UNIVERSIDADE D
COIMBRA

Vera Catarina Abreu Malheiro

Relatórios de Estágio sob a orientação da Dra. Fátima Marques e Dra. Rita Rolim e Monografia intitulada "Exploiting Pharma 4.0 technologies in the Non-Biological Complex Drugs manufacturing: Innovations and Implications", sob orientação da Professora Doutora Filipa Mascarenhas Melo, referentes à Unidade Curricular "Estágio", apresentados à Faculdadade de Farmácia da Universidade de Coimbra, para apreciação na prestação de provas públicas de Mestrado Integrado em Ciências Farmacêuticas.

Setembro de 2023

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setembro de 2023

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Coimbra, 1 de setembro de 2023.

Vera Catarina Abreu Malheiro

(Vera Catarina Abreu Malheiro)

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Capítulo I

Relatório de Estágio em Farmácia Comunitária

Farmácia Fátima Marques

Lista de Abreviaturas

CE Contraceção de Emergência

DIU Dispositivo intrauterino

FFM Farmácia Fátima Marques

MICF Mestrado Integrado em Ciências Farmacêuticas

SWOT *Strenghts, Weaknesses, Opportunities and Threats*

1. Introdução

Com o passar do tempo, as farmácias comunitárias – e, consequentemente, o farmacêutico – , têm vindo a ocupar um papel cada vez mais preponderante na promoção da saúde e no bem-estar dos utentes, atuando não só como ponto de referência no acesso a medicamentos, mas também como local de preferência para a obtenção de informação e resposta a questões relacionadas com a saúde.

De facto, costumo dizer que o farmacêutico é o profissional de saúde mais acessível ao doente e, como tal, acredito que a nossa formação deve fornecer todas as bases necessárias para que possamos estar à altura daquilo que é esperado de nós. Assim, após 5 anos de um plano curricular extremamente completo e enriquecedor, segue-se o estágio curricular, uma última etapa igualmente desafiadora, mas tão bonita! Para tal, escolhi a Farmácia Fátima Marques, localizada em Vila Verde, porque vai de encontro a tudo aquilo que acredito que uma farmácia deve representar: um espaço de confiança que se compromete em atender a todas as necessidades de saúde dos seus utentes, de forma integral e humanizada.

Desta forma, durante o período de 9 de janeiro de 2023 a 26 de abril de 2023, sob a orientação da Dra. Fátima Marques e coorientação dos vários elementos da equipa, pude observar – e experienciar em primeira mão – aquilo que é ser farmacêutico comunitário. E é tanta coisa!

Neste contexto, é com um misto de gratidão e sentimento de realização, que apresento o presente relatório, sob a forma de análise SWOT (acrónimo inglês de *Strenghts, Weaknesses, Opportunities and Threats)*, com o qual pretendo refletir acerca do meu percurso enquanto estagiária da Farmácia Fátima Marques.

2. A Farmácia Fátima Marques

A Farmácia Fátima Marques (FFM) está localizada na Rua dos Bombeiros n,°50/52, no centro urbano de Vila Verde, Braga. Anteriormente, até novembro de 2008, esta farmácia inseria-se no mesmo concelho, mas num contexto rural com uma população predominantemente idosa e com um acesso limitado a informação e a cuidados de saúde, pelo que assumia assim um papel ainda mais preponderante na edução e promoção da saúde dos utentes.

A atual localização envolve uma zona essencialmente residencial que envolve diversas faixas etárias e niveis de literacia, o que exigiu uma adaptação não só no que diz respeito aos produtos comercializados, como também aos serviços que dispõe. As novas instalações destacam-se pela sua estética minimalista, mas simultaneamente moderna e acolhedora.

A minha preferência por esta farmácia no âmbito do estágio curricular prendeu-se, essencialmente, com a grande variedade de serviços que a mesma dispõe e que a diferenciam da concorrência, nomeadamente as consultas de educação sexual, de acompanhamento e reeducação alimentar, de cessação tabágica e, ainda, o acompanhamento dermocosmético.

O horário de funcionamento é das 8.30 às 20.00 horas de segunda a sábado, sendo que a farmácia realiza serviço permanente de 3 em 3 dias, ficando a porta aberta até às 20 horas, com posterior atendimento realizado através do postigo até às 8.30 horas da manhã do dia seguinte.

Relativamente aos recursos humanos, a FFM conta com uma equipa constituída por 9 profissionais, apresentados no Anexo I. Tal como se pode verificar, trabalham na farmácia 6 farmacêuticos, estando em conformidade com o Decreto-Lei n.º 307/2007, de 31 de agosto, que define a necessidade de cada farmácia dispor de, pelo menos, 2 farmacêuticos. (Decreto, 2007)

3. Análise SWOT

A análise SWOT (*Strenghts, Weaknesses, Opportunities and Threats*) é uma ferramenta de gestão que fornece uma análise estruturada de fatores internos – Forças e Fraquezas – e fatores externos – Oportunidades e Ameaças – que podem afetar o sucesso do alvo de análise.

É importante tirar proveito dos pontos fortes, reduzir os fracos, aproveitar as oportunidades e defender das ameaças.

3.1 Forças (*Strenghts*)

3.1.1 Recursos humanos

De entre todos os fatores que contribuem para o sucesso de uma farmácia, considero a sua equipa técnica como sendo um dos mais importantes. Isto porque os seus profissionais são o pilar de qualquer farmácia e, assim, o principal contribuinte para a fidelização – ou falta dela – dos utentes à farmácia.

Os colaboradores da FFM são muito apreciados pelos utentes e foram, sem dúvida, um dos pontos mais fortes do meu estágio. Ao contrário do que inicialmente pensava, a minha integração na equipa foi bastante tranquila e senti-me apoiada e bem recebida desde o primeiro dia.

Trata-se de uma equipa profissional, competente, dinâmica e que, acima de tudo, mantêm o foco no utente. O ambiente foi sempre muito agradável, mesmo nos dias de serviço, em que o excessivo afluxo de utentes nos deixava mais cansados e stressados.

Cada membro da equipa moldou, à sua forma, aquilo em que me fui tornando ao longo dos 4 meses de estágio. Enquanto procurava a minha voz enquanto farmacêutica no mundo real de trabalho, cada um deles – com a sua experiência e a sua forma única – foi, inevitavelmente, marcando um pouquinho de si em mim.

3.1.2 Variedade de serviços farmacêuticos disponibilizados

O facto de a FFM dispor de uma grande variedade de serviços farmacêuticos foi o principal fator que motivou a minha escolha de lá realizar o estágio curricular.

Considero que foi um ponto forte da minha formação, não só porque me permitiu pôr em prática os vários conhecimentos teóricos que fui adquirindo ao longo do meu percurso académico, mas também porque me possibilitou desenvolver várias competências e aptidões em diferentes vertentes da profissão farmacêutica.

Os vários serviços farmacêuticos que pude desempenhar ao longo do meu percurso incluem, por exemplo, a monitorização de doenças crónicas – com medições pontuais de glicémia, tensão arterial, colesterol total e ácido úrico – e a organização e gestão da terapêutica, que consiste na dispensa da medicação do utente organizada por dia e hora de toma, num dispensador próprio. Este último, para além de facilitar a toma da medicação e reduzir os erros que a mesma pode acarretar – especialmente em idosos polimedicados –, permitiu que fosse acompanhando e avaliando a adesão do utente à terapêutica.

A FFM dispõe, ainda, de um leque de serviços farmacêuticos que não pude executar, mas que fui observando, tais como as consultas de dermofarmácia e cosmética, acompanhamento de cessação tabágica e o cantinho da amamentação.

Tudo isto permitiu também que o meu estágio fosse isento de monotonia, uma vez que havia sempre uma atividade diferente em que podia participar.

3.1.*3 Robot* e automatização da farmácia

Em 2018, a FFM passou a incorporar nas suas instalações um *robot* modular de farmácia, *Bd Rowa Smart*, e um sistema de gestão de caixa, *cashlogy*. Para além de agilizar o tempo despendido no armazenamento e dispensa dos medicamentos, o *robot* também permite reduzir a ocorrência de erros na cedência dos mesmos. Da mesma forma, o sistema de gestão de

caixa permite reduzir não só o tempo de pagamento, mas também possíveis erros associados ao mesmo.

3.1.4 Participação em rastreios

Durante o meu estágio, foi-me dada a oportunidade de participar nalguns rastreios de doenças crónicas, nomeadamente da Diabetes *mellitus*, de determinação de parâmetros bioquímicos, como colesterol e ácido úrico, e ainda de despiste de infeção pela *Helicobacter pylori*.

As minhas tarefas passavam pela sensibilização dos utentes da farmácia acerca do rastreio que estava a decorrer no mês vigente e da sua importância na deteção precoce da respetiva patologia, pela determinação dos respetivos parâmetros e pelo tratamento dos dados obtidos. Este foi, claramente, um aspeto muito positivo do meu estágio, uma vez que para além de promover uma relação de maior proximidade com os utentes, também me permitiu desenvolver a capacidade de adaptar o discurso a utentes de literacias diferentes, bem como competências ao nível do tratamento de dados.

3.2 Fraquezas (*Weaknesses*)

3.2.1 Falta de acompanhamento nos primeiros atendimentos

No meu caso, o estágio curricular foi o primeiro contacto com a farmácia comunitária e, como tal, o seu início foi marcado por um grande nível de incerteza e medo de errar. Como tal, esperava que houvesse espaço no meu plano de estágio para um período de observação, em que pudesse acompanhar o atendimento dos vários colaboradores. No entanto, foi-me logo pedido que começasse nos atendimentos sozinha e isso foi, a meu ver, um aspeto negativo na minha adaptação, no sentido em que criou alguns constrangimentos iniciais, por não conhecer grande parte da variedade de produtos que a farmácia dispunha, o que consequentemente poderia afetar a minha credibilidade enquanto profissional aos olhos do utente.

3.2.2 Participação reduzida na preparação de manipulados

A FFM caracteriza-se pela sua vasta experiência na preparação de manipulados, pelo que pensei que seria uma área que iria poder desenvolver e aperfeiçoar durante o meu percurso enquanto estagiária. No entanto, e embora houvesse preparação de manipulados quase semanalmente, considero que o meu contacto com essa área foi muito pouco desenvolvido.

3.3 Oportunidades (*Opportunities*)

3.3.1 Formações

O mercado farmacêutico está em constante evolução e, como tal, o farmacêutico deve sempre procurar manter-se atualizado de forma a prestar um aconselhamento o mais informado e atualizado possível. Neste sentido, a gerência da FFM aposta numa instrução contínua dos seus profissionais e colaboradores, promovendo a realização frequente de formações organizadas pelos laboratórios farmacêuticos e apresentadas nas farmácias por delegados de informação médica.

Para além de fornecerem informação detalhada e dicas de aconselhamento de produtos e gamas já comercializadas, estas formações também servem para dar a conhecer aos farmacêuticos novas formulações, reformulações e/ou fins de linha de produtos.

Durante o meu estágio assisti, essencialmente, a formações no âmbito do aconselhamento dermocosmético, nomeadamente, da ISDIN e da cosmética ativa, onde pude ficar a saber um pouco mais acerca da composição e indicação de alguns cosméticos que dispúnhamos na farmácia. Para além disso, tive também oportunidade de assistir a uma formação sobre o aparelho clini5, concebido pela Callegari Lifescience, que consiste num fotómetro destinado à determinação dos principais parâmetros bioquímicos como, por exemplo, colesterol, LDL, ácido úrico, entre outros. Um aspeto muito positivo que pude experienciar durante as formações foi o facto de constituírem um espaço para troca de impressões entre os vários colaboradores, como por exemplo experiências de *feedback* de utentes em relação a determinado produto.

3.3.2 Heterogeneidade de clientes e situações clínicas

Face à sua localização e acessibilidade, a FFM está sujeita a uma grande afluência de utentes com grande diversificação etária, literacia, socioeconómica e cultural e, fundamentalmente, clínica. Este fator constitui, a meu ver, uma oportunidade não só para a farmácia enquanto negócio, mas também para o meu percurso enquanto estagiária. Isto porque pude lidar, diariamente, com casos muito díspares, desde a dispensa de medicação crónica até ao aconselhamento em afeções menores. Ora, isto permitiu não só alargar os meus conhecimentos enquanto especialista do medicamento, mas também desenvolver as minhas *soft skills* e aprimorar a capacidade de adaptar o meu discurso aos vários tipos de utente.

3.3.3 Plano Curricular de MICF

O plano curricular de MICF fornece uma formação multidisciplinar que permite construir as bases necessárias para uma boa adaptação ao estágio em farmácia comunitária. Desde as unidades curriculares de farmacologia, passando pela de farmácia clínica e até à de indicação farmacêutica, os alunos ficam aptos para iniciar, assertivamente, a atividade do aconselhamento farmacêutico. Gostaria, ainda, de fazer referência à unidade curricular de Organização e Gestão Farmacêutica, na qual nos foi dada a oportunidade de familiarizar com o SiFarma, o que constitui uma mais-valia para a adaptação no estágio.

3.3.4 Dispensa de medicamentos hospitalares nas farmácias comunitárias

A proposta de norma profissional para a dispensa de medicamentos hospitalares em proximidade, desenvolvida pelos Conselhos dos Colégios de Especialidade de Farmácia Comunitária e de Farmácia Hospitalar, foi aprovada para Consulta Pública pela Direção Nacional da Ordem dos Farmacêuticos. (Ordem dos Farmacêuticos, 2023) A meu ver, a concretização desta norma seria uma oportunidade de crescimento para as farmácias comunitárias, não só ao nível do aumento do fluxo de clientes e consequente expansão de serviços, mas também na criação de uma ligação de proximidade com os hospitais, que permitirá uma troca de conhecimentos entre os profissionais de saúde e, consequentemente, uma rede de saúde mais integrada.

3.4 Ameaças (*Threats*)

3.4.1 Constantes alterações de preços

Numa farmácia comunitária, um bom atendimento ao utente está intimamente ligado com uma gestão eficiente no *backoffice.* As constantes alterações de preços a que os medicamentos estão sujeitos, para além de fragilizarem a relação do utente com a farmácia, também podem criar alguns constrangimentos ao nível do trabalho de backoffice e atendimento, uma vez que favorecem o aparecimento de erros.

Durante o mês de março, ao rececionar encomendas, pude experienciar a alteração dos preços de vários medicamentos. Foi necessário ter uma atenção redobrada uma vez que os medicamentos com o preço novo não podiam ser armazenados no robô enquanto não terminasse o *stock* com o preço antigo. Isto resultou numa sobrecarga do armazém da farmácia e, consequentemente, no atraso de alguns atendimentos (quando era necessário ir ao armazém buscar algum medicamento, a procura estava dificultada). Para além disso, mesmo com a atenção redobrada por parte dos colaboradores que estavam nas encomendas, verificaram-se

algumas situações em que o preço no sistema não coincidia com o novo preço, o que reflete a importância da verificação do mesmo no momento da dispensa.

3.4.2 Medicamentos esgotados

A escassez de medicamentos tem sido cada vez mais reportada nos últimos meses, não só em Portugal, mas por toda a Europa. Durante o meu estágio testemunhei ruturas em *stocks* de medicamentos das mais variadas classes terapêuticas – desde os antibióticos, passando pelo paracetamol infantil, xaropes para a tosse e até mesmo (e essencialmente) medicamentos para a diabetes.

Embora seja algo que está além do controlo das farmácias, a verdade é que são os farmacêuticos que estão na linha da frente a "falhar" na resposta às necessidades terapêuticas dos utentes. Durante o meu estágio, foram várias as vezes em que tive de informar o doente que não tinha a sua medicação e que não era possível dar uma previsão de quando estaria disponível e, de facto, nem todos compreendiam que essa falha era devida a fatores externos à farmácia e não a uma má gestão da mesma.

4. Casos Práticos

4.1 Caso Prático 1 – Aconselhamento farmacêutico na contraceção de emergência

PM, 22 anos, dirigiu-se à farmácia e pediu 2 caixas de Postinor®, uma pílula do dia seguinte que contém levonorgestrel, um progestagénio que vai atuar na fase pré-ovulatória precoce, através do bloqueio da ovulação, em média, por 3 dias.

Sendo a contraceção de emergência (CE) um último recurso para evitar uma gravidez não planeada após uma relação sexual desprotegida, não devidamente protegida ou, em casos mais extremos, em situações de crime contra a autodeterminação sexual em mulheres que não utilizam métodos contracetivos, o pedido da utente fez-me alguma confusão, pelo que comecei por fazer algumas questões necessárias a um aconselhamento informado.

Em conversa percebi que uma das caixas seria como método contracetivo de emergência para uma relação sexual desprotegida ocorrida há cerca de 4 dias e que a outra seria para "ficar de reserva", para a eventualidade da situação se repetir. Ficou ainda claro que a utente utilizava contraceção hormonal regular, nomeadamente a pílula Denille® (etinilestradiol 0,03mg + dienogest 2mg), mas que tinha esquecimentos frequentes, razão pela qual recorria frequentemente à contraceção de emergência.

Perante isto, numa primeira fase, procurei explicar-lhe que a correta utilização de um método contracetivo – hormonal ou barreira – é a forma mais segura para a prevenção de uma gravidez indesejada, precavendo a necessidade de recorrer a contracetivos de emergência. Neste sentido, sugeri que programasse um lembrete no telemóvel para relembrar a toma da pilula ou que procurasse junto do médico de família alternativas contracetivas que não implicassem tomas diárias como o anel vaginal ou o DIU (dispositivo intrauterino). Expliquei também que existem diferentes tipos de contraceção de emergência, nomeadamente no que respeita ao período de utilização em que estão indicados, pelo que é importante ter em conta a janela de tempo desde a última relação sexual de risco. Neste caso, como já tinham passado 4 dias, a alternativa mais eficaz seria o acetato de ulipristal, um modelador dos recetores de progesterona que também bloqueia, temporariamente (em média, por 5 dias), a ovulação, mas que, contrariamente ao levonorgestrel, que só está indicado até 72h após a relação sexual, demonstra eficácia até 120h após a mesma. Outro fator a ter considerar na escolha da contraceção de emergência é a fase do ciclo menstrual em que a mulher se encontra. Uma vez que PM estava no início de uma nova carteira da pílula, os esquecimentos estavam associados a um risco significativo de gravidez, pelo que considerei que a toma da CE era justificada.

No final, a cliente mostrou-se bastante compreensiva, concordando em levar apenas uma caixa de ellaone®, que contém 30mg de acetato de ulipristal. Antes de terminar o atendimento, referi que, mesmo tomando a CE, a utente deveria continuar com a toma da Denille® e alertei para a importância de utilizar preservativo durante 14 dias após a toma da CE e para a eventualidade de ocorrerem alguns efeitos secundários ligeiros e transitórios, sem necessidade de terapêutica adicional, como cefaleias, náuseas e dores pélvicas. Mencionei, ainda, a possibilidade de ocorrerem perturbações menstruais que poderiam atrasar a hemorragia de interrupção seguinte, mas que caso o atraso fosse superior a 7 dias, a utente deveria realizar um teste de gravidez.

Ao longo do meu estágio fui-me apercebendo que a área da contraceção está associada a um grande nível de desinformação e que a procura de CE constitui uma oportunidade para o farmacêutico prestar aconselhamento contracetivo e um momento privilegiado para educar para a saúde, com informação adaptada a cada caso, de forma a aumentar os conhecimentos e compreensão para que individualmente se façam as melhores escolhas em questões de saúde sexual.

4.2 Caso Prático 2 – Aconselhamento farmacêutico nas crises de eczema

JM, 35 anos, desloca-se à farmácia com o filho, MM, 13 anos, com queixas de pele seca, prurido intenso – que dificulta o sono e atividades diárias –, vermelhidão e erupções cutâneas em várias zonas do corpo, nomeadamente nos braços e pernas. Relata que MM apresenta história de eczema atópico desde os primeiros meses de vida e que já utilizou vários produtos prescritos pelo dermatologista, mas que de momento lhe falta algo que possa aplicar nas lesões de forma a aliviar a sintomatologia.

O eczema, também conhecido como dermatite atópica, é uma condição inflamatória crónica da pele, muito comum em crianças, e que se caracteriza por lesões vermelhas, prurido e ressecamento da pele. Com períodos de remissão e crise, o eczema implica cuidados diários e consistentes, sempre adaptados ao estado em que a pele se encontra.

Uma vez que JM tinha em casa produtos de limpeza e hidratação adequados ao estado da pele de MM, recomendei apenas, como tratamento local, o Pandermil®, creme, que contém hidrocortisona e está recomendado para alívio dos sintomas inflamatórios e pruriginosos de condições de pele sensíveis a corticoides, como é o caso do eczema atópico. Referi que MM deveria aplicar uma camada fina de Pandermil® nas áreas afetadas, duas vezes ao dia. Além disso, relembrei ainda a importância de implementar medidas não farmacológicas que ajudam no alívio da sintomatologia, nomeadamente: preferir banhos curtos e mornos, evitar coçar as lesões (para prevenir piora dos sintomas e possíveis infeções secundárias), optar por roupas de algodão para minimizar irritação da pele durante as crises e, ainda, evitar exposição prolongada ao sol e aplicar protetor solar várias vezes ao dia nas zonas não afetadas.

4.3 Caso Prático 3 – Aconselhamento farmacêutico na infeção urinária

VM, 35 anos, dirigiu-se à farmácia com uma receita de Fosfomicina para o tratamento de uma infeção urinária. Refere que tem um histórico de infeções urinárias recorrentes e questiona se há algum produto que possa ajudar na prevenção das mesmas. Assim, para além do antibiótico, cedi também o Symbiosys® Cystalia, um suplemento alimentar que contém as estirpes probióticas *Lactobacillys rhamnosus LR06* e *Lactobacillus plantarum LP02* – que inibem a proliferação de bactérias patogénicas – e extrato de arando vermelho, conhecido pela sua capacidade de prevenir a adesão das bactérias prejudiciais à bexiga. Expliquei, ainda, que a utente deveria iniciar o suplemento após terminar o antibiótico e que deveria tomar uma saqueta por dia, durante 30 dias.

Terminei o atendimento alertando para uma série de medidas não farmacológicas que a utente deveria ter em conta, nomeadamente: ingestão diária e abundante de água, implementar boas

práticas de higiene íntima, optar por roupas íntimas de algodão e, ainda, urinar sempre após as relações sexuais.

4.4 Caso Prático 4 – Aconselhamento farmacêutico no tratamento da diarreia

PM, 23 anos, sem histórico médico significativo, desloca-se à farmácia com queixas de diarreia após iniciar o tratamento de uma infeção respiratória com Clavamox® (Amoxicilina + Ácido Clavulânico, 500mg/125mg). Relata que iniciou o antibiótico há dois dias e, desde então, tem tido diarreia frequente, cerca de quatro a cinco episódios líquidos por dia, acompanhados de cólicas abdominais leves. De facto, a diarreia é um efeito secundário conhecido e muito frequente do Clavamox®.

Assim, e excluindo a possibilidade de uma causa infeciosa, decidi aconselhar a toma de UL-250®, um probiótico que contém *Saccharomyces boulardii* e funciona como regulador da flora intestinal e antidiarreico. Expliquei ao utente que deveria tomar uma cápsula, três vezes ao dia, durante 5 dias e recomendei, ainda, uma série de medidas não farmacológicas, nomeadamente a ingestão abundante de água e de alimentos de fácil digestão, como bananas, arroz, maçãs e torradas, que ajudam a acalmar o sistema digestivo.

4.5 Caso Prático 5 – Aconselhamento farmacêutico no controlo infeções vaginais

MO, 28 anos, chega à farmácia com relatos de prurido e irritação na zona vaginal, acompanhados de um corrimento anormal e com odor. Os sintomas coincidiam com uma infeção fúngica, como a candidíase, pelo que decidi aconselhar o *Gyno-Pevaryl Combipack,* que inclui um creme vaginal e 3 óvulos. A ação antifúngica é devida ao econazol que combate o crescimento de fungos na região vaginal, aliviando os sintomas descritos pela utente.

Expliquei à utente que deveria utilizar o aplicador fornecido para inserir um óvulo o mais profundamente possível na vagina, preferencialmente à noite, e aplicar uma camada fina de creme nas regiões externas afetadas, uma vez por dia, durante três dias consecutivos. Frisei, ainda, que antes da aplicação MO deveria lavar bem a área genital com um produto específico e adequado, pelo que acabei por ceder também um gel de limpeza íntima da Lactacyd, que ajuda a limpar a área genital sem perturbar o equilíbrio do pH natural.

5. Considerações Finais

Findado o meu estágio curricular na Farmácia Fátima Marques, não poderia estar mais orgulhosa do meu percurso! Foi, sem dúvida, uma experiência extremamente enriquecedora e uma mais-valia para a minha formação. No fundo, representou não só o início do fim enquanto estudante do MICF, mas também – e essencialmente – a procura da minha voz enquanto futura farmacêutica. Foi uma busca da resposta à pergunta "Que tipo de farmacêutica quero ser?". E hoje, ao terminar o presente relatório, sei que – independentemente da área onde quer que este percurso me leve – quero ser tudo o que a profissão implica. Quero comprometer-me com aconselhamentos de qualidade, fundamentados, sempre realizados com empatia, respeito e adaptados a cada utente. Quero ir além da dispensa dos medicamentos e quero fazer ver que somos muito mais do que isso! Procuro ser uma fonte confiável de informações e cuidados e ter um papel ativo no tratamento e recuperação de todos os doentes que por mim passarem!

Foi um percurso bonito, mas também cheio de desafios, em que o principal receio era não estar à altura, tanto da equipa da farmácia como da profissão em si. No entanto, com a ajuda de todos os colaboradores, fui aos pouquinhos ganhando cada vez mais confiança em mim e segurança nos meus atendimentos.

Desde as longas receções de encomendas, passando pelas contagens físicas e até ao atendimento ao público, estou confiante de que cada momento na farmácia foi preenchido com experiências enriquecedoras e lições valiosas, não só a nível profissional, mas também pessoal, pelo que levarei comigo os valores de dedicação, respeito e empatia que presenciei ao longo do meu percurso.

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7. Anexos

Anexo I - Recursos Humanos da Farmácia Fátima Marques

Pessoal	Função	Formação
Maria de Fátima Barreira Marques	Diretora Técnica	Licenciatura em Ciências Farmacêuticas. Especialista em Farmácia Comunitária pela OF. Mestrado em Engenharia Biológica
Maria de Fátima Gonçalves Pires	Farmacêutica substituta	Licenciatura em Ciências Farmacêuticas
Cátia Manuela Mendes Ribeiro	Farmacêutica	Mestrado Integrado em Ciências Farmacêuticas
Catarina Ferreira Novo	Farmacêutica	Mestrado Integrado em Ciências Farmacêuticas
Horácio Miguel Antunes	Farmacêutico	Licenciatura em Ciências Farmacêuticas
Diana Sofia Azevedo Alves	Farmacêutica	Mestrado Integrado em Ciências Farmacêuticas
Ângela Filipa Macedo Mota	Técnica de Farmácia	Licenciatura em Farmácia
Cindy Nadil Pinto	Técnica de Farmácia	Licenciatura em Farmácia

Anexo 2 - Análise SWOT do estágio na Farmácia Fátima Marques

Forças	Fraquezas
• Recursos Humanos • Variedade de serviços disponibilizados • Robô e automatização da farmácia • Participação em Rastreios	• Falta de acompanhamento nos primeiros atendimentos • Participação reduzida na preparação de manipulados
Oportunidades	**Ameaças**
• Formações • Heterogeneidade de utentes e situações clínicas • Plano curricular de MICF • Dispensa de medicamentos hospitalares nas farmácias comunitárias	• Constantes alterações de preços • Medicamentos esgotados

Capítulo II

Relatório de Estágio em Farmácia Hospitalar

Hospital de Braga

Lista de Abreviaturas

2CA – Centro Clínico Académico

AUE – Autorização de Utilização Excecional

CE – Comissão de ética

CFT – Comissão de Farmácia e Terapêutica

FDS – Fast Dispensing System

FNM – Formulário Nacional de Medicamentos

HB – Hospital de Braga

PPCIRA – Programa de Prevenção e Controlo de Infeções e de Resistências a Antimicrobianos

PrEP – Profilaxia Pré-Exposição da Infeção pelo Vírus da Imunodeficiência Humana

RAM – Reações adversas medicamentosas

SF – Serviços Farmacêuticos

SNS – Serviço Nacional de Saúde

SWOT – Strenghts, Weaknesses, Opportunities and Threats

UASF – Unidade de ambulatório dos serviços farmacêuticos

UCQ – Unidade Centralizada de Quimioterapia

UPE – Unidade de Preparação de Medicamentos Estéreis

UPNE – Unidade de Preparação de Medicamentos Não Estéreis

VIH – Vírus da Imunodeficiência Humana

1. Introdução

A farmácia hospitalar é uma área de atuação do farmacêutico que desempenha um papel fundamental na prestação de cuidados ao utente.

Apesar de, enquanto especialista do medicamento, o farmacêutico ser responsável pela gestão de todo o circuito do mesmo, é importante lembrar que as suas competências e aptidões vão muito além disso. De facto, embora muito lentamente, a profissão farmacêutica está a ser reconhecida como uma mais-valia na integração de equipas multidisciplinares para a prestação de serviços clínicos a doentes internados e/ou de ambulatório.

De facto, esta vertente clínica da nossa profissão é algo que me fascina muito, pelo que ao ser-me dada a possibilidade de estagiar noutra área para além da farmácia comunitária, foi claro que queria fazê-lo numa farmácia hospitalar, especialmente numa que tirasse proveito das competências farmacêuticas no seu todo.

Assim, durante os meses de maio e junho de 2023, completei 280 horas de estágio curricular nos Serviços Farmacêuticos (SF) do Hospital de Braga (HB), sob a orientação da Dra. Rita Rolim, e preparei o presente relatório, segundo o modelo SWOT – acrónimo inglês de *Strenghts, Weaknesses, Opportunities and Threats –,* de forma a apresentar uma análise crítica do mesmo.

2. O Hospital de Braga

O Hospital de Braga, localizado no Lugar de Sete Fontes, São Vítor, foi inaugurado em maio de 2011, substituindo o antigo Hospital de São Marcos. Como parte integrante do Serviço Nacional de Saúde (SNS) em Portugal, o hospital conta com equipas multidisciplinares altamente qualificadas para a prestação de serviços de saúde de excelência, bem como equipamentos com tecnologias inovadoras, o que tem contribuído para o seu reconhecimento.

De facto, desde 2015, o Hospital de Braga tem conquistado consistentemente o primeiro lugar no grupo de melhores hospitais de média/grande dimensão do SNS nos prémios "TOP 5 – A Excelência dos Hospitais", promovido pela IASIST, uma empresa multinacional especializada em benchmarking hospitalar, refletindo o seu compromisso em proporcionar um atendimento de qualidade e uma abordagem centrada no doente.

3. A análise SWOT

3.1 Forças (*Strenghts*)

3.1.1Instalações do Hospital de Braga e dos Serviços Farmacêuticos

O Hospital de Braga (HB) é muito recente e, por isso, destaca-se pelas suas instalações modernas e tecnologias inovadoras.

Os Serviços Farmacêuticos encontram-se, na sua grande essência no piso -1. No entanto, mais recentemente, a farmácia de ambulatório e a farmácia do hospital de dia de oncologia passaram para os pisos 0 e 1, respetivamente. Isto acaba por ser uma mais-valia, não só porque facilita a acessibilidade do utente às respetivas áreas, mas principalmente porque facilita a articulação dos farmacêuticos com equipas de enfermagem e médicos e, consequentemente, a sua integração em equipas multidisciplinares que participam no tratamento do doente.

No que diz respeito aos equipamentos, importa destacar o Kardex® e o Fast Dispensing System (FDS 330®), que agilizam todo o processo de preparação da medicação para distribuição individual em dose unitária. Para além disso, importa também mencionar as câmaras de fluxo laminar vertical que permitem a preparação dos estéreis e citotóxicos, assegurando as condições que as preparações exigem.

3.1.2 Multidisciplinaridade do plano de estágio

No HB, os Serviços Farmacêuticos (SF) encontram-se divididos em várias atividades e distribuídos por diferentes zonas, pelo que o meu estágio foi programado de forma a incluir uma passagem lógica e organizada por todas elas, de forma a proporcionar uma visão global de todo o circuito do medicamento. Assim, o plano de estágio integra um novo serviço a cada semana, pelo que me foi atribuída a planificação apresentada no Anexo 2.

Esta organização possibilitou que a minha passagem pelo hospital fosse isenta de monotonia e permitiu-me ter uma ideia clara da interligação e interdependência dos vários setores de atuação do farmacêutico hospitalar.

3.1.3 Centro Clínico Académico (2CA)

O Centro Clínico Académico de Braga (2CA) é uma parceria entre a Universidade do Minho, o Hospital de Braga e o Hospital CUF do Porto, que visa o desenvolvimento da investigação clínica.

Fundado em 2012, o 2CA está sedeado no Hospital de Braga e disponibiliza de uma infraestrutura própria totalmente equipada, onde se realizam todos as etapas dos ensaios

clínicos, desde as consultas médicas, avaliação de enfermagem, colheita de amostras biológicas, dispensa da medicação experimental, aplicação de questionários e realização de meios complementares de diagnóstico, entre outros procedimentos clínicos.

O facto de o hospital disponibilizar toda uma ala para o 2CA faz com que todo o processo dos ensaios clínicos seja mais cómodo, não só para os doentes/participantes, como também para a equipa multidisciplinar de profissionais que o constituem. Para a minha experiência enquanto estagiária, este aspeto foi também muito positivo porque permitiu que contactasse com várias áreas de atuação dos farmacêuticos nos ensaios clínicos – farmacêuticos de ensaios, coordenadores e monitores – e com toda a restante equipa, num ambiente destinado meramente a esse propósito da investigação clínica.

3.1.4 Farmotecnia

Nos SF, a farmacotecnia encontra-se subdividida em três grandes grupos: Unidade Centralizada de Quimioterapia (UCQ), Unidade de Preparação de Medicamentos Estéreis (UPE) e Unidade de Preparação de Medicamentos Não Estéreis (UPNE), sendo que cada um possui instalações próprias, garantindo a segurança e controlo de qualidade que as respetivas preparações exigem.

Ainda que tenha sido essencialmente observacional, a passagem pelo setor da farmotecnia permitiu-me perceber e experienciar quais as exigências associadas a cada uma das suas subáreas, nomeadamente no que diz respeito aos procedimentos de validação de prescrições e libertação de lotes, especificidades de cada tipo de preparação e, ainda, regras de vestuário e higienização das câmaras de preparação.

Para além disso, na UPE foi-me dada a oportunidade de participar ativamente na formulação, nomeadamente na assistência da preparação das bolsas de nutrição parentérica individualizadas e alguns colírios. Da mesma forma, na UPNE pude também auxiliar na preparação de alguns manipulados, nomeadamente da suspensão oral de ácido ursodesoxicólico, colutórios para os doentes de oncologia e, ainda, papéis de omeprazol para pediatria.

Considero o setor da farmacotecnia um ponto forte do meu estágio curricular, não só por ter sido a área onde me foram atribuídas mais tarefas, mas também porque me permitiu adquirir vários conhecimentos, nomeadamente ao nível da oncologia, nutrição parentérica, tecnologia farmacêutica e farmácia galénica.

3.1.5 Farmacovigilância

Apesar de as notificações de reações adversas medicamentosas (RAMs) ser um dever de todos os profissionais de saúde, a farmacovigilância não está diretamente inserida nos serviços farmacêuticos hospitalares. No entanto, a Unidade Regional de Farmacovigilância de Braga encontra-se inserida dentro do Hospital, mais precisamente nas imediações dos SF, e está ao encargo de uma farmacêutica do hospital.

Isto constituiu, sem dúvida, um ponto forte do meu estágio curricular, uma vez que neste setor consegui perceber todo o racional envolvido nas notificações RAMs, não só na criação de uma notificação, mas também no processamento das mesmas. Considero este um ponto positivo do meu estágio na farmácia hospitalar, uma vez que a área da farmacovigilância é fundamental para a defesa da saúde pública na minimização do risco associado aos medicamentos.

3.1.6 Contacto com novas terapêuticas

Durante a passagem pela farmácia de ambulatório do HB lidei diariamente com medicação inovadora para o tratamento de patologias como hepatites B e C, esclerose múltipla e lateral amiotrófica, doença de Crohn, Vírus da Imunodeficiência Humana (VIH) e Profilaxia Pré-Exposição da Infeção pelo Vírus da Imunodeficiência Humana (PrEP).

Da mesma forma, ao acompanhar o trabalho dos diferentes setores de produção, pude familiarizar-me com terapêuticas para patologias do foro oncológico e, ainda, com a área da nutrição parentérica. O facto de lidar diariamente com terapêuticas que nunca foram abordadas no meu percurso académico e com as quais dificilmente iria contactar na farmácia comunitária foi sem dúvida um aspeto muito enriquecedor do meu estágio.

3.2 Fraquezas (*Weaknesses*)

3.2.1 Falta de recursos humanos e caráter observacional

A especificidade das tarefas executadas pelo farmacêutico a nível hospital acompanhada do reduzido número de recursos humanos e de uma consequente sobrecarga de trabalho foram, a meu ver, um obstáculo à vertente prática da minha experiência enquanto estagiária. A verdade é que a dimensão prática é muito importante para a nossa formação, mas, em ambiente hospitalar, essa é praticamente inexistente. Contrariamente ao que aconteceu durante o meu estágio em farmácia comunitária, senti-me muito pouco ativa e participante ao longo do meu percurso.

Das tarefas que pude executar saliento a contagem semanal do *stock* de psicotrópicos e estupefacientes, a preparação de pedidos da área da distribuição clássica (onde se inserem hemoderivados, psicotrópicos e estupefacientes e medicação para o bloco operatório), a participação na realização do inventário da farmácia de ambulatório e da farmácia do hospital de dia de oncologia e, ainda, a prestação de assistência na preparação dos estéreis e não estéreis.

3.2.2 Pouco contacto com a vertente clínica

É uma verdade universalmente conhecida que o uso incorreto dos medicamentos tem um impacto não só ao nível da morbilidade e mortalidade, mas também a nível económico. Tal facto aliado ao aumento e à complexidade da terapêutica disponível e ao custo crescente associado à utilização de medicamentos tem evidenciado a necessidade de incluir o farmacêutico, enquanto especialista do medicamento, em equipas multidisciplinares que participam ativamente no tratamento e recuperação dos doentes. Esta vertente clínica do farmacêutico permite introduzir melhorias significativas no estado geral de saúde dos utentes e, no Hospital de Braga, pode assumir diferentes formas, nomeadamente (1) no acompanhamento da visita clínica, (2) na reunião de ensino ao cuidador do serviço de medicina interna. (3) na reconciliação da terapêutica no internamento de medicina interna, (4) na prestação de informação aos utentes e profissionais de saúde e, ainda, (5) nas Comissões Técnicas e Grupos de Trabalho.

Por me parecer que a área da farmácia clínica está muito bem aproveitada no Hospital de Braga, considero um ponto fraco do meu estágio o facto de não me ter sido dada a oportunidade de contactar com ela.

3.3 Oportunidades

3.3.1 Dispensa de medicamentos hospitalares nas farmácias comunitárias

Durante o meu estágio na farmácia de ambulatório, percebi que há uma tentativa por parte dos farmacêuticos responsáveis em marcar o agendamento do levantamento da medicação para o dia em que o utente tem consulta no hospital. No entanto, isso nem sempre é possível e a verdade é que, na minha opinião, não faz sentido os doentes terem de se deslocar até ao hospital quando as farmácias comunitárias têm profissionais igualmente qualificados para realizar a cedência da medicação, sempre acompanhada do devido aconselhamento. Assim, considero que a dispensa de medicamentos hospitalares em farmácias comunitárias reflete uma oportunidade de melhoria para a farmácia hospitalar – e consequentemente para a experiência de futuros estagiários – na medida em que permite a alocação dos farmacêuticos

da farmácia de ambulatório hospitalar para outros SF dos hospitais, o que é muito vantajoso tendo em conta a falta de recursos humanos.

3.3.2 Unidade Curricular de Farmácia Hospitalar de MICF

A Unidade de Curricular de Farmácia Hospitalar do MICF fornece uma vasta gama de conhecimentos acerca dos serviços farmacêuticos hospitalares, o que faz dela um aspeto favorável para o sucesso dos alunos que procuram realizar o estágio em farmácia hospitalar. De facto, foram várias as vezes em que, durante o meu percurso no hospital de Braga, recorri aos conhecimentos adquiridos na disciplina, facilitando assim a minha adaptação e integração.

3.4 Ameaças

3.4.1 Rutura de *stocks*

Tal como tem acontecido nas farmácias comunitárias, também nos hospitais se tem verificado a falta de alguns medicamentos, pelo que fui presenciando algumas ruturas de *stock* durante o meu estágio no HB. Apesar de algumas situações terem sido facilmente resolvidas através de um pedido a hospitais de proximidade e/ou farmácias comunitárias, a verdade é que isto nem sempre se verifica. Como tal, trata-se de uma ameaça no sentido em que se traduz numa falha na capacidade dos SF em corresponder às necessidades terapêuticas dos doentes.

3.4.2 Exigências regulamentares

A atividade farmacêutica hospitalar está intimamente ligada com uma série de exigências regulamentares que, apesar de serem necessárias, podem muitas vezes ser uma ameaça no sentido em que representam alguns desafios, custos e atrasos para os SF. Por exemplo, sempre que é necessário prescrever um medicamento que não faça parte do Formulário Nacional do Medicamento (FNM) – e adenda específica do HB –, o médico tem de preencher um extra-formulário que tem de ser, posteriormente, aprovado pela Comissão de Farmácia e Terapêutica (CFT) e pelo Conselho de Administração e, caso se trate de uma utilização off-label, pela Comissão de ética (CE). É, ainda, importante referir que no caso de se tratar de uma Autorização de Utilização Excecional, é ainda necessária a aprovação por parte do INFARMED. Só depois de se verificar todas as aprovações necessárias é que os SF iniciam o processo de aquisição do medicamento, o que pode também estar sujeito a alguns atrasos, dependendo se ele é ou não comercializado em Portugal. Apesar de ter plena consciência de que estas imposições são necessárias, não posso negar o facto de que podem implicar alguns constrangimentos, não só pelos atrasos no acesso ao medicamento, mas também pela complexidade administrativa a que estão associadas e que pode ser uma ameaça à eficiência operacional.

3.4.3 Autonomia dos técnicos de farmácia

À medida que ia percorrendo os diferentes setores dos SF do Hospital de Braga fui-me apercebendo de que algumas funções que em tempos eram da responsabilidade do farmacêutico são agora exclusivas dos técnicos de farmácia.

Embora reconheça a necessidade e benefícios de uma equipa multidisciplinar nos SF hospitalares, considero este facto uma ameaça no sentido em que faz com que a vertente tecnológica do farmacêutico hospitalar esteja, aos poucos, a desaparecer. Isto é evidente no setor da farmacotecnia onde, regra geral, os técnicos são responsáveis por toda a manipulação, enquanto o farmacêutico faz "apenas" a vericação do mesmo.

4. Considerações Finais

Ao finalizar o meu estágio curricular em farmácia hospitalar, encontro-me a um passo mais perto de me tornar, oficialmente, farmacêutica. Independentemente da área de atuação que o futuro tenha reservado para mim, considero que a passagem pela farmácia hospitalar me permitiu desenvolver competências importantes e necessárias para o meu percurso profissional e para que consiga corresponder àquilo que é esperado de mim.

Dada a curta duração do meu percurso no hospital e o caráter observacional do estágio, é compreensível que não tenha – ainda – todas as competências necessárias para dominar a área da farmácia hospitalar. Ainda assim, foi uma mais-valia poder contactar com esse ambiente e experienciar aquilo que é o dia-a-dia dos serviços farmacêuticos do mesmo.

Segundo a Ordem dos Farmacêuticos, o farmacêutico hospitalar "integra uma vasta equipa multidisciplinar de saúde que trabalha nos hospitais, estando diretamente envolvido na aquisição e boa gestão dos medicamentos, na sua preparação e distribuição pelos blocos e enfermarias, gerando a informação de natureza clínica, científica ou financeira que o sistema carece, especialmente na avaliação da inovação terapêutica e monitorização dos ensaios clínicos." Apesar de estar implícito, considero que esta definição devia incluir a possibilidade – e necessidade – da integração do farmacêutico hospitalar em equipas multidisciplinares de forma a aproveitar o seu potencial clínico. De facto, desta experiência fica a certeza de que, independentemente se temos o reconhecimento ou não, nós farmacêuticos temos um papel a desempenhar em tudo o que envolve o medicamento e isso inclui, sem dúvida, o acompanhamento dos doentes. O nosso lugar no hospital vai muito além do armazém do piso -1 e cabe a nós, futuros profissionais, lutar para que consigamos chegar aos pisos superiores, onde estão os doentes.

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6. Anexos

Anexo 1- Análise SWOT do estágio nos Serviços Farmacêuticos do Hospital de Braga

Forças	**Fraquezas**
• Instalações do Hospital de Braga • Multidisciplinaridade do plano de estágio • Centro Clínico Académico (2CA) • Farmotecnia • Farmacovigilância • Contacto com novas terapêuticas	• Falta de recursos humanos e caráter observacional do estágio • Pouco contacto com a vertente clínica
Oportunidades	**Ameaças**
• Dispensa de medicamentos hospitalares nas farmácias comunitárias • Unidade Curricular de Farmácia Hospitalar	• Rutura de *stocks* • Exigências regulamentares • Autonomia dos técnicos de farmácia

Anexo 2 - Cronograma do plano de estágio nos Serviços Farmacêuticos do Hospital de Braga

Área	Data
Farmácia de ambulatório	02-05-2023 a 05-05-2023
Dose Unitária	08-05-2023 a 12-05-2023
Intervenção Farmacêutica	
Distribuição Clássica	15-05-2023 a 26-05-22
Hemoderivados	
Estupefacientes	
Gases Medicinais	
Citotóxicos	29-05-2023 a 02-06-2023
Hospital Dia Oncologia	
Estéreis	05-06-2023 a 09-06-2023
Galénica	
Ensaios Clínicos	12-06-2023 a 16-06-2023
Farmacovigilância	19-06-2023 a 23-06-2023
Gestão	
CFT	
CE	
PPCIRA	
Qualidade	

Capitulo III

Monografia

"Exploiting Pharma 4.0 technologies in the non-biological complex drugs manufacturing: Innovations and Implications"

Abstract

The pharmaceutical industry has entered an era of transformation with the emergence of Pharma 4.0, which leverages cutting-edge technologies in the manufacturing processes. This holds tremendous potential for enhancing the overall efficiency, safety and quality of Non-Biological Complex Drugs (NBCDs), a category of pharmaceutical products that poses unique challenges due to their intricate composition and complex manufacturing requirements. This monograph attempts to provide insight into the application of select Pharma 4.0 technologies, namely machine learning, *in silico* modeling, and 3D printing, in the manufacturing process of NBCDs. Specifically, it reviews the impact of these tools on NBCDs such as liposomes, polymeric micelles, glatiramer acetate, iron carbohydrate complexes, and nanocrystals. It also addresses regulatory challenges associated with the implementation of these technologies and presents potential future perspectives, highlighting the incorporation of Digital Twins in this field of research as it seems to be a very promising approach, namely for the optimization of NBCDs manufacturing processes.

Keywords: Pharma 4.0; Non-Biological Complex Drugs; Additive manufacturing; Three-dimensional (3D) printing; Digital Twins; *In silico* modeling; Machine Learning; Polymeric micelles; Liposomes; Glatiramoid/glatiramer acetate; Iron carbohydrate complexes; Nanocrystals.

Resumo

A indústria farmacêutica entrou numa era de transformação com o surgimento da Pharma 4.0, que aplica tecnologias de ponta nos processos de fabrico. Isto possui um grande potencial para aprimorar a eficiência geral, segurança e qualidade dos Medicamentos Complexos Não-Biológicos (NBCDs), uma categoria de produtos farmacêuticos que apresenta desafios únicos devido à sua composição e requisitos complexos de fabrico. Esta monografia pretende fornecer uma visão da aplicação de determinadas tecnologias da Pharma 4.0, nomeadamente machine learning, *in silico* modeling e impressão 3D, no processo de fabrico dos NBCDs. Especificamente, analisa o impacto dessas ferramentas em NBCDs como lipossomas, micelas poliméricas, acetato de glatirâmero, complexos de carboidratos de ferro e, ainda, nanocristais. Aborda também os desafios regulamentares associados à implementação destas tecnologias e apresenta potenciais perspetivas futuras, destacando a incorporação de gémeos digitais neste domínio de investigação, uma vez que parece ser uma abordagem muito promissora, nomeadamente para a otimização dos processos de fabrico de NBCDs.

Palavras-chave: Pharma 4.0; Medicamentos Complexos Não Biológicos; Impressão 3D; Digital Twins; *In silico* modeling; Machine learning; Micelas Poliméricas; Lipossomas; Acetato de glatirâmero; Complexos de Carboidratos de Ferro; Nanocristais.

Abbreviations

3D – Three-dimensional

AI – Artificial Intelligence

ANN – Artificial Neural Network

API – Active pharmaceutical ingredient

ASP – Antisolvent precipitation

BWM – Ball Wet Milling

CESS® – Controlled Expansion of Supercritical Solution

CMAs – Critical material attributes

CNS – Central Nervous System

CPPs – Critical process parameters

CQAs – Critical quality attributes

Dexi – Dexibuprofen

DMT – Disease-Modifying Treatment

DRZ – Dorzolamide hydrochloride

EAE – Experimental Autoimmune Encephalomyelitis

EUD – Eudragit

FD – Freeze-dried

FDA – Food and Drug Administration

GA – Glatiramer acetate

GI – Gastrointestinal

hERG – Human ether-a-go-go-related gene

HME – Hot-melt extrusion

HPH – High-pressure homogenization

HPMC – Hydroxypropyl methylcellulose

IOP – Intraocular pressure

ISGS – *In situ* gelling system

MD – Molecular Dynamics

MF – Microfluidic technology

MIMO – Multiple-Input-Multiple-Output

MISO – Multiple-Input-Single-Output

ML – Machine learning

MRE – Mean Relative Error

MS – Multiple Sclerosis

NanoPRX – Nanoformed piroxicam

NAP – Naproxen

NBCD – Non-Biological Complex Drug

NN – Neural network

PAL – Palmatine HCL

PAT – Process Analytical Technology

PDI – Polydispersity index

PEO-PPO-PEO – Poly (ethylene oxide)-Poly (propylene oxide)-Poly (ethylene oxide)

PVP – Polyvinyl pyrrolidone

QbD – Quality by Design

RTD – Room temperature-dried

SDS – Sodium dodecyl sulfate

SSE – Semi-solid extrusion

TEER – Transepithelial electrical resistance

TIM – Timolol maleate

TNF-α – Tumor necroses factor-α

1. Introduction

It is widely recognized that bringing a new pharmaceutical drug to the market is a complex, lengthy, and costly process associated with high uncertainty. This process is known as drug development and encompasses various stages, including preclinical research, drug design and production, regulatory filling, clinical trials in humans, obtaining regulatory approval and the subsequent steps of manufacturing and marketing. (Hariry, Barenji e Paradkar, 2022) Throughout the years, the pharmaceutical industry has undergone significant changes and advancements, progressing from Pharma 1.0 to Pharma 4.0, and more recently reaching the era of Pharma 5.0. Even though Pharma 4.0 is a relatively recent development, the truth is that certain pharmaceuticals are already venturing into the 5.0 era. (Sharma *et al.*, 2022)

During Pharma 1.0, the processing of materials derived from minerals, animals and plants underwent a significant transformation. The use of basic hand-operated tools gave way to the introduction of commercial-scale equipment capable of crushing, blending, milling, and pressing a larger quantity of medicines. In fact, certain key machines developed during the Pharma 1.0 era continue to be widely used in the present day, showcasing their durability and effectiveness. (Arden *et al.*, 2021) Subsequently, electricity and early electronic machines ushered in a new era in the evolution of the pharmaceutical industry. This phase witnessed the integration of digital tools into various aspects of pharmaceutical research, development, manufacturing, and distribution. (Sharma, Patel e Shah, 2023) To the pharmaceutical sector, this technological incorporation marked a significant milestone because it allowed a more data-driven and patient-centric approach, besides providing a larger-scale production and more efficient quality control. However, these process controls were far from being perfect since they were confined to pre-determined and static settings, which only allowed for the monitoring of process performance and passive control strategies. (Arden *et al.*, 2021) The third industrial revolution was enabled by the emergence of computers and communication technologies, including networked computing, the internet, and wireless communications. (Sharma, Patel e Shah, 2023) This led to a greater level of automation in processes and equipment, and so, continuous manufacturing and active control. This revolution, known as Pharma 3.0, allowed the implementation of more sophisticated control strategies and higher product and process quality, reducing the need for human operators, and facilitating better tracking of parameters and metrics associated with production. Although some industries are well into Industry 3.0, the pharmaceutical industry is still very much transitioning into it. (Arden *et al.*, 2021) Pharma 3.0 also brought the implementation of advanced process analytical technology (PAT), which provides real-time data on process and product quality. It also enhanced Quality by Design

(QbD) processes, which focus on controlling product quality within specific parameters. (Arden *et al.*, 2021) While Pharma 3.0 already enables a much-improved understanding of how to capture, analyze and secure large amounts of data in pharmaceutical manufacturing, there is still room for further technological advancements to achieve the full potential of PAT and QbD. (Grangeia *et al.*, 2020) Later on, with the appearance of Artificial Intelligence (AI), Cloud Computing, Machine Learning (ML), Big Data Analytics*, In silico* modeling, 3D printing, and other advanced manufacturing technologies, the manufacturing process was actualized, forcing the emergence of another industrial revolution, known as Pharma 4.0. (Inuwa *et al.*, 2022) These advanced manufacturing technologies enable autonomous and self-organizing systems that are able to operate independently, without human intervention. (Arden *et al.*, 2021)

In the pharmaceutical sector, the fourth industrial revolution allowed a shift in the paradigm of formulation development. (Wang *et al.*, 2021)The possibility to integrate various data sources allows the connection of both external and internal information, creating a comprehensive network. In the context of pharmaceutical manufacturing, this integration involves merging external data, such as patient experience, market demand, supplier inventories, and public health emergencies, with internal data encompassing energy and resource management, modeling and simulation results, and laboratory data. This fusion enables unparalleled real-time responsiveness, monitoring, control, and predictive capabilities. (Arden *et al.*, 2021)

In an ever-evolving marketplace characterized by a fast-changing and smartly integrated supply chain and more active participation of patients in the decision-making about their healthcare, pharmaceutical companies face an urgent imperative to maintain their competitive advantage. In this setting, the key factor that sets businesses apart is their ability to meet the expectation of Pharma 4.0, which despite being a complex process to implement, provides enhanced resources for ensuring product safety compliance, safeguarding the supply chain, and fostering pharmaceutical development. (Inuwa *et al.*, 2022) This concept of Pharma 4.0 is closely linked to Artificial Intelligence, a technology-based system involving various advanced tools and networks that can mimic human intelligence. (Arden *et al.*, 2021) It possesses systems and software with the ability to interpret and learn from the input data, enabling them to autonomously make decisions in order to achieve specific objectives. (Mak e Pichika, 2019) AI plays a crucial role in Pharma 4.0 by enabling smart, data-driven decision-making and optimization throughout the entire pharmaceutical value chain. (Paul *et al.*, 2021)

Non-biological complex drugs (NBCDs) are complex in nature, often comprising intricate structures and diverse components. (Rocco *et al.*, 2019) Therefore, traditional quality control

methods may not fully capture the complexities of these drugs. Pharma 4.0 techniques can offer real-time monitoring and predictive quality control, allowing for more effective detection of deviations and potential issues. Besides, since NBCDs manufacturing involves handling a vast amount of data from multiple stages of the production process, these innovative technologies can leverage this data to support data-driven decision-making, enabling manufacturers to identify patterns, trends, and correlations that may impact product quality, stability, and reproducibility. (Zagalo, Sousa e Simões, 2022) In this sense, this monograph presents a view on the application of select Pharma 4.0 technologies namely machine learning, *in silico* modeling, and 3D printing, for enhancing the overall efficiency, safety and quality of Non-Biological Complex Drugs (NBCDs), a category of pharmaceutical products that poses unique challenges due to their intricate composition and complex manufacturing requirements.

However, is important to keep in mind that to attain Pharma 4.0, while embracing cutting-edge manufacturing technologies, is also important to simultaneously overcome regulatory obstacles. (Saha *et al.*, 2022) In this context, this review also addresses these regulatory challenges as well as potential future perspectives, particularly the incorporation of Digital Twins in the field of NBCDs development and manufacturing.

2. Emerging tools of Pharma 4.0

The following sections of this review will highlight and describe emerging tools of Pharma 4.0, such as additive manufacturing (3D printing), *in silico* modeling and machine learning, which are represented in Figure 1.

2.1 Additive manufacturing: Three-dimensional (3D) printing

Additive Manufacturing encompasses all manufacturing techniques that involve the sequential addition of material to build a 3D object. Typically, a digital representation of the desired object is created using computer-aided design software, and then it is produced using one or more additive technologies. (Ragelle *et al.*, 2021)

3D printing, as an additive manufacturing technique, offers immense potential in the pharmaceutical sector. It consists of the layer-by-layer creation of 3D objects based on digital designs and holds promise in the development of versatile release models to meet clinical needs and facilitate patient-centric treatment, such as personalized dosing, accommodating the treatment of specific disease states or patient populations. (Muñiz Castro *et al.*, 2021) The classification of 3D printing techniques can be simplified into three main categories: Printing-

Based Inkjet Systems, Nozzle-Based Deposition Systems, and Laser-Based Writing Systems. (Kotta, Nair e Alsabeelah, 2018)

Spritam® (levetiracetam), an epilepsy medication developed by Aprecia Pharmaceuticals, was the first 3D-printed pharmaceutical to receive approval from the Food and Drug Administration (FDA). (Jacob *et al.*, 2020) It utilizes a unique 3D printing technology called ZipDose®, which allows for the production of a highly porous tablet that dissolves rapidly in a small amount of liquid. This orodispersible tablet, characterized by its porous and soluble matrix composition, demonstrated similar pharmacological efficacy comparable to conventional tablets. However, it exhibited a significant improvement in solubilization time, indicating faster dissolution. (Kotta, Nair e Alsabeelah, 2018) It is worth noting that the approval of Spritam® as a 3D-printed pharmaceutical by FDA was a significant milestone in the field of pharmaceutical manufacturing, as it demonstrated the potential of 3D printing technology in the production of unique drug formulations and opened up possibilities for personalized medicine. (Jacob *et al.*, 2020)

Extensive research has been dedicated to advancing the use of 3D printing techniques in pharmaceutical manufacturing. As these endeavors progress, additive manufacturing technology has not only demonstrated its potential for creating personalized medications tailored to individual patients but has also emerged as a viable option for large-scale manufacturing, thanks to its ability to generate dosage forms with unique performance characteristics, difficult to achieve through traditional methods. (Tracy *et al.*, 2023)

2.1.1 Advancements in the pharmaceutical industry offered by 3D printing technology

In the pharmaceutical industry, 3D printing offers the benefit of creating products with sophisticated external shapes. In fact, this technique was employed to produce orally disintegrating printlets specifically tailored for individuals with visual impairment. These printlets were meticulously designed with Braille and Moon patterns on their surface, allowing patients to identify medications even when removed from their original packaging. This approach shows the potential to enhance accessibility and independence for visually impaired patients in managing their medication regimens, reducing potential errors. (Awad *et al.*, 2020)

3D printing has also demonstrated unprecedented potential in controlling drug release and influencing a drug´s pharmacokinetic profile. In fact, through the use of 3D printing techniques, multiparticulates termed miniprintlets loaded with paracetamol exhibited prolonged drug release patterns, offering a novel approach to drug delivery with remarkable flexibility and

control over release properties. By adjusting parameters such as dimensions and matrix composition, the therapeutic effect can be finely tuned, enabling the production of multi-drug systems. Furthermore, the possibility of creating miniprintles containing two drugs, namely paracetamol and ibuprofen, was also investigated. By utilizing different polymers, one drug was released immediately and the second was sustained over an extended period of time. (Awad *et al.*, 2019)

Another promising advantage of 3D-printing is the ability to delay the drug release, reaching even the colon in the gastrointestinal (GI) tract. This advancement holds tremendous potential as a breakthrough for the treatment of inflammatory bowel diseases. (Tracy *et al.*, 2023) (Melocchi *et al.*, 2021)

For its numerous advantages, this technology has been employed to manufacture an extensive range of pharmaceutical products. These encompass printlets (3D printed tablets), capsules, subcutaneous implants, transdermal microneedles, among other innovative drug delivery devices. (Muñiz Castro *et al.*, 2021) (Picco *et al.*, 2023) (Charoenying *et al.*, 2020)

2.2 *In silico* modeling

In silico modeling refers to the use of computational methods and computer simulations to study and analyze complex systems, typically in the fields of science, engineering, and medicine. (Viceconti *et al.*, 2021)

This approach involves creating virtual representations or models of real-world systems, based on mathematical algorithms, statistical techniques, and biological or physical principles. By simulating the behavior of these models, researchers can gain insights into the underlying mechanisms, predict outcomes, and test hypotheses without the need for costly or time-consuming physical experiments. (Brodland, 2015)

In the pharmaceutical sector, *in silico* modeling is used to predict the behavior of drug molecules, their interactions with biological targets, and their potential efficacy and safety profiles. (Seo *et al.*, 2022) In this context, arises the term "*in silico* trials", which refers to the application of computer modeling and simulation to assess the safety and effectiveness of medicinal products, including drugs, medical devices, diagnostic products, and advanced therapy medicinal products. (Viceconti *et al.*, 2021)

Over the years, numerous reviews have described how *in silico* methods can be used for predicting the absorption, distribution, metabolism, excretion, and toxicity (ADME/TOX) of different drugs. (Hewitt *et al.*, 2015) This plays a crucial role in assisting decision-making since

it is not possible to test experimentally all possible combinations of drug interactions. (Ai, Fan e Ekins, 2015) By simulating the behavior of substances *in silico*, researchers can quickly identify compounds with unfavorable ADME/TOX profiles and prioritize those with higher chances of success for further experimental evaluation, saving time, and resources, and reducing the risk of costly failures in later stages of drug development. (Hewitt *et al.*, 2015)

This technique also provides a mechanistic insight into the underlying processes and interactions involved in ADME/TOX because they can simulate the behavior of substances at the molecular level, allowing researchers to understand the interactions with transporters, enzymes, receptors, and other factors influencing ADME/TOX properties. Such information can help in understanding the mechanisms of action, potential toxicities, and the design of safer and more effective drugs. (Montanari e Ecker, 2015)

In addition, *in silico* models can also be employed to study complex biological systems, such as cellular processes and signaling pathways. These models can help unravel the underlying mechanisms governing these systems and aid in the understanding of diseases, as well as the development of therapeutic interventions. (Sung, 2022) (Tian *et al.*, 2015)

As an example of the applicability of *in silico* modeling in the pharmaceutical field could be taken into consideration the design of these models to predict and comprehend the mechanism of action of the human ether-a-go-go-related gene (hERG) blockers. This is relevant because the hERG gene encodes a crucial ion channel in the heart, namely he hERG potassium channel, which plays a crucial role in regulating the electrical activity of the heart. Certain drugs may inadvertently block the hERG channel, leading to a drug-induced QT prolongation, which can result in a potentially life-threatening heart rhythm disturbance called Torsade de Pointes. Therefore, understanding and predicting the effects of potential hERG blockers through *in silico* methods are vital in drug development and safety assessment. (Villoutreix e Taboureau, 2015)

2.3 Machine Learning (ML)

ML is an Artificial Intelligence-based technology that focuses on constructing computational models by training them with a set of data. It enables machines to automatically analyze and interpret complex patterns and data, improving their performance in making predictions or decisions. For instance, ML might predict the stability of a specific drug formulation by considering data from a range of previous experiments that investigated formulation stability. (Bannigan *et al.*, 2021)

Machine learning algorithms identify patterns, anomalies, and potential risks, enabling proactive quality management, enhancing accuracy, efficiency, and compliance, and ensuring high product standards, regulatory compliance, and patient safety. (Paul *et al.*, 2021) In fact, by automating inspection processes, analyzing data for defects and deviations, and predicting quality outcomes, this AI technology is revolutionizing quality control and assurance processes.

This technology can be broadly categorized into three types: supervised learning, unsupervised learning, and reinforcement learning. (Gupta *et al.*, 2021) In the first one, the algorithm is supplied with training data that includes both recorded observations and their corresponding labels. Utilizing this information, the algorithm constructs a model that can predict the appropriate output label for new observations. (Dinh *et al.*, 2019) Unsupervised learning, on the other hand, deals with unlabeled data, where the algorithm aims to discover hidden patterns or structures in the data without any predefined labels. Basically, the model learns to cluster similar data points or find relationships between the variables. (Eckhardt *et al.*, 2023) Finally, reinforcement learning involves a learning approach that relied on the use of rewards to categorize inputs as "good" or "bad" data based on their interaction with the surrounding environment. Through this process, the algorithm learns to optimize its actions to maximize positive outcomes and minimize negative ones. (Dedeloudi, Weaver e Lamprou, 2023)

The initial applications of machine learning in drug formulation date back to the 1990s when neural networks (NNs) were employed to forecast properties related to immediate-release oral tablets. This involved the preparation and assessment of a diverse array of tablet formulations and the training of the neural network with the acquired data, enabling the prediction of different outcomes such as disintegration time, dissolution rate, and friability. These early experiments marked the pioneering use of machine learning techniques in optimizing drug formulation processes. (Bannigan *et al.*, 2021)

Nowadays, the application of ML in the healthcare sector allows an improved cancer diagnosis, the discovery of new antifibrotic and antibiotic molecules, and the development of self-driving laboratories. It also allows the prediction of the products of certain chemical reactions and, consequently, the optimization of these reactions. (Bannigan *et al.*, 2021)

2.4 Digital twins

In the pharmaceutical industry, digital twins can have several uses and take different forms and are increasingly being adopted to improve efficiency, productivity, and quality control of drug manufacturing processes. For instance, researchers developed computer simulations to create digital twins of dissolution apparatuses, namely USP II, and tablets to mimic their behavior

realistically. By using these digital twins, they could investigate drug release profiles and shear rates that act on the tablet under different paddle speeds in both USP II and biorelevant colon models. The aim was to understand how the USP II could be operated to achieve more realistic hydrodynamic conditions that resemble the conditions in the human colon *in vivo*. To ensure accuracy and relevance in the simulations, the behavior of the tablet and the motility patterns within the colon are derived from experimental data and *in vivo* observations, respectively. Based on their findings, the researchers recommend using an "on-off" operating mode in the USP II rather than a constant paddle speed. This "on-off" mode generates shear rate peaks, which better reflect the *in vivo* conditions of the human colon. This change in operating mode can help achieve more realistic simulation results, providing deeper insights into the tablet´s disintegration and drug release processes in the colon-targeted solid dosage forms. (Schütt *et al.*, 2022)

These digital twins were also employed as a digital representation of the continuous manufacturing process for pharmaceuticals. This allows the prediction of critical process parameters (such as those in the feeders, blender, and tablet press) and critical quality attributes (tablet composition, weight, thickness, and hardness) throughout the manufacturing process. This means that pharmaceutical companies can study the steady-state operation of the process within the design space, examine the impact of different operating conditions, materials, and process parameters, and understand the dynamic response to disturbances or variations in the process. (Moreno-Benito *et al.*, 2022)

In addition, researchers have developed a new and innovative concept called a "neural network-intelligent digital twin" to describe, predict and optimize the outcomes of the manufacturing process of solidified nanosuspensions. The authors have integrated the artificial neural network into the digital twin development process in a stepwise manner. The steps include data sampling, model deployment, and curve fitting. This means that the NN is trained using a dataset containing information about the manufacturing process, and the network´s architecture and parameters are optimized (curve fitting) to effectively represent the behavior of the process. One of the primary roles of the ANN within the digital twin is to augment the amount of available data. Since training a neural network typically requires a significant amount of data, the ANN generates additional simulated data points to further calibrate and validate the model. By doing so, the digital twin can be fine-tuned to better represent the real-world manufacturing process, without the need for extensive physical experiments, and reducing uncertainties in the model´s predictions. Overall, this research introduces a sophisticated approach that combines NN technology and digital twin concepts to improve the

understanding, prediction, and optimization of the manufacturing process for solidified nanosuspensions. This has the potential to lead to more efficient and cost-effective manufacturing processes in the pharmaceutical sector. (Davidopoulou e Ouranidis, 2022)

Another – and very recent – example of the applications of Digital Twins is the use of this technology enabled by process analytical technology (PAT) approaches to improve various aspects of the SARS-COVID-19 vaccine manufacturing process, such as capacity multiplication, reduction of out-of-specification batch failures, personnel training, efficient operation, optimal utilization of resources, and faster product release. Specifically, the focus is on messenger ribonucleic acid (mRNA) vaccine processing and the potential use of digital twins to address bottlenecks and optimize the process. Researchers suggested creating a digital twin of the entire process that converts plasmid deoxyribonucleic acid (pDNA) to mRNA. By combining digital twins with PAT, the vaccine production process can be improved and made more efficient and the manufacturing capacity can be multiplied without compromising the quality and efficiency of the production. In addition, researchers also consider that digital twins can also be used as a training tool for personnel to become qualified in operating the manufacturing process effectively and efficiently. It also allows the optimization of the usage of scarce buffers and chemicals, leading to better resource management in the manufacturing process, and a faster product release, allowing vaccines to be distributed more quickly to meet the global demand. (Schmidt *et al.*, 2021)

In general, digital twins allow enhanced drug formulation development, reduced reliance on costly experiments and improved drug performance assessment. It enables pharmaceutical companies to move towards more data-driven and agile manufacturing processes, leading to better products and reduced costs. However, despite their potential benefits, the pharmaceutical industry has not fully embraced the use of digital twins in their operations. (Davidopoulou e Ouranidis, 2022)

3. Non-Biological Complex Drugs (NBCDs)

NBCDs are defined as medicinal products that are not derived from living organisms but are entirely synthesized through a fully synthetic process. Besides, the active substance comprises multiple structures that cannot be entirely isolated, quantified, characterized, or fully described using physicochemical analytical methods. (Sun, Jiang e Chen, 2020)

NBCDs are closely related to nanoparticles and some examples include fat emulsions, liposomes, polymeric micelles, iron-carbohydrate complexes, dendrimers, swelling cross-linked polymers, glatiramoids, among others. Sometimes, low molecular weight heparins, dry

powder inhalers, ocular/intravenous emulsions and dermal patches are seen as NBCDs as well. (Zagalo, Sousa e Simões, 2022) Figure 2 illustrates the NBCDs that are within the scope of this monograph.

In a conference that took place in Budapest (October 2014), doctor De Vlieger listed a few key attributes for an NBCD: (Hariry, Barenji e Paradkar, 2022)

1. It consists of a multitude of closely related structures.
2. The entire complex is the active pharmaceutical ingredient.
3. The properties cannot be fully characterized by physicochemical analysis.
4. A robust and well-controlled manufacturing process is key to reproducing the product.

Regarding NBCDs, one of the main challenges is the characterization process, specifically in evaluating batch-to-batch similarity and the impact of manufacturing process variations. This sensitivity to manufacturing changes can give rise to challenges in ensuring reproducibility when produced by different manufactures. A noteworthy example of this occurred with follow-on products for iron sucrose complexes, where reports indicated that patient safety was compromised by switching patients to a follow-on product. (Klein *et al.*, 2019) The complex nature of NBCDs may arise from various factors. For instance, the complexity may stem from the active substance itself, as seen with glatiramer acetate, or it may arise from the formulation, as observed with liposomes. (Rocco *et al.*, 2019)

All the mentioned above explains why NBCDs fall under a distinct regulatory framework compared to small molecule drugs. (Crommelin *et al.*, 2015)

3.1 Polymeric micelles

Polymeric micelles are nanoscale particles (sizes ranging between 20 and 200 nm) that consist of a hydrophobic core, serving as a reservoir for poorly soluble active pharmaceutical ingredients (APIs), and a hydrophilic shell that offers colloidal stability and limits protein adsorption and opsonization, leading to extended circulation times. (Ghezzi *et al.*, 2021) Since the physicochemical properties, and the *in vivo* distribution, safety, and efficacy of the final product are highly dependent on the chosen polymer chemistry and manufacturing process, this explains why polymeric micelles are classified as NBCDs. (Hwang, Ramsey e Kabanov, 2020) Despite the challenges associated, these structures hold great promise in drug manufacturing and delivery because they offer several advantages that make them attractive for various therapeutic applications. (Ghezzi *et al.*, 2021) By encapsulating hydrophobic drugs in their core, these structures provide increased solubility and stability, facilitating their delivery to target sites. (Hwang, Ramsey e Kabanov, 2020) Simultaneously, these nanocarriers

also have shown improved therapeutic outcomes when compared to the free drug. (He *et al.*, 2016) In addition, the biocompatibility of many polymers used in micelle formulation makes them well-tolerated by the body, reducing the risk of adverse reactions. (Ghezzi *et al.*, 2021) Moreover, by modifying the surface properties of the micelles, they can be engineered to selectively accumulate at specific disease sites, taking advantage of the enhanced permeability and retention effect of tumor tissues or inflamed regions. (Ghosh e Biswas, 2021)

More recently, researchers have been studying the combination of two or more polymers in order to assemble polymeric mixed micelles. (Cagel *et al.*, 2017) The underlying concept is to combine polymers with complementary characteristics to enhance drug encapsulation, stability, and targeted delivery. Overall, this is a direct and convenient approach to improve the physical stability and enhance the drug-loading capacities of conventional polymeric micelles for drug delivery. (Ebrahim Attia *et al.*, 2011)

3.2 Liposomes

Liposomes are colloidal and spherical vesicles composed of lipid molecules, primarily phospholipids, which have a hydrophilic head and hydrophobic tails, allowing them to form a closed, bilayered structure in an aqueous environment. (Guimarães, Cavaco-Paulo e Nogueira, 2021) Their classification is made according to their size, which can go from 0.025 μm (very small liposomes) to several μm (large liposomes), and their number of double layers. (Akbarzadeh *et al.*, 2013) The formulation of these structures involves the dispersion of the lipid molecules in an aqueous phase to form the vesicles. This can be done through mechanical methods (microfluidization, extrusion), replacement of organic solvents by aqueous media methods (ethanol injection, reverse phase evaporation) and detergent removal methods. (Guimarães, Cavaco-Paulo e Nogueira, 2021) These structures have been studied in several pharmaceutical research as drug delivery systems due to their remarkable capacity to encapsulate molecules with varying solubilities: hydrophilic molecules can be accommodated in the internal core, hydrophobic molecules within the lipid bilayer, and amphiphilic molecules at the water/lipid bilayer interface. Moreover, their exceptional biocompatibility, biodegradability, lack of toxicity, and non-immunogenic nature further enhance their potential as an excellent option in the therapeutic field. (Jensen e Hodgson, 2020)

Liposomes offer a host of additional benefits, including their capability to carry substantial drug loads, their capacity for self-assembly, and the versatility to modify a wide range of physicochemical and biophysical properties, thereby allowing precise control over their biological characteristics. (Guimarães, Cavaco-Paulo e Nogueira, 2021) It is therefore clear

that liposomes are incredibly versatile structures that find applications across diverse fields. In fact, they can be found as a therapeutic alternative for cancer (Saraf *et al.*, 2020) as well for the treatment of skin conditions such as hyperpigmentation, among many others. (Atallah *et al.*, 2022)

Though the years, diverse delivery systems based on liposomes were developed, like niosomes, transfersomes, ethosomes, dendrossomes, of which we highlight the first two.

3.2.1 Niosomes

Niosomes were initially developed for the cosmetic industry but have now a wide range of applications in the pharmaceutical field. (Costa e Santos, 2017) It consists of biodegradable and biocompatible vesicles composed of nonionic surfactants and, sometimes, cholesterol or its derivatives. (Pando *et al.*, 2015) These structures allow us to overcome some limitations associated with liposomes since they are not only more cost-effective and easier to prepare but also demonstrate a higher encapsulation efficiency. (Chen *et al.*, 2019) This explains why niosomes have garnered significant attention in numerous studies for diverse applications, including for several types of cancers and fungal infections. (Aparajay e Dev, 2022)

3.2.2 Transfersomes

Transfersomes are specialized lipid-based nanocarriers composed of phospholipids and edge-active agents. They possess exceptional deformability and flexibility, allowing them to squeeze through the narrow pores of the stratum corneum. (Costa e Santos, 2017) This characteristic enables efficient transdermal drug delivery, offering a non-invasive alternative for systemic drug administration. (Chaudhary, Kohli e Kumar, 2013) Transfersomes have garnered significant attention due to their potential to enhance drug absorption, minimize side effects, and improve patient compliance. (Lei *et al.*, 2013) (Shuwaili, Al, Rasool e Abdulrasool, 2016)

3.3 Glatiramoid/Glatiramer acetate (GA)

Glatiramer acetate (GA), also known as Copolymer-1 or Cop-1, is a heterogeneous mixture of synthetic polypeptides, comprising L-alanine, L-lysine, L-glutamic acid, and L-tyrosine. (Rocco *et al.*, 2019) Its discovery took place in the late 1960s when researchers were investigating the immunological properties of synthetic amino acid polymers in the quest for a synthetic antigen capable of inducing experimental autoimmune encephalomyelitis (EAE), the most commonly used model for studying Multiple Sclerosis (MS). (Weinstock-Guttman *et al.*, 2017) In the US and Europe, GA has been approved as a disease-modifying treatment (DMT) for patients with relapsing forms of MS, a chronic, inflammatory disease of the central nervous

system (CNS), that starts as an autoimmune reaction leading to acute CNS inflammation, along with the disruption of myelin, ensheathing axons and axonal damage. (Weinstock-Guttman *et al.*, 2017)

Despite not being completely random, the amino acid sequences are not completely conserved from batch to batch, even when the process is tightly controlled. Therefore, the quality of these substances heavily relies on the precision of the manufacturing process. (Rocco *et al.*, 2019)

GA falls under the category of NBCDs not only due to its intricate structure and variable composition but also because fully characterizing and analyzing its molecular structure is exceptionally challenging compared to traditional small-molecules drugs. (Rocco *et al.*, 2019) (Melamed-Gal *et al.*, 2018)

3.4 Iron carbohydrate complexes drugs

Iron carbohydrate complexes drugs are effective iron replacement agents for treating iron deficiency anemia. (Nikravesh *et al.*, 2020) This is an area of great interest because it is the most common micronutrient deficiency worldwide. (Percy *et al.*, 2017)

Oral iron supplements in the form of ferrous iron might not be the perfect therapeutic approach because they are associated with gastrointestinal intolerance, prolonged iron store repletion time, and impaired absorption of iron. As a way to overcome these problems, intravenous iron-carbohydrate complexes appear as an alternative approach that can lead to higher hemoglobin levels, as well as faster replenishment of the body iron stores. (Auerbach e Ballard, 2010)

These structures consist of colloidal formulations composed of an iron core and a complex carbohydrate coating with an average particle size at the nanoscale. Different formulations differ in terms of the iron core size, carbohydrate shell coating material and hydrodynamic size of the product. The stability of the iron-carbohydrate complexes and the rate at which iron is released from the matrices is also different among different products. (Zheng *et al.*, 2017) Furthermore, is crucial to have a comprehensive knowledge of the physicochemical characteristics of the various intravenous iron-carbohydrate complexes, to improve the safety and efficacy of the currently available products as well as for the formulation of new iron preparations in the future. (Nikravesh *et al.*, 2020)

3.5 Nanocrystals

Nanocrystals are carrier-free drug particles with sizes in the nanometer range and crystalline characteristics. (Müller, Gohla e Keck, 2011) Thanks to the high drug loading, nanocrystals guarantee efficient drug delivery to cells or tissues and maintain potent therapeutic concentrations to achieve the desired pharmacological effect, and so these transporters have become very attractive to treat various types of diseases. (Mohammad *et al.*, 2019)

This technology of nanocrystallization offers a very promising and effective way to deal with low solubility and poor bioavailability of poorly soluble drugs because, due to the nanosize, they allow an increased dissolution pressure and higher dissolution rate. (Müller, Gohla e Keck, 2011) To produce nanocrystals, several methods have been implemented and they can be divided into three main categories: top-down (nanonization), bottom-up (crystal growth or nucleation), and combination techniques. (Miao *et al.*, 2018)

For all of the advantages mentioned above, these NBCDs have been employed in several ranges of diseases, namely in cancer therapy, inflammatory diseases (due to their capacity of improving the physicochemical properties of Biopharmaceutics Classification System (BCS) class II drugs), in the prevention of preterm birth (as progesterone is a BCS class IV drug, with poor solubility and very low permeability, which difficult the therapeutics), among many others purposes. (Mohammad *et al.*, 2019) (Lin *et al.*, 2014)

4. Applying Pharma 4.0 tools in the production of Non-Biological Complex Drugs

4.1 Additive manufacturing: 3D printing

4.1.1 Polymeric Micelles

3D printing has exhibited promising results in the manufacturing of diverse drug delivery systems, such as polymeric micelles. In a recent investigation, chitosan-based polymeric micelles containing camptothecin (CPT) were integrated into 3D printing systems and coated with an enteric layer. This approach aimed to safeguard the nanosystems from the harsh conditions of the gastrointestinal tract. (Almeida *et al.*, 2021) The manufacturing process involved the use of a bioprinter that combines Fused Deposition Modeling (FDM) – a widely used 3D printing method that involves melting and extruding filament materials layer by layer – and Injection Volume Filling (IVF) – a technique that enables the incorporation of solutions or dispersions ate room temperature into the extruded scaffold. (Linares, Casas e Caraballo, 2019) (Almeida *et al.*, 2021) The internal structure of the printfills is depicted in Figure 3A. The *in vitro* drug release profile showed that both printfills containing the free drug and those

with micelles effectively managed drug release. Consequently, there was no drug release from the printfills within the initial 2-hour period at pH 1.2. However, when pH changed to 6.8, the retarding polymer began to dissolve, permitting the entry of water (Figure 3B). Researchers also concluded that both polymeric micelles and the free drug present in the dissolution media did not exhibit any cytotoxic effects on Caco-2 cells, a colorectal cancer cell line. In fact, these cells showed an increase in metabolic activity of up to 100%, which could be attributed to the presence of simulated gastrointestinal fluids (Figure 3C). Furthermore, as illustrated in Figure 3D, the permeability of CPT from the micelles was observed to be higher than that of the free drug in both Caco-2 standard model (a) and a 3D intestinal model (b), with significant differences becoming evident during the final incubation times. In the 3D model, the CPT permeability reached approximately 27%, representing an enhancement compared to the standard model´s permeability of 20%. This heightened permeability in the 3D model aligns more closely with the *in vivo* human intestine, reflecting a drug permeability that is more akin to real-world conditions. The experiment also demonstrated consistent transepithelial electrical resistance (TEER) maintenance for both micelles and free drug, reflecting the monolayer integrity, and consequently suggesting that the tested formulation is safe. Besides, the apparent permeability coefficients exhibited notable disparities between the micelles and the free drug. In the 3D model, the apparent permeability coefficients of CPT from the micelles indicate a significant increase in CPT permeability and consequently, bioavailability. On the other hand, the free drug maintained an apparent permeability coefficient similar in both models, signifying that the drug´s permeability was nearly half that of the micellar drug, specifically within the context of the 3D model (Figure 3D(c)). Furthermore, to ensure the structural integrity of the membrane following the permeability experiment, hematoxylin, and eosin (H&E) staining was conducted for both models and under all conditions (Figure 3E). This staining process employed two dyes: hematoxylin, a basic dye, and eosin, an acidic dye. Hematoxylin imparts a purple hue to acidic structures like the nucleus, while eosin imparts a pink color to basic structures such as the cytoplasm and extracellular matrix. Considering this staining mechanism, Figure 3E presents a consistent monolayer in both models, which underscores the preservation of cellular membrane integrity. These observations indicate that the membrane remained intact and well-formed throughout and following the permeability assay. Overall. the findings of the study showed that the printfills were able to maintain the micelles intact until they reached the intestinal pH, increasing the CPT intestinal absorption and, consequently, its oral availability. Furthermore, the combination of 3D printing and nanotechnology holds considerable potential for the targeted release of polymeric micelles in the colon. This advancement can enhance the absorption of drugs in the intestines while

safeguarding them from degradation as they go through the gastrointestinal tract. (Almeida *et al.*, 2021)

In another study, researchers focused on creating a bioink suitable for 3D printing a hydrogel implant with controlled drug release capability. To achieve this, simvastatin was loaded into polymeric micelles composed of polylactide/poly (ethylene glycol) triblock copolymers (PLA-PEG-PLA). These micelles were then incorporated into hydrogels through a photo-cross-linking 3D printing process. The resulting simvastatin-loaded triple-network hydrogel demonstrated remarkably long-term drug release over 14 weeks, maintaining a therapeutic concentration. These findings indicate that these micelles hold great promise as a bioink material, providing long-term hydrogel stability, biodegradability, and sustained delivery of hydrophobic drugs, such as simvastatin. (Cisneros *et al.*, 2021)

4.1.2 Liposomes/niosomes

Due to their numerous benefits, liposomes have garnered significant attention, especially in the fields of cancer treatment and vaccinology. However, their development remains a challenge, making it crucial to seek out innovative approaches that enable fast, safe, and consistent production with high-level batch-to-batch reliability. (Sommonte *et al.*, 2022)

In an experimental study, researchers used 3D printing technology to create a 3D-printed niosomal hydrogel (3DP-NH) containing cryptotanshinome (CPT), as a topical delivery system for acne therapy. To formulate the CPT-loaded niosomal hydrogel the CPT-loaded niosomes were carefully added, drop by drop, into the hydrogel. Subsequently, the resulting mixture was printed using an extrusion-based 3D printer to produce a 3D-printed CPT-loaded niosomal hydrogel (3DP-CPT-NH) with specific drug dosage, shape, and size. The findings demonstrated that the 3DP-CPT-NH exhibited a significant anti-acne effect without causing any skin irritation. (Wang *et al.*, 2020)

Another investigation was conducted, combining microfluidic technology (MF) and 3D printing and resulting in the formulation of "diamond-shaped" devices suitable for producing liposomes loaded with lysozyme as a model drug. Computer-aided design software was used to design microfluidic devices with diverse geometries, which were then printed using high-resolution Digital Light Processing (DLP) – 3DP. Stability tests confirmed the consistency of the developed formulations, and an encapsulation efficacy study showed positive results. Overall, this study showcased the effectiveness of combining MF and 3DP, highlighting the potential for synergistic growth in this field. (Sommonte *et al.*, 2022)

4.1.3 Nanocrystals

In the pharmaceutical field, 3D printing has also been making an impact in the manufacturing of nanocrystals, allowing more precise control over drug dosage and release profiles. (Groetsch *et al.*, 2023) For instance, additive manufacturing has been used to encapsulate nanocrystals within polymeric matrices, creating drug-loaded filaments or tablets, and improving the solubility and bioavailability of poorly soluble drugs. The precise control over the placement of nanocrystals in the printed structured allows for enhanced drug delivery and therapeutic efficacy. In fact, a recent study aimed to develop fast-dissolving oral polymeric film formulations loaded with indomethacin nanocrystals using 3D printing technology and the outcomes demonstrated that this offers a promising approach for enhancing solubility in immediate-release formulations. (Germini e Peltonen, 2021)

Another experiment focused on the development of an in situ forming robust injectable and 3D printable hydrogel based on cellulose nanocrystals. The results demonstrated that the hydrogels exhibited excellent injectability and maintained their shape fidelity without the need for additional cross-linking steps. The interlayer bonding between the printed layers was strong, resulting in the formation of stable 3D structures, even up to 10 layers. (Phan *et al.*, 2022)

Additive manufacturing also allows the creation of personalized drug delivery systems by incorporating nanocrystals. For instance, researchers have used 3D printing to fabricate patient-specific tablets containing nanocrystals of poorly soluble drugs. This enables customized dosages and controlled release profiles tailored to individual patient needs. In the first-ever study that included nanocrystals within 3D-printed tablets, albendazole nanocrystals were successfully incorporated into the tablets, achieving a concentration of up to 50% w/w, which is not typically attainable with conventional tablets. Moreover, the printlet formulation with nanocrystals exhibited superior efficacy in improving drug dissolution in HCL 0.1N compared to nanocrystals included in hard gelatin capsules. The nanocrystals demonstrated maintained particle size, crystallinity, and chemical stability before and after 180 days of storage. Overall, the findings demonstrated the promising pharmaceutical potential of combining 3D printing and nanocrystals for the development of stable, fast-release, oral solid dosage forms of poorly soluble drugs. This experiment also involved the use of propyleneglycol as a carrier and showed that this technique holds potential for printing objects using different types of nanocrystals embedded in low melting temperature polymers. (Lopez-Vidal *et al.*, 2022)

4.2 *In silico* modeling

4.2.1 Polymeric micelles

A recent study focused on developing a novel technology called MeltDrops, which used hot-melt extrusion (HME) for continuous manufacturing of *in situ* gelling systems (ISGS), known to prolong the retention time and improve the bioavailability of ophthalmic drugs. This is relevant because the traditional manufacturing of ISGS has been challenging and costly, hindering their industrial scale-up and clinical implementation. However, MeltDrops technology offers a one-step extrusion process to develop these systems (Figure 4A), which overcomes the limitations of batch manufacturing. Based on *in silico* modeling, researchers employed Molecular Dynamics (MD) simulation to analyze the difference in physical properties of two types of MeltDrops – loaded with timolol maleate (TIM) or dorzolamide hydrochloride (DRZ) – at two different temperature conditions, 300 K (room temperature) and 308 K (physiological temperature) (Figure 4B). These simulations provided evidence of enhanced interactions between drug, polymer, and water molecules at the higher temperature (308 K), indicating the formation of ISGS with the desired properties, such as solution-gel transition at physiological temperatures. Researchers also concluded that the in vitro drug release from MeltDrops technology demonstrated sustained and controlled release behavior, while marketed eyedrops showed complete drug release in less than 30 minutes (Figure 4C). Besides, the results also showed a percentage decrease in intraocular pressure (IOP) after administration of MeltDrops and marketed eyedrops indicating the superior IOP-reducing potential of MeltDrops over the conventional ones (Figure 4D). Finally, it was conducted a HET-CAM test in order to evaluate the potential ocular irritancy of MeltDrops. The results showed no signs of irritation, indicating that they are safe and well tolerated for ocular use (Tambe *et al.*, 2023)

Previously, a continuous manufacturing technique utilizing coaxial turbulent jet in coflow was established for the production of paclitaxel-loaded polymeric micelles. More recently, researchers employed coarse-grained molecular dynamics simulations to gain deeper insights into the impact of material attributes (specifically, the drug-polymer ratio and ethanol concentration) and process parameters (such as temperature) on the self-assembly process of polymeric micelles. Additionally, these simulations provided molecular-level information on micelle instability. The findings demonstrated a clear correlation between the micelle shape and drug encapsulation. As the paclitaxel content increased, the micelles transformed from spherical to ellipsoidal structures. Through the simulation data, researchers were able to identify the critical aggregation number, which represents the minimum number of polymer and drug molecules required for this shape transition. Moreover, this investigation indicated

that larger micellar size and reduced solvent accessibility contributed to enhanced structural stability of the micelles. Additionally, researchers conducted an evaluation of the micellar dissociation free energy using steered molecular dynamics simulations across various temperatures and ethanol concentrations. The simulations unveiled thar higher ethanol levels and temperatures led to micellar destabilization, resulting in a more significant release of paclitaxel. This increased drug release was attributed to the solvation of the hydrophobic core, promoting micellar swelling and reducing hydrophobic interactions, ultimately leading to loosely packed micellar structure. In general, the computational predictions provided valuable insights into the micelle self-assembly process, morphological changes, drug release, and thermodynamic instability and showed excellent agreement with experimental results, underscoring its efficacy in studying the impact of material attributes and process parameters on the polymeric micelle formulation during continuous processing. (Duran *et al.*, 2022)

In another study, researchers used coarse-grained molecular dynamics simulations to investigate the behavior of a specific type of block copolymer called poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide) (PEO-PPO-PEO), commonly known as Pluronics or Poloxamers. They studied the effect of polymer and surfactant concentration on the morphology of these bock copolymers and ionic surfactants, namely sodium dodecyl sulfate (SDS), in aqueous solutions. The results showed that when Pluronics and SDS are present together in the solution, they tend to form mixed micelles and that the shape of those micelles depends on the relative concentrations of Pluronics and SDS in the solution. The core of the mixed micelles is made up of PPO chains from Pluronics, the alkyl tail of SDS, and some water molecules, while the shell surrounding the core is composed of PEO chains, water molecules, and the sulfate headgroups of SDS. Basically, they observed that as more SDS is added, the morphology of the mixed micelles changes from spherical to wormlike-cylindrical geometry. Overall, the molecular insights gained from studying the coassembly of an ionic surfactant and an amphiphilic triblock copolymer in aqueous media have potential applications in various complex fluid mixtures. However, the accuracy of the results relies on the coarse-grained force field used, which can be improved with more computationally expensive atomistic simulations for quantitative comparisons with experimental data. (Bhendale e Singh, 2023)

4.2.2 Liposomes / transfersomes

In silico modeling has been employed in the manufacturing of liposomes because it allows researchers to simulate and predict the behavior of these structures, such as their stability, size, composition, drug encapsulation efficiency, and release kinetics. Furthermore, these

models can help optimize the manufacturing process, predict the performance of liposomal formulations, and guide experimental design. (Ramajayam *et al.*, 2020)

In a recent study, the authors constructed computational models to identify active pharmaceutical ingredients (APIs) that can achieve the desired high concentrations in nano-liposomes through remote loading. The models aimed to predict the suitability of APIs for nano-liposomal delivery by considering fixed main experimental conditions, such as liposome lipid composition and size. They added a prediction of drug leakage from the nano-liposomes during storage, which is crucial for ensuring the development of pharmaceutically viable nano-drugs. By using "load and leak" models, they screened two large molecular databases to identify candidates' APIs for delivery by nano-liposomes. Through the screening process, the researchers identified 667 molecules that showed positive results in both the loading and leakage models, indicating high-loading and stable characteristics. Among these molecules, 318 received high scores in both properties and, notably 67 of them are FDA-approved drugs. (Cern *et al.*, 2017) Basically, these findings highlight the use of computational modeling in the optimization of liposomal formulations because by narrowing down the search to molecules that exhibit high-loading and stability characteristics, researchers can focus their efforts on molecules with a higher probability of success, saving time, resources, and costs associated with traditional trial-and-error approaches.

These computational approaches can – and should – be combined with experimental studies because it allows a better understanding of the mechanisms that are being investigated. The computational modeling not only aids in explaining experimental results, but also has the potential to guide and inspire new directions for experimental research in the development of liposomal drug delivery systems. (Bunker, Magarkar e Viitala, 2016)

In a study that aimed to develop active targeting liposomes to deliver anticancer agents to the treatment of hepatocellular carcinoma, computational modeling was used to gain insight into the structure and behavior of the intended targeted liposomal drug delivery systems within the bloodstream. The research showcases the complementary nature of these simulations alongside experimental research, often offering valuable mechanistic context. (Pathak *et al.*, 2016)

Another example of the predictive power of *in silico* modeling in the pharmaceutical industry is an investigation that explored the use of thermosensitive liposomes (TSL) for targeted drug delivery to tumors. The researchers created a three-dimensional computer model to simulate the delivery of the TSL-encapsulated doxorubicin to mouse tumors. To do so, a mouse hind

limb was scanned using a 3D scanner, and the resulting geometry was imported into finite element modeling software. A virtual tumor is added to the model, and the authors simulate the heating process using a surface probe. In addition to the heat transfer model, the researchers also developed a drug delivery model that simulates the kinetics of drug release. It is important to mention that the computed model was validated by performing experimental studies using gel phantoms and *in vivo* fluorescence imaging studies in mice with lung tumor xenografts: by comparing the results of the computer model with the experimental studies, the researchers can assess the accuracy of the model. The results showed that *in silico* modeling accurately reproduces the temperature profile observed in the phantom experiments and that the drug delivery profile simulated by the model also aligns with the results of the in vivo studies. Overall, it demonstrates the feasibility of using a computer model to accurately simulate drug delivery in preclinical studies. (Ramajayam *et al.*, 2020)

To investigate the distribution of three drugs with different polarities (5-fluorouracil, ligustrazine, and osthole) within liposomes and transfersomes, researchers conducted a study using molecular dynamics simulation. To understand the drug distribution, they employed the radial distribution function – which calculates the probability of finding a drug molecule at a specific distance from a reference drug molecule within the vesicle – and the potential of mean force – that describes the potential energy between a drug molecule and the surrounding lipid molecules, indicating the strength of their interactions. By using these measures, the authors were able to characterize the distribution of drugs within the lipid vesicles. The results highlight the potential of molecular simulation technology in understanding the characteristics of lipid vesicles and their interactions with drugs. (Wu *et al.*, 2021)

4.2.3 Nanocrystals

A research study aimed to develop and evaluate an advanced *in silico* modeling for understanding the pharmacokinetics of Foscan®, a formulation containing temoporfin that has received approval for palliative photodynamic therapy of squamous cell carcinoma of the head and neck. The researchers conducted precipitation experiments in the presence of biorelevant media, which means they simulated conditions similar to those found in the human body to observe how Foscan® behaves. When they introduced the drug to these media, they observed that it underwent a process of precipitation, forming nanocrystals. Furthermore, they used nanoparticle tracking analysis to study these nanocrystals, which allowed them to measure the size and analyze the distribution in the sample of these structures. By incorporating the data from these precipitation experiments and nanoparticle tracking analysis, the model predicted how nanocrystals of Foscan® were formed, their size distribution, and how they interacted

with biological fluids in the body. This information could help them explain and predict the Foscan® pharmacokinetics more accurately, as nanocrystals can significantly impact how a drug is absorbed, distributed, and eliminated. (Jablonka *et al.*, 2019)

In another study, to evaluate the impact of polymers in the production of stable dexibuprofen (Dexi) nanocrystals with improved therapeutic potential, researchers combined *in silico* modeling techniques (namely AutoDockVina, Marven Sketch, and Maestro) with experimental studies. The results provided molecular insight into the mechanisms of binding of the optimal polymers to the surface of Dexi nanocrystals, showing that the combination of hydroxypropyl methylcellulose (HPMC)-polyvinyl pyrrolidone (PVP) and HPMC-Eudragit (EUD) was the most effective in stabilizing Dexi nanocrystals. Overall, the combination of computational modeling with experimental studies, allow researchers to save time and resources by focusing on the most promising polymer combinations, thereby expediting the drug development process. Additionally, this integrated approach provides a deeper understanding of the molecular mechanisms underlying the stabilization of nanocrystals, helping researchers make more informed decisions in their pursuit of developing better pharmaceutical formulations. (Ullah *et al.*, 2018)

4.3 Machine learning

4.3.1 Polymeric micelles

Machine learning algorithms can be utilized to predict various properties and behaviors of polymeric micelles. For example, models can be trained using data on the polymer structure, composition, molecular weight, and other relevant parameters, along with experimental outcomes such as micelle size, stability, drug loading, and release profiles. These models can then be used to predict the behavior of new polymeric systems, guiding the design and selection of optimal micellar formulations. (Jones, Ghandehari e Facelli, 2016)

Researchers used an artificial neural network (ANN) to create a model for the release of a chemotherapeutic drug – doxorubicin – from polymeric micelles (specifically Pluronic P105) under two different ultrasound frequencies. Although the exact number of samples used in the study was not explicitly mentioned, the model was trained using experimentally obtained input-output data concerning the release of doxorubicin from the micelles. The developed ANN model was then employed to optimize the application of ultrasound in order to achieve the desired drug release at the tumor site. The ANN method accurately predicted the release behavior and demonstrated maximum prediction errors of 0.002 and 0.001 at ultrasound frequencies of 20 and 70 kHz, respectively. The results demonstrate the successful design and

testing of a controller capable of adjusting the ultrasound frequency, intensity, and pulse length to maintain a constant release of Dox, potentially enhancing targeted drug delivery to tumor sites. (Husseini *et al.*, 2009)

4.3.2 Liposomes/niosomes

By analyzing large datasets of liposomal properties and characteristics, machine learning models can identify patterns and correlations between various liposome components (lipids, encapsulated substances, among others) and their properties (size, stability, drug release profile). This information can guide the selection of optimal liposome compositions and improve formulation success rates. (Han *et al.*, 2023) In addition, ML models can also be trained on existing data to predict important liposomes properties, which may include encapsulation efficiency, drug release kinetics, stability under different conditions, and targeting capabilities. By utilizing historical data and relevant features, machine learning algorithms can provide valuable insights and predictions, enabling more efficient and targeted liposome development. (Kashani-Asadi-Jafari, Aftab e Ghaemmaghami, 2022)

In fact, there are some trials applying machine learning for liposome formulation optimization or prediction. For instance, a study proposed a machine learning framework to address the challenges associated with optimizing the drug entrapment efficiency of niosomal vesicles, showing that these algorithms allow the synthesis of niosomal systems with optimal entrapment efficiency at a lower cost and time. (Kashani-Asadi-Jafari et al., 2022) In another study, scientists have built an artificial neural network (ANN), and advanced machine learning model, to optimize the percentage of cytarabine entrapped in the liposome, showing that ANN provides more accurate prediction formulations when compared with the multiple regression analysis method. (Subramanian, Yajnik e Murthy, 2004) An ANN model was also developed to predict size and polydispersity index of liposomes made of DOPC (1,2 Dioleoyl-sn-glycero-3-phosphocholine), cholesterol, and DSPE-PEG 2000 1,2 Distearoyl-sn-glycero-3-phosphoethanolamine-N [amino (polyethylene glycol)-2000] (ammonium salt)) using a microfluidic system. The results demonstrated that microfluidic-based preparation techniques assisted by computational tools can accelerate the development and clinical translation of nano-based pharmaceutical products. (Rebollo *et al.*, 2022)

Recently, machine learning has been combined with molecular descriptors, which are a set of quantitative values or features that represent various properties of a molecule´s structure, composition, and behavior. These are used to encode complex chemical information into numerical data, which can then be used as input for various computational analysis and machine

learning models. Basically, by learning from patterns in these data, ML models can predict the properties of new molecules without physically synthesizing or testing them. (Baptista *et al.*, 2022) (Han *et al.*, 2023) To illustrate this, an ANN was built to create computational models aimed at optimizing a continuous liposome manufacturing system, where these vehicles were formed using a co-axial turbulent jet in a co-flow technology. This means that two phases were used – an ethanol phase with lipids and an aqueous phase – to create liposomes of uniform sizes. The ANN was used to optimize this manufacturing process and so, it took various input parameters known as critical material attributes (CMAs) and critical process parameters (CPPs). CMAs include characteristics of the raw materials, such as the length of the hydrocarbon tail in lipids, the percentage of cholesterol, and the type of buffer used. CPPs include process conditions, such as solvent temperature and flow rate. The ANN´s purpose was to predict critical quality attributes (CQAs) of the liposomes. In this study, the CQAs were the particle size and polydispersity index (PDI), which indicate how uniform the liposome sizes are. Thereby, two types of ANN architectures were evaluated, namely a Multiple-Input-Multiple-Output (MIMO) model – which take multiple inputs and produce multiple outputs – and a Multiple-Input-Single-Output (MISO) model – which takes multiple inputs but produces a single output (Figure 5A) The study found that the MISO architecture outperformed the MIMO architecture in terms of accuracy for the task at hand. Apart from developing the ANN model, a graphical user interface was also created to help end-users perform interactive simulated risk analysis and visualize the predictions made by the ANN model (Figure 5B). Evaluations demonstrated that the developed graphical user interface yields accurate predictions for both liposome particle size and PDI, as long as the chosen inputs fall within the scope of the studied conditions during the initial ANN training. Such predictions have the potential to support the formulation of a control strategy aimed at mitigating the influence of process disturbances on liposome particle size. Utilizing the five input features mentioned earlier, an ANN was trained with the primary goal of minimizing the Mean Relative Error (MRE), which was successfully achieved at a level below 5%. It was notable a very low error for predicting particle size, as evident from the comparison between the target and predicted values presented in Figure 5C. However, the prediction accuracy for PDI was notably inadequate, as indicated by the results displayed in Figure 5D. Basically, despite the successful predictions for particle size, the model encountered challenges in accurately forecasting PDI values. To mitigate the training error, researchers introduced molecular descriptors as supplementary inputs to the ANN. These were obtained from PaDEL-Descriptor Software and helped the ANN understand the characteristics of the raw materials. The combination of CMAs, CPPs, and molecular descriptors was used to train the MISO ANN model and allowed

for to reduce of errors during both training and testing, indicating improved model performance (Figure 5E) Overall, by using a combination of critical material attributes, process parameters, and molecular descriptors, this study improved the accuracy of predicting the quality attributes of liposomes. (Sansare *et al.*, 2021)

In another study, ML techniques were used to create prediction models capable of individually predict crucial parameters of liposomes, such as size, PDI, zeta potential, and encapsulation efficiency. To validate the predictive prowess of these models, liposome formulations were created for two distinct compounds: naproxen (NAP) and palmatine HCL (PAL), representing insoluble and water-soluble molecules, respectively. Recognizing the significance of drug properties in liposome behavior, further investigation into the molecular interactions and behaviors of NAP and PAL within liposomes was undertaken through coarse-grained molecular dynamics simulations. Figure 6A and 6A1 depict the initial configurations of the two systems, of which ten underwent dynamic simulations lasting 1 microsecond. Snapshots captured during the modeling process are illustrated in Figures 6B and 6B1, while the ultimate structures of the respective liposomes are displayed in Figures 6C and 6C1. Additionally, the size distribution was assessed, and the structures of the liposomes containing NAP and PAL were characterized using transmission electron microscopy, showcased in Figures 6D and 6D1. These simulations unveiled that NAP molecules tend to integrate into the lipid layer, while a majority of PAL molecules aggregate within the inner aqueous phase of the liposome. The marked disparity in the physical states of NAP and PAL underlines the pivotal role of drug properties in formulating liposomes. Additionally, formulation attributes were ranked to offer significant insights for designing effective formulations. Given that logS (logarithm of a compound´s aqueous solubility), molecular complexity (an assessment of the intricacy of a structure), and XLogP3 (represent a predictive estimation of the octanol-water partition coefficient, determined through a specific algorithm) of the drug molecules held significant influence over encapsulation efficiency, their correlation was illustrated using a heatmap, depicted in Figure 6B. This heatmap employed color visualization in a two-dimensional format to depict the data relationship effectively. Basically, drug molecules with certain properties, such as a logS value between -3 and -6, a molecular complexity between 500 and 1000, and a XLogP3 value greater than or equal to 2, are considered a priority for formulating liposomes with better encapsulation. Finally, in Figure 6C it is possible to verify a congruence between predicted and experimental outcomes, which serves as confirmation of the ML models ´s satisfactory accuracy. In summary, the researchers established comprehensive prediction models for anticipating liposome formulations, and the influences of key factors were dissected

by combining ML techniques with molecular modeling. The study successfully validates the availability and rationality of these intelligent prediction systems, offering promising applications for the future development of liposome formulations. (Han *et al.*, 2023)

Based on all of that, it is safe to say that machine learning plays a valuable role in the development of liposomes by assisting in formulation design, predicting liposome properties, optimizing drug loading and release, analyzing characterization data, and optimizing manufacturing processes. By leveraging machine learning techniques, researchers can expedite the development and improve the performance of liposomal formulations for drug delivery and other biomedical applications. (Rathore *et al.*, 2023)

4.3.3 Nanocrystals

Machine learning techniques have been increasingly employed in the field of nanocrystals development. For instance, it can be trained to predict the properties of nanocrystals, by using data from a variety of sources, including experimental measurements, theoretical calculations, and molecular descriptors. These predictive models can assist in the design and selection of nanocrystals with desired properties, saving time and resources by reducing the need for extensive experimental testing. In fact, to address this issue, researchers collected data on nanocrystal size (910 data points) and polymer dispersity index (341 data points) using three different preparation methods – ball wet milling (BWM) method, high-pressure homogenization (HPH) method, and antisolvent precipitation (ASP) method –, in order to construct prediction models. The results indicated that the machine learning performed well in predicting those properties for BWM and HPH methods but showed relatively poor predictions for the ASP method. The researchers speculated that the poor prediction for the ASP method might be due to the lower quality of data resulting from the poor reproducibility and instability of nanocrystals prepared using this method. They also found that the majority of commercialized nanocrystals products were manufactured using BWM and HPH approaches. ML helped rank the factors influencing nanocrystal properties, indicating that milling time, cycle index, and stabilizer concentration were crucial factors for nanocrystals prepared by BWM, HPH, and ASP methods, respectively. The accuracy of these predictions was further confirmed by experiments with newly prepared nanocrystals. Overall, the results demonstrate that ML can be successfully utilized for predicting nanocrystals properties when prepared using BWM and HPH methods. It also highlights the potential of using machine learning in nanotechnology manufacturing, providing a promising alternative to the traditional, labor-intensive approaches in nanocrystals formulation development. (He *et al.*, 2020)

4 Regulatory issues

Regulatory agencies, including FDA, believe that the incorporation of computational methods into the field of pharmaceutics can enhance product quality. By using these methods, a deeper understanding of the process involved in product design is achieved, aligning with the principles of QbD. (Wang *et al.*, 2021) In fact, FDA has been moving towards performance-based regulation, focusing on measurable outcomes rather than prescriptive processes, which aligns well with Pharma 4.0 and its extensive data capabilities. (Arden *et al.*, 2021)

To attain Pharma 4.0, it is essential to embrace cutting-edge manufacturing technologies while simultaneously surmounting regulatory obstacles. (Saha *et al.*, 2022) For instance, initially, there was a noticeable absence of a well-defined regulatory framework to assist innovators in integrating digital technologies and traditional processes persisted due to the lack of regulatory precedents. However, more recently, significant strides have been taken in this direction. In particular, FDA has taken a proactive step by establishing the Digital Health Center of Excellence, aiming to adopt a comprehensive approach to digital health technology. (Trenfield *et al.*, 2022)

Moreover, filing regulatory applications across different jurisdictions with varying expectations can be burdensome, particularly for emerging manufacturing technologies. Achieving international regulatory convergence could provide clarity and certainty for manufacturers. Besides, the industry may simultaneously comprise companies operating under Pharma 2.0, 3.0, and 4.0 paradigms. Regulating such a diverse landscape requires flexible frameworks to enable the adoption of new technologies without disrupting supply from older technology-based manufacturers. (Arden *et al.*, 2021)

It is important to notice that, to this day, FDA has already approved several 3D printed products, which encompass not only drug products – such as Spritam® – but also – and essentially – a diverse range of medical devices, that include orthodontic implants, prosthetics, anatomical models, and reaction-wares. (Pravin e Sudhir, 2018) In December 2017, FDA released a guidance titled "Technical Considerations for Additive Manufactured Medical Devices", which provides guidelines covering various aspects, including software and hardware requirements, quality control, and process validation procedures. However, considering the complexity of medicinal products, which often have more demanding requirements than medical devices, separate regulatory considerations are needed. APIs present additional challenges, such as potential incompatibilities and the stability of the active substance during the printing process. (Bom *et al.*, 2021)

Nonetheless, due to the variability of additive manufacturing methods, it is challenging to devise a universal set of guidelines applicable to all 3D printing techniques. The truth is that, given the multitude of factors influencing the quality of computationally designed dosage forms and the safety of their use, the establishment of appropriate regulatory requirements is of utmost importance. However, currently, there are no valid regulations pertaining to the design, manufacturing process, and quality testing considerations specific to three-dimensional printing in the pharmaceutical industry. (Jamróz *et al.*, 2018) Recently, it has been emphasized that 3D printing, as a manufacturing process, does not pose regulatory limitations as long as the final product meets the established requirements. For instance, the previously mentioned approved 3D printed tablet, Spritam®, includes the same excipients that are found in conventional tablets. The only difference lies in the production process. Consequently, it is reasonable to assume that similar quality requirements apply in this case as they do for other orally disintegrating tablets. (Preis e Öblom, 2017)

Overall, as the pharmaceutical industry is transitioning into Pharma 4.0 era, regulatory agencies are exploring ways to adapt and accommodate the advancements brought by these new technologies. (Trenfield *et al.*, 2022)

5 Future Prospects

Pharma 4.0 technologies have demonstrated significant promise in the manufacturing of NBCDs. The integration of advanced digital techniques, automation, and data analytics in the pharmaceutical industry has the potential to optimize processes, enhance quality control, enable customization, and improve supply chain efficiency, ultimately leading to improved production and delivery of NBCDS.

However, there is still much potential for further development and some areas where ongoing work and future efforts can be focused. For instance, these technologies can extend to various other NBCDs, such as glatiramer acetate and iron carbohydrate complexes as, to the best of our knowledge, there are no experimental studies available that access the impact of pharma 4.0 in these NBCDs. Is also expected to assist in the implementation of digital twins to simulate and optimize NBCDs manufacturing. By integrating real-time data from sensors and process models, digital twins can enable virtual testing, scenario analysis, and optimization of manufacturing operations to enhance productivity and efficiency. It is important to take into consideration that as the implementation of Pharma 4.0 techniques progresses, regulatory frameworks need to evolve to accommodate the use of advanced technologies in NBCDs manufacturing. This includes addressing data security and privacy concerns, establishing

guidelines for the validation and qualification of digital systems, and ensuring compliance with evolving regulatory requirements.

In addition, is also important to keep in mind that the implementation of Pharma 4.0 principles and technologies implies a reevaluation and readjustment of economic policies, a legal framework, and the establishment of financial stability to accommodate these emerging techniques. This also calls for a transformation in the academic curriculum to facilitate the acquisition of necessary skills, upskill the workforce, and foster system-wide awareness. (Inuwa *et al.*, 2022)

Overall, the future prospects of Pharma 4.0 in the manufacturing of NBCDs are very promising. The implementation of advanced digital technologies and data-driven approaches can optimize processes, improve quality assurance, enhance customization capabilities, and streamline supply chains, ultimately leading to more efficient and effective manufacturing of NBCDs.

While the concept of Pharma 4.0 continues to grow and its techniques are being slowly applied, there is an ongoing discussion about the potential evolution of the pharmaceutical industry beyond the current Pharma 4.0 framework. In fact, the term Pharma 5.0 has already been mentioned. It represents a possible future stage in which the integration of advanced technologies and data-driven approaches in the pharmaceutical sector goes even further, so the future prospects are very ambitious, considering the potential of these tools, but also a challenge, in particular for the regulatory follow-up that will have to be given in this context.

6 Conclusion

Pharma 4.0 brings significant alterations in the field of pharmaceutical manufacturing. Through the utilization of cutting-edge technologies such as 3D printing, *in silico* modeling, and machine learning, Pharma 4.0 enables improved process efficiency, enhanced product quality, and greater regulatory compliance.

Concerning Non-Biological Complex Drugs manufacturing, Pharma 4.0 tools allow for enhanced overall production efficiency by streamlining operations and reducing production time, ultimately leading to cost savings. Additionally, the increased automation and use of real-time data analytics have improved process monitoring and control, minimized the risk of errors, and ensured a higher level of product quality and consistency. Furthermore, the integration of artificial intelligence and machine learning algorithms has also accelerated drug

development and formulation processes, leading to a more personalized and precise approach to healthcare.

However, despite the remarkable progress made, it is important to acknowledge the challenges associated with the adoption of these technologies, such as the need for skilled personnel capable of operating and maintaining advanced technologies, ensuring data security and privacy, and addressing regulatory concerns regarding the validation and qualification of these novel manufacturing processes. Overall, it is safe to say that the implementation of Pharma 4.0 technologies in the manufacturing of NBCDs represents a transformative approach and a paradigm shift in the pharmaceutical industry. As we move forward, continuous research and innovation will pave the way for a more sustainable and patient-focused pharmaceutical landscape.

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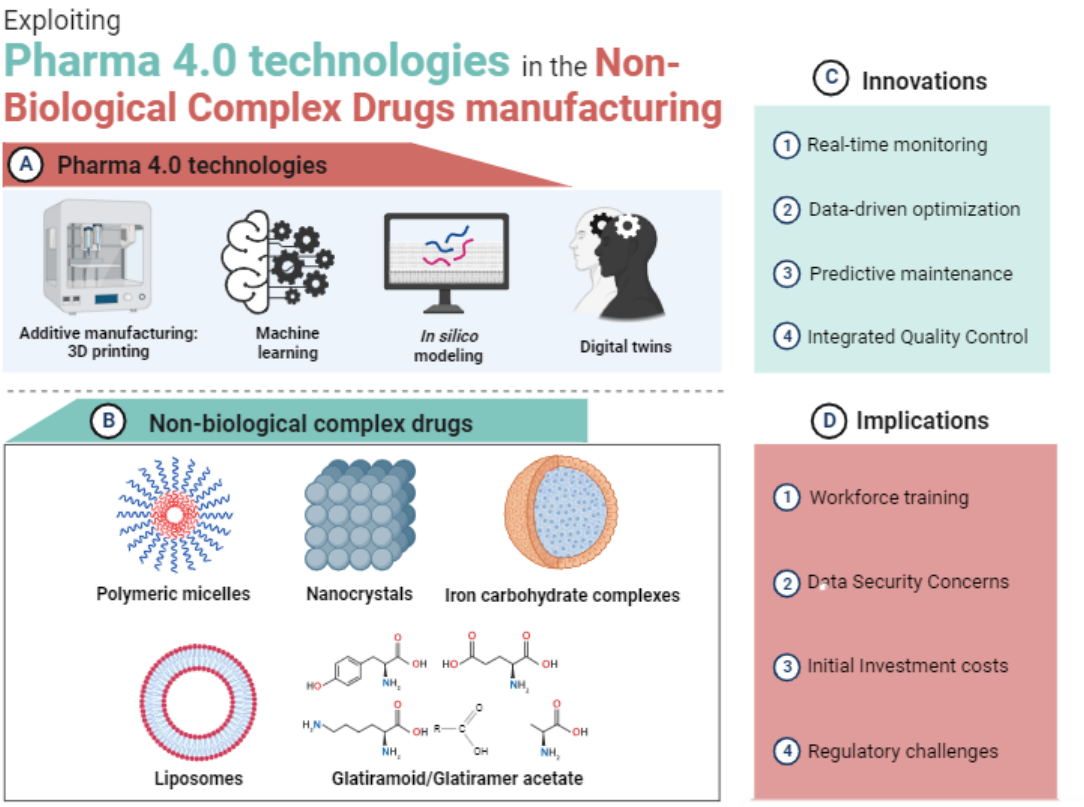
8 Annexes

Graphical Abstract



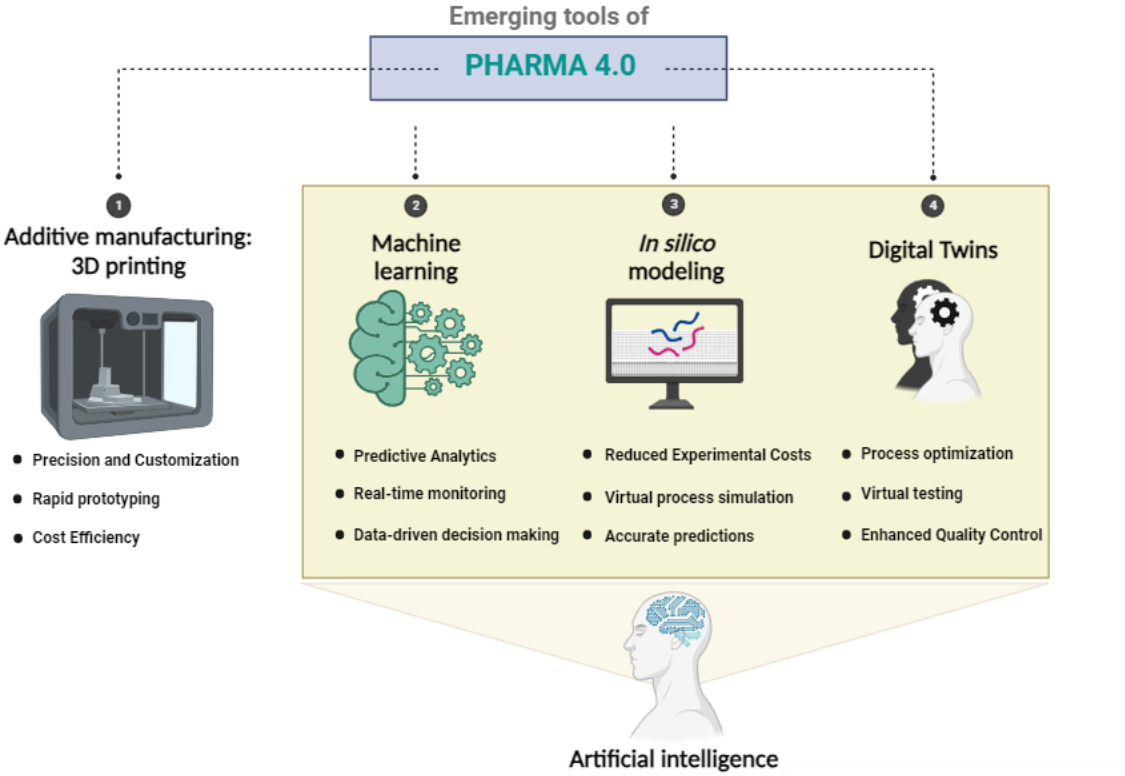


Figure 1- Emerging tools of Pharma 4.0 and their main advantages in Drug manufacturing.

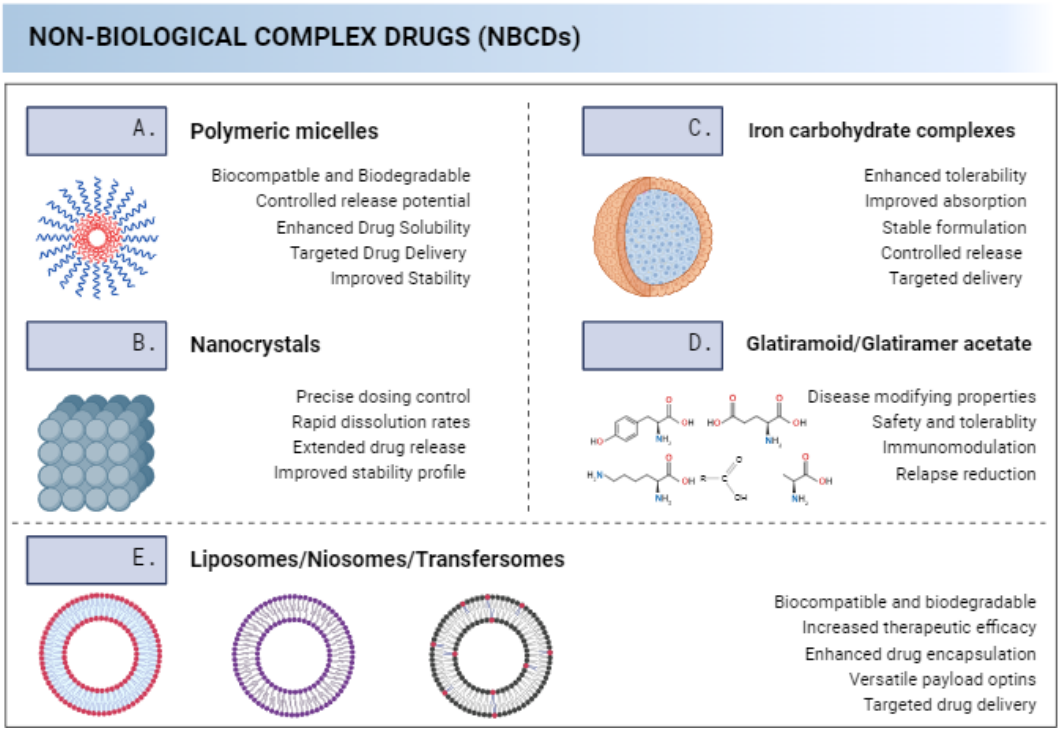


Figure 2 - Illustrative depiction of Non-Biological Complex Drugs (NBCDs) and description of their main technological advantages.

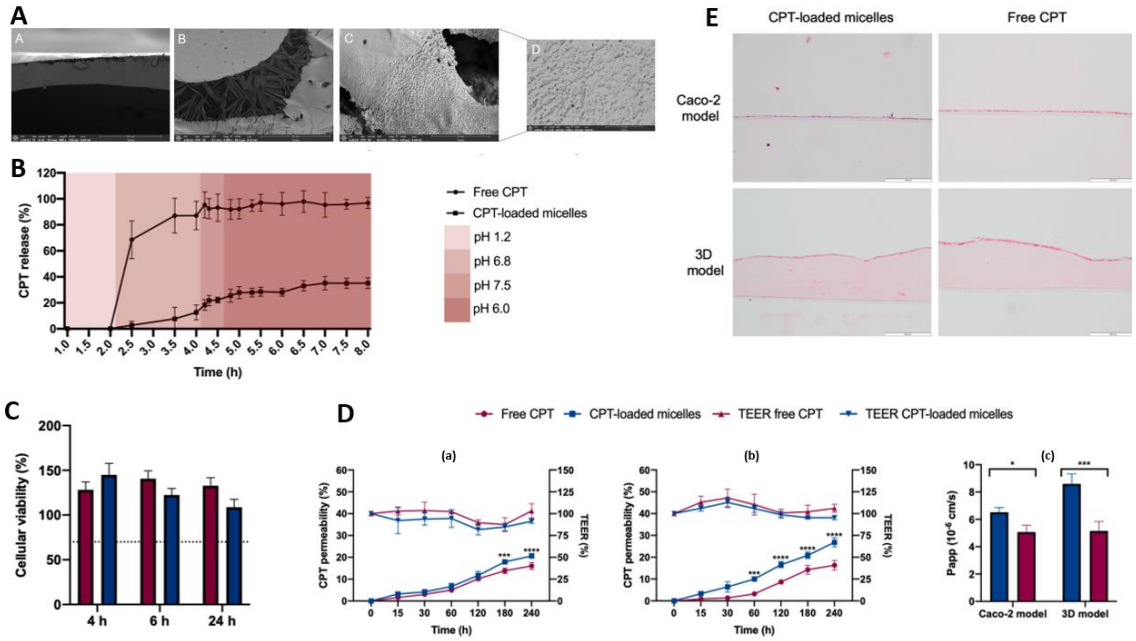


Figure 3 - (A) Images obtained through scanning electron microscopy of (A) top layer of Eudragit in the printfills, (B) CPT crystals within the printfills, (C) micelles loaded with CPT inside of the printfills and (D) magnified polymeric micelles inside the printfills; (B) Cumulative release of CPT from the printfills in simulated gastrointestinal fluids. The release of CPT-loaded micelles is depicted by squares, while the release of free CPT is indicated by circles; (C) The cell viability of the dissolution medium sourced from the printfills containing CPT-loaded micelles (depicted by blue columns) and free CPT (illustrated by pink columns) was assessed following 4,6 and 24 hours of incubation with Caco-2 cells; (D) Intestinal permeability and respective TEER values of CPT across a standard Caco-2 cell model (a) and across a 3D intestinal model (b) and apparent permeability coefficients of CPT-loaded micelles (blue) and free CPT (pink) in both Caco-2 monoculture model and the 3D model; (E) H&E staining to assess cellular integrity following exposure to the dissolution medium containing CPT-loaded micelles and free CPT during permeability assay. The cytoplasm was stained in pink, while the nucleus was

stained in purple. The transwell membrane, positioned just beneath the cellular monolayer, remains transparent. (Almeida *et al.*, 2021)

CPT: camptothecin**; H&E:** hematoxylin, and eosin**; TEER:** transepithelial electrical resistance

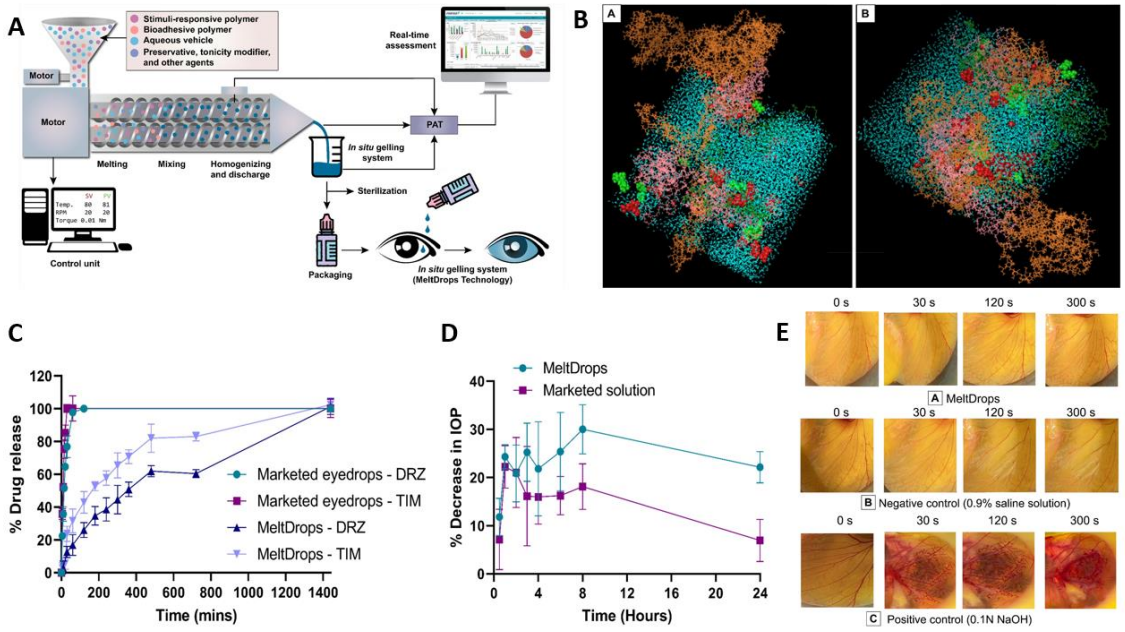


Figure 4 - (A) Schematic depiction of the ISGS manufacturing process through the MeltDrops technology; (B) Molecular interactions forming between the components of the formulation at two different temperatures: 300 K (A) and 308 K (B); (C) Cumulative release of timolol maleate (TIM) and dorzolamide hydrochloride (DRZ) over time from both MeltDrops and commercially available solutions; (D) Percentage decrease in IOP following the administration of MeltDrops and conventional marketed eyedrops; (E) HET-CAM test results after the application of (A) MeltDrops with no signs of irritation, (B) 0.9% w/v saline solutions, also showing no signs of irritation, and (C) 0.1N Sodium Hydroxide solution, revealing features like vascular lysis, coagulation, and hemorrhage. (Tambe *et al.*, 2023)

DRZ: dorzolamide hydrochloride; **IOP:** intraocular pressure; **ISGS:** in situ gelling system**; TIM:** timolol maleate**.**

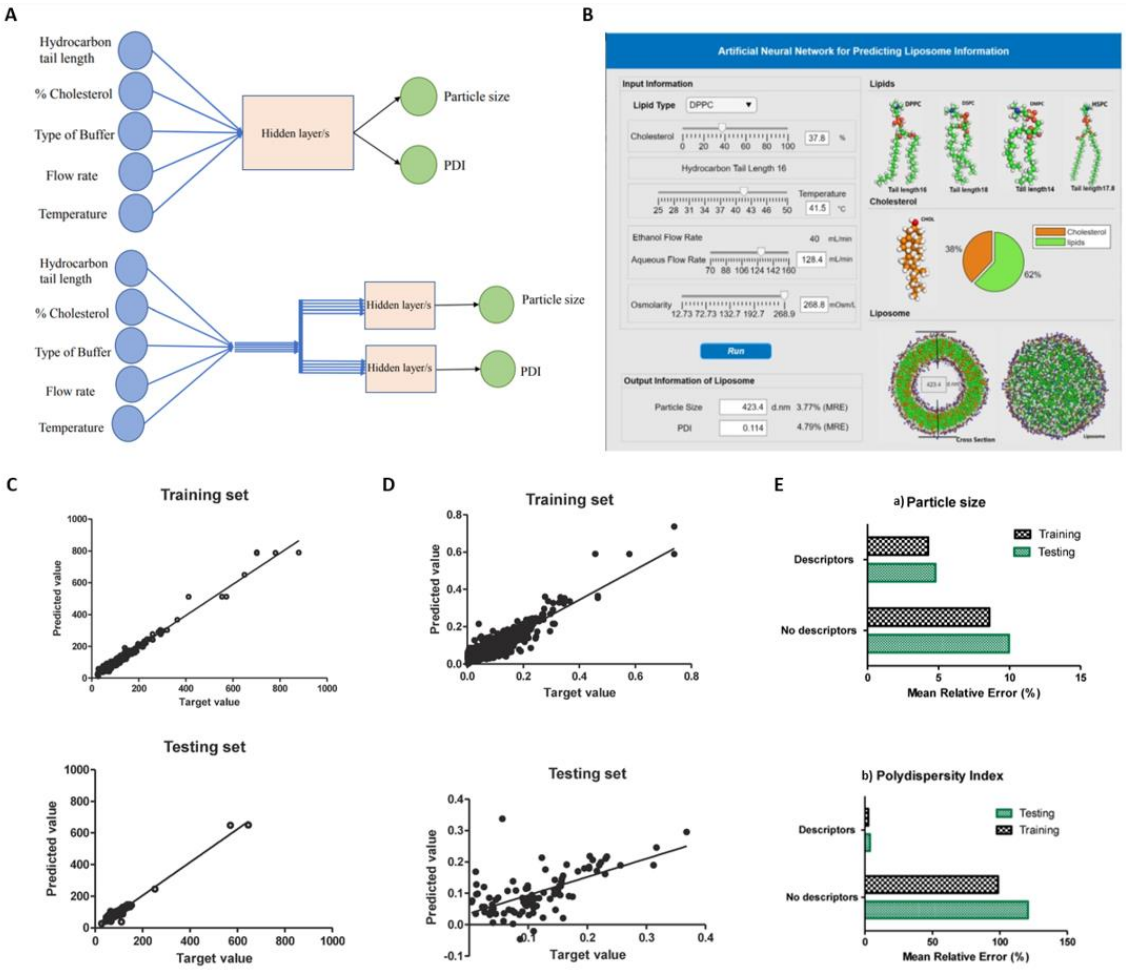


Figure 5 - (A) Comparative illustration of MIMO model (a) and MISO model (b); (B) Graphical user interface of the ANN for liposome particle size and PDI prediction in continuous liposome manufacturing; (C) Comparison of predicted vs. target values for liposome particle size in the training and testing sets, without molecular descriptors; (D) Comparison of predicted vs. target values for liposome PDI in the training and testing sets, without molecular descriptors; (E) Evaluation of MRE with and without incorporating molecular descriptors in the ANN input: (a) particle size and (b) PDI. (Sansare *et al.*, 2021)

ANN: Artificial neural network; **MIMO:** Multiple-Input-Multiple-Output**; MISO:** Multiple-Input-Single-Output**; PDI:** polydispersity index**; MRE:** Mean Relative Error

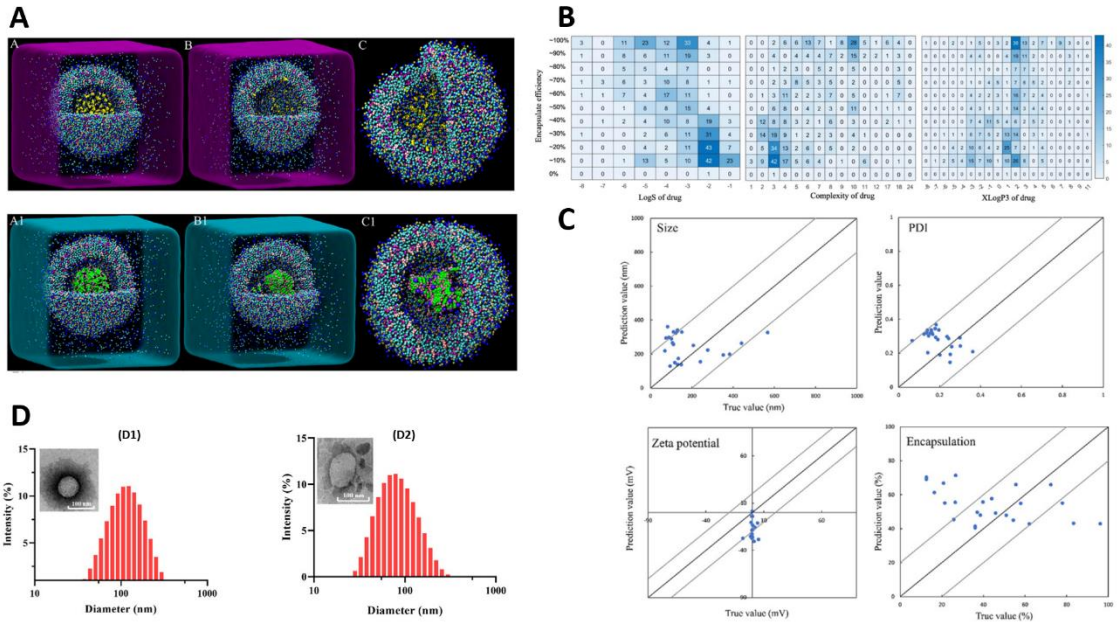


Figure 6 - A) Snapshots captured during 1 microsecond of molecular dynamics simulations, alongside the experimental size distribution of NAP liposomes (A, B, C, and D) and PAL liposomes (A1, B1, C1 and D1); (B) Heat map assessment illustrating the connection between logS, molecular complexity, and XLogP3 of the drug with encapsulation within liposomes. The numerical values within each matrix indicate the frequency of encapsulation occurrences corresponding to each specific property; (C) A scatter plot displaying the comparison between experimental and predicted values for size, PDI, zeta potential, and encapsulation.

NAP: naproxen; **PAL:** palmatine HCL; **PDI:** polydispersity index.