UNIVERSIDADE D
COIMBRA

João Daniel Nunes Simão

Relatório de Estágio e Monografia intitulada "Development of bilayer tablets by Quality by Design: Focus on Manufacturing parameters" referentes à Unidade Estágio Curricular, sob a orientação do Dr. André Paiva e do Professor Doutor António Ribeiro apresentado à Faculdade de Farmácia da Universidade de Coimbra, para apreciação na prestação de provas públicas de Mestrado Integrado em Ciências Farmacêuticas.

Outubro de 2021

1 2  9 0

UNIVERSIDADE D
COIMBRA

João Daniel Nunes Simão

Relatório de Estágio e Monografia intitulada "Development of bilayer tablets by Quality by Design: Focus on Manufacturing parameters" referentes à Unidade Estágio Curricular, sob a orientação do Dr. André Paiva e do Professor Doutor António Ribeiro apresentado à Faculdade de Farmácia da Universidade de Coimbra, para apreciação na prestação de provas públicas de Mestrado Integrado em Ciências Farmacêuticas.

Outubro de 2021

Eu, João Daniel Nunes Simão, estudante do Mestrado Integrado em Ciências Farmacêuticas, com o n.º 2016228538, declaro assumir toda a responsabilidade pelo conteúdo do Documento Relatório de Estágio e Monografia intitulada "Development of bilayer tablets by Quality by Design: Focus on Manufacturing parameters" apresentado à Faculdade de Farmácia da Universidade de Coimbra, no âmbito da unidade de Estágio Curricular.

Mais declaro que este Documento é um trabalho original e que toda e qualquer afirmação ou expressão, por mim utilizada, está referenciada na Bibliografia, segundo os critérios bibliográficos legalmente estabelecidos, salvaguardando sempre os Direitos de Autor, à exceção das minhas opiniões pessoais.

Coimbra, 25 de outubro de 2021.

João Daniel Nunes Simão

(João Daniel Nunes Simão)

Agradecimentos

Aos meus pais, por serem o meu alicerce, por toda a confiança depositada em mim e por me apoiarem em todas as decisões da minha vida. Ao meu irmão por ser a minha referência, por todos os conselhos e por me fazer recordar que não há amor como o de irmãos.

Aos meus avós, pelo amor que me transmitem e assim me tornarem numa pessoa melhor.

Ao Diogo, ao Luís, à Marta e à Marisa, pelo caminho percorrido, pela compreensão e pelas conquistas ao longo destes cinco anos. À Beatriz, que sendo família, me fez sentir em casa.

Ao Pedro, pela sua disponibilidade, por todos os ensinamentos e pela ajuda que me ofereceu ao longo de todo o meu percurso académico.

A toda a equipa da Farmácia Estádio, pelo conhecimento transmitido, pela paciência e vontade em me fazer crescer enquanto pessoa e futuro farmacêutico.

Ao Professor Doutor António Ribeiro pela disponibilidade, exigência, rigor e confiança depositada em mim. A sua colaboração foi fundamental para a realização da monografia.

Ao Professor Doutor Chris Vervaet, à Dra. Elisa de Pauw e à Universidade de Ghent, pela oportunidade que me proporcionaram em realizar um estágio que serve de forte complemento à minha formação.

À Faculdade de Farmácia da Universidade de Coimbra, por todos os anos de formação e crescimento que fizeram de mim uma pessoa mais competente.

Índice

Parte I

Relatório de Estágio em Farmácia Comunitária

Farmácia Estádio

Lista de Abreviaturas

AINEs - Anti-inflamatórios Não Esteróides

APCER - Associação Portuguesa de Certificação

FE - Farmácia Estádio

MICF - Mestrado Integrado em Ciências Farmacêuticas

MNSRM - Medicamentos Não Sujeitos a Receita Médica

PIM - Preparação Individualizada da Medicação

I. Introdução

O Mestrado Integrado em Ciências Farmacêuticas (MICF) é constituído por 5 anos letivos obrigatórios e, cada ano, compreende 2 semestres. No total, 8 semestres estão destinados a aulas com componente teórica e prática e, no último ano, o primeiro semestre inclui apenas aulas teóricas enquanto que o segundo semestre é destinado à realização do estágio curricular em farmácia comunitária. Ao longo destes 5 anos, contactei com uma forte e sólida componente teórica que nos serve de base para os estágios que decidirmos realizar no último semestre do curso.

Relativamente ao estágio em farmácia comunitária, é de extrema importância na medida em que, enquanto farmacêuticos comunitários, entre muitas funções, temos como principal a de conhecer e entender ao máximo o medicamento de forma a aconselhar e a garantir que os doentes recebam a medicação da forma mais correta e informada possível. Sendo assim, neste estágio, aplicam-se os conhecimentos adquiridos ao longo dos anos no contacto direto com o doente e como objetivo final é o de sairmos o mais bem preparados possível para a vida profissional.

A farmácia comunitária é o último e, por vezes, o único contacto que os doentes têm com um profissional de saúde antes de tomarem a medicação. O farmacêutico comunitário, além de todo o conhecimento acerca do medicamento, tem que ser dotado de uma elevada capacidade social para entender, compreender e interagir da melhor forma possível com os utentes. A farmácia é um espaço público e existe uma grande variedade no que toca ao tipo de pessoas que aí se deslocam e, assim, consoante a necessidade dos utentes, o farmacêutico terá que adequar a sua atuação e ter uma grande capacidade de adaptação.

A farmácia que escolhi para a realização do meu estágio foi a Farmácia Estádio (FE), em Coimbra, e tive como orientador de estágio o Dr. André Paiva. Neste relatório de estágio, apresentado sob a forma de análise SWOT (*Strengths, Weaknesses, Opportunities and Threats*), vou enumerar os pontos fortes e fracos do ponto de vista interno (*Strengths* e *Weaknesses*) bem como do ponto de vista externo à farmácia (*Opportunities* e *Threats*). Vou ainda apresentar alguns casos clínicos nos quais me deparei ao longo destes meses.

II. Análise SWOT

2.1 *Strengths* - Pontos Fortes

2.1.1 Recursos humanos

A FE, sob direção técnica da Dra. Ana Isabel Rebelo, é constituída por uma equipa multidisciplinar e combina a energia, conhecimento e proatividade dos seus membros mais jovens com a experiência dos trabalhadores com mais anos de casa.

Há uma elevada organização no que toca à divisão de tarefas tendo, cada membro integrante da equipa, determinadas funções específicas. Esta forma de trabalhar faz com que o trabalho seja realizado de forma mais eficaz, com menos erros e, dividindo o peso das tarefas entre todos, faz com que, a longo prazo, sejam menos os sinais de fadiga e de desgaste psicológico.

No que toca à relação com os estagiários, desde início notei a disponibilidade para com os estagiários e, como reflexo, foi notória a vontade em ajudar, ensinar e fazer-nos crescer tendo, ao máximo, proporcionado um ambiente profissional e feito com que nos sentíssemos como se estivéssemos em casa. Além disso, a forma como abordam a questão do utente, pretendendo, sempre que possível, zelar pela sua saúde e bem-estar, fez-me crescer e aprender muito durante os meses em que trabalhei com esta equipa técnica.

2.1.2 Reuniões "*Kaizen*"

Kaizen é uma filosofia que surgiu no Japão pós-segunda guerra mundial que, introduzida nas farmácias, consiste num sistema e cultura de potencialização da capacidade de resposta ao utente, redução do desperdício nas atividades operacionais e aumento da sua rentabilidade através de um alinhamento da equipa com os objetivos definidos [1].

Semanalmente eram realizadas reuniões nas quais eram definidos pontos chave, de forma a permitir a melhoria contínua do desempenho de todos. Como objetivo principal, as reuniões serviam para abordar assuntos de forma a todos terem conhecimento e comunicar à equipa certos resultados. A mim sempre me foi permitida a presença nestas reuniões e, quando estava preparado, passei a ter um papel ativo nas mesmas.

2.1.3 Controlo de qualidade

Sendo certificada pela Associação Portuguesa de Certificação (APCER) quanto ao cumprimento da Norma NP EM ISSO 9001:2015 e das Boas Práticas de Farmácia, a FE garante que o serviço é prestado diariamente com qualidade pelos seus trabalhadores, sendo cumpridos todos os requisitos necessários para proporcionar ao utente o melhor atendimento possível [2].

O levantamento dos riscos e oportunidades para o desempenho da farmácia, a identificação e acompanhamento constante dos objetivos e indicadores de negócio, a definição de autoridades e responsabilidades assim como avaliações periódicas da atividade (exemplo: revisão pela gestão) constituem exemplos de documentos e registos obrigatórios para obtenção e manutenção desta certificação. Manutenção esta que obriga a auditorias realizadas anualmente tanto por entidades internas como externas, garantindo assim a continuidade da qualidade prestada.

2.1.4 Serviços farmacêuticos

A farmácia comunitária e os seus colaboradores, como agentes prestadores de saúde, têm, incluídos no seu dia-a-dia, diversos serviços de fácil e rápido acesso à comunidade que permitem o estreitamento de relações com os utentes. Esta conexão mais próxima reflete-se na saúde do doente através do aumento da proximidade no acompanhamento e consequentemente diagnóstico a eficácia dos tratamentos.

Alguns dos serviços farmacêuticos que são atualmente prestados nas farmácias portuguesas são: Preparação Individualizada da Medicação (PIM), utilização de meios auxiliares de diagnóstico, apoio domiciliário, administração de medicamentos, administração de vacinas não incluídas no Plano Nacional de Vacinação e consultas de nutrição.

A FE, pela quantidade e qualidade dos serviços prestados, tem um papel muito importante na população de Coimbra e, ao longo dos meses em que decorreu o meu estágio, aprendi e assisti a essa prestação de serviços e fui, ainda, parte ativa em alguns deles.

Dentro dos serviços prestados, destaco os seguintes:

- Meios auxiliares de diagnóstico/ Medição de parâmetros bioquímicos e fisiológicos

Os utentes podem dirigir-se à farmácia e, de forma rápida e acessível, medir parâmetros que devem estar diariamente controlados como o nível de açúcar no sangue, o valor da pressão arterial e o colesterol total.

Destaco ainda o importantíssimo papel que a farmácia teve durante o Inverno perante o aumento do número de casos de infeção pelo novo Coronavirus. A FE foi das primeiras no distrito a ser autorizada à realização de testes para deteção do novo Coronavirus. Perante este cenário, foi de extrema importância porque, devido ao elevado número de casos, os laboratórios e os centros de diagnóstico não conseguiam testar as pessoas ao ritmo desejado. Tendo uma parte ativa na deteção de infeções na comunidade, a FE conseguiu ajudar na deteção de casos, bloqueio de cadeias de transmissão e ainda aconselhamento farmacêutico no que toca aos sintomas e às muitas dúvidas pelas quais a população atravessava naquela fase

difícil. A nível pessoal, foi uma experiência interessante porque contactei de perto com a realidade que era e continua a ser a pandemia. Com esta aprendizagem, fiquei familiarizado com os sintomas e sinais do "doente COVID" e pude aprender, junto dos farmacêuticos, qual a abordagem e o que deve ser aconselhado a utentes nesta situação. Para o futuro, saio mais preparado em lidar com utentes com problemas respiratórios e em diferenciar esta patologia de outras do foro respiratório, com sintomas semelhantes. A avaliação caso a caso numa situação destas é importante uma vez que a decisão de direcionar, ou não, o utente ao médico pode ser decisivo para a sua saúde.

- PIM

A FE proporciona aos utentes a possibilidade de aderirem ao PIM. O farmacêutico, de acordo com a guia de tratamento e, através da revisão do plano terapêutico, prepara a medicação separando-a por dias da semana e por horários de refeição, facilitando e garantindo, assim, a sua toma e adesão.

A polimedicação é um dos fatores críticos no que toca à efetividade do tratamento do doente idoso, uma vez que compromete a adesão e a manutenção do tratamento para doenças de cariz crónico [3]. Desta feita, ao proporcionarmos ao utente a possibilidade de obterem a medicação separada por dias da semana e por horário de refeição, evitamos erros, confusões e esquecimentos no que toca à toma dos medicamentos.

A nível individual, ao ter participado no serviço PIM, ajudou-me, não só a compreender de forma mais ativa esta problemática, como também me permitiu contextualizar com alguma medicação do doente crónico e a consolidar conhecimentos relacionados com a farmacologia e a farmacoterapia adquiridos ao longo dos anos.

- Consultas de nutrição

Na FE, uma nutricionista, semanalmente, acompanha diversos utentes. Foi uma possibilidade para mim, enquanto estagiário, poder conhecer os produtos que são indicados podendo, além disso, exercer a minha função de aconselhamento farmacêutico no que toca à saúde alimentar.

- Apoio domiciliário

Para os utentes com maior dificuldade de deslocação à farmácia a entrega ao domicílio é uma realidade. A FE fá-lo sem qualquer remuneração zelando apenas pelo bem-estar do utente e com o objetivo de que toda a medicação lhe chegue a horas e nas condições adequadas. Tive a oportunidade de participar em entregas ao domicílio, o que me permitiu

desenvolver capacidades de comunicação e entender as necessidades que alguns utentes têm e que não lhes permite a deslocação à farmácia.

2.1.5 Plano de estágio

O primeiro dia dos estagiários na FE consiste sempre na apresentação e explicação do plano de estágio. Numa reunião com a Dra. Ana Isabel Rebelo e com o Dr. André Paiva, foi-me fornecido, em formato papel, um documento contendo informação acerca da farmácia: a sua história, equipa técnica e instalações. Além disso, inclui, tal como o nome indica, o plano de estágio da farmácia. Foi-me explicada toda a informação que constava no documento e, saí da reunião, com uma ideia muito clara do meu papel enquanto estagiário e das várias fases pelas quais iria passar ao longo dos meses.

Pessoalmente achei bastante positivo este primeiro contacto, uma vez que fiquei com uma ideia bastante marcada da forma como o meu estágio iria proceder e deu a possibilidade de me preparar da melhor forma para as diferentes etapas do decorrer do estágio.

2.1.6 Cor das batas

O meu estágio foi todo realizado usando uma bata que se diferenciava dos restantes farmacêuticos. Consistia numa bata verde, claramente distinta das restantes, e com a devida identificação do estagiário.

A meu ver, facilita o meu trabalho no que toca à relação que temos com o utente uma vez que, ao ser automaticamente identificado como estagiário, salvaguarda uma possível reação menos positiva por parte da pessoa que está a ser atendida. Além disso, caso queira, a meio do atendimento, esclarecer algum tipo de dúvida com os farmacêuticos, as pessoas são muito mais compreensivas se lhes pedirmos que aguardem enquanto procuramos ajuda.

Posto isto, a eventual opção dum determinado utente por um colega que tenha uma bata branca é um mal menor tendo em conta o acima mencionado e o objetivo do estágio, que é o de aprender ao máximo nas melhores condições possíveis.

2.2 *Weaknesses* - Fraquezas

2.2.1 Manipulados

A FE está equipada com um laboratório e possui todas as certificações e exigências legais para a preparação de manipulados. O Dr. André Paiva é o responsável por esta área de funcionamento da farmácia. Durante o meu estágio foram muitos os pedidos para a preparação de manipulados mas, por falta de tempo e de recursos humanos, não fui parte integrante dessa tarefa, sendo que apenas participei em algumas tarefas simples como a pesagem de cápsulas e a rotulagem dos preparados. Pelo explicado, e por achar que o nosso curso me preparou

muito bem no que toca aos medicamentos manipulados, considero que tenha sido um espaço por preencher no que toca ao meu percurso enquanto estagiário.

No entanto, coincidi com a fase em que os manipulados de ivermectina eram muito prescritos por parte da comunidade médica para combater os efeitos da COVID-19 (doença provocada pelo novo Coronavírus SARS-COV-2) demonstrando a importância que tem a preparação de manipulados e, mais uma vez, o farmacêutico na comunidade.

2.2.2 Dermocosmética, veterinária e homeopatia

A dermocosmética e a veterinária são categorias de produtos muito vendidas nas farmácias portuguesas em geral e, no caso dos produtos homeopáticos, têm uma grande expressão de vendas na FE devido à proximidade de uma clínica de medicina integrativa.

O aconselhamento farmacêutico no que toca aos produtos cosméticos é algo bastante importante e, dentro destas categorias, foi a que senti que poderia prestar mais aconselhamento. Por outro lado, em relação à veterinária, não considerei o meu papel tão fundamental. Contudo, enquanto farmacêutico tenho que ter conhecimento em todas as áreas ligadas à farmácia e, assim, estar preparado para aconselhar também o utente que procura respostas a questões deste tema.

Relativamente à homeopatia, o desconhecimento das marcas e da forma como os produtos atuavam e a grande variedade de produtos fez com que me sentisse incapaz de ajudar os utentes e responder às questões por eles colocadas.

2.2.3 A pandemia do Coronavírus e o número de estagiários

Quando iniciei o meu estágio, em janeiro, a pandemia havia obrigado a farmácia a trabalhar por turnos de forma a prevenir um possível fecho caso alguém ficasse infetado. Esta situação obrigou, naturalmente, a que trabalhássemos em dias intermitentes. Ao trabalharmos dia sim dia não, a margem de progresso é mais reduzida porque o trabalho não é contínuo e contribui, de maneira negativa, para a aprendizagem, para a adaptação e para a evolução do meu trabalho enquanto estagiário.

A FE, pela sua capacidade de organização e infraestruturas, costuma acolher um número considerável de estagiários. Desta vez não foi diferente mas, pelo acima mencionado, tivemos dificuldade na conclusão do nosso estágio visto que o tempo na farmácia tinha que ser gerido de forma a que todos os estagiários tivessem as mesmas oportunidades e qualidade de ensino.

Foi, portanto, um ponto negativo que afetou o decorrer do meu estágio. No entanto, com o esforço de todos e a disponibilidade da farmácia em fazermos horas durante os fins de

semana, noites e nos meses de agosto e setembro foi possível a conclusão do estágio curricular sem quaisquer problemas.

2.3 *Opportunities* - Oportunidades

2.3.1 Instituições

A FE é parceira de diversas instituições como lares de idosos e de caráter social. Diariamente são enviados, através de correio eletrónico, os pedidos de medicação por parte dessas instituições onde vem identificado o médico prescritor e os dados referentes ao utente, como o tipo de medicação e a devida dosagem. Posteriormente, a farmácia fatura a medicação e procede à preparação da mesma.

A FE, com o objetivo de proporcionar um melhor serviço, adquiriu recentemente um equipamento de PIM de uma forma automatizada, que permite uma melhor rastreabilidade dos medicamentos incluídos na terapêutica dos utentes e uma também importante diminuição de erros. Durante o meu estágio, a Dra. Ana Cardoso e o Dr. André Paiva eram os responsáveis por manipular a máquina. Explicaram-me todo o processo e fui parte ativa nesta tarefa. Considero uma oportunidade no sentido em que, desde que os medicamentos chegam à farmácia até que são distribuídos pelas instituições, participei na separação da medicação e observei o posterior controlo da máquina, o que me permitiu associar diversos princípios ativos aos respetivos nomes comerciais e, ainda, familiarizar-me com a medicação que muitos destes utentes tomam sendo, na sua grande parte, medicação crónica, o que me ajudou na fase final do meu estágio que foi o atendimento ao público.

Este serviço prestado dá um enorme destaque à FE a nível da zona centro devido à importância que tem na comunidade e demonstra, uma vez mais, o papel fundamental que o farmacêutico tem na saúde, tanto pública como individual. Além disso, queria reforçar que, enquanto estagiário, e lidando com serviços como este, interiorizei que a necessidade de inovação tanto a nível de equipa como individual é importante e uma mais-valia para a profissão de farmacêutico.

2.3.2 Formações

Durante o estágio tive a oportunidade de participar em diversas formações, nomeadamente de produtos e marcas de cosméticos.

Com estas formações extra, adquiri conhecimentos que me são úteis visto que, estrategicamente, as marcas alteram a sua gama de produtos e é necessária uma constante atualização para corresponder da melhor forma às necessidades dos utentes. Além disso, ajudou-me a assumir uma postura mais confortável perante o atendimento.

2.3.3 Serviço Permanente

Foi-me dada a possibilidade de integrar o período de funcionamento noturno da farmácia.

Fi-lo juntamente com o Dr. Luís Cavaleiro e, durante essas horas, consciencializei-me com a realidade, diferente, que é a do utente durante a noite. É mais uma vertente para a qual o farmacêutico tem que estar preparado visto que as necessidades e as indicações para as quais os utentes solicitam apoio são distintas das que normalmente acontecem durante o dia.

2.3.4 Épocas diferentes, necessidades diferentes

Por ter realizado um segundo estágio, que foi iniciado ainda não tendo terminado o de farmácia comunitária, tive a oportunidade de trabalhar em diferentes fases do ano: de janeiro a abril deparei-me com a habitual época de Inverno, caracterizada por muitos problemas a nível respiratório, gripes, constipações e o muito falado Coronavírus. Ainda durante esse período, convivi com as muitas alergias que aparecem devido à época primaveril. Voltei, após terminar o outro estágio, à farmácia, em agosto, altura do ano em que as necessidades dos utentes são totalmente distintas. Neste caso, problemas relacionados com a exposição solar foram muito frequentes.

2.3.5 Cartão das Farmácias Portuguesas

Em resposta à crise e também ao constante aumento da venda de medicamentos fora das farmácias foi criado o Cartão das Farmácias Portuguesas. Com este cartão, as pessoas ao adquirirem determinados produtos vão acumulando pontos e, atingindo determinada pontuação, podem trocá-los por produtos ou rebatê-los em compras. Com esta estratégia, as farmácias tentam atrair as pessoas na compra de determinados produtos garantindo, assim, um aconselhamento correto. Consoante o balanço entre a atribuição e rebate de pontos, é atribuído um saldo que, quanto mais positivo for, mais negativo financeiramente é para a farmácia.

Na FE, por meio de reuniões, analisávamos a situação de cada colaborador da farmácia e, consoante os objetivos a cumprir, eram definidas metas a cada um. Esta avaliação de desempenho, que era realizada semanalmente, deu-me a entender a realidade existente neste mercado a nível de marketing e negócio.

2.4 *Threats* - Ameaças

2.4.1 Medicamentos esgotados

Perante a elevada procura de alguns medicamentos, em determinadas situações certos medicamentos esgotavam e, muitas vezes incompreendidos, tinha que explicar o porquê aos utentes. Nesses momentos, a confiança do utente em mim, caso não se lhe fosse explicada a situação de forma correta, poderia ficar comprometida.

Além disso, a falta de determinado medicamento pode complicar a terapêutica ao utente. Uma alternativa e resposta ao problema, no caso de totalmente esgotados nos fornecedores e sem genéricos correspondentes é, por exemplo, reencaminhar os utentes aos médicos para que se lhes fosse alterada a terapêutica por outra igualmente eficaz.

Havia uma necessidade de gestão quase perfeita dos *stocks* por todos os trabalhadores para responder de forma eficaz a toda e qualquer falta de medicamento que pudesse surgir e, como estagiário, foi uma ameaça ao meu estágio pois nem sempre foi possível resolver a situação contactando os fornecedores ou outras farmácias.

2.4.2 Venda de MNSRM (Medicamentos Não Sujeitos a Receita Médica) fora das farmácias

A minha formação ensinou-me, entre muitas coisas, que o medicamento e os produtos farmacêuticos devem ser utilizados com a máxima segurança e, sempre que possível, com a indicação médica e o aconselhamento farmacêutico.

A possibilidade de venda de MNSRM em Portugal, fora das farmácias, incentiva à automedicação e torna mais complicado o acompanhamento dos utentes por parte dos profissionais de saúde. A situação é agravada pela facilidade dos grandes espaços comerciais apresentarem preços aliciantes em relação às farmácias. A resposta a este problema passa por disponibilizar à população, nas farmácias, o melhor atendimento e prestação de serviços possíveis de forma a que os utentes coloquem, nos farmacêuticos, a máxima confiança para que sejam parte integrante na melhoria do estado de saúde.

Durante o tempo em que estagiei em farmácia comunitária pude prestar aconselhamento aos utentes em relação a MNSRM, suplementos alimentares e produtos cosméticos. Sem este aconselhamento, a utilização indevida pode gerar problemas de saúde ao utente.

III. Casos Clínicos

Caso Clínico 1: Senhor dirige-se à farmácia queixando-se de que tinha sido mordido durante a noite por insetos, no braço, e que sentia muito ardor e comichão e solicitou Fenistil®. A zona das picadas estava bastante vermelha e com um estado de inflamação já avançado. Devido aos sintomas e sinais que apresentava o utente, expliquei que era importante não coçar a zona afetada e colocar gelo nos primeiro dias e, ainda, aconselhei a levar um creme de hidrocortisona, para aplicar 2 a 3 vezes por dia e não ultrapassar os 5 dias de tratamento e, em caso e melhoria, ir reduzindo o número de aplicações. Finalmente, expliquei que seria importante acompanhar sempre o estado de evolução da lesão.

Caso Clínico 2: Senhora chega à farmácia queixando-se de dor de garganta, algum cansaço nos últimos 2 dias e uma ligeira dor de cabeça. Pretendia algo que melhorasse a sua situação rapidamente pois não queria que isso a afetasse durante o trabalho.

Tendo em conta a sintomatologia ligada à COVID-19 apresentada, tentei perceber se tinha febre, tosse ou dificuldades respiratórias uma vez que são sintomas muito relacionados com esta doença, ao que a utente referiu que não tinha dificuldades em respirar, mas que de manhã sofreu com alguma tosse e sentiu a temperatura corporal mais alta que o habitual. Além disso, perguntei se suspeitava ter contactado com alguém infetado e a resposta foi negativa. Sugeri, então, à utente, que realizasse o teste rápido de antigénio à COVID-19, explicando que, tendo em conta a sua situação, ainda que achasse não ter contactado com nenhum positivo, o mais acertado seria realizar o teste pois, numa eventual infeção, poderia infetar outras pessoas caso estivesse com elas nos dias seguintes. A utente decidiu realizar o teste e o resultado foi positivo. Ajudei-a depois, ligando para a Saúde 24 e fornecendo os dados da utente de forma a que passasse a ser seguida devidamente pelas autoridades de saúde. Recordei a utente de que seria importante, nos dias seguintes, manter o distanciamento social e tomar certas medidas como o uso de máscara e, no caso de viver acompanhada, usar uma divisão da casa apenas para si e lavar os utensílios a altas temperaturas. Por fim, dispensei à utente paracetamol para tomar em *SOS*, referi ser importante a ingestão de muita água e que fosse acompanhando os seus sintomas reportando às autoridades e profissionais de saúde no caso de pioria do seu quadro clínico.

Caso Clínico 3: Utente habitual da farmácia informa que teve uma consulta recente no reumatologista e que lhe foi diagnosticado artrose no joelho. Informa que nos últimos dias tem sentido um aumento da dor e sofrido de uma tosse intensa. Pediu ibuprofeno para as dores e antitússico para a tosse.

Tendo em conta o historial do utente, uma vez sendo asmático, explico que a toma desse tipo de anti-inflamatórios está totalmente desaconselhada no doente asmático e aconselho a tomar, no seu caso, paracetamol e a optar por medidas não farmacológicas como exercício físico de baixo impacto (caminhar, natação, bicicleta), que estão a nível de eficácia similar em relação aos AINEs (Anti-inflamatórios Não Esteróides), no que toca a este tipo de doença articular. Em relação à tosse, comecei por tentar perceber se a asma estava controlada, perguntando se tinha sintomas além da tosse e com que frequência estava a utilizar a medicação de emergência. O utente respondeu que não tinha mais sintomas e que não alterou o padrão de utilização da medicação de emergência e, nesse caso, tentei perceber se a utilização do inalador, por parte do utente, estava a ser efetuada de forma correta, uma vez que a tosse poderia ser irritativa resultante da má utilização do inalador. Após me explicar como utilizava o dispositivo e, percebendo que o fazia de forma correta, expliquei que não poderia dispensar o antitússico uma vez que a tosse é um dos sintomas do mau controlo da asma e, sendo assim, aconselhei o senhor a dirigir-se ao seu médico para que lhe fosse revista a sua situação clínica.

IV. Conclusão

Durante o estágio na FE apercebi-me da importância que o farmacêutico comunitário tem na sociedade. Em termos de conhecimentos, estes devem estar totalmente consolidados para dar resposta às questões colocadas e, sendo que grande parte do nosso trabalho é passado a interagir com os utentes, as qualidades sociais são uma mais-valia para o bom exercer desta profissão.

Tendo sido o momento mais desafiante dos meus cinco anos de curso, este estágio proporcionou-me uma aprendizagem completa que se destacou a vários níveis: evoluí bastante em termos de farmacoterapia e no entendimento das guias de tratamento seguidas pelos utentes; tornei-me mais capaz e confiante no atendimento e aconselhamento farmacêutico, desenvolvendo capacidades comunicativas e de relacionamento com os utentes; em termos de *back-office*, tornei-me totalmente autónomo no que toca ao processo de receção de encomendas e validação das mesmas, ganhei uma elevada perceção em relação à gestão de *stocks* necessária ao bom funcionamento da farmácia e, ainda, saí consciencializado da

documentação e legislação que são indispensáveis e se encontram ligadas aos psicotrópicos; dos serviços prestados pela FE, por ter sido parte integrante dos mesmos considero ter sido uma mais valia no meu estágio, dando destaque ao meu papel na medição dos parâmetros bioquímicos e fisiológicos.

Saio, deste estágio, preparado para exercer a minha função enquanto farmacêutico e sensibilizado do papel importante que podemos, enquanto profissão, exercer na vida do utente e da comunidade em geral.

V. Bibliografia

1. Imai, Masaaki - **Kaizen (Ky'zen), the Key to Japan's Competitive Success**. New York: Random House Business Division, 1986.
2. Instituto Português da Qualidade (2015**)** - **NP EN ISO 9001:2015 – Sistemas de gestão da qualidade** – Requisitos.
3. Osterberg L., *et al.* - Adherence to Medication. ISSN: 04797876. **The new england journal of medicine** 2005, 353:487-97.

Parte II

Monografia

"Development of bilayer tablets by Quality by Design: Focus on Manufacturing parameters"

List of Abbreviations

AIDS - Acquired Immunodeficiency Syndrome

API - Active Pharmaceutical Ingredient

BA - Bonding Area

BBB - Box-Behnken Design

BS - Bonding Strength

IBS - Interfacial Bonding Strength

CMA - Critical Material Attributes

CMC - Carboxymethylcellulose

CPP - Critical Process Parameters

CQA - Critical Quality Attributes

CR - Controlled Release

DoE - Design of Experiments

EMA - European Medicines Agency

ER - Extended Release

FDA - Food and Drug Administration

FDC - Fixed-Dose Combination

FTIR - Fourier-transform Infrared Spectroscopy

HCL - Hydrochloric Acid

HCTZ - Hydrochlorothiazide

HIV - Human Immunodeficiency Virus

HPLC - High Performance Liquid Chromatography

HPMC - Hydroxypropylmethyl Cellulose

ICH - International Council for Harmonisation

ILS - Interfacial Layer Strength

IR - Immediate Release

IS - Interfacial Strength

MCC - Microcrystalline Cellulose

P1 - Pressure Exerted on First Layer

P2 - Pressure Exerted on Second Layer

PAT - Process Analytical Technology

QbD - Quality by Design

QbT - Quality by Testing

QTPP - Quality Target Product Profile

RAM - Risk Assessment and Mitigation

RSM - Response Surface Methodology

SR - Sustained Release

Table Index

Figure Index

Abstract

Fixed-dose combinations, where bilayer tablets are included, have gained market and investor confidence in recent years due to their ability to solve problems. Examples of these problems are the lack of medication adherence by people who take a high number of pills daily and possible interactions between active pharmaceutical ingredients.

However, bilayer tablets manufacture depends on a set of parameters and processes that must be monitored in order to obtain the final pharmaceutical form with the best physical and chemical characteristics. The optimization of formulation and manufacturing processes during critical stages of its production, such as compression and ejection, will avoid problems such as delamination which are very frequent in the production of this type of pharmaceutical form.

This review article, in addition to the discrimination of bilayer tablets' advantages, addresses some of the most important factors affecting their manufacture, with focus on delamination by using Quality by Design as a strategy. The role of material properties, elasticity and plastic recovery, pre-compression and main compression, moisture and punch shape on tablets properties is covered in this article. Finally, the Quality by Design methodology, more precisely its applicability is discussed with examples in double-layer tablet technology.

Keywords: Fixed-dose combinations; Polymedication; Bilayer tablet manufacturing; Delamination; Quality-by-Design.

Resumo

As associações de fármacos em terapia combinada, onde se incluem os comprimidos de dupla camada, têm vindo a conquistar mercado e a confiança dos investidores nos últimos anos devido à sua capacidade de solucionar problemas como a falta de adesão à medicação por doentes que tomam um elevado número de comprimidos diariamente e a presença de interações entre princípios ativos.

No entanto, o seu correto fabrico está dependente de um conjunto de parâmetros e processos que devem ser monitorizados de forma a obtermos a forma farmacêutica final com as melhores características físicas e químicas. A otimização da formulação e dos processos de fabrico durante etapas críticas da sua produção, como a compressão e a ejeção, vai evitar problemas como a delaminação, que são muito frequentes na produção deste tipo de forma farmacêutica.

Este artigo de revisão, além de evidenciar as vantagens deste tipo de forma farmacêutica, aborda alguns dos mais importantes fatores que afetam o seu fabrico, focando-se na delaminação através duma estratégia de Qualidade programada. As propriedades dos materiais, a elasticidade e a recuperação plástica, a pré-compressão e compressão, a humidade e a forma dos punções são alguns dos parâmetros abordados neste artigo. Finalmente, é sumariamente explicada a metodologia da Qualidade Programada e abordada a sua aplicabilidade, com exemplos, na tecnologia dos comprimidos de dupla camada.

Palavras-chave: Terapia em dose combinada; Polimedicação; Produção de comprimidos de dupla camada; Delaminação; Qualidade programada.

I. Introduction

Over the years, polymedication has proved to be one of the most important barriers regarding adherence and maintenance of treatment in various diseases [1]. Diseases like hypertension, type 2 diabetes and AIDS (Acquired Immunodeficiency Syndrome) need to be treated in a chronic way and such treatment often includes taking several drugs concomitantly, otherwise we will not achieve optimal disease control [2, 3, 4].

A good solution to this problem is the use of Fixed-dose combinations (FDCs). They combine 2 or more active pharmaceutical ingredients (APIs) in the same pharmaceutical formulation (tablet or capsule). Besides that, in combinations like telmisartan and amlodipine efficacy can be improved and reduced side effects can be achieved [5]. Even if, concerning to compliance there are no great doubts about the advantages of these pharmaceutical formulations, a very careful evaluation is necessary when these are the chosen therapy modality [6] as limitations associated with interactions between drugs, among others, have been reported to have greater implications for FDC intake when comparing to an isolated drug [7].

There are 3 types of FDCs that stand out: multi-layer systems, monolithic systems and multiparticulate systems [8]. Multi-layer tablets, in recent years, have been particularly studied and results have shown important advantages over other pharmaceutical forms [9, 10]. Some of the reasons for the success and interest in this pharmaceutical formulation are, for example, its high flexibility (incompatible APIs in the same tablet and the possibility of generating different release profiles) [11] and better adherence to therapy by the patient [12].

Layered tablets composed of two layers are referred to as bilayer tablets. Bilayer tablets can provide product performance objectives hardly achievable by conventional tablets, still, a new set of challenges is expected with regard to formulation and manufacturing parameters controls and product performance requirements [13]. At the time of its production, there is a need to evaluate and optimize certain parameters and procedures because, otherwise, the tablets produced will have associated problems. One of the most common problems during the production of bilayer tablets is delamination. This problem occurs initially in the compression process and it is necessary to study the tendency towards delamination and a quality control of the processes is required in order to prevent this from happening during manufacture, manipulation and storage [14]. In a recent study, pre-compression proved to be a more compromising parameter of adhesion between layers, compared to the main compression [11].

The pharmaceutical development of bilayer tablets is quite challenging considering the influence of several formulation and process parameters on tablet properties. Thus, a rationale multiapproach based on factorial design is likely to meet the challenge. Formulation development upon Quality by Testing (QbT) approach ensures the quality of the drug product but it is not guaranteed. For more than a decade, Quality by Design (QbD) strategy has become the most preferred regarding redefined quality. The ICH (International Council for Harmonisation) guidelines for industry such as Q8 R2: Pharmaceutical development has clearly defined key operators for the QbD based pharmaceutical development such as Quality Target Product Profile (QTPP), Critical Quality Attributes (CQA), Risk Assessment and Mitigation (RAM) and Design Space.

This review focuses on bilayer tablet technology. Its advantages and manufacturing process are described taking into account a QbD methodology as a tool to overcome the challenges of the most relevant processes and formulation factors making the development process more effective and efficient.

II. Bilayer tablets

2.1 Polymedication: we must insist on bilayer tablets

Polymedication is a problem often associated with chronic diseases [15]. Within this category, diseases such as diabetes, hypertension and AIDS are some examples in which a large percentage of patients have more than one drug as prescribed therapy for many years [16, 17]. The elderly, a population group that suffers a lot from chronic diseases, also take a high number of pills daily. In this case, it has several consequences such as interactions between drugs, reduced adherence to treatment by the patient and fluctuation between excessive and reduced effectiveness of the treatment of different pathologies [18].

Hypertension is one of the examples of diseases that have been increasing in prevalence in recent years [19]. For several reasons, including the need to take more than one pill a day, adherence to treatment by hypertensive patients after one year of treatment, is reported to be less than half [20]. Non-adherence to treatment for hypertension is associated, of course, with uncontrolled blood pressure and high blood pressure peaks, but also with some dangerous cardiovascular events such as heart failure and stroke and, in extreme cases, death can occur [19, 21].

In the case of patients infected with HIV (human immunodeficiency virus) it can be considered a recent problem, considering that, due to the improvement in therapy over many years, HIV-infected patients are less susceptible to the disease and their average life expectancy

has increased. In addition to antiretrovirals, AIDS patients take on average more medications than the rest of the population [18]. A study carried out in children revealed that adherence to treatment is negatively related to the pill burden of antiretroviral drugs thus promoting the feasibility of using FDCs in children [22].

It is, therefore, of great importance to make adherence to therapy as effective as possible. One of the ways to combat polymedication is to reduce the pill burden and, in line with this strategy, FDCs (which include bilayer tablets) are a real and effective option [18, 19]. When starting or changing the usual medication for FDCs, the patient's adherence effectively increases [18].

Table I. List of bilayer-tablet based fixed-dose combinations marketed for various indications approved by either Federal Drug Administration or European Medicines Agency (EMA). Every formulation is discriminated whenever possible for its indication, active pharmaceutical ingredients, the rationale for its production, the technology by which the API is released and trademark name.

Indications	Formulation	Specific technology[1]	Rationale[2]	Example of brand name	Approval date	REF
T2D	Metformin HCl and Pioglitazone	(SCOT™)	Synergistic effect	Actoplus MET XR	2009	FDA data
T2D	Metformin and Glipizide	-	Synergistic effect Interaction between drugs	Metaglip	2002	FDA data
T2D	Glimepiride and Pioglitazone HCl	-	Interaction between drugs	Duetact	2006	FDA data
T2D	Alogliptin and Pioglitazone	Film-coated tablet	Interaction between drugs	Incresync	2013	EMA data
T2D	Sitagliptin and Metformin HCl	Metformin core coated with sitagliptin	Synergistic effect and ER of metformin	Janumet XR	2008	EMA data
T2D	Pioglitazone and glimepiride	-	-	Tandemact	2007	EMA data
Diabetes mellitus / Dyslipidemia	Sitagliptin and Simvastatin	-	Interaction between drugs	Juvisync	2011	FDA data
Hypertension	Telmisartan and Hydrochlorthiazide	-	Interaction between drugs	Kinzalkomb	2002	EMA data
Hypertension	Enalapril maleate and Felodipine	Press-coating	ER of felodipine	Lexxel	1996	FDA data
Hypertension	Telmisartan and amlodipine	-	Interaction between drugs	Twynsta	2009	FDA data
Tuberculosis	Rifampicin and Isoniazid	Coated tablet	Interaction between drugs	Rifinah	1999	EMA data
Bacterial Infections	Amoxicillin and Clavulanate	Film-coated bilayer scored tablet	Combo and ER of amoxicillin	Augmentin XR	2002	FDA data
HIV	Efavirenz,Emtricita-bine and Tenofovir disoproxil fumarate	Film-coated tablet	Incompatibility between drugs	Atripla	2007	EMA data
Pain	Tramadol and Acetaminophen	Film coated capsule-shaped tablet	Synergistic effect	Ultracet	2001	FDA data
Migraine	Sumatriptan and Naproxen sodium	Film-coated tablets	-	Treximet	2008	FDA data
Expectorant	Guaifenesin and Pseudoephedrine	-	IR of guaifenesin / ER of guaifenesin and pseudoephedrine	Mucinex D	2004	FDA data

Allergic rhinitis	Desloratadine and Pseudoephedrine sulphate	-	ER of pseudoephedrine sulphate	Clarinex-D	2005	FDA data
Allergies	Cetrizine HCl and Pseudoephedrine HCl	-	IR/ ER of pseudoephedrine HCl	Zyrtec – D	2007	FDA data
Rheumatoid arthritis and oste oarthritis	Misorostol and Diclofenac	Enteric-coated core	Incompatibility between drugs	Arthrotec	1997	FDA data

API - Active pharmaceutical ingredient; EMA - European medicines agency; ER - Extended Release; FDA - Food and drug administration; HCl - Hydrochloric acid; HIV - Human immunodeficiency virus; IR - Immediate Release; REF - Reference; SCOT™ - Single composition osmotic technology; T2D - Type 2 Diabetes.

[1] Other than classical bilayer obtained by compression;

[2] According to disclosed information in common technical document (CTD).

2.2 Applications

Bilayer tablets can consist of only one API or two distinct ones, in the same pharmaceutical formulation. One layer can be used for immediate release (IR) and the other for controlled release (CR) of the drug. This technology allows us to obtain an initial high concentration of drug in the blood and also to prolong this action over time [23, 24]. As mentioned above, this contributes to a better adherence to therapy by the patient. In table II, we have a summary of the applicability of bilayer tablets in solving problems when it comes to pharmacotherapy and drug development.

Table II. Problems related to therapeutics, pharmaceutical drug development and discrimination of the solutions provided by bilayer tablet technology.

Limitation associated with therapeutics or drugs	Solution offered by bilayer tablet technology	REF
Need for combination therapy	Drugs in two distinct layers, physically separated	12, 25
Chemical and physical incompatibility		26, 27
Need to control the release profile	Immediate and extended release profiles	23
Need to reduce dose frequency		
Polymedication	Reduction in the number of pills per day (by combining 2 drugs in the same formulation)	28
Treatment adherence		
Patent term	Good alternative to increase the patent time of a certain drug product	
Efficacy	Synergistic effect between drugs	
"Burst effect"	Control of initial drug release	29
Manufacturing costs	Low-price (compared to the drug products individually) and suitable for industrially production	30
Microbial and chemical stability	Improved with bilayer tablets	12
Smell and flavor	Can be camouflaged by coating technique	30
Low half-life drugs	Increase of bioavailability	

2.3 Manufacturing

Bilayer tablets manufacturing process is complex although most of the equipment and technology is similar to those being used for classic tablets. Its production has been extensively studied but manufacturing problems can still occur if operating conditions are not optimized [26].

Direct compression can be used when we have a mixture of APIs with excipients having good flow properties so their movement into the matrix is predictable and reproducible thus not requiring any intermediate process such as granulation (dry or wet granulation). In reality, few materials meet these requirements thus direct compression can hardly be used making the selection of excipients a fundamental step toward the best physical and chemical properties and consequently suitable for compression. These excipients may have, in the formulation, the function of lubricants (stearic acid, magnesium stearate), disintegrants (Croscarmellose sodium (e.g. Ac-Di-Sol®; Explocel®)), diluents (Microcrystalline cellulose (e.g. Avicel® pH-102)), Mannitol (e.g. Pearlitol®), among others.

However, parameters about the formulation and manufacturing processes must be optimized and understood as much as possible, in order to obtain the final product with the best possible quality. In the next chapter, some of the difficulties and challenges that arise when choosing the formulation until obtaining a bilayer tablet through direct compression will be addressed.

The flowchart depicted in figure 1 describes the main steps corresponding to the production of the bilayer tablet as well as its final appearance, after the final ejection step.

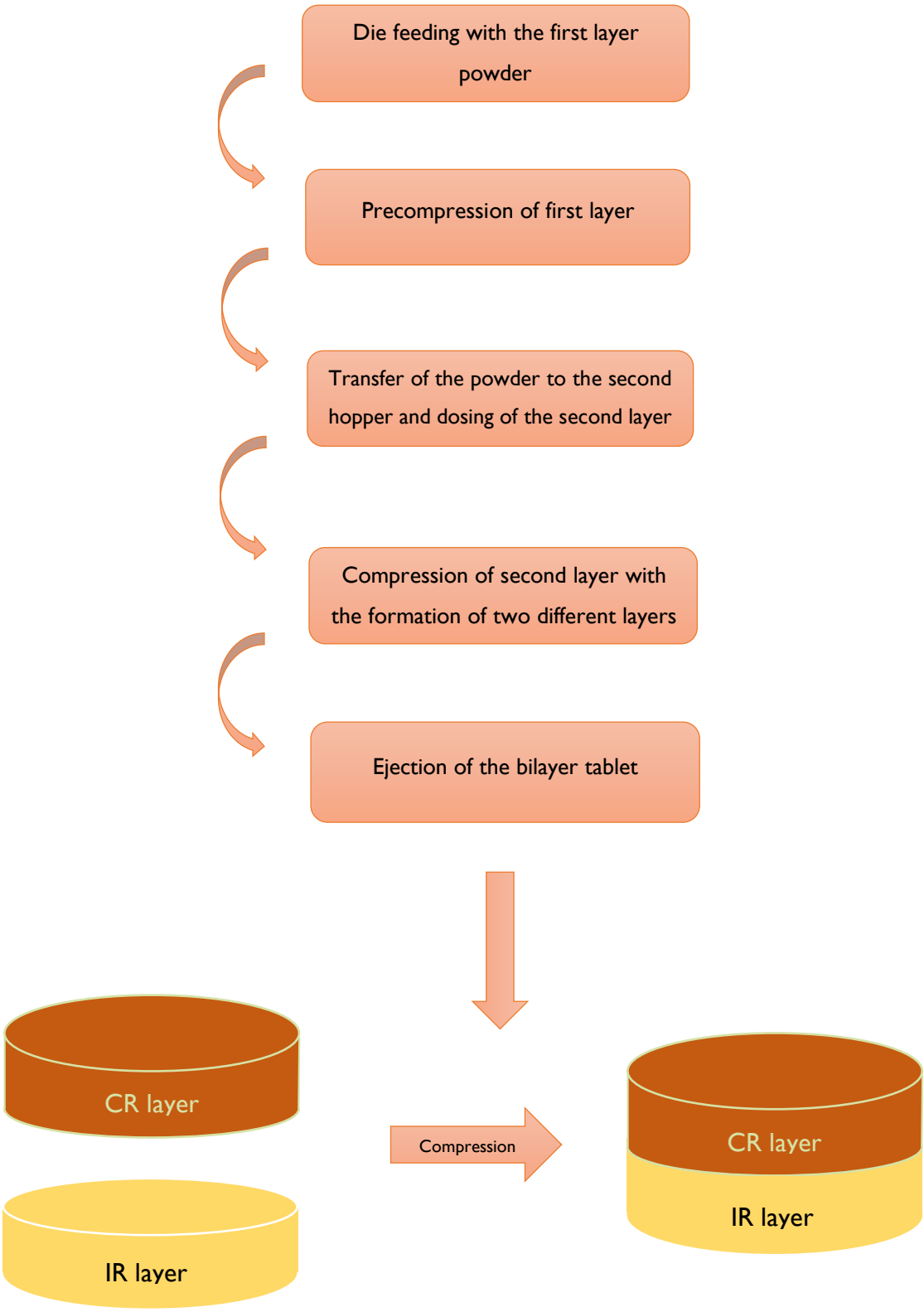

Figure 1. Scheme of the steps in the manufacturing of a bilayer tablet, starting from feeding the die and production of the first layer and finishing with the ejection of the complete tablet. The result is a tablet constituted by two layers physically separated, in this case identified as controlled release (CR) layer and immediate release (IR) layer.

III. Critical factors in manufacturing bilayer tablets

There are many factors that need to be optimized, more specifically the ones related to materials (API and excipients) physical chemical properties and others related to formulation and equipment used during their production. Assuring compacted layers' mechanical adhesion within the tablet requires the understanding of the parameters influencing the stress state, the mechanical properties of every layer and the overall tablet.

3.1 Material properties

The materials, both APIs and excipients, must be chosen carefully as their properties (plasticity and brittleness, among others), must be chosen carefully as their influence on the bilayer tablet compaction process should not be neglected. For plastic materials, if their elasticity limit point is not exceeded, plasticity has no impact [23] whereas brittle materials when subjected to compression do not suffer any plastic deformation behavior before particle fragmentation [31].

During tablets formulation overall materials' compressibility and compatibility are key players toward a strong and cohesive tablet.

Adhesion and bonding behavior at the interface between the adjacent layers is of outmost importance when manufacturing bilayer tablets. Interfacial crack often results in residual stresses in the tablet thus promoting delamination or layer-separation, usually not visible immediately after compaction, such as packaging, storage, or shipping [23].

If the same type of material is used in both layers, bonding area (BA) is the major concern as bonding strength (BS) remains constant. On the other hand, if different materials are used the formation of pores is more accentuated with less compressible materials, which are more resistant to compression, later facilitating the penetration of particles while adding the second layer [32].

Furthermore, the amount of material is likely to have impact on layers BS. In tablets with both layers consisting of mixtures of microcrystalline cellulose (MCC) (plastic material) and lactose (brittle material), an increase in the % of MCC in the first layer led to an increase in IBS (interfacial bonding strength) despite the decrease in BA [33]. However, after 20% of MCC, the negative effect of BA outweighed the benefit of BS whilst the situation was reversed with MCC % closer to 80%. When tablets consisting of an IR/ER (extended release) combination, materials such as hydroxypropylmethyl cellulose (HPMC) are often used in the second layer. Although the use of HPMC has a lowering effect on BS the effect of increasing the percentage of MCC has shown the same influence in the BA-BS ratio and its contribution to IBS [24].

Another important parameter to control is the amount of lubricant used. By using low amount of lubricant in tablets obtained with materials with reduced elasticity mismatch, reduced pre-compression force and high main compression force greater adhesion between the two layers was favored [26, 34, 35].

After compression, bilayer tablet elastic recovery can lead to different stresses. Stress not supported by the tablet undergoes to structure failures and tablet capping or lamination may occur upon tablet high rate and degree of elastic recovery. On the other hand, tablet brittle fracture during decompression leads to fracturing of surfaces. Tablet plastic deformation is time dependent and it is a different way to relieve stress.

The required force to fracture the tablet may allow determination of mechanical properties of materials, such as Young's modulus, E, defined as the ratio of stress over strain deformation ($E = \sigma/\varepsilon$). Furthermore, apparent Modulus has been an indicator of a tablet's breaking force and viscoelasticity. A tablet consisting of layers with different values of Young's modulus is prone to an elastic mismatch generation promoting on tablet a radial stress along the interface which may lead to delamination [26, 36].

The environmental conditions among which humidity, moisture and temperature can affect the compactness of materials. Significant changes in temperature and humidity during bilayer tablets production and storage can mean loss of quality and adhesion between the layers in the tablets [23].

Humidity influence on the Young's modulus should be considered as humidity high values decrease Young's modulus leading to tablet delamination easier [28]. To prevent this from happening, it is recommended pre-conditioning of the materials [37].

Humidity can have several effects, more precisely on the fluidity of the powders, on their compressibility and tensile strength and later in the storage of the drug product [38]. Tablets composed of Avicel-lactose and lactose-Avicel showed a lower strength with increasing humidity and storage time, whilst strength of tablets made of lactose-lactose increased under the same conditions [34].

Hygroscopic materials made tablets revealed to be more prone to changes due to radial stresses (negative effect on adherence) while in tablets composed of non-hygroscopic materials, the reduction in the adhesion of the layer is dependent only on the storage time [38].

As well as Young's modulus, friability, weight variation and thickness, hardness is one of the parameters that is crucial to be measured when studying bilayer tablets [39].

The hardness will then depend on the composition of the materials (both qualitative and quantitative), which at the time of compression directly affects the tendency to deform [28].

The hardness and Young's modulus are both related to the plasticity and elasticity of the materials. The hardness and the Young's modulus have a proportional relationship with each other, regardless of the material used, making it possible to infer one from the other and it is advisable to measure the hardness, since it is an easier parameter to measure. The relationship of both with the tensile strength is similar. A balance between brittleness and plasticity is one of the important milestones when we want to obtain quality tablets as both have influence on the IBS [40].

3.2 Process parameters

It is somehow difficult to systematize main process parameters influence on bilayer properties without referring materials attributes, particularly their brittle and plastic properties.

The compression force is one of the most important parameters to control in the production of bilayer tablets [23] and the impact of its influence is material dependent. For plastic materials, if P1(pression exerted on first layer) is too high the surface roughness is decreased and the delamination of the tablet it is mostly to occur [12, 35, 41]. A minimal P1 ensures first layer sufficient roughness upon contact and adhesion to the second layer [26]. For brittle materials, there is no tendency to delamination even when high compressive forces are used in the first layer [28]. Regarding P2 (pression exerted on second layer), even though it is not so crucial, it has a complementary role and should also be well studied [42].

Compression forces have a substantial impact on IBS. IBS will depend on both BA and BS. The larger the BA and the greater the BS, the greater IBS will be [32]. Upon compaction with reduced compression force, powder particles rearrange themselves whilst increasing the compression force particles they go through processes such as plastic and elastic deformation [42].

BA is influenced by porosity and waviness [32]. A higher P1 reduces porosity and increases the compaction of the powder decreasing BA and, consequently, leading to lower IBS. On the other hand, a higher P2 positively influences waviness, and facilitates the interpenetration of particles, improving IBS [32].

Interesting results on how the shape of the punches influences the interfacial resistance of the layers have been disclosed. Punches shape has an influence on the strength of the produced bilayers: convex or concave punches comparing to the flat ones have a greater

capacity to enhance the interactions between the two layers because during the pre-compression process an increased surface area is achieved. This effect is directly proportional to the compression force applied [9].

The use of convex punches in pre-compression presented better results. Increasing the curvature of punches interfacial resistance also increased and deeper punches revealed to be the ones mostly contributing to the interfacial strength.

3.3 Control strategy

Bilayer and classical monolayer tablet manufacturing shares several common unit operations as both products are formed by powder compaction [28]. Great advances in compaction area have led to improvements in quality and efficiency of pharmaceutical tableting, still, there are a number of technological challenges ahead to bring bilayer tablet design and manufacturing to similar standards of robustness as found in classical monolayer tablets. These issues range from drug product characterization, to material/parameters/equipment selection, as well as modeling [28]. General manufacturing unit operations, process parameters and quality attributes have been exhaustively described for pharmaceutical tablet dosage forms [43, 44]. Bilayer tablets are heterogeneous systems composed of two layers separated by a discrete interface. This heterogeneity remains the main source for the additional challenges in the manufacture and control of bilayer tablets. Bilayer properties such as hardness and lamination tendency depend on both the formulation and the deformation behavior of each layer during and after compression. For bilayer tablets, further studies related to the interdependency between first and second layer interactions, including thickness, weight and force, are required [28]. A planned set of controls derived from tablet properties aimed to achieve and process can ensure process performance and product quality.

The main problem that occurs during the manufacturing of bilayer tablets is delamination [13, 14]. It is thus critical to have a robust method to quantify interfacial strength and this relevance has increased with the implementation QbD in the manufacturing of bilayer tablets. The IBS of bilayer tablets has been determined mostly by tensile and shear measurement methods [45].

IV. QbD in pharmaceutical development

The QbD approach, highly investigated in recent years, is one of the most promising approaches to the pharmaceutical industry. Through a perception of the risks, understanding of the formulation and parameters related to the process, with the QbD strategy we can obtain a better-quality product [46]. If we understand the causes of variability we can, throughout the manufacturing process, adapt our procedure in order to reduce this variability [29]. QbD is preferable to QbT as it guarantees the predefined quality in the final product [47].

Based on scientific fundamentals and the application of a design strategy it is intended, as much as possible, to know the product and the processes in order to achieve certain objectives [48].

The main objective is, by understanding the relationship between critical material attributes (CMAs) and critical process parameters (CPP) as schematically represented in Figure II, to obtain a final product with the appropriate pre-defined quality attributes [49]. High risk parameters are initially defined from the risk assessment and will be part of the Design of experiments [29, 50]. A DoE and response surface methodology (RSM) constitute two important pieces which together will allow obtaining mathematical models that will provide output responses through input variables. The better the input variables are adjusted, the better the quality of our formulation and the closer to the objectives.

4.1 Relevant steps

The first step is to define the QTPP which includes the final specifications of the product we want to obtain. It is a strategy that is developed taking into account the final result [29, 49]. The QTPP - dosage form, dosage, delivery system, route of administration - needs to be guided taking into account the CQAs - biological, physical or microbiological properties that must be within determined values - and, to do so, we must have a broad knowledge of the processes as well as about the substances that will be part of the formulation, which is very important because it will reduce the amount of necessary tests and thus reduce manufacturing costs. Related to the CQAs, is the Risk Assessment which will be discussed next.

After defining our design goal, we have the process design space, phase in which we take into account the CPPs. From design space, we aim to ensure the maximum quality for our product, improving the relationship between process parameters and material attributes. Through literature, experimental methods or prior knowledge, possible future problems will be avoided at this stage of QbD.

In the continuation of process design space, we can define the control design space. In this step, we will be able to keep complex processes under control. For this, let's compare the output of a process with a reference one, and one of the widely used techniques is DoE. From this step, we hope to minimize the effort and causes of possible unexpected results.

Finally, but not the least, the operating space often defined as "the best set of parameters, statistically-supported determined and accommodating any natural changes in CPPs and CQA". For generics, the operating space has to be in accordance with the control space while for new products, it must be guided in accordance with the design space.

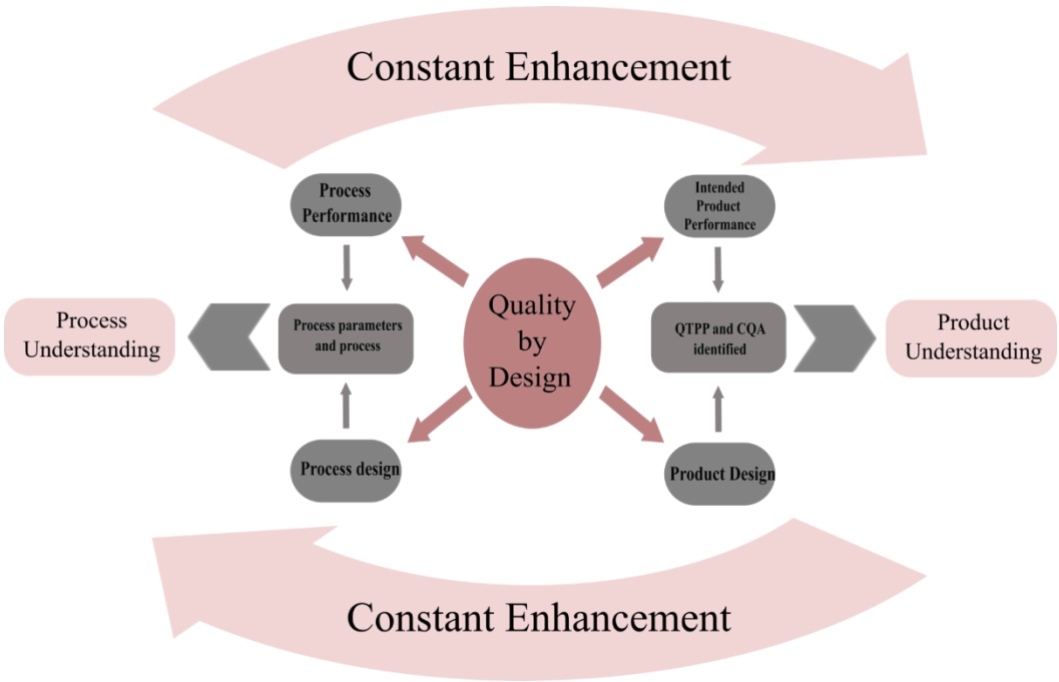

Figure II. Representative scheme of the QbD process in which we can divide it into two parts: process and product understanding. The result is a complete understanding of both parts that will guarantee us that the final product has the specifications we defined as critical, thus ensuring the highest possible quality.

4.2 Useful tools

4.2.1 Prior Knowledge

Prior knowledge is something that cannot be acquired through literature or education, but through experience. Therefore, the public cannot take advantage of this knowledge. This knowledge acquired by researchers through previous studies will allow to approach all QbD steps in a more rational and effective way [43].

4.2.2 Risk Assessment

According to the ICH guideline, "Risk assessment is a valuable science-based process used in quality risk management that can aid in identifying which material attributes and process parameters potentially have an effect on product CQAs." With a tendency to take place at the beginning of the process, it will help to identify the crucial parameters and later these can be studied in more depth in order to have an understanding as complete as possible of the product development [43].

4.2.3 DoE

After defining the highest risk factors, experimental strategies such as the DoE are used to study and better understand the process. It is a structured method and will permit us to have a more effective control of the process, being useful, for example, to understand the output responses that may arise from the input factors.

4.2.4 PAT (Process Analytical Technology)

By using PAT we will better understand the processes related to manufacturing [51, 52]. Based on the condition that quality must be inherent to the products, and using in-line, on-line and at-line measurements, it is a strong aid in the control, design and analysis of manufacturing processes. This will allow us to obtain real-time information on critical processes. The ideal scenario is the real-time release of the product.

As mentioned above, measurements in the PAT environment can be of 3 types: at-line: the sample taken and isolated is analyzed close to the sampling point; on-line: the sample is removed and can eventually be put back in the process and, finally, in-line: in this case the sample is never removed from the process stream [53].

V. QbD in manufacturing bilayer tablets

The process of bilayer tablet design, at the beginning mostly dependent on the quality by testing approach, has greatly changed for and nowadays a deep understanding of the impact of formulation and process parameters on the bonding properties of bilayer tablets is required so comprehensive DOE can be plotted with focus on QbD by exploiting the prior knowledge. Table III refers to a summary of the applicability of QbD in optimizing bilayer tablets.

Table III. Applications of QbD to the pharmaceutical development and optimization of bilayer tablets. Whenever possible the purpose, the design used and the variables evaluated in studies are discriminated.

Objective and purpose of the research	Formulation	Initial risk assessment[1]	Definition of QTPP and CQAs identification	DOE (Software)	Independent variables	Dependent variables	Output	Ref.
Risk assessment; effect of CPP and CMA on CQA; optimization.	Simvastatin SR labetalol HCl IR	Ishikawa fishbone diagram; preliminary hazard analysis tool	Yes Yes	3^2 full factorial design (Design-Expert® 9)	Compression pressure; concentration of superdesintegrants and desintegrant	Tablet crushing strength, tablet porosity and tablet friability	RA by FMEA revealed control strategies minimum impact on CQA; compression speed and compression force were optimized.	49
Effect of CMA on CQA; optimization.	HCTZ in IR and SR	Yes	No Yes	2^2 full factorial design (Design Expert 8.0.4)	Concentration of superdisintegrants and drug: polymers blend in IR and SR layers, respectively	Disintegration time (DT) and T100%	Independent variables significant effect over the dependent responses; statistical tools usefulness; good match predicted values-experimental values.	29
Identification of CMA; optimization; QTPP based on marketed control formulation.	Telmisartan and amlodipine	Yes	Yes Yes	X^y (Design-Expert® 10)	**Telmisartan layer** D-mannitol; MCC and crospovidone. **Amlodipine layer** CCM-Na;PVP; K25.	**Telmisartan layer** CI; friability; hardness; DDP up to 45 min. **Amlodipine layer:** Hardness of tablet, friability of tablet, DDP up to 45 min.	Good match predicted values-experimental values; optimized formulation high stability; the *in vivo* pharmacokinetic data indicated bioequivalence with control formulation.	54
Effect of CMA on CQA; optimization.	Empagliflozin and metformin HCl SR	Yes	No No	3^2 (two factor, three level) factorial design	Binder concentration (sodium CMC) and ER polymer (HPMC K100M CR/ PEO/ Carbopol)	DDP at 1, 4 and 10 h	Independent variables significant impact on the responses; effect of CPP on drug release could be predicted by polynomial equations; optimized batch showed assay and drug release results within specifications.	55
Identification of CQA; optimization; impact of CMA on drug release.	Fexofenadine HCl IR and montelukast sodium SR	Prior knowledge, experience and literature	Yes Yes	A three-factor, three-level BBB (Design-Expert 11.0.5.0)	**IR layer** Amount of drug, sodium starch glycolate and bicarbonate **SR layer** Amount of drug, HPMC and magnesium stearate	**IR layer** DDP and disintegration time **SR layer** DDP	Optimization model successfully validated using ANOVA and diagnostic plots; impact of CMA on responses was determined; cronomodulated time release to overcome the obstacle of nocturnal asthma.	56
Effect of CMA on drug release; optimization;	IR and SR layers containing lexoprofen	Yes	No No	BBD 3^3 (Design-Expert software 8.0.4)	Drug in the IR layer/ total drug; HPMC/ drug in the SR layer; Eudragit	DDP at 30 min; DDP at pH 1.2 at 2 h; DDP at pH 6.8 at 12 h.	Responses fitted to suitable models and statistical validation upon analysis of	57

impact of CMA on drug release.					RL/PEO/ drug in the SR layer.		variance, response surface graphs and contour plots; good match predicted values-experimental values suggested the success of the BBD; Optimized formulation better stability than commercial product.	
Effect of CMA on drug release; optimization.	IR and SR layers of dextrometho-rphan	-	No No	-	Binder; superdisintegrant and coating concentrations.	Hardness; thickness; weight variation; friability; content uniformity; disintegration; dissolution profile	Control results within the limits; extended release layer showed a decreased release as concentration of the polymer increases; drug release followed first order kinetics; optimized formulation studied for FTIR was found to be compatible due to no shifts of main peaks of drug.	58
Prediction of dissolution profiles of APIs	No discrimination of API in both layers	-	-	3^3 SIMCA 14.1 (Umetrics-Sartorius, Umeå, Sweden)	**API A layer** PSD of API A **API B layer** PSD of API B **Bilayer tablet** Hardness	NIR spectra; HPLC-quantification dissolution testing; relation between NIR spectra and dissolution testing	The API in each layer was identified through PCA; PCA study on spectral data was able to classify bilayer tablets hardness: PCA was able to classify API A but not API B with respect to the levels of PSD; A good match HPLC-NIR spectroscopy.	59
Evaluation of the effect of process parameters on layer adhesion	No API Combinations of immediate and controlled drug release excipients	-	No No	CCD of Experiment levels for each factor (JMP® Pro 13)	Pre-compaction; main compaction; TRS.	Layer adhesion	A shear test was used successfully to measure the layer adhesion on bilayer tablets; main compaction pressure and TRS were the most CPP.	11
Effect of CMA and CPP on drug product properties; optimization.	IR layer of saxagliptin and SR of metformin	-	Risk estimation matrix and taguchi design	BBD (Design expert)	**IR layer** MS level, kneading time and lubrication time. **SR layer** HPMC, Compritol and MS levels.	CI; content uniformity; DDP at 30 min CI; DDP at 2 h, 5 h and 10 h	Influence of various formulation parameters on CQA of drug products was understood with fewer experiments; cost can be reduced using QbD in the development of FDC for improving patient compliance.	1
Optimization of a HBS system; Multiple linear regression analysis of dependent variables	IR layer of HCTZ and SR of LP	-	-	2^3 full factorial designs	Concentration of swelling agent (HPMC K4M); concentration of gas spawning agent (sodium bicarbonate); Buoyancy enhancer (ethylcellulose 4cps)	DDP at 12h; time required to 50% of drug discharge; Floating lag time.	Optimized bilayer table was developed by QbD; three-month stability at 40°C/75% RH; biphasic drug release floating bilayer tablets.	60

Impact of CPP and CMA on the delamination of coated tablets; create models more sensitive to equipment and scale changes	API not disclosed	.	-	2^3 full factorial design (JMP®8)	Tablet hardness, spray rate and exhaust temperature	Tablet survival tests predicting the percent of tablet failure at the 7th, 14th and 21st day time points.	Impact of the tablet-bed microenvironment experienced during coating on the delamination tendencies of bilayer tablets in open storage conditions; The models created using primary DOE factors were more sensitive to equipment and scale changes	[61]
The effect of CMA interfacial adhesion; Develop a new flexural test to assess interfacial strength; validation	No APIs	-	-	MODDE 9.1 software (Umetrics, Sweden).	**Layer 1** CP, Lactose PS, MCC, HPMC **Layer 2** CP, Lactose PS, MCC, HPMC	ERt1, ERt2, DERt	New methodology to measure interface layer strength (ILS) of tablets. Excipients critical effect on ILS; the cohesion of tablets is higher for excipients with close elastic recovery.	[36]
Effect of CPP on drug product properties; optimization; PAT.	Metformin HCl SR and evogliptin tartrate IR	Yes	Yes	MODDE 12 software (Umetrics Inc., Sweden) CCD	-	-	-	[62]

BBD-Box-Behnken design; CI-Carr's index; CMA-Critical material attributes; CPP-Critical process parameters; CQA-Critical quality attribute; CCD-Central composite design; CP-Encompress Premium; DERt-Difference of total elastic recovery; DDP-Dissolved drug percentage; DNA-Does not apply; ERt1-Elasticity of the material in the layer 1; ERt2-Elasticity of the material in the layer 2; FCCCD-Face-centered center composite design; FMEA-Failure mode effect analysis; FTIR-Fourier-transform infrared spectroscopy; HBS-Hydrodynamically balanced system; HCTZ-Hydrochlorothiazide; HPLC-High performance liquid chromatography; HPMC-Hydroxypropyl methylcellulose; IR-Immediate release; LP-Losartan potassium; MS-Magnesium stearate; PAT-Process analytical technology; PCA-Principal component analysis; PEO-Polyethylene oxide; PLS-Partial least squares; PS-Pregelatinized starch; PSD-Particle size distribution; QbD-Quality by Design; RA-Risk assessment; RH-Relative humidity; SR-Sustained release; TRS-Turret rotation speed; $T_{X\%}$ (time required to release X% of the drug).

1 For formulation development

2 Design name and software

A simvastatin (sustained release (SR)) and Labetalol Hydrochloric acid [63] (IR) bilayer tablet was developed using QbD strategy [49]. After the identification of the QTPP and performing the risk assessment, both the independent and dependent variables were selected. The statistical tool used was a 3^2 factorial design and obtained values showed correlation with the predicted ones. An interplay between the independent variables and the respective responses was found. Formulation was optimized and the usefulness of QbD in the production of bilayer tablets was demonstrated.

Hydrochlorothiazide (HCTZ) bilayer tablets were developed by using QbD [29]. From the risk assessment, it was concluded that the concentration of superdisintegrant (croscarmellose sodium) and polymers (hydrophilic polymers) were two critical parameters in the formulation. The DoE was designed using as methodology, in this case, a 2^2 full factorial design. The disintegration time of tablets decreased as the concentration of the superdisintegrant increased and also the concentration of polymer revealed to be the most relevant factor in the release of the drug from the SR layer. The QbD-based strategy proved to be a very important support in the perception of the variables that may influence the performance of the bilayer tablet and also demonstrated effectiveness in obtaining a formulation with the highest quality.

QbD was used as a strategy in the industrial development of antihypertensive tablets [54]. In addition to prior knowledge, authors used control drug product (Twynsta®) target values to determine the factors (control and responses). The design used, D-optimal mixture, led to the best formulations. Telmisartan and amlodipine tablet (Telmiduo®) showed greater physical stability compared and evaluating the pharmaceutical and biological equivalence, results demonstrated that this tablet can be produced more cost-effectively.

The reliability of the RSM technology was demonstrated in the optimization of empagliflozin and metformin hydrochloride bilayer tablets [55]. Through this methodology, a major effect of the concentration of binder as well as that of the ER polymers on the release of the drug from the ER part was found. The binder used was sodium carboxymethylcellulose (CMC) and for the polymers HPMC K100M CR / polyethylene oxide / carbopol. The formulation that best suited the predefined parameters contained 5% CMC combined with the HPMC K.

Eudragit-coated bilayer tablets consisting of IR layer of fexofenadine HCl and SR of montelukast sodium were previously screened for CQA and optimized following a Box-Behnken design (BBB) [56]. The formulation was developed, and the CQAs were identified.

Statistics tools and diagnostic plots confirmed the relevance and goodness of fit with regard to the used model. The bilayer tablet after Eudragit coating provided an IR action for the first hour and a SR effect for more than 8 hours.

BBD was used as DOE of loxotrofen tablets. By BBD, models and statistical validation, the responses were properly analyzed using graphs and contour plots. The final result was an optimized loxoprofen tablet (better stability than the commercial product) that demonstrated the feasibility of using QbD in pharmaceutical development and the possibility of using BBD in the formulation of this type of tablets instead of other approaches already on the market [57].

A QbD strategy was successfully applied in an IR/ER dextromethorphan tablet. The formulation was optimized using tools like the design space and Fourier-transform Infrared Spectroscopy (FTIR). The dissolution output was better for this formulation than for the others available on the market [58].

The prediction of bilayer tablets dissolution can be done through Near Infrared (NIR) spectroscopy, as demonstrated in this study [59]. Their dissolution profiles were influenced by the hardness. After comparing the results with the reference dissolution profiles provided by high performance liquid chromatography (HPLC) it was concluded that the results were very similar with the NIR having the advantage of not destroying the sample.

Lamination is a common bilayer tablet defect occurring in tablet manufacturing. The influence of some tableting process parameters, more precisely, pre-compression, main compression pressures, and their interactions on layer adhesion of bilayer tablets was evaluated [11]. Elasticity of the material was estimated upon elastic recovery. A central composite DoE was performed on each formulation, made of immediate and CR excipients, using layer adhesion as response. Main compaction followed by turret rotation speed was the main parameter leading to delamination of tablets formulated with plastic materials and a more pronounced effect was found at high pressures as the difference in elasticity of excipients was higher. No effect of the rotation speed on layer adhesion was found in formulations with brittle excipients.

A bilayer tablet containing saxagliptin in the IR layer and metformin in the SR layer was developed in four stages using QbD [1]. In the first step QTPP of tablet was defined, and CQAs were identified. In the second and third steps, IR layer containing saxagliptin and SR layer containing metformin were optimized, respectively. Final step consisted of preparation and characterization of bilayer tablet. The effect of independent parameters on dependent

parameters, estimated for both layers using BBB led to optimized formulations while performing few experiments.

Gastro retentive bilayer tablets directing Losartan and HCTZ as a FDC were primed through direct compression method [60]. Losartan-containing floating layer was formulated with HPMC K4M using ethyl cellulose (4cps) and sodium carbonate as buoyancy enhancer and gas spawning agent, respectively. Critical formulation parameters effect on floating lag time, total floating time, T50% and % drug release, were investigated to get optimized formulation. The responses were analyzed using analysis of variance, and polynomial equation stood created for every retort using Multiple linear regression analysis. The optimized formulation upon revision for storage stability exhibited no substantial alteration in drug product specifications thus biphasic drug release design floating bilayer tablets were successful developed.

Pyrobutton data loggers were used to measure the microenvironment influence on bilayer tablets. The layer adhesion was evaluated during the pan coating operation. The independent variables and their responses were carried out using a 2^3 full factorial design strategy. As a result, coating spray rate and hardness affected the layer adhesion while coating exhaust temperature had no significant effect, indicating that the conditions under which pan coating is processed will have an impact on the tendency of delamination of tablets on storage [61].

Adhesion at the interface of bilayer tablets has been considered critical for their design although its characterization it is hardly to achieve. The effect of the elasticity of several materials on the interfacial adhesion in bilayer tablets was investigated [36]. Elasticity was characterized by tablets' total elastic recovery after compaction and for evaluation of the tablets 'interfacial layer strength (ILS) a flexural test was proposed. Correlation of breaking force with both the ILS strength and fracture occurring over the interface or in one of tablet layers revealed to material dependent. The highest breaking forces were mostly obtained when the materials had close ER whilst reduced breaking forces were obtained for materials with different elastic recovery. Statistically analysis of interfacial mechanical strength changes confirmed the relevance of QbD concept in pharmaceutical industry. Another test, with an easy implementation, for the characterization of the interfacial adhesion of bilayer tablets was proposed by the research group [35]. The proof-of-concept of this test, consists in applying a half cylindrical punch at the interface of bilayer tablets, was based on its reliability regarding the effects of some CPPs and CMAs on the interfacial adhesion of tablets. Good match between obtained results and those obtained with other groups confirmed the potential of such breaking test for the measurement of ILS.

A bilayer tablet, consisting of metformin HCl in a SR layer and evogliptin tartrate in an IR layer, was developed using a QbD approach [62]. High risk tableting process parameters were optimized through a central composite face-centered design. Optimized drug products that satisfied the established QTPP were obtained. Evogliptin tartrate content in the tablet prepared on a large scale was confirmed by at-line transmittance Raman spectroscopy as a process analytical technology. Furthermore, *in vitro* drug release and *in vivo* pharmacokinetic studies revealed both drugs bioequivalence compared to those of the reference drugs. Optimized bilayer tablet showed stability during both storages under long-term and accelerated conditions.

VI. Conclusions

As pharmaceutical technology advances, healthcare systems quality and solutions quantity increase thus fighting diseases becomes more effective and average life expectancy increases.

Bilayer tablet-based fixed dose combinations have significant advantages over other dosage forms and they have already proven to be effective in several diseases.

Manufacturing process of bilayer tablets studies revealed concerns related to tablets stability after compression thus requiring deep studies as variations in one single parameter often result in changes not only in the properties of both layers but also in the interface.

In order to overcome main obstacles occurring during production of bilayer tablets, with delamination being one of the most common, a deep knowledge of critical materials and parameters and their interplay must be assessed to assure that the final product meets both the technological and therapeutic expectations, as well as the regulatory requirements.

To solve the problems identified as critical, a strategy that has been developed and widely used in recent years is QbD. In a pharmaceutical development perspective, formulation prior knowledge and an early understanding of the process represents an effective way of manufacturing bilayer tablets, demonstrating good reasons to be one of the most effective strategies in pharmaceutical development.

Very effective approaches such as PAT and DoE have been used in recent studies that demonstrate their effectiveness. For example, concentrations of superdisintegrant and polymers were evaluated leading to an optimization of HCTZ tablets avoiding much of the time and resources required for a traditional approach such as QbT and sources of variability substantially decreased.

QbD based strategy has showed remarkable progresses in the development of bilayer tablets containing different drugs at large different doses. It revealed to be effective toward low dose-containing IR layer tablets scale up for commercialization using Raman spectroscopy as a PAT.

Robust techniques to assess IBS in bilayer tablets have been validated and applied in their formulation through QbD thus making easier the control of critical events occurring in their manufacture, such as the delamination, including the comparison between tensile and shear determination techniques.

In general, the QbD strategy is presented as a promising concept in terms of pharmaceutical development. The development and production guided by this type of technique aims to reduce as much as possible all problems related to the quality of the product that may arise and, as a future perspective, the direction of pharmaceutical research and development based on QbD appears to be one of the great challenges in the pharmaceutical industry in the coming years.

VII. Bibliography

1. Amit, K., *et al.* - Development of Bilayer Tablet Containing Saxagliptin Immediate Release and Metformin Sustained Release Using Quality by Design Approach. ISSN: 1574-8855/2212-3903. **Current Drug Therapy** 2021, 16:184-203. DOI:http://dx.doi.org/10.2174/1574885516666210315100848.

2. An, J.J., *et al.* - Fixed-Dose Combination Medications for Treating Hypertension: A Review of Effectiveness, Safety, and Challenges. ISSN: 1522-6417. **Current Hypertension Reports** 2020, 22 (**95**). DOI:10.1007/s11906-020-01109-2.

3. Vijayakumar, T.M., *et al.* - Safety, Efficacy, and Bioavailability of Fixed-Dose Combinations in Type 2 Diabetes Mellitus: A Systematic Updated Review. ISSN: 0011-393X. **Current Therapeutic Research-Clinical and Experimental** 2017, 84:4-9. DOI:10.1016/j.curtheres.2017.01.005.

4. Vitoria, M., *et al.* - Current and future priorities for the development of optimal HIV drugs. ISSN: 1746-630X. **Current Opinion in Hiv and Aids** 2019, 14:143-149. DOI:10.1097/coh.0000000000000527.

5. Balraj, M.S.;Faruqui, A.A. - Efficacy and safety of triple drug fixed-dose combination of telmisartan, amlodipine and hydrochlorothiazide in the management of hypertension. ISSN: 2320-6012. **International Journal of Research in Medical Sciences** 2017, 3:1858-1862. DOI:10.18203/2320-6012.ijrms20150291.

6. Van Galen, K.A.;Nellen, J.F.;Nieuwkerk, P.T. - The Effect on Treatment Adherence of Administering Drugs as Fixed-Dose Combinations versus as Separate Pills: Systematic Review and Meta-Analysis. ISSN: 2090-1240. **Aids Research and Treatment** 2014, **967073**. DOI:10.1155/2014/967073.

7. Godman, B., *et al.* - Fixed dose drug combinations – are they pharmacoeconomically sound? Findings and implications especially for lower- and middle-income countries. ISSN: 1473-7167. **Expert Review of Pharmacoeconomics & Outcomes Research** 2020, 20:1-26. DOI:10.1080/14737167.2020.1734456.

8. Fernandez-Garcia, R., *et al.* - Oral Fixed-Dose Combination Pharmaceutical Products: Industrial Manufacturing Versus Personalized 3D Printing. ISSN: 0724-8741. **Pharmaceutical Research** 2020, 37:22. DOI:10.1007/s11095-020-02847-3.

9. Zhang, J.Y., *et al.* - Interfacial strength of bilayer pharmaceutical tablets. ISSN: 0032-5910. **Powder Technology** 2018, 337:36-42. DOI:10.1016/j.powtec.2017.12.025.

10. Castrati, L., *et al.* - Comparison of breaking tests for the characterization of the interfacial strength of bilayer tablets. ISSN: 0378-5173. **International Journal of Pharmaceutics** 2016, 513:709-716. DOI:10.1016/j.ijpharm.2016.10.005.

11. Bellini, M.;Walther, M.;Bodmeier, R. - Evaluation of manufacturing process parameters causing multilayer tablets delamination. ISSN: 0378-5173. **International Journal of Pharmaceutics** 2019, 570 (**118607**). DOI:10.1016/j.ijpharm.2019.118607.

12. Desai, D., *et al.* - Formulation design, challenges, and development considerations for fixed dose combination (FDC) of oral solid dosage forms. ISSN: 1083-7450. **Pharmaceutical Development and Technology** 2013, 18:1265-1276. DOI:10.3109/10837450.2012.660699.

13. Vaithiyalingam, S.R.;Sayeed, V.A. - Critical factors in manufacturing multi-layer tablets—Assessing material attributes, in-process controls, manufacturing process and product performance. ISSN: 0378-5173. **International Journal of Pharmaceutics** 2010, 398:9-13. DOI:https://doi.org/10.1016/j.ijpharm.2010.07.025.

14. Podczeck, F. - Theoretical and experimental investigations into the delamination tendencies of bilayer tablets. ISSN: 0378-5173. **International Journal of Pharmaceutics** 2011, 408:102-112. DOI:10.1016/j.ijpharm.2011.02.007.

15. Vrijens, B., *et al.* - Current Situation of Medication Adherence in Hypertension. ISSN: 1663-9812. **Front Pharmacol** 2017, 8. DOI:10.3389/fphar.2017.00100.

16. Derington, C.G.;Cohen, J.B.;Bress, A.P. - Restoring the upward trend in blood pressure control rates in the United States: a focus on fixed-dose combinations. ISSN: 0950-9240. **Journal of Human Hypertension** 2020, 34:617-623. DOI:10.1038/s41371-020-0340-6.

17. Calcagno, A., *et al.* - Medication burden and clustering in people living with HIV undergoing therapeutic drug monitoring. ISSN: 0306-5251. **British Journal of Clinical Pharmacology** 2021, Online ahead of print. DOI:10.1111/bcp.14869.

18. Freedman, S.F., *et al.* - Older HIV-infected adults: complex patients (III)polypharmacy. ISSN: 1878-7649. **European Geriatric Medicine** 2019, 10:199-211. DOI:10.1007/s41999-018-0139-y.

19. Burnier, M.;Egan, B.M. - Adherence in Hypertension A Review of Prevalence, Risk Factors, Impact, and Management. ISSN: 0009-7330. **Circulation Research** 2019, 124:1124-1140. DOI:10.1161/circresaha.118.313220.

20. Hill, M.N., *et al.* - Adherence and persistence with taking medication to control high blood pressure. ISSN: 1933-1711. **Journal of the American Society of Hypertension** 2011, 5:56-63. DOI:10.1016/j.jash.2011.01.001.

21. Corrao, G., *et al.* - Better compliance to antihypertensive medications reduces cardiovascular risk. ISSN: 0263-6352. **Journal of Hypertension** 2011, 29:610-618. DOI:10.1097/HJH.0b013e328342ca97.

22. Foca, M. - Fixed-dose combination therapy for paediatric HIV infection. ISSN: 2352-4642. **Lancet Child & Adolescent Health** 2017, 1:3-4. DOI:10.1016/s2352-4642(17)30015-9.

23. Akhtar, M., *et al.* - Bilayer tablets: A developing novel drug delivery system. ISSN: 1773-2247. **Journal of Drug Delivery Science and Technology** 2020, 60:10. DOI:10.1016/j.jddst.2020.102079.

24. Chang, S.Y.;Sun, C.C. - Interfacial bonding in formulated bilayer tablets. ISSN: 0939-6411. **European Journal of Pharmaceutics and Biopharmaceutics** 2020, 147:69-75. DOI:10.1016/j.ejpb.2019.12.009.

25. Prasanthi, B., *et al.* - Design and evaluation of bilayer tablets of metformin hydrochloride and pioglitazone hydrochloride as combination drug therapy. ISSN: 2093-6214. **Journal of Pharmaceutical Investigation** 2017, 47:497-505. DOI:10.1007/s40005-016-0276-6.

26. Blicharski, T., *et al.* - Challenges in technology of bilayer and multi-layer tablets: a mini-review. ISSN: 2084-980X. **Current Issues in Pharmacy and Medical Sciences** 2019, 32:229-235. DOI:10.2478/cipms-2019-0039.

27. Tao, J., *et al.* - Understanding the Delamination Risk of a Trilayer Tablet Using Minipiloting Tools. ISSN: 0022-3549. **Journal of Pharmaceutical Sciences** 2017, 106:3346-3352. DOI:10.1016/j.xphs.2017.07.005.

28. Abebe, A., *et al.* - Review of bilayer tablet technology. ISSN: 0378-5173. **International Journal of Pharmaceutics** 2014, 461:549-558. DOI:10.1016/j.ijpharm.2013.12.028.

29. Dholariya, Y.N., *et al.* - Design and optimization of bilayered tablet of Hydrochlorothiazide using the Quality-by-Design approach. ISSN: 2230-973X. **International Journal of Pharmaceutical Investigation** 2014, 4:93-101. DOI:10.4103/2230-973x.133058.

30. More, S., *et al.* - Multilayered tablet: a novel approach for oral drug delivery. ISSN: 0975-8232. **International Journal of Pharmaceutical Sciences and Research** 2018, 9:872-882. DOI:10.13040/ijpsr.0975-8232.9(3).872-82.

31. Beer, F.P., *et al.* - Mechanics of materials, New York: McGraw-Hill, 2012.

32. Chang, S.Y.;Sun, C.C. - Insights into the effect of compaction pressure and material properties on interfacial bonding strength of bilayer tablets. ISSN: 0032-5910. **Powder Technology** 2019, 354:867-876. DOI:10.1016/j.powtec.2019.07.021.

33. El-Mohsen, M.A., *et al.* - Distribution of H-3 trans-resveratrol in rat tissues following oral administration. ISSN: 0007-1145. **British Journal of Nutrition** 2006, 96:62-70. DOI:10.1079/bjn20061810.

34. Kottala, N., *et al.* - Evaluation of the Performance Characteristics of Bilayer Tablets: Part I. Impact of Material Properties and Process Parameters on the Strength of Bilayer Tablets. ISSN: 1530-9932. **AAPS PharmSciTech** 2012, 13:1236-1242. DOI:10.1208/s12249-012-9845-9.

35. Busignies, V., *et al.* - Development of a new test for the easy characterization of the adhesion at the interface of bilayer tablets: Proof-of-concept study by experimental design. ISSN: 0378-5173. **International Journal of Pharmaceutics** 2014, 477:476-484. DOI:https://doi.org/10.1016/j.ijpharm.2014.10.051.

36. Busignies, V., *et al.* - Role of the elasticity of pharmaceutical materials on the interfacial mechanical strength of bilayer tablets. ISSN: 0378-5173. **International Journal of Pharmaceutics** 2013, 457:260-267. DOI:https://doi.org/10.1016/j.ijpharm.2013.09.009.

37. Podczeck, F. - Methods for the practical determination of the mechanical strength of tablets-From empiricism to science. ISSN: 0378-5173. **International Journal of Pharmaceutics** 2012, 436:214-232. DOI:10.1016/j.ijpharm.2012.06.059.

38. Klinzing, G.;Zavaliangos, A. - Understanding the Effect of Environmental History on Bilayer Tablet Interfacial Shear Strength. ISSN: 0724-8741. **Pharmaceutical Research** 2013, 30:1300-1310. DOI:10.1007/s11095-012-0969-0.

39. Reddy, M.S.;Kumari, G. - Formulation and Evaluation of Bilayer Tablets of Ramipril as Immediate Layer and Propranolol Hydrochloride as Sustained Layer. ISSN: 0973-8398. **Asian Journal of Pharmaceutics** 2018, 12:43-48. DOI:http://dx.doi.org/10.22377/ajp.v12i01.1917.

40. Sun, W.J.;Kothari, S.;Sun, C.C. - The relationship among tensile strength, Young's modulus, and indentation hardness of pharmaceutical compacts. ISSN: 0032-5910. **Powder Technology** 2018, 331:1-6. DOI:10.1016/j.powtec.2018.02.051.

41. Akseli, I., *et al.* - Mechanistic characterization of bilayer tablet formulations. ISSN: 0032-5910. **Powder Technology** 2013, 236:30-36. DOI:10.1016/j.powtec.2012.05.048.

42. Kottala, N., *et al.* - Influence of compaction properties and interfacial topography on the performance of bilayer tablets. ISSN: 0378-5173. **International Journal of Pharmaceutics** 2012, 436:171-178. DOI:10.1016/j.ijpharm.2012.05.026.

43. Yu, L.X., *et al.* - Understanding Pharmaceutical Quality by Design. ISSN: 1550-7416. **Aaps Journal** 2014, 16:771-783. DOI:10.1208/s12248-014-9598-3.

44. Martin, N.L., *et al.* - Process Modeling and Simulation of Tableting-An Agent-Based Simulation Methodology for Direct Compression. ISSN: **Pharmaceutics** 2021, 13:24. DOI:10.3390/pharmaceutics13070996.

45. Chang, S.Y.;Li, J.X.;Sun, C.C. - Tensile and shear methods for measuring strength of bilayer tablets. ISSN: 0378-5173. **International Journal of Pharmaceutics** 2017, 523:121-126. DOI:10.1016/j.ijpharm.2017.03.010.

46. Mishra, V., *et al.* - Quality by design (QbD) approaches in current pharmaceutical set-up. ISSN: 1742-5247. **Expert Opinion on Drug Delivery** 2018, 15:737-758. DOI:10.1080/17425247.2018.1504768.

47. Parmar, C., *et al.* - Formulation and optimization of enteric coated bilayer tablets of mesalamine by RSM: In vitro - In vivo investigations and roentogenographic study. ISSN: 1773-2247. **Journal of Drug Delivery Science and Technology** 2018, 44:388-398. DOI:10.1016/j.jddst.2018.01.008.

48. EMA/CHMP/ICH/167068/2004. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use considerations (ICH) guideline Q8 (R2) on pharmaceutical development-Step 5, 2017.

49. Bhujbal, S.M. - A research article on an integrated, Quality by Design (QbD) approach for design, development and optimization of bilayer tablet formulation of containing simvastatin as sustained release and labetalol HCl as immediate release. ISSN: **Journal of Pharma Research** 2019, 8:208–213.

50. Kausch, I.;Doehn, C. - Molecular Therapy. In: Schwab M., ed. *Encyclopedia of Cancer*. Berlin, Heidelberg: Springer Berlin Heidelberg, 2011; 2364-2367.

51. Yu, L.X. - Pharmaceutical quality by design: Product and process development, understanding, and control. ISSN: 0724-8741. **Pharmaceutical Research** 2008, 25:781-791. DOI:10.1007/s11095-007-9511-1.

52. Dadou, S.M., *et al.* - The optimization of process analytical technology for the inline quantification of multiple drugs in fixed dose combinations during continuous processing. ISSN: 0378-5173. **International Journal of Pharmaceutics** 2021, 592. DOI:10.1016/j.ijpharm.2020.120024.

53. De Beer, T., *et al.* - Near infrared and Raman spectroscopy for the in-process monitoring of pharmaceutical production processes. ISSN: 0378-5173. **International Journal of Pharmaceutics** 2011, 417:32-47. DOI:10.1016/j.ijpharm.2010.12.012.

54. Lee, A.R., et al. - Quality by Design (QbD) approach to optimize the formulation of a bilayer combination tablet (Telmiduo (R)) manufactured via high shear wet granulation. ISSN: 0378-5173. **International Journal of Pharmaceutics** 2017, 534:144-158. DOI:10.1016/j.ijpharm.2017.10.004.

55. Chinta, R.;Pilli, R. - Formulation design of empaglifozin and metformin hydrochloride extended release tablets: optimization of formulation using statistical experimental design ISSN: 0975-8232. **International Journal of Pharmaceutical Sciences and Research** 2020, 11:6434-6447. DOI:10.13040/ijpsr.0975-8232.11(12).6434-47.

56. Singh, B., *et al.* - Optimized chronomodulated dual release bilayer tablets of fexofenadine and montelukast: quality by design, development, and in vitro evaluation. ISSN: 2314-7253. **Future Journal of Pharmaceutical Sciences** 2019, 5:5. DOI:10.1186/s43094-019-0006-9.

57. Tak, J.W., *et al.* - Preparation and Optimization of Immediate Release/Sustained Release Bilayered Tablets of Loxoprofen Using Box-Behnken Design. ISSN: 1530-9932. **AAPS PharmSciTech** 2017, 18:1125-1134. DOI:10.1208/s12249-016-0580-5.

58. Nadeem, M.;Babu, M.S. - Application of Quality By Design (Qbd) In Formulation Development of Immediate and Extended Release Bilayered Tablets of Dextromethorphan As A Model Drug. ISSN: **Indo American J of Pharm Sci** 2014, 1.

59. Baranwal, Y., et al. - Prediction of dissolution profiles by non-destructive NIR spectroscopy in bilayer tablets. ISSN: 0378-5173. **International Journal of Pharmaceutics** 2019, 565:419-436. DOI:10.1016/j.ijpharm.2019.05.022.

60. Maddiboyina, B., et al. - Formulation and evaluation of gastro-retentive floating bilayer tablet for the treatment of hypertension. ISSN: 2405-8440. **Heliyon** 2020, 6:e05459. DOI:10.1016/j.heliyon.2020.e05459.

61. Zacour, B.M., et al. - Correlating bilayer tablet delamination tendencies to micro-environmental thermodynamic conditions during pan coating. ISSN: 0363-9045. **Drug Development and Industrial Pharmacy** 2014, 40:829-837. DOI:10.3109/03639045.2013.788014.

62. Won, D.H., et al. - Optimization of bilayer tablet manufacturing process for fixed dose combination of sustained release high-dose drug and immediate release low-dose drug based on quality by design (QbD). ISSN: 0378-5173. **International Journal of Pharmaceutics** 2021, 605:120838. DOI:https://doi.org/10.1016/j.ijpharm.2021.120838.

63. Dyer, A.M., et al. - Nasal delivery of insulin using novel chitosan based formulations: A comparative study in two animal models between simple chitosan formulations and chitosan nanoparticles. ISSN: 0724-8741. **Pharmaceutical Research** 2002, 19:998-1008.