UNIVERSIDADE D
COIMBRA

Henrique Rodrigues Franco Mendes

Relatórios de Estágio e Monografia intitulada "*Nanomedicine: Applications and current challenges in pediatrics*" referentes à Unidade Curricular "Estágio", sob a orientação do Dr. André Paiva, da Dra. Mariana Rocha e da Professora Doutora Ana Rita Figueiras, apresentados à Faculdade de Farmácia da Universidade de Coimbra, para apreciação na prestação de provas públicas de Mestrado Integrado em Ciências Farmacêuticas.

Setembro de 2021

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Declaração de Autoria

Eu, Henrique Rodrigues Franco Mendes, estudante do Mestrado Integrado em Ciências Farmacêuticas, com o n.º 2016234018, declaro assumir toda a responsabilidade pelo conteúdo do Documento Relatórios de Estágio e Monografia intitulada "*Nanomedicine: Applications and current challenges in pediatrics*" apresentados à Faculdade de Farmácia da Universidade de Coimbra, no âmbito da unidade de Estágio Curricular.

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Coimbra, 15 de setembro de 2021.

Henrique Rodrigues Franco Mendes

(Henrique Rodrigues Franco Mendes)

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A todos vós, obrigado.

Contents

PARTE I

RELATÓRIO DE ESTÁGIO EM FARMÁCIA COMUNITÁRIA

LISTA DE ABREVIATURAS E ACRÓNIMOS

FE: Farmácia Estádio

MICF: Mestrado Integrado em Ciências Farmacêuticas

MM: Medicamento manipulado

TRAg: Testes rápidos de antigénio

INTRODUÇÃO

No âmbito do plano de estudos do Mestrado Integrado em Ciências Farmacêuticas (MICF) realizei o meu segundo estágio curricular em farmácia comunitária na Farmácia Estádio (FE) sob a orientação do Dr. André Paiva.

A farmácia comunitária é a área profissional com o maior número de farmacêuticos [1] e a sua importância na sociedade é incontestável. É a "cara" do setor farmacêutico perante a população, tendo um papel fundamental na prestação de cuidados de saúde. Por este motivo, a realização de um estágio em farmácia comunitária torna-se essencial e também uma excelente oportunidade para a minha formação enquanto futuro farmacêutico.

Os motivos que me levaram a escolher a FE para a realização do meu estágio foram vários, o *feedback* positivo por parte de anos anteriores, a localização e por ser uma farmácia bastante equipada. Muitos destes motivos vão ser aprofundados e fundamentados ao longo deste relatório.

O presente relatório vai descrever, na forma de uma análise SWOT, aspetos pertinentes do meu estágio curricular na FE, que decorreu de 12/04/2021 a 13/08/2021.

ANÁLISE SWOT

A análise SWOT é uma técnica de planeamento estratégico e irá servir para analisar e realçar pontos importantes do meu estágio curricular na FE que influenciaram, de uma forma positiva ou negativa, a realização do mesmo. Os pontos destacados estão divididos em Pontos Fortes (*Strenghts*), Pontos Fracos (*Weaknesses*), Oportunidades (*Opportunities*) e Ameaças (*Threats*).

***Figura 1*:** Análise SWOT referente ao Estágio em Farmácia Comunitária.

1. PONTOS FORTES

1.1. Equipa

A FE possui uma equipa constituída por cinco farmacêuticos, uma técnica de farmácia, duas técnicas auxiliares de farmácia e um caixeiro sobre a coordenação técnica da Dra. Ana Isabel Rebelo. É uma equipa jovem, dinâmica, trabalhadora, e profissional, exibindo um nível exemplar de responsabilidade e dedicação para a profissão. A equipa da FE contribuiu bastante para o meu estágio curricular, uma vez que sempre se mostraram disponíveis para ajudar com qualquer questão ou dificuldade que sentisse, tendo tido um papel muito importante para a minha formação enquanto futuro profissional de saúde.

1.2. Localização

A FE encontra-se localizada no edifício do estádio municipal Cidade de Coimbra, partilhando o mesmo com o centro comercial Alma Shopping. É uma zona da cidade bastante movimentada e com diversas clínicas nas proximidades, por este motivo, tem uma boa afluência de utentes, bastante diversificados, de todas as faixas etárias e com necessidades variadas. Esta diversificação contribuiu bastante para o meu estágio na medida em que tive a oportunidade de contactar com várias situações distintas durante o atendimento ao público, pondo à prova as minhas competências e contribuindo para fomentar bastante o conhecimento adquirido ao longo do curso do MICF.

1.3. Preparação Individualizada da Medicação

Segundo a norma geral da Preparação Individualizada da Medicação (PIM), esta define-se como o "serviço a partir do qual o farmacêutico organiza as formas farmacêuticas sólidas, para uso oral, de acordo com a posologia prescrita, por exemplo, em um dispositivo de múltiplos compartimentos (ou em fita organizada por toma em alvéolos), selado de forma estanque na farmácia e descartado após a sua utilização" [2]. A FE realiza a PIM para alguns utentes e para diversas instituições da zona de Coimbra. Tive a oportunidade de poder auxiliar em várias fases desse processo, na reposição da medicação, na verificação da mesma, e também na entrega a instituições e utentes. Considero uma mais-valia para o meu estágio, pelo que pude compreender a importância deste serviço e ter uma participação ativa no mesmo.

1.4. Serviços Farmacêuticos

As farmácias não servem apenas para dispensar medicamentos aos utentes, tendo a capacidade e responsabilidade de ter um papel ativo na sua saúde. Os serviços farmacêuticos

consistem em serviços prestados aos utentes, pela farmácia, com o objetivo de promover a saúde e bem-estar dos mesmos. Serviços estes podem ser apoio domiciliário, administração de primeiros socorros, medicamentos e vacinas, entre outros [3], [4]. A FE dispõe ao serviço dos seus utentes os seguintes serviços: avaliação da glicémia, colesterol, triglicerídeos e pressão arterial, teste rápido de antigénio (TRAg) para deteção de infeção por SARS-CoV-2, pesquisa de anticorpos para o SARS-CoV-2, consultas de nutrição e podologia, e preparação individualizada da medicação. Tive a oportunidade de realizar, ou pelo menos ter uma intervenção ativa, em todos estes serviços. Considero que foi um ponto forte do meu estágio na medida em que, me permitiu não só ter uma maior intervenção e proximidade para com o utente, mas também desenvolver competências que irão ser importantes para o meu futuro papel como farmacêutico.

2. PONTOS FRACOS

2.1. Erros e faltas de Stock

Algo com que me deparei várias vezes durante o atendimento ao público foram discrepâncias entre o *stock* informático e o *stock* real dos produtos da farmácia. Estas discrepâncias podiam ter várias causas, nomeadamente, erros no atendimento, na receção de encomendas, nas reservas ou até devido à falta de espaço no *robot*. Isto originava situações um pouco difíceis, na medida em que demorava demasiado tempo do atendimento à procura um certo produto para depois ter que informar o utente que afinal não o tínhamos na farmácia.

Outro problema relacionado com os *stocks* da farmácia e que considero que tenha afetado negativamente o meu estágio foi a frequência de faltas de *stock*. Em muitas ocasiões o *stock* da farmácia não correspondia aos produtos solicitados pelos utentes, não só de certos laboratórios de medicamentos sujeitos a receita médica, mas também de produtos de venda livre. A consequência disto foi a frequência de atendimentos em que era necessário encomendar um certo produto, fazendo com que o utente tivesse que voltar à farmácia para o levantar, o que levava a algumas queixas por parte dos mesmos e, em alguns casos, a que desistissem do atendimento por terem alguma urgência na aquisição do produto.

Em suma, considero estes dois pontos fraquezas do meu estágio, uma vez que tiveram uma influência significativa na perceção dos utentes, pondo em causa a competência e profissionalismo do atendimento.

2.2. Diferenciação dos Estagiários

Os estagiários da FE utilizam uma bata de cor diferente (verde) dos restantes elementos da equipa. Esta diferenciação serve para informar o utente que está perante uma pessoa em formação, de modo a que estes sejam mais compreensivos a possíveis falhas, sem prejudicar o estagiário ou a farmácia. Enquanto na teoria considero que a diferenciação tenha um bom propósito, na prática o que acabava por acontecer era, ocasionalmente, o utente recusar-se a ser atendido por alguém com uma bata verde e, mesmo quando eram atendidos, muito mais facilmente desvalorizavam o aconselhamento do estagiário, tornando o atendimento muito mais difícil. Portanto, considero que este ponto tenha afetado consideravelmente o meu estágio curricular.

2.3. Elevado Número de Estagiários

Durante o primeiro mês do meu estágio houve uma sobreposição dos estagiários do primeiro turno com os do segundo, resultando num total de seis estagiários em simultâneo na farmácia. Enquanto numa fase inicial considero que tenha sido algo positivo visto que ainda era inexperiente e precisava de apoio em muitas tarefas, assim que comecei a ter autonomia revelou-se um obstáculo à minha formação, na medida em que o número de tarefas a realizar não chegava para o número elevado de estagiários.

2.4. Medicamentos Manipulados

Segundo a Portaria n.º 594/2004, um medicamento manipulado (MM) define-se como *"qualquer fórmula magistral ou preparado oficinal preparado e dispensado sob a responsabilidade de um farmacêutico"*. A preparação de MMs, embora não seja muito frequente, tem uma elevada importância no ajuste da terapêutica dos utentes, permitindo a preparação de dosagens ou formas farmacêuticas que não existem no mercado. A FE possui um laboratório bastante equipado para a realização de manipulados, tendo uma procura significativa dos mesmos por parte dos utentes. No entanto, devido ao elevado movimento da farmácia, não tive oportunidade de poder participar na preparação de MM e considero que teria sido enriquecedor para a minha formação.

3. OPORTUNIDADES

3.1. Participação em formações

De modo a garantir uma prestação de cuidados de saúde sempre atualizada e que os utentes recebam sempre o maior benefício possível dos seus tratamentos, é necessário

garantir um desenvolvimento constante dos conhecimentos e da prática farmacêutica. Na prática isto é feito através de formações, sejam estas em eventos ou na própria farmácia. Durante o meu estágio tive a oportunidade de participar em algumas formações, embora que em número reduzido. Estas tiveram um grande impacto no meu atendimento ao longo dos meses que passei na FE, e permitiram expandir o meu conhecimento dos produtos que aconselhava aos utentes, levando a um aconselhamento muito mais completo, factual e seguro.

3.2. Sifarma

O SIFARMA® é uma ferramenta de gestão e atendimento das farmácias comunitárias desenvolvida pela GIlint®. É um sistema que permite às farmácias fazer a gestão de *stocks* e de encomendas e também auxiliar no processo de atendimento ao público, permitindo um atendimento mais fluído, eficiente e completo. De todas as farmácias comunitárias em Portugal, cerca de 90% utilizam o SIFARMA® [5]. É uma ferramenta bastante difusa nas farmácias de Portugal, sendo, portanto, essencial aprender a trabalhar com a mesma e conhecer em todas as suas funcionalidades. A FE utiliza o SIFARMA 2000® para a receção de encomendas, gestão de *stocks* e para algumas funcionalidades que apenas são possíveis nesta versão, utilizando o novo módulo para o atendimento ao público. Considero que a utilização do SIFARMA 2000® e do novo módulo de atendimento, foi uma excelente oportunidade para a minha formação, tendo em conta que não teria contactado com este sistema, não fosse pelo estágio curricular, e que as minhas capacidades referentes à utilização deste *software* ficaram bastante enriquecidas e completas.

3.3. Diversidade dos atendimentos

Uma das características do trabalho em farmácia comunitária é a diversidade de atendimentos e situações com que nos podemos deparar. Podem-nos aparecer queixas, por parte dos utentes, relacionadas com qualquer área da saúde, e, como profissionais de saúde, temos que estar preparados para lidar com qualquer tipo de situação. Durante o meu estágio na FE deparei-me com casos bastante distintos, com os quais não tinha tido nem formação, nem preparação prévia, tendo, portanto, que pedir a um colega para me auxiliar. Este tipo de situações foram uma excelente oportunidade para aprender como lidar com cada caso específico de modo a, mais tarde, poder aplicar em atendimentos futuros.

3.4. Contacto com outros Profissionais de Saúde

A saúde engloba várias componentes, com diversas áreas e diferentes profissionais de saúde, nomeadamente médicos, farmacêuticos, enfermeiros, psicólogos, nutricionistas,

fisioterapeutas, entre outros. Levando à necessidade de uma multidisciplinaridade na terapêutica do doente, sendo que, quanto maior for a capacidade de comunicação e cooperação entre profissionais de saúde, melhor será o cuidado e a qualidade no tratamento do utente. Ao longo do meu estágio foi necessário, por diversos motivos, contactar com outros profissionais de saúde e considero que tenha sido uma experiência enriquecedora, pelo que me ajudou a abrir os horizontes na importância desta matéria e a desenvolver competências neste tipo de comunicação.

4. AMEAÇAS

4.1. Situação Pandémica SARS-CoV-2

Um dos fatores que mais influenciou o meu estágio curricular na FE foi a situação pandémica atual devido ao vírus SARS-CoV-2, por diversos motivos. Nomeadamente a realização de testes rápidos de antigénio, a utilização de máscaras e redução da frequência de formações.

A FE realiza, nas suas instalações, os TRAg para rastreio de infeção por SARS-CoV-2. Numa primeira análise, posso considerar a participação em todas as fases deste processo, à exceção da realização do teste em si, um aspeto positivo por me permitir aprender e trabalhar em algo diferente, podendo assim contribuir para o rastreio da população e ter um papel ativo conta a propagação do vírus. No entanto, considero uma ameaça à minha formação no sentido em que a realização do pré-registo, comunicação e emissão do certificado de testagem eram tarefas morosas, sendo que a realização das mesmas me impedia de realizar outras tarefas mais importantes para a minha formação enquanto futuro farmacêutico, nomeadamente o atendimento ao público. Para além disso, a realização dos TRAg, acrescentado às funções normais de uma farmácia comunitária, levou a uma carga de trabalho bastante exaustiva de toda a equipa.

Outro fator foi a utilização da máscara nos atendimentos, não só da minha parte, mas também por parte dos utentes. Levou não só, em certos utentes, a problemas de comunicação, mas também a uma diminuição de proximidade para com os mesmos, pelo que a ocultação das expressões faciais criava uma "barreira", tornando todo o contacto com os utentes muito mais impessoal.

Por último, devido às restrições atuais, e por muitas indústrias estarem em teletrabalho, notou-se uma diminuição do número de formações e, como referi anteriormente, estas são essenciais para o desenvolvimento profissional, sendo especialmente importantes para os estagiários.

4.2. Não realização de um estágio de verão

Um dos maiores obstáculos que senti durante as primeiras semanas do estágio e durante os primeiros atendimentos foi o facto de não ter realizado um estágio de verão em farmácia comunitária. Embora tenha um boa e rápida capacidade de aprendizagem, considero que o estágio de verão teria sido benéfico para compreender melhor a realidade e contexto do trabalho numa farmácia.

4.3. Plano de estudos do MICF

O plano de estudos do MICF da Faculdade de Farmácia da Universidade de Coimbra é bastante diversificado, e completo para algumas áreas da atividade farmacêutica, no entanto, considero a farmácia comunitária uma área negligenciada em certos aspetos. Os conhecimentos adquiridos durante o curso, em pouco me prepararam para os casos com que me deparei durante o atendimento. Embora considere que muitos dos conhecimentos necessários para a prática farmacêutica numa farmácia só conseguem ser realmente interiorizados na prática, e reconheça que o estágio curricular faça parte do plano de estudos do MICF, existem certas lacunas que poderiam ser preenchidas com aprendizagem teórica mais enquadrada na realidade, nomeadamente nos produtos veterinários e dermocosméticos.

CONCLUSÃO

A realização do meu estágio curricular na farmácia estádio foi, sem dúvida, uma experiência muito enriquecedora, não só a nível profissional, mas também a nível pessoal. Correspondeu, de uma forma positiva, às minhas expetativas, e ajudou-me a desenvolver várias competências, principalmente a responsabilidade, proatividade, autonomia e comunicação necessárias para o exercer da prática profissional. Ajudou a cultivar, de uma forma prática, muitos dos conhecimentos adquiridos durante o MICF, como também a capacidade de lidar com situações de elevada carga de trabalho e *stress*.

Resta-me então agradecer a toda a equipa da FE pela oportunidade, pela preocupação para com a minha formação, pela assistência sempre que precisa e por contribuírem bastante para o meu desenvolvimento profissional.

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PARTE II

RELATÓRIO DE ESTÁGIO EM INDÚSTRIA FARMACÊUTICA

LISTA DE ABREVIATURAS E ACRÓNIMOS

AR: Assuntos Regulamentares

FV: Farmacovigilância

M&SA: Medical & Scientific Affairs

MICF: Mestrado Integrado em Ciências Farmacêuticas

INTRODUÇÃO

No âmbito do plano curricular do Mestrado Integrado em Ciências Farmacêuticas (MICF) realizei o meu estágio curricular em indústria na Owlpharma – *Consulting, LDA.* sob a orientação da Dra. Mariana Rocha. A Owlpharma é uma consultora farmacêutica com departamentos em assuntos regulamentares (AR), farmacovigilância (FV), garantia de qualidade, e *medical & scientific affairs* (M&SA) [1]. Fui inserido no departamento de FV e, ocasionalmente, tive a oportunidade de trabalhar com o com o departamento de M&SA.

Decidi realizar o meu primeiro estágio curricular (sendo o segundo em farmácia comunitária) em indústria por ser uma área bastante complexa e diversificada, com a qual não temos muito contacto direto durante os cinco anos do MICF, sendo este contacto principalmente de uma forma teórica, e, portanto, este estágio é uma excelente oportunidade para uma experiência prática nas diversas áreas de indústria farmacêutica. Escolhi a Owlpharma devido ao meu interesse pelas áreas de AR e FV, gerado pelo contacto com as cadeiras de Assuntos Regulamentares do Medicamento/Gestão de Processos Regulamentares e Farmacovigilância e Farmacoepidemiologia, respetivamente.

Considero que tenha sido uma oportunidade única, não só para o meu desenvolvimento pessoal, mas também profissional. Equipou-me com competências fundamentais para o meu futuro percurso profissional, nomeadamente ritmo de trabalho, comunicação em equipa, responsabilidade, resolução de problemas, entre outras. Adicionalmente também tive a oportunidade de participar em diversas formações, que à frente irei descrever mais detalhadamente.

Este relatório irá descrever aspetos pertinentes do meu estágio na Owlpharma na forma de uma análise SWOT (Figura 1), dividida em pontos fortes, pontos fracos, oportunidades e ameaças.

ANÁLISE SWOT

A análise SWOT é uma técnica de planeamento estratégico e irá servir para analisar e realçar pontos importantes do meu estágio curricular na Owlpharma que influenciaram, de uma forma positiva ou negativa, a realização do mesmo.

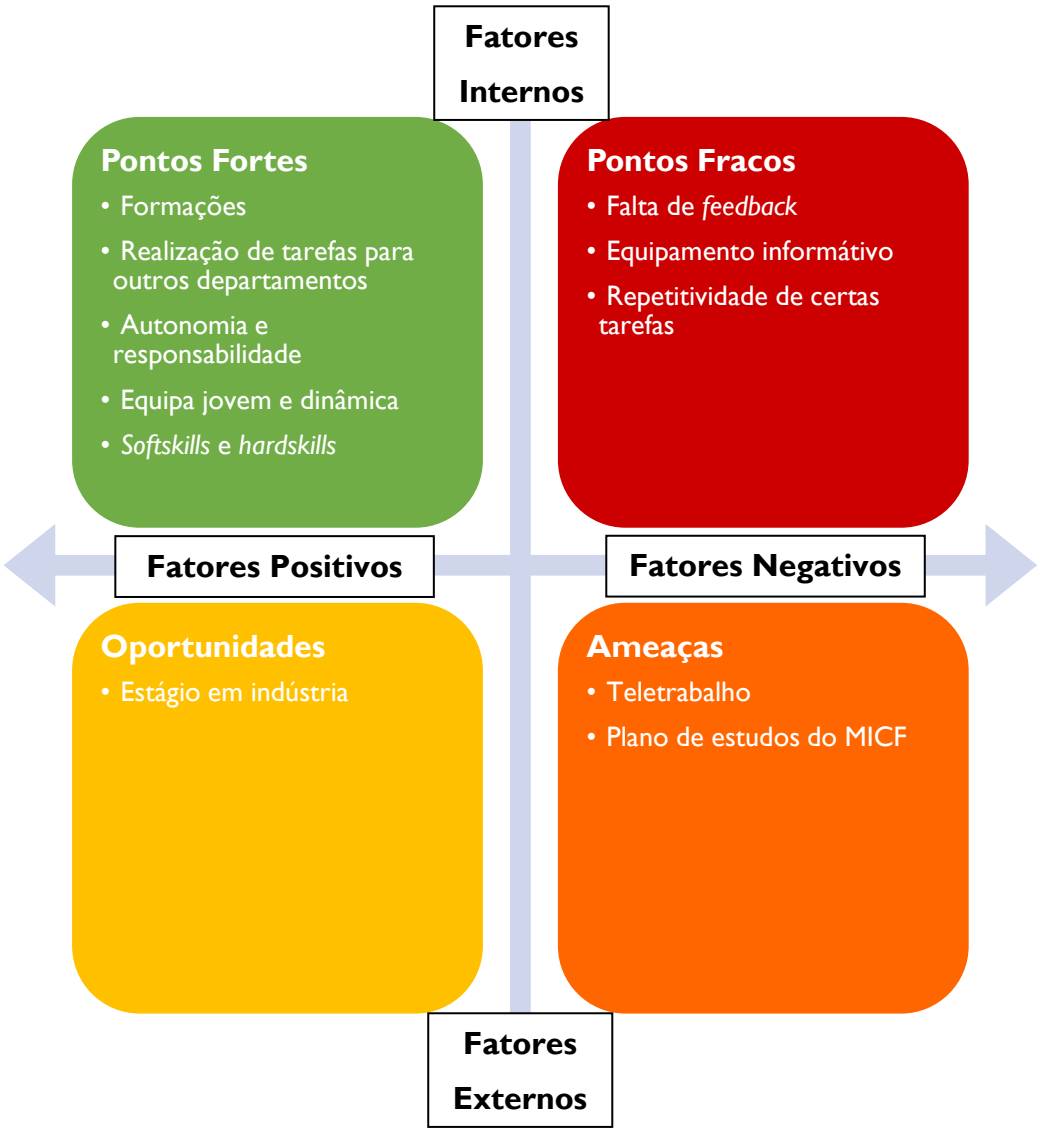

Figura 2: Análise SWOT referente ao Estágio em FV na Owlpharma.

1. PONTOS FORTES

1.1. Formações

O plano curricular do MICF é caracterizado pela sua abrangência nas diversas áreas que englobam o papel do farmacêutico. Esta diversidade, embora possa ser um ponto forte, inevitavelmente traz os seus problemas, nomeadamente uma falta de especificidade e especialização em certas áreas. Considero que duas dessas áreas sejam os AR e a FV, embora o MICF nos dê algumas bases essenciais para o conhecimento destas áreas, é necessária uma aprendizagem contínua de modo a garantir um conhecimento atualizado e completo. Nesta vertente, o meu estágio curricular na Owlpharma foi uma mais-valia, sendo que desde o primeiro dia tive a oportunidade de assistir a diversas formações nas áreas de FV, AR e M&SA que foram essenciais para o meu trabalho.

1.2. Realização de tarefas para outros departamentos

Durante os três meses de estágio na Owlpharma estive inserido no departamento de FV, no entanto, tive a oportunidade de trabalhar também ocasionalmente com o departamento de M&SA. Considero este aspeto como um ponto forte do meu estágio na medida em que me permitiu conhecer outro departamento com responsabilidades e uma dinâmica de trabalho diferente, desenvolver novas competências inerentes ao trabalho desse departamento e, também, fazer uma gestão do trabalho dos dois departamentos de modo a otimizar o tempo despendido para cada um.

1.3. Autonomia e responsabilidade

Embora todas as tarefas que efetuasse fossem sempre revistas, mais tarde, por alguém experiente, após serem dadas orientações e esclarecidas as dúvidas sobre cada uma, sempre me foi dada autonomia na realização das mesmas. Foi-me também explicada a importância dos trabalhos que estava a elaborar, promovendo um bom sentido de responsabilidade que me motivou ainda mais para a realização dos mesmos. Considero a autonomia e o sentido de responsabilidade duas competências essenciais no mercado de trabalho, tendo sido, portanto, um ponto positivo do meu estágio.

1.4. Equipa jovem e dinâmica

As relações interpessoais e o ambiente de uma equipa são fatores muito importantes para promover uma boa cooperação e um ritmo de trabalho saudável. Uma boa dinâmica de equipa tem influência na criatividade, produtividade e na eficácia do trabalho. O departamento

de FV da Owlpharma, coordenado pelo Dr. Ricardo Andrade e pela Dra. Mariana Rocha, tem uma equipa bastante jovem, dinâmica e profissional, desde a primeira semana que fui bem integrado, participando todas as semanas numa reunião semanal onde era visto como parte da equipa. Durante estas reuniões era posto a par de outros projetos que o departamento estava a desenvolver, e eram discutidos assuntos com os quais não tinha tido ainda contacto, sendo, portanto, uma boa oportunidade para adquirir novos conhecimentos da área da FV e familiarizar-me com diferentes aspetos da mesma. Para além disso, sempre me foi esclarecida qualquer questão que tivesse e nunca senti falta de abertura para as colocar.

1.5. Softskills e hardskills

Softskills são competências não quantificáveis que são essenciais para uma boa prestação no local de trabalho, exemplos de *softskills* são a comunicação, relacionamento interpessoal, ética de trabalho, negociação, entre outras. *Hardskills* são competências técnicas e quantificáveis que um indivíduo utiliza no local de trabalho, estas podem ser competências informáticas, linguísticas, entre outras. Durante o meu estágio na Owlpharma pude desenvolver e fomentar várias *hardskills* como o uso do inglês, do *Microsoft office*® e outras competências informáticas, tradução, redação de textos, entre outras. No caso das *softskills* notei uma melhoria no meu trabalho em equipa, capacidade de comunicação, pensamento crítico, resolução de problemas e gestão de tempo.

2. PONTOS FRACOS

2.1. Falta de feedback

O *feedback* é uma componente muito importante da comunicação para o processo de aprendizagem, impede-nos de cometer erros repetidos e garante, especialmente para um estagiário, que estamos a trabalhar da forma correta, sendo uma ferramenta essencial para a melhoria contínua. Após realizar uma tarefa nova na Owlpharma, em alguns casos, não me era dado nenhum *feedback* acerca da mesma, deixando-me a questionar se havia algo a melhorar. Este ponto deixou de ser um problema a partir do momento em que comecei a procurar, eu próprio, o *feedback* das tarefas que realizava.

2.2. Equipamento informático

No primeiro dia do estágio na Owlpharma foi-me fornecido um computador portátil para poder trabalhar a partir de casa. No entanto, esse computador era antigo e já não estava em muito bom estado, sendo bastante lento a responder. Para além disso, no último mês do

meu estágio deixou completamente de funcionar e fui obrigado a utilizar o meu computador pessoal. Ter que trabalhar com este computador da afetou bastante a eficiência do meu trabalho visto que demorava muito mais tempo a realizar tarefas simples.

2.3. Repetitividade de certas tarefas

Outro aspeto que afetou negativamente o meu estágio foi a pouca diversidade de tarefas em certas alturas. Embora tenha tido contacto com outros departamentos e tenha tido a oportunidade de trabalhar em várias tarefas diferentes, havia semanas em que o trabalho se tornava bastante monótono por estar a elaborar sempre os mesmos relatórios ou a fazer o *screening* da literatura nacional ou internacional por longos períodos de tempo. Embora compreenda a importância deste trabalho, por vezes tornava-se muito repetitivo o que afetava a minha produtividade e motivação. De forma a combater esta vertente, uma opção seria apostar na rotatividade de tarefas de modo a não estagnar numa só.

3. OPORTUNIDADES

3.1. Estágio em Indústria

O plano de estudos do MICF aborda quase todas as áreas relacionadas com a indústria farmacêutica, no entanto, não é possível aprender todos os aspetos de uma determina área sem experiência direta com a mesma. A possibilidade de realizar um estágio em indústria, na área de FV, foi, sem dúvida, uma excelente oportunidade que me foi proporcionada pela Faculdade de Farmácia da Universidade de Coimbra e pela Owlpharma. Sempre me interessei pelas áreas de AR e FV e a realização de um estágio numa destas áreas contribui bastante para o meu desenvolvimento e é uma mais-valia para o meu futuro profissional.

4. AMEAÇAS

4.1. Teletrabalho

O desenvolvimento de relações interpessoais e o *networking* são oportunidades que são proporcionadas pelo contacto e partilha de espaço num local de trabalho. No entanto, devido à pandemia provocada pelo vírus SARS-CoV-2, a Owlpharma passou para um regime de teletrabalho a tempo inteiro. Embora considere que a Owlpharma se tenha adaptado muito bem às condições atuais e que o meu trabalho não tenha sido diretamente afetado (além do ponto 2.2), não tive a oportunidade de trabalhar a partir de um escritório e considero que

essa mudança de ambiente teria sido bastante benéfica para o desenvolvimento de competências pessoais.

4.2. Plano de estudos do MICF

Outro aspeto que considero uma ameaça ao meu estágio curricular em FV foram os conteúdos lecionados no plano de estudo do MICF, especificamente na cadeira de Farmacovigilância e Farmacoepidemiologia. Embora sejam abordados os conceitos básicos e mais importantes da FV, apenas de uma forma mais superficial e não muito direcionada para a realidade profissional. A área de FV é bastante complexa, não seria possível abordar, de forma aprofundada, todos os tópicos necessários para a exerção de tarefas na mesma, no entanto, considero que podia ser dada mais atenção à formação dos estudantes nesta área. Como já referi anteriormente, a Owlpharma forneceu um leque de formações bastante completo, e como tal, não senti quase nenhum constrangimento ou impedimento devido aos meus conhecimentos.

CONCLUSÃO

Concluído o meu estágio em FV na Owlpharma gostaria de agradecer a toda a equipa pela oportunidade, integração e por todo o apoio prestado. Durantes os três meses do estágio senti que fiz realmente parte da equipa e que o meu trabalho era valorizado.

Considero, de um modo geral, que tenha sido uma experiência bastante enriquecedora, tive a oportunidade de aprender bastante sobre várias áreas pelas quais tinha interesse, principalmente na FV e M&SA por trabalhar diretamente em projetos nestas áreas. Adicionalmente, tive a oportunidade de adquirir novos conhecimentos na área de AR graças ao leque bastante completo de formações fornecido pela Owlpharma.

Como já referi anteriormente, desenvolvi muitas competências que considero essenciais para o meu futuro. A oportunidade de contactar com um ambiente profissional será benéfica para a próxima fase do meu percurso. A realização deste estágio na Owlpharma foi, sem dúvida, uma mais-valia para complementar a minha formação do plano de estudos do MICF e para ganhar experiência numa das minhas áreas de interesse.

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PARTE III

"NANOMEDICINE: APPLICATIONS AND CURRENT CHALLENGES IN PEDIATRICS"

LIST OF ABBREVIATIONS AND ACRONYMS

ADME: Absorption, distribution, metabolism, and excretion

Ape1: Apurinic endonuclease 1

BBB: Blood-brain barrier

BD: Biodistribution

BSA: Body surface area

CL: Clearance

CNS: Central nervous system

EMA: European Medicines Agency

FDA: Food and Drug Administration

GET: Gastric emptying time

GFR: Glomerular filtration rate

GIT: Gastrointestinal tract

HCT: Hydrochlorothiazide

NAC: N-acetyl-L-cysteine

NF: Nanoformulation

NLC: Nanostructured lipid carriers

NP: Nanoparticle

NT: Nanotherapeutic

PD: Pharmacodynamic

PEG: Poly(ethylene glycol)

PK: Pharmacokinetic

PP: Pediatric population

SLN: Solid lipid nanoparticles

Vd: Volume of distribution

ABSTRACT

The current landscape of pediatric medicine is characterized by a lack of approved therapeutic indications for this population. This is caused by a shortage of pediatric inclusion in clinical trials and drug development, the heterogenicity of pediatric patients, the maturational differences between children and adults, among other factors. Nano delivery systems have seen major developments in medicine in the past decades, with applications in various fields, and have been used to tackle various challenges related to pediatric medicine, namely the organoleptic properties of these formulations, the lack of age-appropriate pharmaceutical forms, the ease of dose adjustments, and problems with bioavailability and targeting. Different types of nanoparticles (NPs) have been studied for pediatric administration, some examples include polymeric NPs, dendrimers, lipid, and metallic NPs. Understanding the pharmacokinetics of these nano delivery systems plays a major role in drug development, affecting not only the effectiveness of these formulations, but also their toxicity. Many challenges are associated with the introduction of novel delivery systems, especially in the pediatric population. Pharmaceutical industries will have to deal with safety concerns, biological challenges, costs of large productions, and the current regulatory landscape. This review will present and discuss the topics mentioned above.

Keywords: Nanoparticles, nanomedicine, polymeric, dendrimers, lipid nanoparticles, metallic nanoparticles, pediatrics, and pharmacokinetics

RESUMO

O panorama atual de medicamentos pediátricos é caracterizado por uma falta de indicações terapêuticas para esta população. Isto é causado por uma falta de inclusão pediátrica em ensaios clínicos e no desenvolvimento de fármacos, pela heterogeneidade dos doentes pediátricos, pelas diferenças de maturação entre adultos e crianças, entre outros fatores. Nas últimas décadas, os nanosistemas viram um grande desenvolvimento em medicina, com aplicações em várias áreas, e têm sido utilizados para responder a vários desafios relacionados com os medicamentos pediátricos, nomeadamente as propriedades organoléticas destas formulações, a falta de formas farmacêuticas apropriadas à idade pediátrica, a facilidade de ajustes de dose e problemas com biodisponibilidade e terapêutica dirigida. Diferentes tipos de nanopartículas têm sido estudados para administração pediátrica, alguns exemplos incluem nanopartículas poliméricas, lipídicas, metálicas e dendrímeros. Compreender a farmacocinética destes nanosistemas é importante para o desenvolvimento de medicamentos, afeta não só a eficácia destas formulações, mas também a sua toxicidade. Vários desafios estão associados à introdução de sistemas inovadores, especialmente na população pediátrica. Indústrias farmacêuticas terão que lidar com preocupações relacionadas com a segurança, desafios biológicos, custo de produções em grande escala e panorama regulamentar atual. Esta revisão vai apresentar e discutir os tópicos mencionados em cima.

Palavras-chave: Nanopartículas, nanomedicina, poliméricas, dendrímeros, nanopartículas lipídicas, nanopartículas metálicas, pediatria e farmacocinética.

INTRODUCTION

The development of pediatric formulations, suitable for every stage of childhood maturation, can be a challenging task. Although there has been a rise in new pediatric medicines and indications, there is still a lack of approved drugs for various diseases that affect, exclusively or not, this population group. This is a consequence of many different factors, including: 1) the physiological differences between children and adults; 2) the lack of clinical studies and trials directed at children; 3) the shortage of age-appropriate pharmaceutical forms; 4) the lack of high-quality Pharmacokinetic (PK) and pharmacodynamic (PD) data; 5) lower financial profit for pharmaceutical companies; 6) the existence of diseases that only affect children. Among other factors [1].

The pediatric population (PP) can be divided into 5 age groups according to developmental stages - preterm newborn infants/neonates, term newborn infants/neonates (0-27 days), infants and toddlers (1 month to 23 months), children (2-11 years) and adolescents (12-16 or 18 years) [1]. For the purpose of this review and discussion, the term "children" will be utilized in a general sense, according to the Oxford English Dictionary to reference *"a young human who is not yet an adult"* [2].

Nanomedicines are defined by the European Medicines Agency (EMA) as a system designed for clinical application, with at least one nano-scale sized component, and resulting in definable specific characteristics and properties [3]. Nanomedicine is a field of medicine that has seen great interest in the past decade. A PubMed search with the term "nanomedicine" in the year 2010 shows 974 results, compared to 5334 in 2020, an over five-fold increase [4], and justifiably so, the use of nanoparticles has revolutionized modern medicine, with applications ranging from novel delivery systems to diagnosis and imaging [5]. Nanoformulations (NFs) can be utilized to deliver drug agents by encapsulation or attachment and deliver them to the target tissue in a more precise and controlled released [6]. Nanocarriers have numerous advantages compared to the conventional drug form, namely the manipulation of particle size and surface characteristics, enabling various routes of administration that otherwise were not possible, high drug loading, controlled and sustained drug release, reduction in side effects, and drug incorporation without the use of chemical reactions. All of these advantages contribute to an improved therapeutic efficacy of these drugs [7], [8]. Nanoparticles, owing to these properties, have recently been explored for their applications in pediatric medicine.

This review will highlight the current paradigm and challenges of pediatric therapy, the use of nano-delivery systems as a possible solution to a few of these challenges, the PK

differences between adults and the PP and how these differences affect NFs, the safety and other issues related to the application of these novel delivery systems and will include a discussion about the future of nanomedicine in pediatrics.

1. CURRENT CHALLENGES IN PEDIATRIC MEDICINE

Pharmaceutical industries, researchers, and physicians face many challenges when dealing with pediatric medicine, most drugs are not approved for pediatric use, and so, must be prescribed "off-label" by the physician, based on their clinical knowledge and past experiences rather than clinical research data. This practice, while common and necessary, has risks, due to the shortage of reliable clinical evidence on the use of these drugs in pediatric patients, the chances for a possible lack of efficacy and/or toxicity are higher. There are several reasons for the lack of approved drugs in pediatrics, such as the lack of pediatric representation in clinical trials, the lack of financial incentives for industries to develop pediatric medicine, the lack of age-appropriate pharmaceutical forms and dosage, undesirable organoleptic properties, limited drug development for pediatric diseases, and the lack of PK and PD data for these patients [9].

1.1. Challenges with drug development

1.1.1. Clinical trials

From an ethical point of view, any research that involves children always has some constraints associated. Clinical research is the study/studies intended to verify the effects of one or more investigational drugs, using, for this purpose, subjects with the aim of creating generalized knowledge. In adult studies, ethical problems can be easily circumvented by the voluntary and informed consent of the research subjects, however, children under 18 (in most European countries) cannot give consent on their own behalf [10], and so, parents, recruiters, and regulators must determine whether or not the risk/benefit is acceptable to allow for the research to advance [11].

Clinical trials are essential for the advancement of medical knowledge and patient well-being. However, clinical trials in children, much due to the vulnerability of this age-group, are plagued with a history of abuse and public concern that led to their absence from these studies. The EU Clinical Trials Register displays 2032 trials, with an EudraCT protocol, in patients under 18 from 2001 to 2010, and 4143 trials from 2011 to 2020 [12]. Although the inclusion

of the PP in clinical studies has been steadily increasing, it is still insufficient [13]. This lack of pediatric clinical trials has resulted in insufficient data regarding dosing, efficacy, and safety information. Possibly preventing an important drug treatment from being used in children because it was not properly tested in this age-group [9]. Pediatric clinical studies are also harder to carry out than regular clinical trials; there is a need for age-appropriate equipment and medical techniques, a "child-friendly" environment, and pediatric specialists. Simple procedures such as urine and blood sample collection are more difficult to perform in children. Recruiting is also a significant problem since many recruiters have difficulty in reaching a meaningful number of children, resulting in delays in conducting and completing these studies [14].

1.1.2. Financial incentives

Another reason for the lack of approved medicine in pediatrics is the lack of financial incentives for pharmaceutical companies to study this age group. The cost of development for pediatric drugs is generally greater than that of adults and the drug market for children is comparatively smaller, and so, investment is less financially attractive [15].

1.1.3. Limited drug development for pediatric diseases

One of the problems with pediatric medicine is the limited targeting of drug development towards children. In a general sense, pediatric drug development is driven by adult drug development. This is not so much of a problem in cases where a disease affects both populations groups (e.g. asthma). It is, however, a problem when a disease only occurs in the PP. In the case of oncology, there are several drug compounds approved or in development for cancers that affect both age groups (e.g. leukemia). On the other hand, diffuse intrinsic pontine glioma, a pediatric brain cancer that rarely affects adults, has very limited treatment options and very few compounds in development [1], [16].

1.1.4. Lack of pharmacokinetic and pharmacodynamic data

Despite the advancements made in our understanding of a child's maturation and developmental changes in the past decades, the lack of high-quality PK data remains one of the major challenges of pediatric drug development. The impact of age-related effects on PKs, PDs, and dosage needs is not fully understood. [17] Furthermore, pediatric patients have distinct medicine-related toxicity, and preferred routes of administration; and both the active drug and formulation excipients sometimes have altered bioactivity in children. Rapid growth and development during childhood exacerbates dosing issues, with dosages of certain

formulations fluctuating 100-fold during this time [1]. In comparison to adults, children display metabolic and biological differences, which are caused by the maturation and growth of various organs and biological systems after birth; and thus, present differences in absorption, distribution, metabolism, and excretion (ADME) [18]. Consequently, this lack of extensive PK data in the various subgroups of the PP constitutes a problem in the development of age-appropriate formulations, which leads to an increase in the risk of toxicity or sub-therapeutic dosing caused by off-label use of drugs by clinicians [19].

1.1.5. Pharmaceutical form and dosage

Choosing the most adequate pharmaceutical form is a challenge in pediatric medicine. An ideal formulation for pediatric use must: allow minimal dosage and frequency; have one dosage form that fits all necessities or a full range of pharmaceutical forms; have minimal impact on lifestyle; have minimal and non-toxic excipients; be easily produced, stable, cheap, commercially viable; and have a convenient and easy administration. It is important for pharmaceutical formulations to have the ability to handle dose requirement changes during development, which can vary greatly. There are also changes in preference of different dosage forms - small volume oral liquid medicine is more appropriate for the younger age groups, while tablets and capsules are more convenient for adolescents [20].

Dosage for the PP is too often derived by adjusting adult dosages to body weight; however, the PK (ADME) of a drug is substantially different between adults and children, this topic will be explained more in-depth later on. Not only are the physiological differences important between these two age groups, but, as mentioned previously, the PP can also be divided into different age groups according to developmental stages. Therefore, the body's response to a certain compound will vary according to the growth and maturation of the individual [1]. These developmental differences between pediatric patients result in different dosage needs. Consequently, the steps needed for clinical translation of a drug in pediatrics are much more complex than the standard dose adjustment, often needing safety and efficacy studies. Furthermore, dosage can greatly affect patient adherence, since frequent doses and regimen complexity is associated with poor patient adherence [9], [21], [22].

1.1.6. Organoleptic properties

The organoleptic characteristics of a drug are crucial when dealing with pediatric patients, an unpleasant taste, smell, or even texture can lead to poor patient adherence and, consequently, treatment failure. Appearance also has an impact on the acceptability of a drug and may even influence the perception of taste, for example, a yellow-colored tablet is

expected, by a child, to taste like lemon. The organoleptic properties of drug formulations can be modulated with the use of edulcorates and colorants, however, these substances can have unfavorable toxicity profiles in pediatric patients, and their use is associated with safety concerns. All of this is particularly significant in cases of chronic therapies, where the treatment regimen requires multiple daily administrations [1], [23].

2. NANO DELIVERY SYSTEMS FOR DRUGS USED IN PEDIATRICS

Nanoparticles (NPs) are solid or colloidal particles ranging from 1-100 nm, consisting of macromolecular materials, in which the active ingredient is trapped, dissolved, encapsulated, absorbed, or attached. These particles hold great potential as an effective drug delivery system, releasing the drug substance in a controlled manner with the possibility of drug targeting [24]. The use of NPs in medicine is based on three basic applications: nanomaterials which can be used as transporters of active substances or as biosensors, aiding in treatment. Knowledge of molecular medicine in various fields, such as genetics, and nanotechnologies which can be utilized for therapy and/or rapid diagnosis, repair genetic material, and improve cell functions [25]. This article focuses more on the use of NPs as transporters of active substances and the benefits for pediatric administration.

2.1. Potential benefits

The use of NPs as a delivery system for pediatrics, although not having been thoroughly studied, already shows potential benefits that support its development: improving the organoleptic properties of certain active substances and/or excipients, enabling the development of new pharmaceutical forms that otherwise were not possible, allow for easier dose adjustments, increasing bioavailability, decreasing the number of daily administrations, and improving drug targeting.

2.1.1. Organoleptic properties

The use of nano delivery systems has commonly been discussed as a solution to taste-related patient non-adherence in pediatrics. As explained before, the organoleptic properties of a drug play a major role in pediatric formulations, with taste, smell and texture being some of the reasons for patient non-adherence [26].

In the study of Prebianca G, *et al.* 2020, an alcohol-free liquid dosage form of polymeric coated NPs containing ritonavir was formulated [27]. Ritonavir is an antiretroviral drug indicated for the treatment of HIV-1 in adults and children older than 2 years old [28], [29]. The available liquid pharmaceutical forms have been reported to have a bitter taste, which affects patient adherence; and, consequently, therapeutic efficacy. Therefore, the development of ritonavir in polymeric NPs was studied as a potential solution. Ritonavir NPs were obtained by polymeric coating with Eudragit® L 100-55. These coated NPs showed low size distribution and high absolute zeta potential, which suggests high kinetic stabilization. The results of this study were evaluated using the Likert scale, with higher values representing greater bitterness, and lower values a more tolerable taste. Non-encapsulated ritonavir solution presented a score of 2.8, the ritonavir NPs without coating a score of 3.5, and finally the Eudragit® L-coated ritonavir NPs a score of 2.6. It was proposed that the differences in score between ritonavir solution and non-coated NPs were due to the bitter masking effect of the ethanol content in the ritonavir oral solution. The authors concluded that NP preparation followed by polymeric coating showed a promising alternative for bitter taste masking [27].

In another study, Krieser K*, et al.* 2020, developed nanostructured liquid formulations of saquinavir, using Eudragit RS100 and Pullulan as polymers, with the goal of improving the formulation's stability and taste-masking properties. Saquinavir is an antiretroviral drug indicated for the treatment of adult patients with HIV-1 [30]. This drug substance presents a bitter, metallic, and astringent taste; these properties make treatment adherence in children a problem as explained previously. Moreover, there are no liquid formulations of saquinavir currently available in the market. Eudragit RS100 is a cationic, water insoluble, pH-independent polymer used for the preparation of controlled-release oral dosage forms. Pullulan is a biodegradable carbohydrate produced by the fungus *Aureobasidium pullulans* with the ability of creating polymeric films. The NP suspensions were prepared using the interfacial polymer technique. Four formulations of different Eudragit RS100 and Pullulan ratios were tested, with four formulations without saquinavir serving as control. The taste evaluation was performed using an electronic tongue and demonstrated that the formulations prepared had the capability of masking the taste of saquinavir. The results revealed that the encapsulation of saquinavir succeeded in the stabilization of the drug in a liquid formulation, without the use of alcohol, sugar or antioxidants, and with suitable nanotechnological characteristics, such as sustained release and taste-masking properties [23].

Rath SP, et al. 2014 tested the taste-masking properties of quinine sulphate loaded solid lipid nanoparticles (SLN). Quinine sulphate is indicated for the treatment of sensitive plasmodium strains, resistant to chloroquine [31]. Although this drug substance has been used

in the past decades, there are still very few commercially available liquid formulations. Tablets, which would require breaking for dose adjustment, might not provide an accurate dose. Intramuscular administration has the risk of lower limb paralysis if administrated incorrectly; and rectal administration has low bioavailability and can sometimes be expelled from the rectum. Additionally, quinine sulphate has an extremely bitter taste, making it unsuitable for pediatric treatment. Therefore, there is an urgent need for a liquid antimalarial oral formulation, with the aim of improving palatability, accuracy, and reliability of dosing in children. For this reason, SLN of quinine sulphate were developed to study their potential in improving the palatability of this therapy. These SLN were prepared by ultrasonic solvent emulsification, using glyceryl monostearate as a lipid in a 1:3 drug to lipid ratio and three different surfactants. The NPs with the best results used poloxamer 188 as a surfactant, showing high entrapment efficiency, negligible release in simulated salivary fluid, and close to 100% release at stomach pH. The NPs created showed good physiochemical properties, achieving taste-masking capabilities, allowing flexibility for dose adaptation, and showing potential for increased patient compliance [32].

The taste-masking properties of NPs have been studied substantially in the past couple of years, as emphasized by the articles previously mentioned. Nonetheless, more intricate and larger-scale clinical trials are still required. Although the results of these studies have supported the palatability improvement of NP formulations, pediatric patients were not used as subjects; instead, adults or analytical methods were used to verify the results. While these methods provide some validity to the results, use of the target population would still be preferred due to the intricate and variable aspects of the PP mentioned above. For these reasons, more clinical trials and investments are incentivized.

2.1.2. Pharmaceutical forms and dosage

Other drawbacks from current pediatric formulations include the available pharmaceutical forms and dosing requirements. As previously explained, pediatric patients require different formulations at different developmental stages, which is often not possible, not only due to the development costs of these formulations but also because of a potential incompatibility or instability of the active substance. The clear necessity for more diverse pharmaceutical forms and easier dose adjustments in pediatrics is a problem that has been tackled using nano-based pharmaceutical forms. Nanoencapsulation can solve problems with solubility that hinder drug formulation into certain pharmaceutical forms.

Such is the case of Diefenthaeler HS, *et al.* 2020, in which researchers developed a suspension containing NPs of omeprazole for pediatric administration. Omeprazole is an

irreversible proton pump inhibitor used for the treatment of secretory dysfunctions [33]. It presents, in its base form, chemical instability in acid environments, being sensitive to heat, light, humidity, and organic solvents. As a result, all oral formulations are enteric-coated solid forms, with no currently available liquid pharmaceutical forms, which becomes a problem for its use in pediatric patients. For this reason, in this study, omeprazole-loaded NPs were developed using the nanoprecipitation method, with Eudragit® RS100 as the skeleton material in the inner core and with pH sensitive Eudragit® L100-55 as the outer core. *In vivo* pharmacological studies showed a protective effect of these NPs, protecting the stomach of mice against ulcer formation. The particles prepared also displayed good physiochemical properties, thus presenting a potentially effective therapeutic strategy for omeprazole administration in the PP population, in a liquid pharmaceutical form [34].

In another study, Dharshini KP, *et al.* 2020, chitosan NPs loaded with dolutegravir were prepared for pediatric anti-HIV therapy. Dolutegravir is indicated for the treatment of adults, adolescents and children HIV positive [35] - an integrase inhibitor available only in oral tablets. Downsides associated with the conventional form of dolutegravir are difficulty in swallowing and the variation in pediatric dose of 5 to 10 mg/day. *Dharshini KP, et al.* proposed the development of biodegradable polymeric nano-carriers as a delivery system, with the possibility of mixing these particles with food for convenient administration in children. Chitosan, isolated and extracted from novel crab shells, was chosen as the polymeric carrier due to its biodegradability, non-toxicity, and biocompatibility properties. The dolutegravir loaded chitosan NPs were produced using the spray drying technique and were shown to have favorable physio-chemical properties as well as less toxicity compared to the free drug. This chitosan-based NF in powder form could help solve the problems with swallowing and dose adjustments mentioned above, helping with the administration in HIV pediatric patients without compromising therapeutic efficacy [36].

2.1.3. Bioavailability

Bioavailability of a drug formulation is the extent to which the active substance is absorbed from its pharmaceutical form to become available at the site of action. This can be affected by many factors; in the case of oral drug delivery, the preferred route of administration for pediatric patients, it is mostly affected by the aqueous solubility and intrinsic dissolution rate (which is the amount of drug dissolved per unit of time and area), the lower the water-solubility and dissolution rate of the drug, the lower the bioavailability [37]. One other factor that affects oral bioavailability is poor gastrointestinal permeability, drugs with poor membrane permeability generally have to be administered in a higher dose to achieve

the therapeutic concentration [38]. Improving the bioavailability of pediatric drugs has several benefits, especially concerning therapeutic adherence. Increasing the bioavailability of a drug substance allows for a reduction of the dose required for therapeutic efficacy; thus, potentially reducing the number of daily administrations and/or quantity of drug administered, which in some cases can be a determining factor in the effectiveness of therapy [1].

Nanotechnology has been used to improve the bioavailability of oral drug formulations through various mechanisms, higher surface area, protection against chemical and enzymatic degradation, better drug permeation, reduced efflux, increased water-solubility, increased dissolution rate and enhanced lymphatic transport. Many studies have taken advantage of these mechanisms, such is the case of Cirri M, *et al.* 2017, in which researchers developed a hydrochlorothiazide-cyclodextrin complex incorporated into SLN. Hydrochlorothiazide (HCT) is a short acting diuretic indicated for the treatment of hypertension and edema, mostly used in combination with other antihypertensive drugs. According to the Biopharmaceutical Classification System, HCT is considered a class IV drug [39], due to having poor solubility and low membrane permeability, which results in poor oral bioavailability. Additionally, HCT is reported to have stability problems in aqueous solutions. The SLN were prepared by the hot high-shear homogenization method, followed by ultrasonication. After HCT-cyclodextrin complexation, the SLN based on Precirol® ATO5 were loaded with the aid of Pluronic® as a surfactant. The SLN prepared not only displayed good physiochemical properties, but also displayed in *in vivo* studies a prolonged HCT pharmacological effect when compared to the simple drug suspension of HCT. These results demonstrate the effectiveness of this approach in pediatric formulations for the improvement of bioavailability [40].

2.1.4. Targeting

Another function of NPs that shows potential for its use in the PP is the use of targeting. There are two types of targeting commonly used in nanotechnology, that is, active targeting and passive targeting. Active targeting consists in the molecular targeting of NP drug carriers with the goal of enhancing therapeutic specificity and reduce toxicity. Ligands specific to the target cell's receptors are conjugated on the surface of the NP, which can potentially increase the delivery of the therapeutic drug to the desired site, while simultaneously decreasing the delivery to unwanted sites [41]. This is especially beneficial when implemented in the PP, for the importance of avoiding toxicity in healthy tissues considering the age of these patients; and because there is a lack of data on the toxicity of drugs used in pediatrics [42]. NP targeting is commonly studied in cancer therapy; chemotherapies frequently fail to improve the patient's mortality or morbidity because of the severe side effects on normal cells; targeted NPs can be

designed to only affect tumor cells whilst sparing healthy tissue, and consequently sparing dose-limiting side effects [43]. Passive targeting deposits a drug at a specific location, as a consequence of the NP physiochemical properties, taking advantage of the NP accumulation in relation to individual molecules or drugs in the microenvironment of the target site; as a result of increased permeation and retention of these particles; and, in the case of cancer, the permeable vasculature and damaged lymphatic drainage of solid tumors [44], [45].

This strategy was observed in the study of Kievit FM, *et al.* 2015, where a NP-based siRNA delivery vehicle was developed to silence a specific gene expression conferring tumor resistance to radiotherapy. Medulloblastoma and ependymoma are two of the most common pediatric brain tumors; radiotherapy is a vital component in the treatment of these cancers. However, it is accompanied by radiation-induced developmental and psychosocial adverse events. For this reason, there is a clear need for the development of strategies that increase sensitivity of brain tumor cells to radiotherapy, whilst not affecting healthy adjacent brain tissue. Apurinic endonuclease 1 (Ape1) is an enzyme that has been linked to radiation resistance in cancer cells. Suppression of Ape1 expression in cancer cell lines has been demonstrated to increase sensitivity to both radiation and alkylating agents. With this objective, a NP-based siRNA delivery system was developed to silence the Ape1 gene expression. Iron oxide NPs were prepared via the co-precipitation method, coated with chitosan-Poly(ethylene glycol) copolymer and polyethyleneimine, and loaded with siRNA. These NPs were able to reduce Ape1 expression by over 75% in medulloblastoma cells and 80% in ependymoma cells; and this reduction in Ape1 correlated with an increase in DNA post-radiation treatment damage; thus, resulting in reduced cell survival in clonogenicity assays. These results demonstrate that NP-mediated active targeting might be an effective tool in pediatric cancer treatment [46].

These are some of the potential applications of nano delivery systems in pediatrics. Although already showing promise, there are still very few studies on this subject, not only because nanomedicine is a relatively new field, but our understanding of pediatric development and therapeutic needs is also incomplete. With future advancements in both fields, more applications will be discovered, and the benefit/cost ratio of this approach will be appropriately accessed.

2.2. Types of nanoparticles for pediatric administration

The expansion of nanotechnology over the past decades gave rise to various types of NPs for the purpose of therapeutic administration, such as polymeric NPs, dendrimers, micelles, liposomes, exosomes, SLN, metallic NPs, among many others. This next chapter will highlight a few types of NPs that have been used or studied with the purpose of pediatric administration.

2.2.1. Polymeric Nanoparticles

Polymeric NPs (Figure 1) are a type of nanosystem with a matrix consisting of natural, semi-synthetic or synthetic polymers, being classified according to their origin, and can also eighter be biodegradable or non-biodegradable. Biodegradable NPs show more significance for pediatric medicine since non-biodegradable polymeric NPs can induce a high immunological response and chronic toxicity. Synthetic polymers already approved by the Food and Drug Administration (FDA) include PLGA, PGA, PLA, these are generally well tolerated as they are degraded to carbon dioxide and water. Natural polymers are usually proteins or polysaccharides obtained from an animal or vegetable source, examples include albumin, collagen, zein, chitosan, cellulose, etc. NPs built on these polymers (synthetic or natural) display favorable properties, such as biodegradability, low toxicity, high loading capacity, as well as improving both the PKs and PDs of the formulated drug, thus increasing safety and being more suitable for pediatric formulations [47].

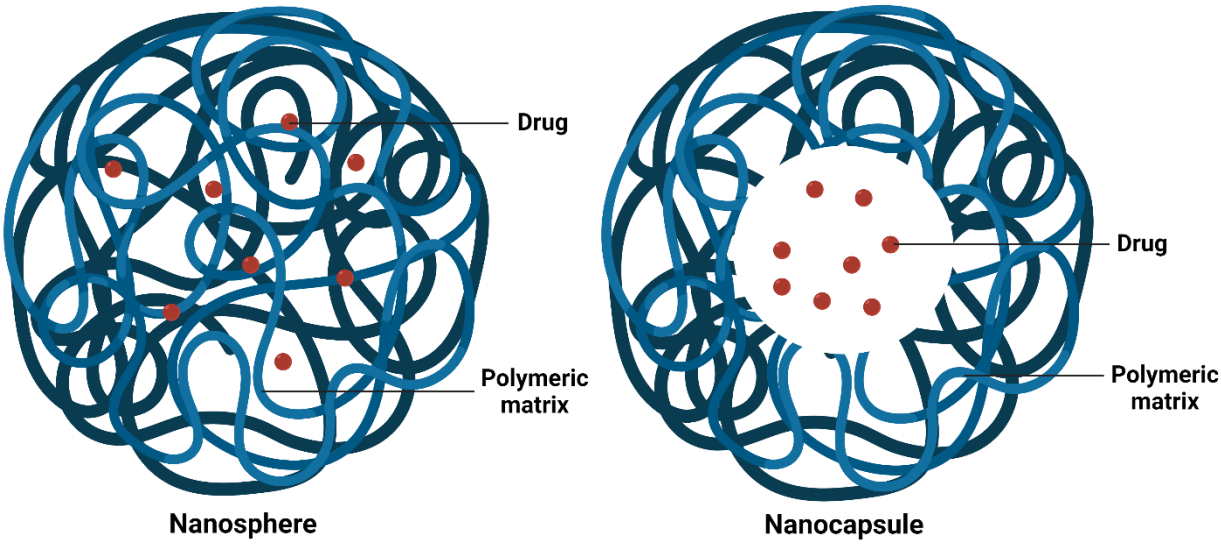

***Figure 1*:** Representation of two polymeric NPs.

Albumin is a biodegradable animal protein that is water-soluble, non-toxic, and non-immunogenic. This protein can improve drug bioavailability and decrease drug resistance. Albumin-polymer conjugates are very versatile, being able to deliver a variety of drugs, reduce

the side-effects by removing toxic vehicles, allow for higher drug loading, all of which leads to an increased drug activity [48], [49]. Paclitaxel-albumin NPs (Abraxane®) have been shown to have increased efficacy in adults with solid tumors and is the first natural polymeric NP to be used in pediatrics. Paclitaxel is a chemotherapeutic agent commonly used in breast and lung cancer, as well as advanced ovary carcinoma [50]. In a pre-clinical trial, the albumin-bound paclitaxel showed an improved safety profile and increased activity in mice with bone sarcoma, resulting in temporary regression and increased survival [51]. In a phase I clinical trial, patients aged ≥6 months to 18 years old with non-central nervous system (CNS) solid tumors were treated with Abraxane®. Results showed a manageable safety profile across all doses, showing promising preliminary clinical activity [52]. These results further prove the potential of albumin-bound NP formulations as there are ongoing phase II clinical trial that include pediatric patients [53].

Chitosan is another natural polymer used in NP formulations. It is an altered natural carbohydrate-based derivative that is obtained from animals, insects, fungi, and marine vertebrates. Because it is a natural polymer, chitosan is characterized by its biocompatibility and biodegradability [49]. In the study of Chen Y, *et al*. 2015, prednisolone-loaded chitosan NPs were prepared for the management of pediatric asthma. Prednisolone is a glucocorticoid used for its anti-inflammatory, anti-neoplastic, immunosuppressive, and vasoconstrictive effects [54]. The NPs were produced by ionotropic external gelation technique, with Tween® 80 and tripolyphosphate serving as a surfactant and crosslinker, respectfully, and developed into fast disintegrating oral tablets by direct compression. These chitosan NPs showed good physiochemical properties and the potential for its use in pediatric patients who have problems with swallowing other dosage forms, with the goal of improving patient compliance [55].

Poly(ethylene glycol) (PEG) is a non-ionic hydrophilic polyester widely used in the field of nanotechnology. It is not biodegradable, being excreted in its unaltered form by the kidney, however, it does not accumulate in the tissues due to its hydrophilic nature. Because of this hydrophilic nature it can be used to stabilize the NPs in the aqueous medium, avoid aggregation, and increase solubility. Moreover, PEG suppresses opsonization, and so it is not as easily detected by the immune system as an external substance [49]. Krishnan V, *et al*. 2013 developed dexamethasone-loaded NPs based on an amphiphilic block of the biodegradable copolymer, comprising of PEG and poly(ε-caprolactone), through the nanoprecipitation method to treat leukemia in the PP. *In vitro* and *in vivo* studies showed no toxicity with the unloaded formulation, and the dexamethasone-NPs demonstrated a significant improvement

in the quality of life and survival of mice compared to the free drug. These NPs showed potential to treat childhood leukemia and to reduce the dose of dexamethasone needed to induce cell death and improve survival [56].

2.2.2. *Dendrimers*

Dendrimers (Figure 2) are radially symmetric nano-sized macromolecules with homogenous, monodisperse, and well-defined structures consisting of tree-like branches built around a small molecule or a linear polymer core. The term "dendrimer" is only an architectural pattern and not a compound [57].

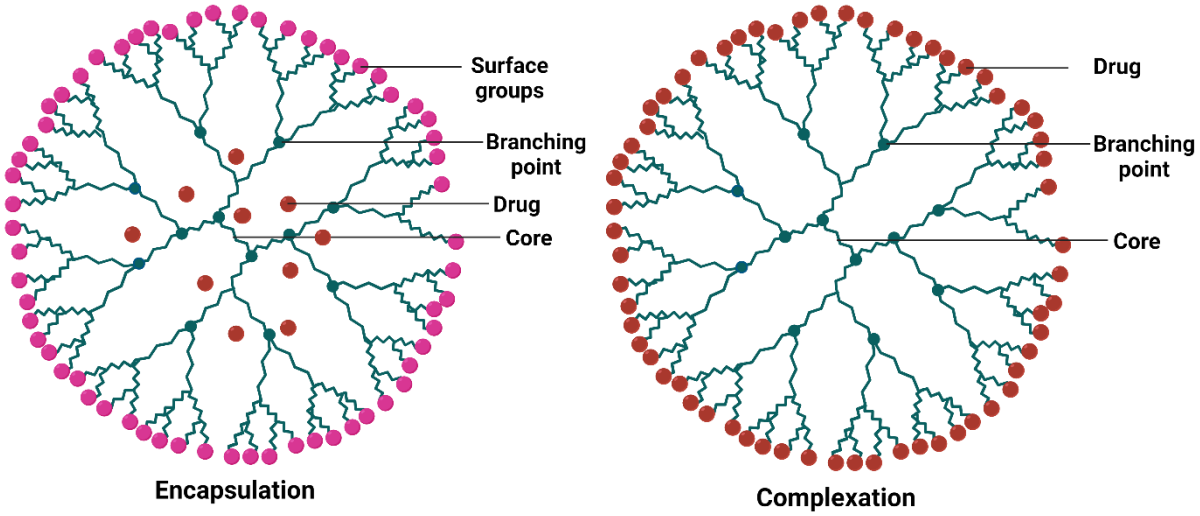

***Figure 2*:** Representation of two types of dendrimers.

In the study of *Yellepeddi, et al. 2018* a pediatric oral formulation of N-acetyl-L-cysteine (NAC) dendrimer conjugate containing Capmul® MCM as a penetration enhancer was developed. NAC is commonly used as an antidote for acetaminophen poisoning and has shown promise in treating neurological disorders such as cerebral palsy. It suffers, however, from a few drawbacks, such as poor oral bioavailability and poor blood-brain barrier (BBB) permeability, which limits its clinical success, requiring high doses for therapeutic activity. For this reason, a NAC-dendrimer conjugate was formulated, results revealed it to be stable in simulated gastrointestinal fluids and its oral absorption enhanced in the presence of Capmul® MCM. These dendrimer-based NPs could be beneficial for the treatment of pediatric patients with neuroinflammation [58].

2.2.3. *Lipid Nanoparticles*

Lipid-based NP delivery systems can be emulsions, vesicular or particulate systems. The most used are liposomes, SLN, and nanostructured lipid carriers (NLC). These

nanosystems are good for encapsulating poorly water-soluble, lipophilic and poorly permeable drugs [59].

Liposomes (Figure 3) consist of vesicles with one of more phospholipid bilayers, with each phospholipid having a hydrophilic and a hydrophobic tail, the tails face each other whist the heads are oriented towards the external aqueous medium. Hydrophilic drugs occupy the internal compartment while lipophilic drugs are internalized in the liposomal lipidic bilayer membrane, these particles have a size ranging from 20 nm to 10 μm [59].

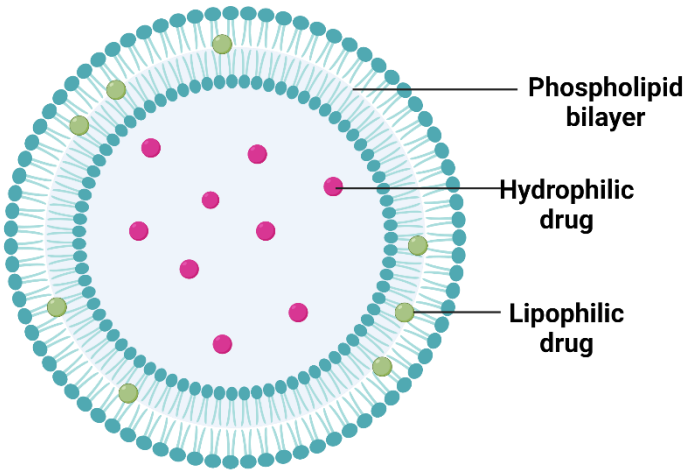

***Figure 3*:** Representation of a lipossome with a hydrophilic and a lipophilic drug load.

There are several liposomal drugs in the market that have been evaluated for the use in children. Marqibo® is a vincristine sulphate liposome injection used in lymphoblastic leukemia treatment, composed of sphingomyelin and cholesterol; with a particle size of 100 nm, that was approved by the FDA in 2012. A phase I clinical trial was reported with this drug substance in patients aged <21 years old with leukemia, chemotherapy-refractory tumors, or relapsed solid tumors. The results of this study did not show dose-limiting neurotoxicity with the FDA-approved adult dose. Furthermore, nonclinical studies showed that these liposomes could potentially increase the accumulation in the tumor site, the time of residence, and the controlled release of vincristine in the tumor when compared to the its conventional form [60], [61].

SLN (Figure 4) are comprised of a solid lipid core stabilized by surfactants in an aqueous medium. These particles have a spherical shape and a size of 50 nm to 1 µm. They are well tolerated and have been proven to reduce systemic and cellular toxicity, thus exhibiting high biocompatibility. Because of their biocompatibility, these particles can be administered through all routes of administration. SLN enhance drug bioavailability and improve its stability, protecting from chemical and enzymatic degradation, allowing a controlled drug release and improving the delivery to its target site [59].

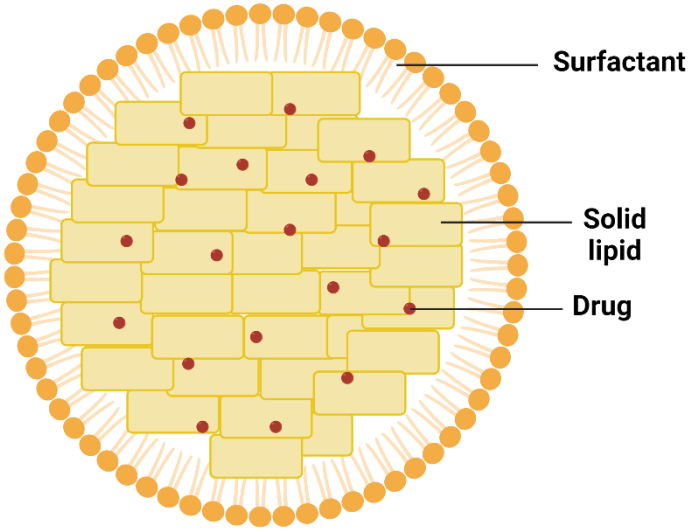

Figure 4: Representation of a SLN.

As mentioned before, in the study of Cirri M, *et al.* 2017, an innovative pediatric oral formulation of HCT was formulated. An HCT-cyclodextrin complex was incorporated into Precirol® ATO5-based SLN with Pluronic® F68 as a surfactant. The SLN formulated showed improved bioavailability of HCT and sustained release properties, being suitable for the treatment of hypertension in pediatric patients [40].

NLC (Figure 5) are another type of lipid nanoparticles, they differ from SLN by having a nucleus made up of both solid and liquid lipids. NLC also show higher drug loading capacity than SLN since their core is less organized [59].

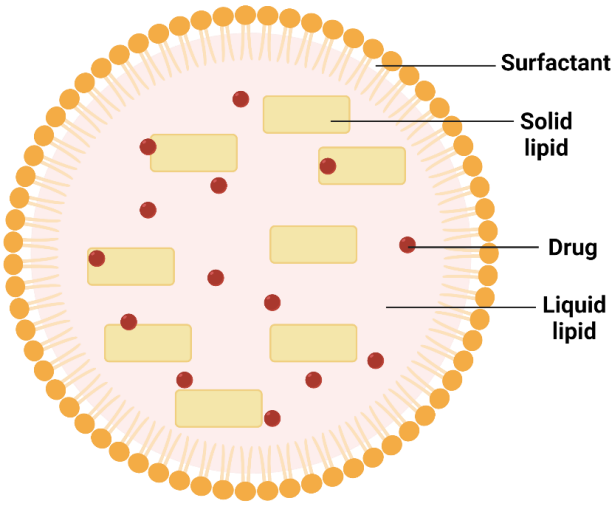

***Figure 5*:** Representation of a NLC.

The same authors from Cirri M, *et al.* 2017 developed NLC containing HCT for pediatric administration. The NPs were produced using the microemulsion technique. The NLC with the superior results contained Precirol® ATO5 as the solid lipid, Tween® 80 and Tween® 20 as a surfactant and co-surfactant, respectively, and castor oil as the liquid lipid. The formulation was orally administered in Sprague-Dawley rats and the results showed better sustained drug release and diuretic effect than the SLN [62].

2.2.4. Metallic nanoparticles

Metallic NPs (Figure 6) are another type of nanosystem that has been studied for the purpose of pediatric drug delivery. These systems are solid, colloidal, particles whose size can range from 10 to 1000 nm and possess good physiochemical properties, high reactivity, high stability, as well as plasmonic and photothermal properties, which make them potent drug carriers [63]. Metallic NPs can be gold NPs, silver NPs, magnetic NPs, quantum dots, iron oxide NPs, among other types [64].

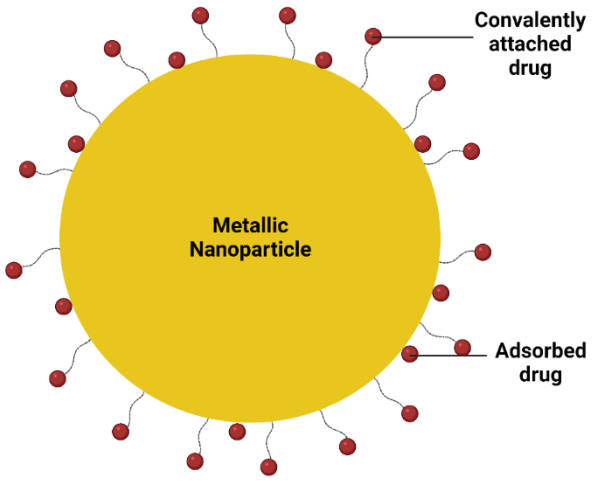

***Figure 6*:** Representation of a metallic NP.

In the study of Liu Zuliang, *et al.* 2017, gold NPs coated with a polymeric shell composed of PEG, chitosan, and polyethyleneimine were loaded with siRNA for pediatric ependymoma and medulloblastoma cells. As mentioned previously, a reduction in Ape1 gene expression is associated with increased DNA damage after radiation. The gold NPs produced loaded with siRNA reduced Ape1 gene expression and, consequently, increased the effect of radiation treatment in ependymoma and medulloblastoma cells lines. These results show a promising approach in reducing pediatric brain tumor resistance to radiation therapy using metallic NPs as a delivery system [65].

Although many NP-based formulations already show potential and safety for pediatric administration, they still require more studies to properly evaluate their effectiveness. The amount of clinical data of nanotherapeutics (NTs) on these patients is still only a small fraction of adult data, for that reason, there is a clear need for more clinical trials with the inclusion of pediatric patients. There are more nanostructured drug formulations that have not been studied in the PP, more studies on these formulations will open more alternatives for pediatric drug therapy, with the potential of improving these treatments.

2.3. Developmental and maturational changes that affect the pharmacokinetics of nanoformulations

PKs in pediatrics play a major role in drug formulation, dose recommendations, and toxicity evaluations. Developmental changes in the maturation of a child will affect the dose needed for therapeutic efficacy, as well as the toxicity of a certain active substance. Studying the differences in a child's biology comparatively to an adult and how these differences will affect the PK profile of a NF will allow for more accurate dose adjustments and facilitate clinical translation.

PK studies comprise the passage of drugs through the body. It is the study of the ADME of a drug or compound. These are the processes that occur from the moment of a drug/compound administration to its elimination from the body. Absorption is the process by which a compound enters the body, from the site of administration to the blood flow. In most routes of administration, the drug passes through various anatomical barriers, such as the intestinal epithelium, the skin epithelium, the BBB, etc. Oral absorption is heavily influenced by the drug's solubility/dissolution in the gastrointestinal tract (GIT), as well as its permeability across intestinal membranes. Distribution is the mechanism by which a compound travels from

the intravascular space into tissues and organs. This process is influenced by factors such as solubility, volume of distribution (Vd), and protein binding. Clearance (CL) refers to the sequence of processes by which a drug compound is irreversibly removed from the body, consisting of metabolism, which is the chemical or enzymatic alteration of a compound into its metabolites, and excretion, the process by which it leaves the body, promoted by renal or biliary CL [66]–[68].

2.3.1. Absorption

The absorption of NFs throughout the neonatal period is affected by the gastric pH, which is relatively high during this phase, differences in gastric pH affect drug dissolution, solubility, release, stability, and permeability [66]. While adults have a healthy gastric pH of 1,5-3,5 [69], a study on 150 neonates showed that the average gastric pH value at birth via vaginal delivery is 6; while via cesarean section revealed a higher pH value of 6.79 [70]. Another study found that gastric pH of neonates, in a fasting state, at 2-3 weeks of life was around 2.6, which is considerably lower than that the average pH of 4.6 of neonates at 2-6 days of life [71]. Succinctly, after being neutral at birth, the gastric pH lowers to 1-3 within the first hours of life, it returns to neutral values after week 1, and then decreases slowly. By age 3, the gastric acid secretion by kilogram of body weight is similar to adult secretion [72]. These discrepancies in gastric acidity result in differences in absorption since it is heavily influenced by local pH, weak basic drugs have increased dissolution and absorption in acid environments like the stomach, while weak acidic drugs are dissolved and absorbed more in basic environments like the intestine. Therefore, an increase in neonatal gastric pH compared to adult pH will result in an increased absorption of weak acids, while decreasing the absorption of weak bases when compared to adults. Some examples of weakly basic drugs include ketoconazole, itraconazole, dazatinib, indinavir, among others [73]–[75]. Drugs like ampicillin, amoxycillin and erythromycin, which are susceptible to acid environments, will have an increased absorption when administered orally in the neonate [76], [77].

Another important aspect that affects the absorption of NFs in pediatric patients is the increased gastric emptying time (GET) of neonates comparatively to adults. Adult males have a GET of 45 min, 60 min for adult females, and 75 min for neonates. Consequently, drug peak concentration will be lower and the time that takes to reach it will be longer [74]. Intestinal transit time is also extended in neonates due to reduced motility and peristalsis; although in older infants the opposite seems to occur, due to increased intestinal motility, the intestinal transit time is shorter; and so, sustained release formulations suffer incomplete absorption.

The reduced surface area in children is also responsible for reduced intestinal absorption [19], [67], [78], [79].

Others PK factors related to oral absorption need to be taken into consideration when developing NFs for children, such as the immaturity of the intestinal mucosa, which is characterized by increased permeability, reduced intestinal mobility, and reduced enzymatic activity. Although permeability is increased, transport systems are immature; therefore, several transporter-mediated interactions may impede therapeutic absorption [67]. There are also variations in the intestinal microflora, the GIT is sterile during fetal life and microbial colonization occurs after birth, reaching normal levels in adolescence. Maternal or artificial milk intake can also influence microbial composition, which causes even more variability among children [19]. For these reasons, drug bioavailability, bioactivity and toxicity are influenced by the enzymatic transformation of drug structures and by the gut microbiome, affecting safety and efficacy in children [80].

Rectal administration is not as affected by maturational changes. However, depending on the absorption site, whether it is in the lower or the upper rectum, absorption is expected to vary [67]. Developmental aspects that distinguish younger children, especially neonates, from older children or adults and that affect intramuscular administration are the decreased blood flow into the muscle, reduced muscle-mass ratio, and higher water proportion. This route has been found to be unreliable in clinical practice due to being unpredictable [17], [67]. Transdermal administration is mostly affected by the greater surface body area to weight ratio, better hydration, and reduced thickness of the epidermis of neonates, infants, and young children. Absorption through other routes of NT administration are also affected by developmental changes, such as transmucosal and intrapulmonary [19].

2.3.2. Distribution

Several processes are involved in NT distribution, which are distinct between neonates and infants when compared to adults - those being plasma protein binding, membrane permeability, and extracellular fluid volume [81].

The BBB is a selectively permeable membrane that regulates the passage of various large and small molecules into the brain. At birth, the BBB is not fully mature and due to reduced permeability in neonates and infants, drug substances may cause toxicity through access to the CNS. Another aspect that affects intrathecal NT dosing in the PP is the relatively large volume of the CNS compared to their body surface area (BSA) - the CNS reaches 80-90% of the adult volume by the age of 4-6 years old, while BSA only reaches adult values by 16-18 years of age [74], [82].

In neonates and infants, the unbound fraction of drugs substances is frequently higher for several reasons; not only is the binding protein concentration usually lower, but these proteins commonly have reduced binding properties. Another reason is the increased concentration of non-esterified fatty acids, bilirubin and other endogenous substances that competitively bind to albumin. α-1-acid glycoprotein, another drug binding protein whose levels are also low at birth, increasing over the first year of life until reaching normal adult values. Plasma protein binding affects the biodistribution (BD) of NPs; protein binding can change NPs size, surface charge, and even influence the internalization of these NPs into macrophages. Albumin binding seems to promote a prolonged NP circulation time in the blood. Since albumin levels are lower in neonates, NP circulation time is also expected to be lower, however, other factors also influence NP circulation time and more studies are needed on this subject [19], [67], [76], [83], [84].

The total body water to body weight ratio in young infants is significantly higher compared to adults (80-90% and decreases to 55-60% by adult age). The extracellular water content is also higher in neonates (45% compared to 20% in adults). And the total body fat is lower (10-15% compared to adult men, and women at 11-20% and 16-30%, respectively). The consequences of this are a higher Vd in neonates and infants of water-soluble drugs, and reduced Vd of fat-soluble drugs [19], [67], [76].

2.3.3. Metabolism

The mechanisms of drug metabolism can be classified into phase I and phase II reactions, phase I reactions involve structural alterations of the drug molecule, oxidation, reduction and hydrolysis, and phase II reactions consist of conjugation with another more water-soluble molecule, both metabolic pathways can be immature at birth and be subject to maturational changes. Metabolism in children differs from adults because of cytochrome enzyme immaturity, which are responsible for the transformation of exogenous and endogenous substances to, subsequently, eliminate them from the body. Children have an increased hepatic blood flow compared to adults; and so, drugs with high extraction ratios, which are dependent on hepatic blood flow, will have an increased hepatic clearance, and consequently less therapeutic effect. However, due to the immaturity of metabolic enzymes, which have a predominant role in drug metabolism, drugs with low extraction ratios, which are dependent on protein binding and hepatocyte metabolic activity, will generally have a prolonged half-life. Furthermore, a drug with high or low extraction ratios in adults will not necessarily have that same category in children, since extraction ratios are dependent on protein binding and the importance of metabolic pathways to a certain compound. Dosage

recommendations should take this into account, not only the developmental age of the patient, but also specific drug metabolic pathways [66], [67], [76]. The hepatobiliary system is the primary route of elimination for blood-circulating particles that do not undergo renal CL, they undergo enzymatic degradation and are subsequently excreted in the bile. The reticuloendothelial system in Kupffer cells is also responsible for cellular removal of particles in the liver [66]. Furthermore, Cyp-nanoparticle interactions can also impact the metabolism of xenobiotics by inhibiting certain cytochrome enzymes, while the mechanisms involved are not fully understood, careful consideration should be advised when considering complex therapies [85]. Although there are very few studies on the matter, various factors can affect NP distribution, and so, the metabolic pathways of each NF should be carefully analyzed as to correctly evaluate dosing recommendations.

2.3.4. Excretion

Drug excretion by the kidney is reliant on 3 processes - glomerular filtration, tubular secretion, and reabsorption. The glomerular filtration rate (GFR) is considerably lower at birth, increasing during the first two weeks of life, and reaches adult levels by six months of age. This rapid improvement in GFR leads to a rapid increase in the renal CL of GFR-dependent drugs, and a diminished risk of drug accumulation. Tubular secretion increases during the first months of life, reaching adult levels at around seven months of age, taking more time than glomerular filtration to reach adults values. When the elimination of a drug is dependent on renal tubular mechanisms, the disproportionate rate in development of glomerular filtration and tubular function can have complex and variable effects on drug renal CL, since a low GFR may be paired with an even greater reduction in tubular reabsorption. Renal blood flow at birth is only 5-6% of cardiac output; it reaches 15-25% by year one, only reaching adult levels by two years of age. During the neonatal period, the elimination of drugs, which are excreted in its unchanged form, is restrained by the immaturity of glomerular filtration and tubular secretion. However, a similar or even greater rate of elimination of some drugs has been observed from plasma in late infancy/childhood compared to adults. Infant urinary pH levels are lower than adult levels, which may influence the reabsorption of weak organic acids and bases [19], [66], [67], [74], [86].

The study of developmental and maturational differences between pediatric patients and adults plays a very important role in understanding the PK profile of NPs in these patients. There are still very few studies that directly explore the relationship between these differences

and nano delivery systems. All these aspects must be fully taken into consideration when determining the right dose for pediatric administration.

2.4. Safety issues and challenges

Although many benefits of nano delivery systems have been pointed out for their use in pediatrics, there are still some concerns and challenges that must be considered. The implementation of nanomedicine in this population suffers from a few of the same challenges of conventional therapeutics, as well as challenges related to the use of novel delivery systems. It is of utmost importance that any occurring side-effects are analyzed, discussed, and studied before the approval of a nanosystem for pediatric treatment. This is especially important considering the susceptibility of this population group. Each subtype of NP should be tested as an individual case, since no general rule can be formulated and the available data on the subject suggests broad results [87].

2.4.1. Safety

The safety of NTs is a complex subject, for clinical translation to be possible, a detailed assessment on the safety of these products is necessary. However, at present, there is a shortage of methods and standards for this evaluation, as the methods used for conventional drugs cannot evaluate the safety of NPs accurately. As mentioned previously, due to the nature of these medicines, physiochemical properties such as morphology, size, surface area and aggregation may alter the BD and interactions with target cells. To increase the odds of success for clinical translation it is important to understand the physiochemical properties of NP, the toxicity profile of known drugs, and the properties of nanocarriers [88].

2.4.2. Biological challenges

The biological challenges for NT development revolve mostly around BD and biological barriers. As with every pediatric drug, the introduction of new nano-based delivery systems to pediatrics will face adversities related to the maturation and development of this age group, which, as touched upon in previous segments, will affect BD and interactions with biological barriers, both external (organ and skin) and internal (cellular). The impact of these interactions on efficacy, targeting and safety of NPs must be well studied and characterized. For this purpose, imaging modalities and quantitative methods must be developed, and be well adapted for use in children. Another important factor that affects BD is the heterogeneity of human

diseases, as well as the difference between humans and animals, this becomes especially apparent in clinical studies [88].

2.4.3. Scale-up and cost

Large-scale synthesis of drug products with high repeatability in the manufacturing process is crucial for clinical translation. Many NTs do not meet the requirements for scale-up synthesis and reproducibility. Because of their complexity, challenges in large-scale drug preparation are greater for NPs than those of conventional drugs. In clinical studies and preclinical investigations NPs are mostly synthesized in small batches, since it is easier to control and optimize the formulation. Oppositely, large-scale production is significantly affected by small variations in the manufacturing process, which can result in critical changes to the physiochemical properties of NPs and influence the therapeutic outcomes. Moreover, the development of these drugs often requires large costs compared to traditional drugs, not only in the scale-up, but also in preclinical and clinical development. A strategy often employed to circumvent this issue is the development of NTs of conventional drugs that are already approved, this approach entails a considerably lower financial risk and increases the likelihood of success. The cost is a very important issue since the exorbitant costs of a drug product can, not only impede its development, but also prevent it from being implemented as a mainstream treatment [88].

2.4.4. Regulation and Standards

Another challenge that poses a barrier in the development of NTs is the lack of standards and regulation in quality control, manufacturing practices, efficacy evaluation and safety evaluation. There is also lack of standardization in the assessment, as a unique category, of nanomedicines for clinical translation, the examination of new NTs by the FDA, EMA and other regulatory agencies is done on an individual product basis, this leads to significant differences between geographical regions, causing some drugs to be approved in one country and not in other countries [89], [90]. Furthermore, NP-based medicines have multiple components that can affect the pharmacological behavior of the active drug, which contrasts with standard drugs where there is usually only a single active agent and other compounds, the excipients, serve as inactive formulation aids. All of these aspects contribute to the complexity of the regulatory pathways necessary for the efficient development and approval of these drugs [88], [91], [92].

FUTURE PERSPECTIVES AND FINAL REMARKS

Although NPs have seen an exponential rise in the past few years and have been proven to be a promising option in resolving some of the problems associated with pediatric therapy. It is still far from a perfect option, the costs associated with the development of NTs, coupled with the small market of pediatric patients, the regulatory challenges, and the task of developing a drug for such a diverse population group is enough to deter potential investment in this field. However, there has been a rise in initiatives by regulatory agencies like the FDA and the EMA with the goal of promoting pediatric drug development and increasing the number of available options for these patients. A good example is the Center for Pediatric Nanomedicine, founded in 2011, an effort to develop and research effective, therapeutic nanomedicine applied to pediatric diseases. In the future, with the rise of more initiatives, advancements in NPs research, increased knowledge of pediatric diseases and PKs, improvement of pediatric clinical trials, and possible reduction in the development cost of NTs, the use of NPs to treat pediatric diseases will most likely be more and more frequent, as the benefits overcome the drawbacks.

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