tool as an alternative assay to evaluate of the accuracy of tablets splitting, presenting statistical correlation with weight variation test. Regarding to splitting procedure, splitter tablet demonstrates advantage related to knife, presenting a better behavior in weight loss and friability tests. Oblong, coated and scored tablets had better results after split than round, uncoated and nonscored tablets. More plastic diluents, as microcrystalline cellulose and lactose monohydrate, affect adversely the tablet splitting performance, promoting more weight variation and weight loss comparing to dibasic phosphate dehydrate and starch. Finally, it was not found equivalence between generics drugs and their reference drugs in all five drug selected regard the splitting process, which indicates the necessity of review the health regulations for registration of generic drugs.

Keywords

coating; generic drug; image analysis; score; splitting procedure; tablet composition; tablet shape; tablet splitter; tablet splitting.

4.1 INTRODUCTION

Tablets for oral administration are the most common commercially dosage form and its division at the time of intake is a fairly usual practice (1,2). Splitting tablet is performed for several reasons, such as dose adjustment, dosage titration, swallowing facilitating and reducing of treatment costs (3–5).

The main problem with this practice is the wide dosage variation in tablets fragments, which can compromise medication therapy owing to a subtherapeutic or a toxic dose, particularly critic for drugs with narrow therapeutic index (5–10). Formulation technology, as found modified released tablets, can be impaired by the splitting process, leading to disastrous outcomes (11,12). Elderly and children patients are especially affected by splitting due to high frequency which they use this procedure and the vulnerable health of these target groups (6,11,13).

Although scored tablets suggest the possibility of splitting, it is not something regulated in most countries and it is up to the pharmaceutical industry manufacturer decides to put or not score mark in tablets and give information about splitting. Even generic drugs do not have obligation to have similarity with the reference medicine in this aspect (14).

The available literature is not sufficient to establish with certainty which tablet production conditions impact tablets splitting process and the importance of each variable in this practice. The interference of shape, surface, composition, or coating in splitting process is discordant. Even if the presence of score is a favorable factor for the accuracy of tablets splitting is contradictory (9,15–18).

The best way to split tablets it is not a consensus as well. There are many different procedures as splitting by hands, with scissors, with a kitchen knife or using tablet splitter. Studies show contradictory findings about those methods and it is not possible to reach a conclusive result using the scientific basis available (5,15,19,20).

Considering this scenario and the relevance of the subject, this study was designed in order to investigate the influence of technological aspects of production, such as score, shape and coating, as well as methodological procedure of split, in the accuracy of fifteen selected medicines splitting.

4.2 METHODS

4.2.1 Material

The choice of medicines aimed to achieve good representation of the technological variables studied. Five drugs often split in clinical practice by elderly patients were selected - immediate release oral tablets of atenolol 50mg, captopril 25mg, hydrochlorothiazide 25mg, losartan 50mg, and sertraline 50mg. For each one of these drugs, three sorts of drug products available in brazilian market were chosen: the reference product and two generics (one scored and other nonscored), totaling 15 different medications.

4.2.2 Study protocol

Tablets were split using both a commercial tablet splitter and a kitchen knife. The different products, were submitted to mechanical and physical tests to asses the impact of split in weight, hardness, friability and disintegration. The study protocol is outline in Figure 2.

It was also analysed the after split behavior of generic drugs tablets and reference drugs tablets in order to examine the interchangeability of medicines after split.

Additionaly, comparisons were made between splitting methods (knife and tablet splitter), score (scored and nonscored tablets), shape (round and oblong) and coating (uncoated and coated tablets). A further qualitative analysis of tablets dilluents starch, lactose monohydrate, microcrystalline cellulose (MCC) and dibasic phosphate dehydrate (DCP) (presence and ausence) was performed.

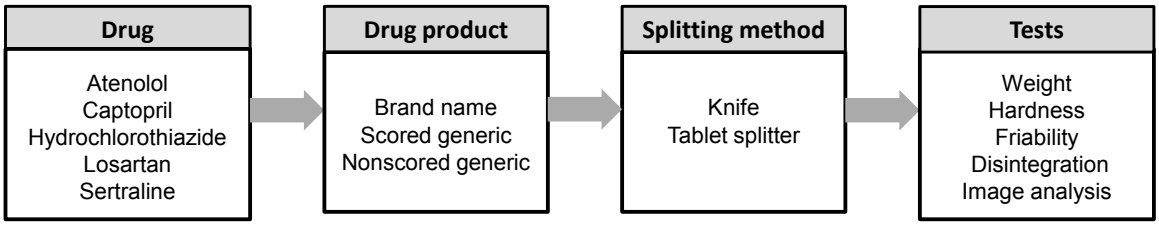

Figure 2. Scheme of the experimental protocol followed for evaluating the splitting tablets.

4.2.3 Mechanical and physical characterization of tablets

4.2.3.1 Weight

Twenty tablets of each medicine were individually weighed using precision balance Shimadzu model AUY 220, before and after splitting. Weight variation was measured by the difference between experimental weight of half tablets and their theoretical weight which was the whole tablet weight divided by two. Weight loss was calculated as the difference between the weight of the whole tablet and the sum of the module of each split tablet. Results were expressed in percentage as mean and standard error values.

4.2.3.2 Hardness

Hardness of ten whole tablets or halves of each medication was obtained using a durometer Nova Etica model 298-AT. The results were expressed as hardness variation, calculated by the difference between hardness of whole tablets and split tablets expressed in percentage as mean and standard error values.

4.2.3.3 Friability

Tablets friability were measured as the percentage of weight loss of twenty whole tablets or halves of each medication tumbled in a friabilometer Nova Etica model 300 working at 25 rpm for 4 min. The results were expressed as friability variation, calculated by the difference between friability of whole tablets and split tablets, expressed in percentage as mean and standard error values.

4.2.3.4 Disintegration time

Tablets disintegration time was measured in water at 37 °C in a disintegration tester Nova Ética model 301-6. For each group, six randomly selected tablets were tested. The results were expressed as disintegration time variation, calculated by the difference between disintegration time of whole tablets and split tablets, expressed in percentage as mean and standard error values.

4.2.3.5 Image analysis

Ten tablets from each group were analyzed using a stereomicroscope Stereo Zoom Microscope XTL connected to a videocamara. The images were captured with software ISCapture Version 2.5.1 and processed with software Image-Pro Plus version 4.5.0.29, where tablets surface area were measured and compared. Results were expressed as surface area variation, calculated by the difference between the surface area of whole tablet and split tablet, expressed in percentage as mean and standard error values.

4.2.4 Statistical analysis

Statistical analysis was performed taking into account splitting method and information related to technical characteristics of tablets as drug, registry group, shape, surface, presence of score, presence of coating and excipients. Statistical analysis was carried out using the SPSS (Statistical Package for the Social Sciences) version 17.0 and Prism version 5.0 softwares. The mechanical and physical characterization of tablets data were expressed as mean ± SEM (standard error of mean) and values of $p<0.05$ were considered statistically significant. Quantitative variables were tested for normal distribution with the Shapiro-Wilk test. Possible differences among groups were investigated by performing ANOVA or the Kruskal-Wallis test (data not normally distributed), followed respectively by Bonferroni's or Dunn's multiple comparison tests. When two groups were compared, we used the Student t test or Mann-Whitney U test (data not normally distributed). On the other hand, data of the quantitative variables (the mechanical and physical characterization of tablets data) were grouped into two groups - above or below a reference value (median) in order to verify the effects of qualitative variables (splitting method, score, table shape, coating). Thus, the chi-square test or Fisher's exact test was performed. All correlations between the tests characterization of tablets data were determined with the use of Pearson product-moment estimates (r). Reference values for each quantitative variable were 7.49 for weight variation, 0.76 for weight loss, 54.94 for hardness variation, 0.37 for friability variation, 12.52 for disintegration time variation, and 10.85 for surface area variation.

4.3 RESULTS AND DISCUSSION

The overall mean data for each of the studied answers are compiled in Table 1.

Table 1. Mean and standard deviation (SD) of mechanical and physical tests for all tablets tested.

	Hardness variation	**Friability variation**	**Disintegration time variation**	**Weight loss**	**Weight variation**	**Surface area variation**
Mean (%)	- 53.3	+ 0.7	- 22.3	- 2.3	9.9	15.2
SD	15.8	0.7	32.8	3.9	10.0	14.1

Hardness and friability assays are designed to evaluate mechanical strength of tablets to ensure the structural integrity of this dosage form under conditions of storage, transport, and handling. It was noticed a dramatic reduction in hardness of split tablets with values around 50% lower than whole tablets (Table 1). Studies show that hardness is influenced by size and shape of tablets, which may explain, in part the enormous variation in this assay for halved tablets (21). There are no studies in the literature about hardness of split tablets to compare.

Similarly, tablets halves were 0.7% more friable than whole tablets (Table 1), which is consistent with a previous research (6). Tablet splitting weakens the dosage form structure generating sharp corners that are easily eroded by the mechanical friction of disintegration test. For ordinary tablets, the maximum value accepted by pharmacopoeia for friability assay is 1.0% (22). In this study, several medicines presented themselves outside this limit after the split, namely hydrochlorothiazide reference scored knife split (friability = 3.14%), captopril generic scored knife split (friability = 2.31%), captopril reference scored knife split (friability = 2.28%), hydrochlorothiazide generic nonscored knife and tablet splitter split (friability = 1.63%), sertraline generic nonscored knife split (friability = 1.57%), and finally captopril reference scored tablet splitter split (friability = 1.03%).

Since the difficulty of keeping the pharmacopoeial limits after splitting, US health agency (FDA) recommends extend the friability limit to 3% for tablets after splitting (23).

In general, splitting process compromises in an important way the mechanical strength of tablets. It seems correct to conclude that changes in tablet shape after split makes it less resistant to mechanical forces and the new surfaces of halve tablet present fragile edges that are more susceptible to mechanical impact. So, it would be prudent recommending the use of the halves as soon as possible avoiding manipulation and store stress.

Disintegration of tablets halves was about 20% faster than whole tablets (Table 1). This result could be explained considering the irregular distribution of lubricants in tablets (24). These excipients might be concentrated on tablet surface and due to its lipophilic characteristics tend to hinder the tablet disintegration. Tablet splitting creates a new face in the dosage form by increasing its surface area and exposing tablet core, which may explain the faster disintegration of tablet halves. The disruption of tablets aesthetic coat, added to the increase of the specific surface can also justify the fast disintegration of split tablets (25). In absolute terms, however, changes in these parameters, representing up to 4.5 minutes (in case of atenolol generic scored split by splitter tablet), which should have little impact on dissolution and bioavailability of these products.

The weight loss related to tablet fragmentation and crumbling caused by split was up to 2% (Table 1). This data seems compatible with other studies that have found values of average weight loss ranging from 0.2 to 3.8% (8,10,18,26,27). It is of note the high coefficient of variation for this test. Some studies pointed out high individual weight loss as 23.5% (10) and 19.4% (8). In this study, the highest values were found to sertraline (generic nonscored split with knife) with a weight loss of 38.9% and to hydrochlorothiazide (generic nonscored split with knife) with 19.1%. As might be expected, there is a statistical correlation between this response (weight loss) and the friability variation ($r = 0.432$; $p=0.001$), which is in line with Ferreira and col. findings (17).

Weight variation is one of the most important response to set the security of a splitting process, since it is directly related to dose. Our data shows a mean weight variation of 9.9% ± 10.0 (Table 1). Once again, the variation was high with split tablets exhibiting weight variation within the range 0 to 50%. These data are in

accordance with the study conducted by Van Riet Nales and col. that identified an average weight variation of 7%, and some cases of products with variation of up to 40% (28).

Literature describes a large variation in weight of halves tablets, suggesting that this variable is conditioned by several factors that go beyond the drug chosen. Studies describe variations higher than 10% on the expected weight of halves tablets on a portion of tested medications ranging from 16% to 41% (8,9,18,26). Weight variations greater than 20% are described for approximately 12% of the tested tablets in two of these studies (8,9).

The utility of image analysis used to measure areas of split tablets and comparing them with expected theoretical areas (surface area variation) was evaluated. The goal was to quantify variations in specific surface and relate them to the weight variation. The software analysis is illustrated in Figure 3.

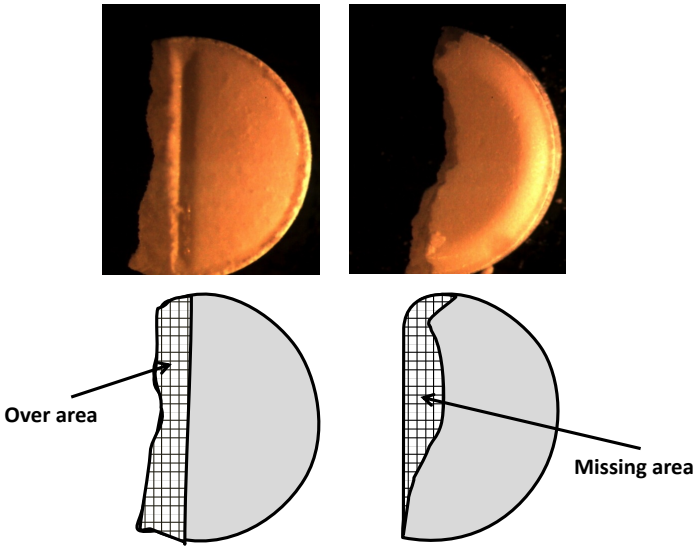

Figure 3. Illustrative image of image analysis test performed to determine the difference between the expected theoretical area and the area found in split tablets.

Split tablets presented an average variation in surface area of 15.2% (Table 1). As expected, surface area variation response showed a statistical correlation with weight variation ($r= 0.169$, $p=0.001$). These two responses were affected in an equivalent manner in all studied variables. Assumed the lack of specific quality control tests to evaluate the tablets splitting process, image analysis, used in this

work for the first time to this objective, proves to be a simple and powerful analytical tool for this proposes.

Brazilian health agency (ANVISA) follows international parameters similar to North American (FDA) and European (EMEA) health agencies in the regulation of generics drugs. Generic drugs must have many of the same characteristics as the corresponding reference, including bioequivalence, meaning that the amount of absorption of a generic product must be within a certain range relative to the reference product making them therapeutics equivalents (29). This study compared the performance of a reference product and two of its generics (one scored and other nonscored), after being submitted to splitting.

Surprisingly, the five drugs studied showed statistical differences between the reference product and their generics at least in 3 control assays (Figure 4). Leastways regarding to the splitting performance, reference products are not equivalents to their generics, as they are also different from each other. These differences are associated not only with the presence of score, since all five drugs showed statistical differences considering only the scored tablets (reference product and scored generic). This kind of issue was also reported by Wilson and col., who did not find equivalence in splitting for generic and reference micronized glyburide tablets (30)

In this sense, FDA has already anticipated the problem and includes the concept of *functional score* (23). Pharmaceuticals must not only add a score in generic whose reference also has, but also should assess the results of tablets in splitting process.

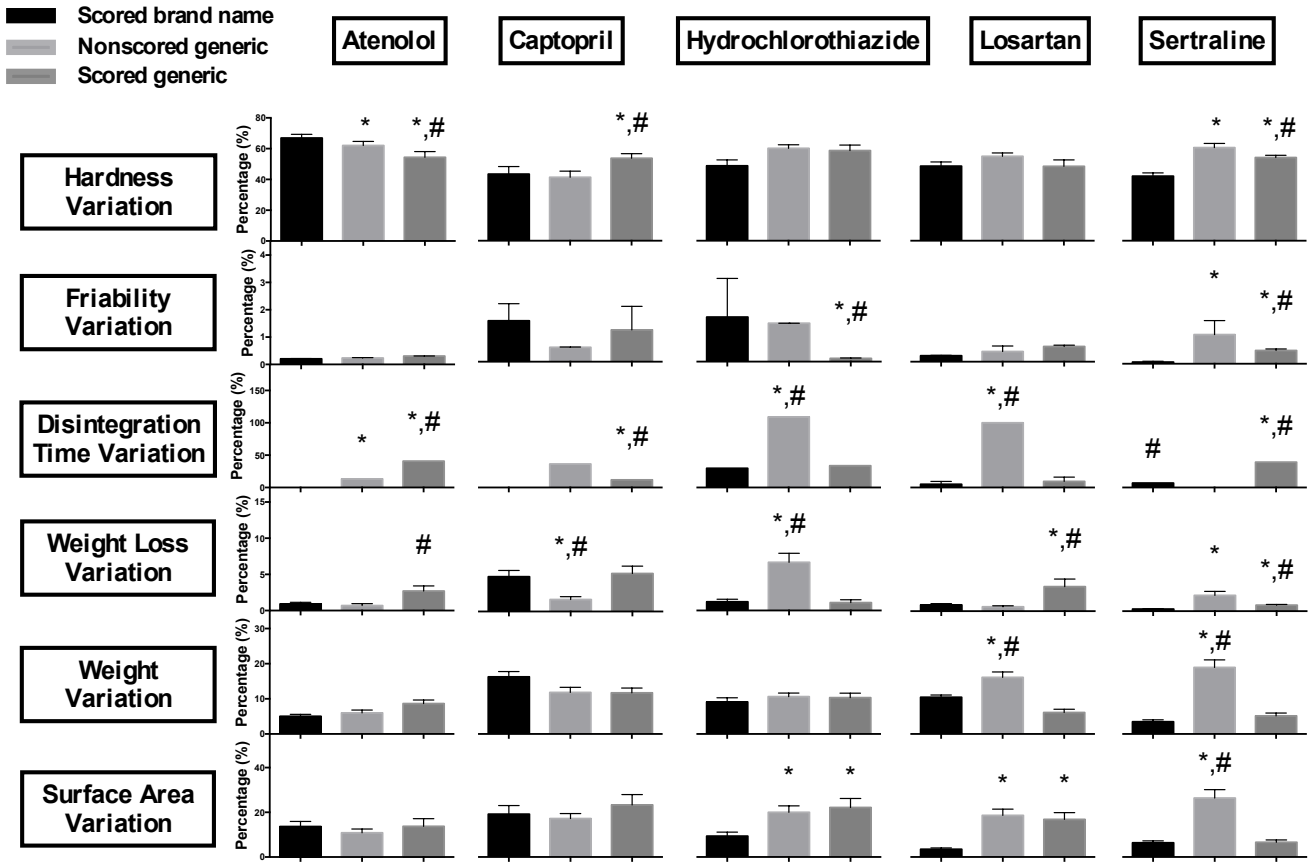

Figure 4. Responses of reference and generics after splitting. Statistic significances are indicated by asterisk (difference between reference and generic) and by hashtag (difference between scored or nonscored generics) ($p < 0.05$).

The most pronounced differences in this comparison occurred with sertraline (Figure 4), which showed statistical differences in all evaluated answers ($p<0.05$). In the specific case of this antidepressant drug, its side effects as nausea, insomnia and diarrhea can be exacerbated by the splitting process (31).

A better understanding of splitting process consist the first step for designing a more suitable tablet for this propose. Thus, a detailed evaluation of technological variables and methodological aspects that could affect the splitting process was carried out.

According to Figure 5, there is no statistic difference between knife and tablet splitter in conducted tests with main values for the tested medicine ($p>0.05$). However, Fisher's exact test pointed out that splitter tablet produce lower values in weight loss and friability variation compared to knife ($p<0.001$ and $p=0.002$,

respectively). In theory, tablet splitter helps to centralize the tablet and allow a section in a most appropriate place.

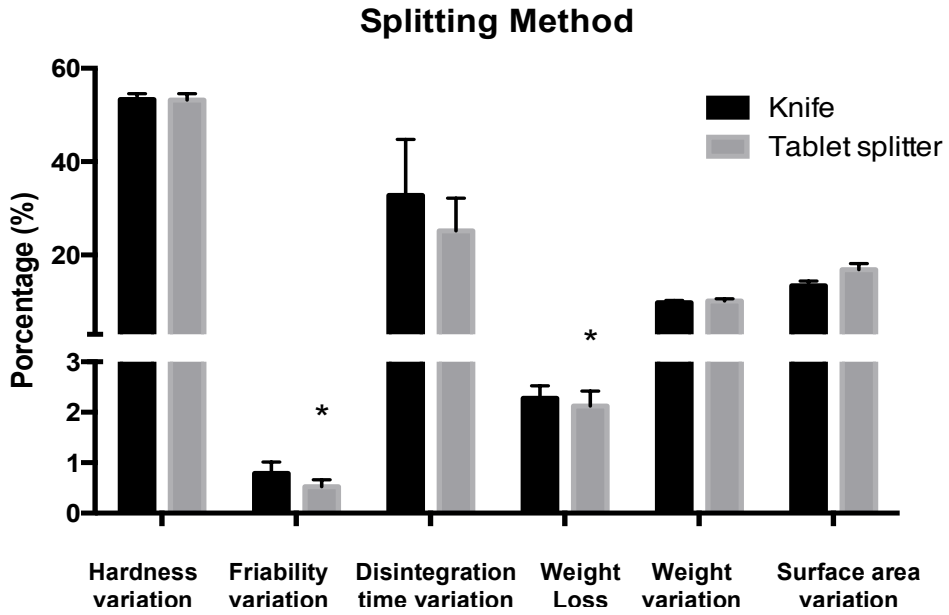

Figure 5. Evaluation of splitting method. Asterisk indicates statistical difference between groups ($p < 0.05$).

Literature show contradictories conclusions for this question with other researches that indicated better performance using tablet splitter rather knife (5,19,32). Nonetheless, two studies found no difference between manual and tablet splitter, whereas Teng and col. showed superior results in split tablets using razor blade instead manual and tablet splitter (15,20,33).

Figure 6 shows the responses obtained in splitting score and nonscore tablets. Scored tablets presented a lower weight variation (8.6% ± 0.4, $p = 0.000$) compared with nonscored tablets (12.6% ± 0.7). This is in accordance with other studies (9,17,18,34).

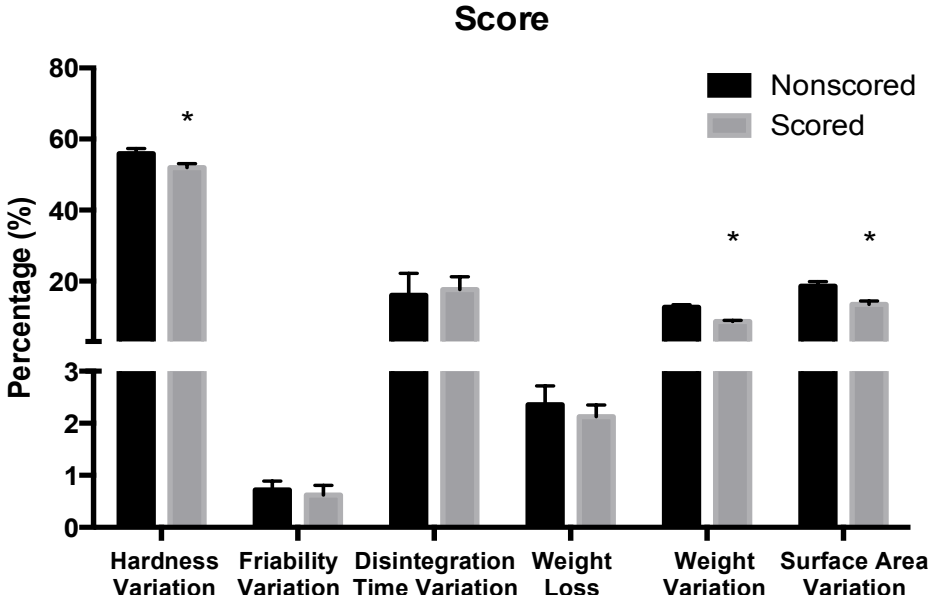

Figure 6. Evaluation of scored and nonscored tablets in splitting tablet. Asterisk indicates statistical difference between groups ($p < 0.05$).

Hardness variation was also lower for scored tablets (52.0% ± 1.2) in comparison with nonscored (55.9% ± 14.6, $p = 0.031$). A possible reason for these behavior may be the more regular forms of split scored tablets. Nonscored halves present irregular surface with points of weakness which can reduce the strength of such dosage form when subjected to crushing.

Figure 6 also shows variation in surface area of nonscored tablet (18.6 ± 1.3%, $p = 0.000$) compared to scored one (13.4 ± 1.0%). Also, statistical relationship between the answers surface area variation and hardness variation support this inference ($r = 0.101$; p=0,013).

Influence of tablet shape on split was analysed. Tablet shape is usually chosen considering aesthetics and marketing over the technical aspect. However, this variable shows an effect with statistical significance in two of the six evaluated answers (weight loss and surface area variation, $p = 0.000$ for both) when examining average (Figure 7). Round tablets exhibited weight loss (2.6% ± 0.2), and surface area variation (17.6% ± 1.0) noticeably higher than those obtained for oblong tablets (0.7% ± 0.8 and 5.5% ± 0.5, respectively). These results agrees with other researches, which show facility and best outcomes splitting oblong tablets rather than

round ones (8,34). This could be explained by the surface contact area for split, which is smaller in oblong tablets (34).

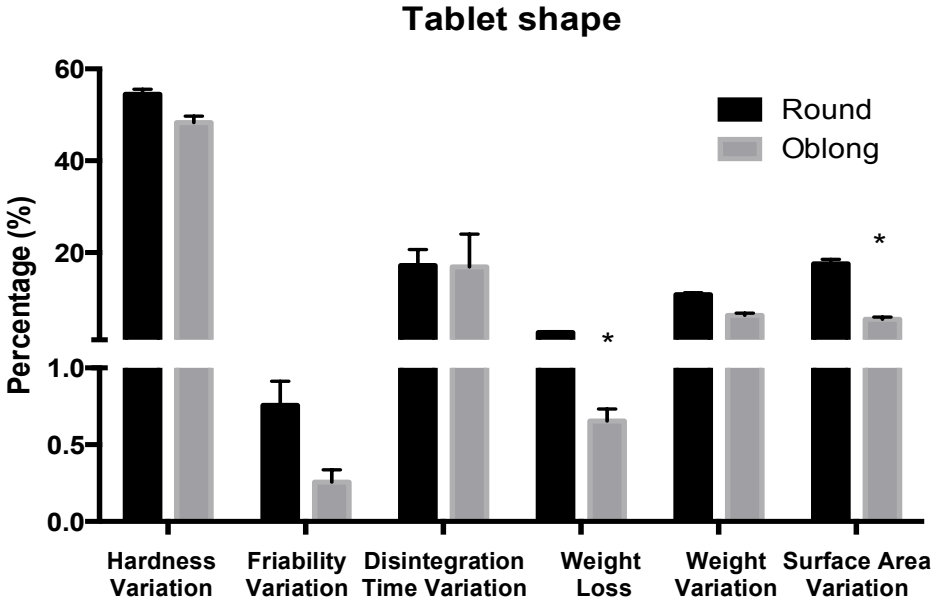

Figure 7. Evaluation of tablet shape in splitting tablet. Asterisk indicates statistical difference between groups ($p < 0.05$).

Hardness and weight variations showed statistical relevance at first sight, but this result was attributed to the presence of coating. There are no differences for those responses comparing only coated round and coated oblong tablets ($p=0.811$ and $p=0.523$, respectively).

Coating proved advantages for tablets submitted to splitting (Figure 8). Coated tablets presented inferior weight loss ($p = 0.000$), hardness ($p = 0.022$) and surface area ($p = 0.009$) variations with values of 1.4% ± 0.2, 51.5% ± 1.2 and 13.0% ± 1.2, respectively, compared with uncoated tablets that presented 2.8% ± 0.3, 54.4% ± 1.3, and 16.6% ± 1.1, respectively. Coating have inherent strength and elasticity, so can hold the core together after splitting, reducing weight loss and hardness variation, which is connected to film properties (35). McDevitt and col., and Sedrati and col. found better results splitting coated tablets as well (8,36).

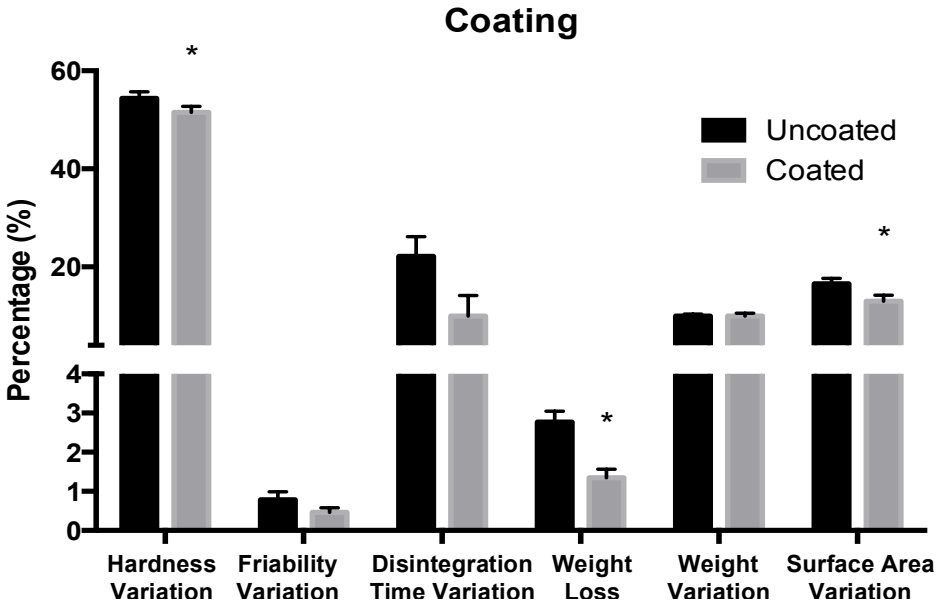

Figure 8. Evaluation of coating in splitting tablet. Asterisk indicates statistical difference between groups ($p < 0.05$).

The qualitative composition of drug products studied was identified in order to analyze the possible influence of diluents on tablet splitting. The following diluents were found in the selected tablets studied: starch, lactose monohydrate, MCC and DCP. Figure 9 shows the assessment made for the answers that showed statistical significance.

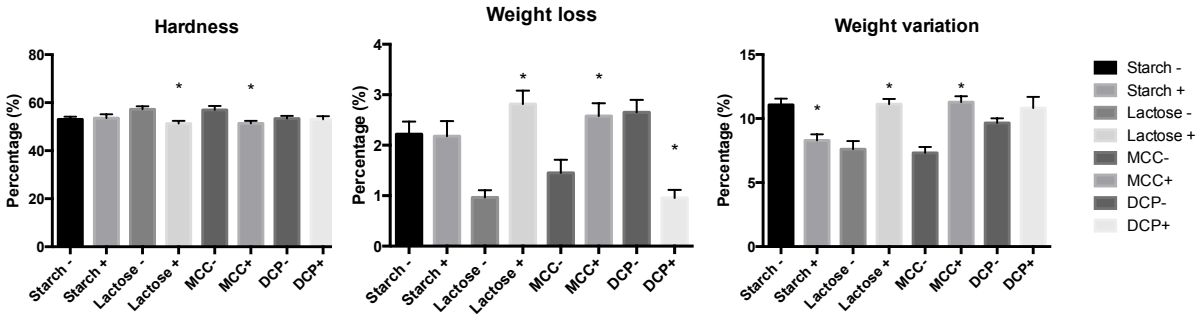

Figure 9. Impact of presence or absence of diluents in splitting tablet responses. Asterisk indicates statistical difference between groups ($p < 0.05$).

Regarding hardness, as might be expected, the presence of plastic materials – MCC and lactose - showed better performances (absence of lactose: 57.2% ± 1.3, presence of lactose 51.3% ± 1.2; p = 0.010; absence of MCC 57.0% ± 1.7, presence of MCC 51.4% ± 1.1; p = 0.004). However, in important responses as weight change and weight loss, lactose and MCC have a negative effect on the splitting, increasing weight variation (absence of lactose: 7.6% ± 0.6, presence of lactose 11.1% ± 0.4; absence of MCC 7.3% ± 0.5, presence of MCC 11,3% ± 0.5) and weight loss (absence of lactose: 1.0% ± 0.1, presence of lactose 2.8% ± 0.3; absence of MCC 1.5% ± 0.3, presence of MCC 2.6% ± 0.3), whereas tablets containing starch and DCP have a beneficial effect in one of these responses (weight variation - absence of starch: 11.1% ± 0.5, presence of starch: 8.3% ± 0.5, p = 0.000; weight loss - absence of DCP: 2,7 % ± 0.3, presence of DCP: 1.0% ± 0.2; p= 0.000).

The excipient had important influence on compressibility factors and on consolidation behavior of each material (37). MCC and lactose present plastic deformation, predominantly, whereas starch and DCP show fragmentation and or elastic conduct (38–40). In this study, the latter group seems to be more suitable for splitting process. Possibly, materials with predominantly plastic deformation when subjected to pressure that culminates in the rupture of the structure may collapse and cause major variations in weight than those materials that can undergo elastic deformation and fragmentation that are able to split without suffering major structural damage.

These findings are in agreement with Bridgeman and col. found that DCP as the filler showed a significantly lower weight variability and weight loss upon splitting as compared to the tablets prepared with lactose (27). Shah and col. tested HPMC and stach as binders and observed better results in content uniformity using starch compared to HPMC (6).

4.4 CONCLUSIONS

The laboratory tests used to evaluate the effect of tablets splitting are adaptations of pharmacopoeial assays for unbroken tablets. In this context, the proposal of using image analysis, considering their correlation with the weight variation, prove to be a useful analytical tool.

The refined statistical analysis makes possible to identify the contribution of technological variables and methodological aspects in the performance of tablets subdivision. Tablet production factors such as composition, shape, score and coating influenced the outcome of split. According to this experimental study, a tablet should have the following desirable characteristics to be subdivided - oblong shape, presence of score and coating. Fisher's exact test analysis pointed out advantages in using splitter tablet instead knife kitchen in regard to the friability test and loss of weight. Considering the visual impairment of some groups as elderly, the use of splitter tablet helps to centralize the tablet allowing splitting better results.

Performance on splitting has not been considered by most health agencies around the world in the regulation of generic drugs. This neglect may ultimately compromise the equivalence between the drugs. In this study, it was not found equivalence between generics drugs and their references drugs in all five drug selected, which indicates the necessity of review the health regulations. The evaluation of splittability score, currently demanded by FDA, could be an option to solve this issue.

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CAPÍTULO 5

CONSIDERAÇÕES FINAIS

A partição de comprimidos é uma prática corriqueira no cuidado hospitalar e doméstico, mas que apresenta riscos para a segurança do paciente, especialmente para crianças e idosos, que mais frequentemente necessitam recorrer a esse artifício. No Brasil e no restante da América do Sul, não há qualquer regulamentação sanitária que verse sobre o tema, e somente a agência sanitária norte-americana (FDA) normatiza em caráter ainda rudimentar o fracionamento de comprimidos. Na maioria dos casos, os laboratórios fabricantes se isentam de qualquer recomendação a respeito da partição, deixando a decisão de realizá-la aos prescritores, profissionais de saúde, cuidadores, e em última instância, aos próprios usuários.

Apesar do número crescente de estudos que abordam o tema, o embasamento científico disponível no momento é controverso, impreciso e está longe de oferecer as certezas necessárias para a realização segura da partição. No que diz respeito à melhor forma de realizar a divisão, a maioria das pesquisas apontam que a quebra manual ou com a ajuda do partidor de comprimidos tem um desempenho superior levando a uma menor variação e perda de peso. Nesse cenário, características de produção, tais como a presença e profundidade do sulco e a dureza do comprimido se tornam fatores preditivos relevantes da facilidade de fracionamento. Outras características dos comprimidos como tamanho, forma, superfície e presença de revestimento influenciam a precisão da quebra, sendo que comprimidos maiores, oblongos, planos e revestidos se mostraram mais aptos para uma divisão uniforme na maioria dos trabalhos.

O descompasso entre os ensaios de laboratório e alguns estudos clínicos expõem a necessidade de se propor especificações analíticas *in vitro* mais adequadas para a avaliação da performance da partição de comprimidos. A simples adaptação dos ensaios de controle de qualidade para comprimidos íntegros parece não ser capaz de estimar todas as nuances envolvidas na avaliação da aptidão de um comprimido para a partição.

Os achados encontrados na literatura estão em consonância com os resultados do estudo experimental conduzido com os cinco medicamentos de uso geriátrico e seus respectivos genéricos, em que se observou a superioridade do partidor de comprimidos na partição, comparado ao uso da faca, obtendo-se menor perda de peso e variação da friabilidade após a divisão. Esse estudo revelou ademais, que comprimidos oblongos, sulcados e revestidos apresentam-se mais adequados para a partição. A análise de imagem mostrou ser um ensaio de caracterização de simples execução e que pode ser de grande utilidade na avaliação da partição de comprimidos devido a sua correlação com a variação de peso ocasionada pelo processo de fracionamento.

Este mesmo estudo coloca em cheque o desempenho dos medicamentos genéricos no que diz respeito ao seu comportamento em relação ao fracionamento. Verificou-se que os medicamentos genéricos não são equivalentes aos medicamentos referência quando partidos, o que pode comprometer sua intercambialidade. Há, portanto a necessidade urgente de modificar a regulação de equivalência e bioequivalência de genéricos, inserindo a questão da partição.

Pode-se concluir que a decisão sobre a partição de um comprimido, vai muito além da verificação das informações sobre a janela terapêutica do fármaco, passando por questões metodológicas e de produção que contribuem de maneira sinérgica para que a prática possa ser realizada de forma segura. As informações e avaliações trazidas nesse trabalho vêm a esclarecer alguns pontos importantes, porém a partição de comprimidos está longe de ser um assunto esgotado.