UNIVERSIDADE D
COIMBRA

Alexandra Benedita Bastos de Campos Carvalho

Relatórios de Estágio e Monografia intitulada "Nanocarrier-based strategies to improve the topical treatment of psoriasis" referentes à Unidade Curricular "Estágio", sob orientação da Dra. Ana Leite e Silva, da Dra. Andreia Silva e da Professora Doutora Filipa Alexandra Mascarenhas Melo e apresentados à Faculdade de Farmácia da Universidade de Coimbra, para apreciação na prestação de provas públicas do Mestrado Integrado em Ciências Farmacêuticas.

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Declaração de autoria

Eu, Alexandra Benedita Bastos de Campos Carvalho, estudante do Mestrado Integrado em Ciências Farmacêuticas, com o n.º 2016222184, declaro assumir toda a responsabilidade pelo conteúdo do Documento Relatórios de Estágio e Monografia intitulada "Nanocarrier-based strategies to improve the topical treatment of psoriasis" apresentados à Faculdade de Farmácia da Universidade de Coimbra, no âmbito da unidade de Estágio Curricular.

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Coimbra, 28 de outubro de 2021.

Alexandra Benedita Bastos de Campos Carvalho

(Alexandra Benedita Bastos de Campos Carvalho)

Agradecimentos

Aos meus pais, as minhas duas pessoas preferidas do mundo, por todo o apoio incondicional em cada uma das minhas etapas, por me transmitirem sempre os valores corretos e me oferecerem todas as oportunidades.

Aos meus irmãos, por serem sempre capazes de me animar nas situações menos boas, mesmo quando a minha paciência é escassa. Ainda assim, serão sempre os melhores do mundo.

Aos meus avós, os maiores entusiastas da minha entrada em Coimbra e os meus anjinhos da guarda. O vosso maior defeito é não ser eternos.

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A todos os restantes colegas e amigos com quem tive a sorte de me cruzar, sem vocês não seria a mesma coisa.

À Dra. Ana Leite pelo profissionalismo, simpatia e excelente forma como me recebeu e ensinou, dando-me sempre oportunidade de crescer e aprender pela autonomia e independência que tanto caracterizaram o meu estágio.

À Professora Doutora Filipa Mascarenhas Melo, pela incrível paciência e disponibilidade demonstradas ao longo da realização da presente monografia.

Por último, a ti Coimbra! Que me ensinaste a crescer, me viste rir e chorar e me deste as mais bonitas amizades que levarei comigo para a vida. A minha segunda casa durante 5 anos onde prometo sempre regressar.

A todos, o meu muito obrigada!

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Parte I

Relatório de Estágio em Farmácia Comunitária

Farmácia Coimbra

Lista de Siglas e Acrónimos

ANF – Associação Nacional das Farmácias

FC – Farmácia Coimbra

IMC – Índice de Massa Corporal

ISEC – Instituto Superior de Engenharia de Coimbra

MICF – Mestrado Integrado em Ciências Farmacêuticas

MNSRM – Medicamentos Não Sujeitos a Receita Médica

MNSRM-EF – Medicamentos Não Sujeitos a Receita Médica de Venda Exclusiva em Farmácia

MUV – Medicamentos de Uso Veterinário

SWOT – *Strengths, Weaknesses, Opportunities and Threats*

1. Introdução

Desde muito cedo, o farmacêutico desempenha um papel fundamental na sociedade enquanto especialista do medicamento e promotor da saúde. Numa farmácia de oficina, para além de agente de saúde pública, é muitas vezes um conselheiro e amigo para os que por lá passam.

Assim, os 5 anos do Mestrado Integrado em Ciências Farmacêuticas (MICF) culminam com a realização obrigatória de um estágio curricular em Farmácia Comunitária. Escolhi a Farmácia Coimbra para realizar o meu estágio, que teve a duração de 12 de abril a 30 de julho, completando um total de 810 horas.

O objetivo deste estágio é consolidar e aplicar os conhecimentos adquiridos, objetivos esses que foram cumpridos, bem como uma experiência pessoal enriquecedora.

O presente relatório aborda as atividades e tarefas por mim desenvolvidas perante uma análise SWOT (*Strengths, Weaknesses, Opportunities and Threats*), onde destaco os pontos fortes, pontos fracos, oportunidade e ameaças decorrentes do meu estágio.

2. Farmácia Coimbra

A Farmácia Coimbra (FC) fica localizada na Avenida Mendes Silva, em Coimbra, inserida dentro do centro comercial CoimbraShopping. Assim, e por estar situada num centro comercial, tem uma vasta variedade de clientes que pela farmácia passam.

Não só pelo CoimbraShopping, está também nas proximidades do Instituto Superior de Engenharia de Coimbra (ISEC) e na zona do Vale das Flores e Bairro Norton de Matos.

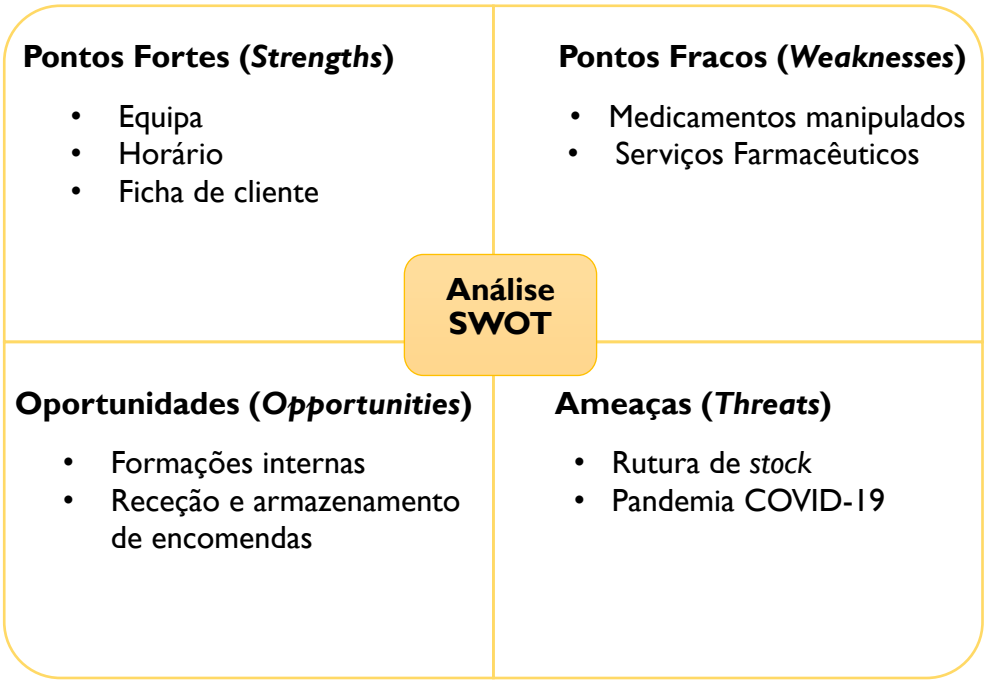
O horário laboral da farmácia rege-se pelo horário do Continente, sendo das 9h às 23h de segunda a quinta-feira, das 9h às 00h às sextas-feiras e sábados, e no domingo das 9h às 22h.

A FC é constituída por dois pisos, sendo que no rés-do-chão é a zona de atendimento ao público. Para esse mesmo efeito, dispõe de seis balcões de atendimento, sendo que durante o meu estágio apenas quatro estavam a ser utilizados. Deviamente organizada, divide-se entre produtos de dermocosmética, puericultura, solares e medicamentos não sujeitos a receita médica (MNSRM) e medicamentos de uso veterinário (MUVs) estão localizados atrás dos balcões. Tem ainda dois gabinetes, um deles destinado ao atendimento individualizado do cliente, determinação de parâmetros bioquímicos ou realização de consultas, sendo que a farmácia tinha um serviço de consultas de nutrição e ecografias 4D. O outro gabinete é o da direção técnica, onde se efetua a contabilidade da farmácia e arquivo de documentação necessária.

Ainda no piso inferior temos um outro espaço onde ocorre o armazenamento de medicamentos não sujeitos a receita médica de venda exclusiva em farmácia (MNSRM-EF) organizados por ordem alfabética e medicamentos que estão reservados. Aqui está também o frigorífico onde são armazenados os medicamentos que exigem condições de conservação especiais.

O piso superior está maioritariamente destinado à gestão e receção de encomendas.

3. Análise SWOT



Quadro 1: Representação esquemática referente à análise SWOT do estágio em Farmácia Comunitária.

3.1. Pontos Fortes

3.1.1. Equipa

A equipa da FC é uma equipa jovem e dinâmica, constituída pela Dra. Ana Leite, Diretora Técnica, quatros farmacêuticos, três técnicos de farmácia e um auxiliar.

Desde o momento em que cheguei à farmácia foram todos muito prestáveis, com uma prontidão e disponibilidade incríveis para o que quer que eu precisasse. Senti-me sempre muito à vontade, e o facto de ser uma equipa praticamente toda jovem ajudou a que o ambiente fosse sempre muito acolhedor e amigável.

Esta postura de todos era um dos motivos pelos quais os próprios clientes se dirigiam à farmácia muitas vezes apenas pela simpatia e agrado com que eram recebidos.

O que torna a equipa em si um dos pontos mais fortes, é também o facto de quando cometia erros ou não me explicava tão bem perante o cliente, a primeira atitude era sempre no sentir de me ensinar e me corrigir de modo a que na próxima vez o atendimento corresse na perfeição. Nunca em momento algum me senti inferiorizada por ser uma estagiária, ou não ter tanta prática e falta de conhecimento.

3.1.2. Horário

No meu estágio em farmácia comunitária eu tinha que estagiar 810h. Uma vez que não realizei apenas o estágio em farmácia comunitária, mas também em indústria farmacêutica, esse número de horas traduzia-se em 4/5 meses de estágio caso eu apenas fizesse 8h diárias O facto de ser uma farmácia de *shopping* e ter um horário alargado ajudou-me bastante, pois permitiu-me fazer mais horas por dia, de modo a conseguir terminar o estágio aquando os meus colegas.

3.1.3. Ficha de cliente

A FC não está inserida na rede Farmácias Portuguesas da Associação Nacional das Farmácias (ANF), não sendo assim aderente do cartão Saúda.

Por outro lado, dispõe da criação de ficha de cliente, o que se torna benéfico tanto para o cliente como para o farmacêutico que lhe está a prestar serviço. Relativamente ao farmacêutico, é útil pois tínhamos acesso à medicação que o cliente costumava tomar e quais os seus laboratórios usuais, tendo assim a possibilidade de escolher os mesmos laboratórios por forma a não baralhar as caixas, desde a forma à cor, uma vez que muitos dos clientes já eram idosos. Em relação ao cliente, tinham a vantagem de cada vez que fizessem uma compra na farmácia acumular pontos, pontos estes que quando atingissem um certo número se traduziam em descontos.

3.2. Pontos Fracos

3.2.1. Medicamentos manipulados

Apesar da FC possuir um laboratório com todas as condições necessárias à preparação de medicamentos manipulados, sendo que é onde ocorre a preparação de xaropes quando requisitada pelo cliente, o reduzido número de pedidos de medicamentos manipulados não justifica a permanência das matérias-primas na farmácia. Assim, quando requisitado, encaminha-se o pedido para a Farmácia Porto (pertencente ao mesmo grupo de farmácias), que mais tarde quando preparado envia o medicamento manipulado de volta para a FC.

Durante o meu estágio, este foi um ponto menos positivo, uma vez que não pude aplicar certos conhecimentos adquiridos durante o MICF.

3.2.2. Serviços Farmacêuticos

Infelizmente, durante o meu estágio na FC, não foi possível prestar serviços farmacêuticos individualizados como a medição da pressão arterial, da glicémia, do Índice de Massa Corporal (IMC) e do colesterol. Não por despreocupação da farmácia, mas porque o gabinete designado para tal foi necessário para a realização a tempo inteiro de testes rápidos à COVID-19.

Em situações normais, este tipo de serviços é prestado pela FC com o devido custo acrescido.

3.1. Oportunidades

3.3.1. Formações internas

Durante o estágio, tive o privilégio de assistir e participar em várias formações que a FC teve. Os representantes comerciais de diversos laboratórios iam regularmente à farmácia falar de novos lançamentos ou apenas relembrar o modo de tomar/usar, dosagens e indicações de produtos já existentes no mercado.

Para além de ser uma mais-valia enquanto estagiária pois permitiu-me um conhecimento mais aprofundado dos MNSRM e MNSRM-EF que dispúnhamos na farmácia, de modo a poder prestar o melhor serviço possível, abriu-me também portas no mundo profissional no sentido de conhecer diferentes laboratórios e os diversos produtos que cada um desenvolve e comercializa.

3.3.2. Receção e armazenamento de encomendas

Quando cheguei à FC, inicialmente foi-me feita uma visita pelos diferentes gabinetes, incluindo o *back-office*, e área aberta ao público. No início do estágio, durante aproximadamente mês e meio, o meu trabalho de estagiária passou pela receção e armazenamento de encomendas. Através do SIFARMA 2000® dava a entrada de encomendas, desde reservas feitas no dia anterior a encomendas mais generalizadas que iam chegando, desde produtos cosméticos a MSRM e MNSRM. Após a entrada feita, seguia-se o armazenamento dos produtos. No caso de reservas, era impresso um talão com o nome, contacto e respetivo produto, pago ou não pago, da pessoa que mais tarde seria contactada para vir levantar a reserva feita. No caso de MNSRM e MNSRM-EF, estes eram encaminhados para o piso inferior para serem posteriormente guardados e repostos nos respetivos lineares e atrás dos balcões. Por sua vez, os MSRM eram armazenados no *robot.*

Quando estas tarefas terminavam, ia então para a zona dos balcões observar o atendimento dos meus colegas.

Achei, sem dúvida, uma etapa muito importante no meu estágio. Foi uma primeira fase mais observacional que me ajudou a estar mais preparada e mais à vontade quando chegou a minha altura de atendimento ao público. O processo de rececionar e armazenar as encomendas que chegavam ajudou-me a ir reconhecendo as caixas, os diferentes laboratórios e, não menos importante, a perceber como funciona a farmácia também no *back-office* e todo o trabalho necessário a fazer à parte do atendimento ao público.

3.4. Ameaças

3.4.1. Rutura de *stock*

Uma vez que a FC faz parte de um grupo de farmácias, as encomendas feitas estavam ao encargo da Farmácia Porto, também uma das farmácias do grupo. Contudo, estas encomendas apenas eram feitas no início do mês, o que, inevitavelmente, ao ser uma farmácia com bastante movimento, se fazia sentir no final do mês.

A FC trabalha muito à base de reservas feitas pelos clientes. Como mencionado anteriormente, a ficha de cliente para além de acumular pontos, era também essencial para se fazer a reserva de um produto. Assim, no final do mês, as reservas de medicamentos aumentavam exponencialmente, pois a farmácia não tinha em *stock* os medicamentos procurados, o que prejudicava também os atendimentos que acabavam algumas vezes por se transformar apenas em reservas.

3.4.2. Pandemia COVID-19

A pandemia COVID-19 durante os meses de abril a julho começou a estar um pouco mais controlada, com o início da vacinação e diminuição de casos e mortes. Ainda assim, tivemos períodos de confinamento em que a FC se viu forçada a trocar várias vezes de horário de atendimento, bem como o fluxo de clientes na farmácia sofreu também algum decréscimo.

A FC para além de vender auto-testes rápidos à COVID-19, também realiza testes de antigénio à COVID-19, e com a chegada do verão muitos dos atendimentos baseavam-se apenas na marcação ou venda de testes, uma vez que é necessário um teste negativo ou certificado de vacinação ao realizar *check-in* em qualquer tipo de estadia ou restaurante.

4. Casos Clínicos

Caso 1

Senhora adulta, cerca de 60 anos, dirige-se à farmácia com as mãos visivelmente gretadas. Questionei se sofria de alguma patologia dermatológica, ao que me respondeu negativamente, dizendo que se tratava do uso excessivo de desinfetante devido à pandemia COVID-19. Aconselhei o creme de mãos da gama Cicalfate da Avène que iria acalmar, proteger e reparar rapidamente as camadas mais superficiais da pele.[1]

Caso 2

Jovem do sexo masculino, cerca de 25 anos, desloca-se à farmácia com grande "dificuldade em ir à casa de banho". Após algumas questões colocadas, verifiquei que é uma questão pontual. Numa primeira abordagem recomendei algumas medidas não farmacológicas tais como ingerir muita água, comer alimentos mais ricos em fibra e praticar exercício físico, no sentido de ajudar a regular o trânsito intestinal. Aconselhei ainda a toma de DulcoSoft® que iria ajudar a amolecer as fezes de uma forma mais continuada, tomando uma saqueta todos os dias ao deitar. Caso a situação se agravasse, nessa altura então atuaríamos com um laxante mais forte, que depois poderia ser utilizado apenas em SOS.

Caso 3

Senhora adulta dirige-se à farmácia com o seu bebé, de aproximadamente 1 ano e meio, mencionando que este está com tosse muita seca, pingo e muito ranho. Para resolver a congestão, indiquei a utilização de água do mar que vai limpar e remover as excreções. Relativamente à tosse, aconselhei o uso de um anti-histamínico, neste caso o Fenistil Gotas®, uma vez que especialmente em crianças a tosse muitas vezes tem causa alérgica. Faz o anti-histamínico 3 vezes ao dia, consoante o peso da criança. A mãe informou-me que a criança pesava aproximadamente 9kg, e uma vez que a posologia indica uma gota por cada kg, neste caso seriam então 9 gotas.

5. Conclusão

A profissão farmacêutica está em constante evolução, estando a sua prosperidade e valorização nas mãos dos farmacêuticos.

A realização do estágio em Farmácia Comunitária é indubitavelmente uma etapa imprescindível no final do MICF, tendo o estágio na Farmácia Coimbra me dado diariamente inúmeras valências para agora poder ser uma excelente profissional. Aprendi a aliar e corelacionar os conteúdos práticos com os teóricos, pondo em prática o que fui aprendendo ao longo de 5 anos de curso, desenvolvi *soft-skills* e capacidades gestoras.

Também a nível pessoal saí mais rica deste estágio. Pelas pessoas que conheci, pelo "desenrascar" que foi necessário em diversas situações e a mente "aberta" que por vezes é exigida.

Ciente do longo caminho que ainda falta percorrer, concluo o estágio com um obrigada a toda a equipa da Farmácia Coimbra por toda a aprendizagem e amizade com que me receberam desde o início. Termino esta etapa certa de que serei uma ótima profissional, promovendo sempre a saúde pública.

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Parte II

Relatório de Estágio em Indústria Farmacêutica

Laboratórios Basi

Lista de Siglas e Acrónimos

AIM – Autorização de Introdução no Mercado

AR – Assuntos Regulamentares

CTD – *Common Technical Document*

DCI – Denominação Comum Internacional

eCTD – *Eletronic Common Technical Document*

FFUC – Faculdade de Farmácia da Universidade de Coimbra

FI – Folheto informativo

IF – Indústria Farmacêutica

MICF – Mestrado Integrado em Ciências Farmacêuticas

RCM – Resumo das Características do Medicamento

SWOT – *Strengths, Weaknesses, Opportunities and Threats*

1. Introdução

O farmacêutico, como especialista do medicamento, cada vez mais tem parte integrante em todo o processo que envolve este, desde o seu desenvolvimento, produção, controlo de qualidade, distribuição e, consequente, dispensa.

O Mestrado Integrado em Ciências Farmacêuticas (MICF) da Faculdade de Farmácia da Universidade de Coimbra (FFUC) tem como última etapa do 2° ciclo de estudos a realização de um estágio curricular. A FFUC exige um estágio em farmácia comunitária, contudo dá oportunidade aos estudantes de realizar outro estágio numa outra área. Assim, através de protocolos estabelecidos com as diferentes entidades, é-nos oferecida a possibilidade de estagiar noutras áreas do medicamento, nomeadamente em Indústria Farmacêutica.

Numa sociedade tão evoluída e com perspetivas futuristas, a regulamentação torna-se um elemento essencial assegurando a efetividade, segurança e qualidade do medicamento. Deste modo, optei por realizar um estágio na área de Assuntos Regulamentares (AR) nos Laboratórios Basi, com duração de aproximadamente 3 meses, com início a 11 de janeiro e término a 9 de abril.

O seguinte relatório compreende as atividades realizadas e competências adquiridas por mim enquanto estagiária, dispondo-se sob a forma de análise SWOT (*Strengths, Weaknesses, Opportunities and Threats*).

2. Laboratórios Basi

Os Laboratórios Basi são uma empresa farmacêutica de referência situados na zona industrial de Mortágua.

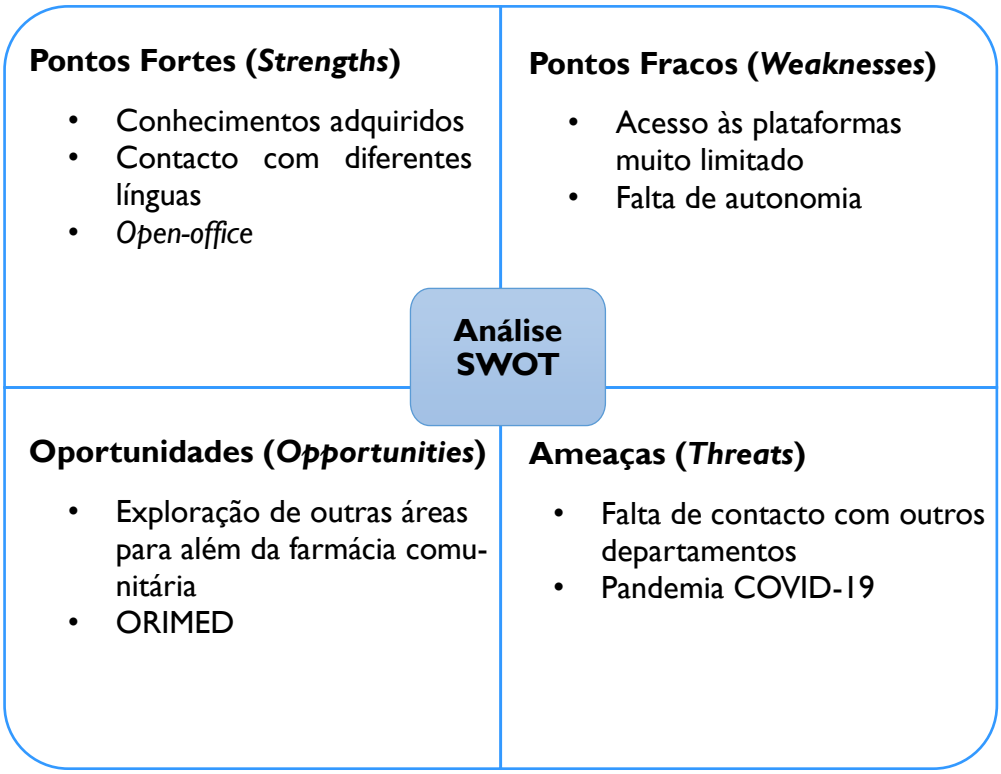
Iniciaram a sua atividade em 1956, e atualmente têm como missão o desenvolvimento, fabrico, comercialização e distribuição mundial de medicamentos. [1]

Os Laboratórios Basi baseiam a sua atividade em 4 pilares chave: flexibilidade, inovação, competitividade e eficiência.[1]

Estão integrados no grupo FHC, dos quais também fazem parte a Empifarma, a Overpharma, associada à comercialização de produtos hospitalares, a Phagecon, associada a serviços de consultoria farmacêutica e ainda a Zeone, consultora da área informática.

Dentro da área de AR, há inúmeros postos de trabalho e diferentes funções, sendo que o departamento em que estagiei foi o de *Registration*.

3. Análise SWOT



Quadro 1: Representação esquemática referente à análise SWOT do estágio em Indústria Farmacêutica.

3.1 Pontos Fortes

3.1.1. Conhecimentos adquiridos

Ao longo do estágio fui aprimorando conhecimentos já adquiridos durante o curso de MICF, nomeadamente na unidade curricular Assuntos Regulamentares do Medicamento.

A informação respetiva de cada medicamento essencial ao seu registo no formato *Common Technical Document* (CTD) é obrigatória. Mais recentemente, tornou-se obrigatória a submissão do dossier em formato eCTD, isto é, a versão eletrónica do CTD. Em MICF é-nos ensinada a parte teórica da composição de um CTD, enquanto que no estágio tive oportunidade de ver na prática como se constrói o documento.

Trabalhei maioritariamente com o Módulo 3, e dentro do Módulo 3, temos o módulo S que corresponde à/às substâncias ativas e o módulo P que diz respeito ao produto acabado.

Os Basi, apesar de serem uma empresa maioritariamente ligada ao desenvolvimento de medicamentos genéricos, estão também recentemente envolvidos na produção de suplementos alimentares e produtos dermocosméticos, apesar destes últimos estarem ainda em desenvolvimento e, portanto, o único contacto que experienciei foi uma formação relativa à regulamentação necessária para a sua introdução no mercado. Ainda assim, sendo um assunto de grande interesse pessoal, mostrou-se incrivelmente vantajosa essa formação na área da dermocosmética, uma vez que na altura do meu estágio pude aliar os conhecimentos que estava a adquirir nos Basi com os conhecimentos adquiridos na faculdade durante a unidade curricular de Dermofarmácia e Cosmética.

Tive também a oportunidade de ver como se realiza um pedido de Autorização de Introdução no Mercado (AIM) e, após resposta do INFARMED, as alterações necessárias a fazer.

As submissões de AIM, alterações ao *dossier* técnico e outras tarefas importantes passam todas pela utilização de plataformas e serviços online fornecidos pelo INFARMED, desde a SMUH para submissão de AIM, SMUH-ALTER quando pretendemos fazer alterações de AIM e ainda o INFOMED, para consultar RCMs e FIs, bem como condições de conservação de medicamentos.

A consolidação de CTDs foi também uma das tarefas que realizei, que consiste na atualização dos diferentes módulos à medida que vão sendo revistos.

3.1.2. Contacto com diferentes línguas

Uma vez que os Laboratórios Basi contactam e comercializam os seus produtos mundialmente, é necessária a tradução de diversos documentos de acordo com a língua para onde estes vão ser enviados. No decorrer do estágio tive oportunidade de realizar diferentes tarefas abrangendo diferentes produtos, neste caso específico de suplementos alimentares, desde traduções do e/ou para o inglês, francês e espanhol de documentos técnicos, tais como folhetos informativos (FI), rotulagens e cartonagens.

Considerei essas tarefas bastante enriquecedoras, uma vez que para além de estar a trabalhar com FIs que me ajudaram a desenvolver conhecimentos científicos relativos aos suplementos com que estava a trabalhar, pude também aprimorar os meus conhecimentos linguísticos.

3.1.3. *Open-office*

A disposição do departamento de AR dos Laboratórios Basi está organizado sob a forma de *open-office,* isto é, não há separação física entre as secretárias de cada trabalhador. Enquanto estagiária, esta organização do departamento facilitou a minha integração, bem como quaisquer dificuldades que eu tivesse acerca das tarefas que me tinham sido destacadas eram rapidamente e muito mais facilmente esclarecidas.

Também entre equipa, a comunicação entre colegas acerca de questões que pudessem surgir era facilitada, tornando-se num melhor ambiente de trabalho.

3.2. Pontos Fracos

3.2.1. Acesso às plataformas muito limitado

O trabalho em AR é maioritariamente dependente do uso de computadores e uma empresa como os Basi, logicamente, tem vários documentos e plataformas protegidos por palavra-passe. Enquanto estagiária senti que nesse sentido não pude beneficiar de tudo o que podia aprender, uma vez que muitos documentos e caminhos me estavam interditos.

3.2.2. Falta de autonomia

Decorrente do ponto anteriormente referido, muitas das tarefas que podia ter realizado, não pude devido à falta de acesso e falta de autonomia que me eram impostos. Acredito que seja da natureza dos Laboratórios Basi não ceder acesso total aos estagiários

por uma questão de proteção de dados, bem como algumas dessas tarefas requererem supervisão.

3.3. Oportunidades

3.3.1. Exploração de outras áreas para além da Farmácia Comunitária

A oportunidade que a FFUC nos proporciona para além da obrigatória passagem pela farmácia de oficina é, na minha opinião, uma mais-valia a nível profissional, quer escolhamos realizar estágio em Indústria Farmacêutica, quer Farmácia Hospitalar, ou outras.

Para além disso, o facto da FFUC ser a única faculdade a tornar possível o estágio em Indústria Farmacêutica é um fator bastante diferenciador e que nos destaca bastante relativamente a outros estudantes. Na IF, e neste caso nos Laboratórios Basi, as oportunidades são imensas e bastante abrangentes, desde o departamento de AR, ao Controlo de Qualidade, ou Investigação e Desenvolvimento, entre outros.

3.3.2. ORIMED

O ORIMED é uma plataforma usada para introduzir todas as informações relativas a um produto, seja medicamento, genérico ou não, suplemento alimentar, dermocosmético, híbrido, entre outros.

Grande parte do meu estágio passou pelo preenchimento do ORIMED, uma vez que todas estas informações estavam compiladas em folhas de Excel, o que tornava a consulta das mesmas não tão intuitiva e de mais difícil acesso.

Assim, alguns dos campos que ficaram ao encargo do meu preenchimento passavam pelo nome por Denominação Comum Internacional (DCI) da substância ativa, dosagem, país de exportação, quantidades dos excipientes, prazos de validade e condições de armazenamento, entre outros.

Uma vez que os Laboratórios Basi exportam os seus produtos para países de todo o mundo, esta tarefa tornava-se um pouco repetitiva, contudo o facto de ler e executar recorrentemente as mesmas tarefas permitiu-me uma melhor compreensão das mesmas.

3.4. Ameaças

3.4.1. Falta de contacto com outros departamentos

Apesar de ter sido necessário o tempo que foi despendido para adquirir os conhecimentos que adquiri, considero o contacto com os outros departamentos igualmente importante. Inicialmente estava previsto uma semana rotativa entre os diferentes departamentos, contudo após entrarmos em "tele-trabalho", ao qual farei menção posteriormente, não foi possível essa experiência.

Ter uma noção geral de como os departamentos interagem entre si e se co-ajudam seria benéfico para o meu estágio, mas também para ficar com uma noção mais ampla das várias opções de empregabilidade da IF.

3.4.2. Pandemia COVID-19

A pandemia COVID-19 com que vivemos há já 2 anos tornou-se um problema de saúde público que causou inúmeras mortes e prejudicou incontáveis negócios. O estágio iniciou-se presencialmente, porém uma semana após começar fui mandada para casa. Uma vez que o meu estágio era mais trabalho de escritório, foi possível dar continuidade ao estágio em modo "teletrabalho". Foi-me emprestado um computador da empresa, no qual eu já tinha começado a trabalhar presencialmente, e no final do estágio regressei aos Laboratórios Basi para o devolver.

4. "Tele-trabalho"

Após as medidas tomadas pelo Estado, foi-me informado que o estágio iria decorrer normalmente, mas sob o formato de "tele-trabalho". Uma vez que o estágio em AR é maioritariamente realizado em computador, não haveria problema.

As reuniões bissemanais que tínhamos passaram a ser realizadas na plataforma "TEAMS", assim como as dúvidas que iam surgindo eram também esclarecidas por lá.

Pessoalmente, o estágio em "tele-trabalho" não foi benéfico, pois sinto que podia ter aprendido mais em ambiente mais profissional, bem como muitas outras dúvidas pertinentes poderiam ter surgido caso estivesse em contacto direto com os outros colegas, tendo o trabalho em casa tornado-se um pouco monótono.

5. Conclusão

Com o mundo do trabalho cada vez mais competitivo, a necessidade de nos destacarmos e estarmos em constante formação acerca das mais diversas áreas é essencial. Apesar de relativamente curto, o estágio de 3 meses nos Laboratórios Basi permitiu-me contactar com a IF pela primeira vez, e sair da minha zona de conforto.

Ajudou-me a perceber o quão importante é a legislação e a atenção e pormenorização que exige, pois qualquer pormenor por mais pequeno que pareça pode atrasar todo o processo da entrada do medicamento no mercado. Durante o estágio, foram várias as vezes em que surgiam novas tarefas para realizar que se tornavam mais urgentes do que aquelas que já estavam a ser realizadas, isto porque o trabalho da empresa depende das necessidades dos clientes. Esta troca de tarefas tornou-se também uma mais-valia a nível pessoal, obrigando-me a ter mais responsabilidade e a gerir e organizar o meu tempo de modo a que fosse possível fazer tudo o que me era pedido da forma mais próxima possível ao que era esperado de mim.

Concluo esta experiência sabendo que irá influenciar a minha postura no futuro, tendo conhecido pessoas fantásticas que me deram valências tanto a nível profissional como pessoal.

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Parte III

Monografia

"Nanocarrier-based strategies to improve the topical treatment of psoriasis"

Resumo

A psoríase é uma doença crónica inflamatória não contagiosa caracterizada por uma inflamação multissistémica com placas avermelhadas e escamas esbranquiçadas com maior incidência nos joelhos, mãos e pés, cotovelos, couro cabeludo e região lombar. Globalmente afeta 2% da população, sendo que a sua fisiopatologia é considerada bastante complexa e ainda com muitos aspetos por compreender.

Atualmente, esta doença ainda não tem cura, contudo pesquisas estão a ser conduzidas para encontrar terapêuticas mais eficazes e seguras, bem como alternativas para diminuir as crises e complicações.

A investigação de nanotransportadores para o desenvolvimento de formulações tópicas surge para tentar ultrapassar alguns obstáculos que os tratamentos convencionais apresentam, sendo que se têm destacado devido à melhor solubilidade que apresentam, melhor libertação do fármaco e menores efeitos secundários apresentados.

No entanto, torna-se necessário conhecer melhor os seus efeitos toxicológicos a curto e a longo prazo, quer para o utilizador quer para o ambiente.

Além da fisiopatologia da psoríase e dos seus tratamentos convencionais, neste trabalho serão apresentadas e discutidas estratégias nanotecnológicas para aplicação cutânea que pretendem fornecer um tratamento mais eficaz, destacando-se ainda aspetos de contexto regulamentar e toxicológico.

Palavras-chave: Doença inflamatória; Nanotecnologia; Nanotransportadores; Psoríase; Tratamento convencional.

Abstract

Psoriasis is a chronic inflammatory non-contagious disease normally characterized by a multisystemic inflammation with reddish plaques and whitish scales with greater incidence in the knees, feet, and hands, elbow, scalp, and sacral areas. The global incidence of psoriasis rounds about 2% of the population and it is established that the pathophysiology of this skin disease is quite complex and still misunderstood.

Nowadays, this pathology still has no cure, however, efforts are being made to find more effective and safe treatments as well as trying to decrease the occurrence of crises and complications.

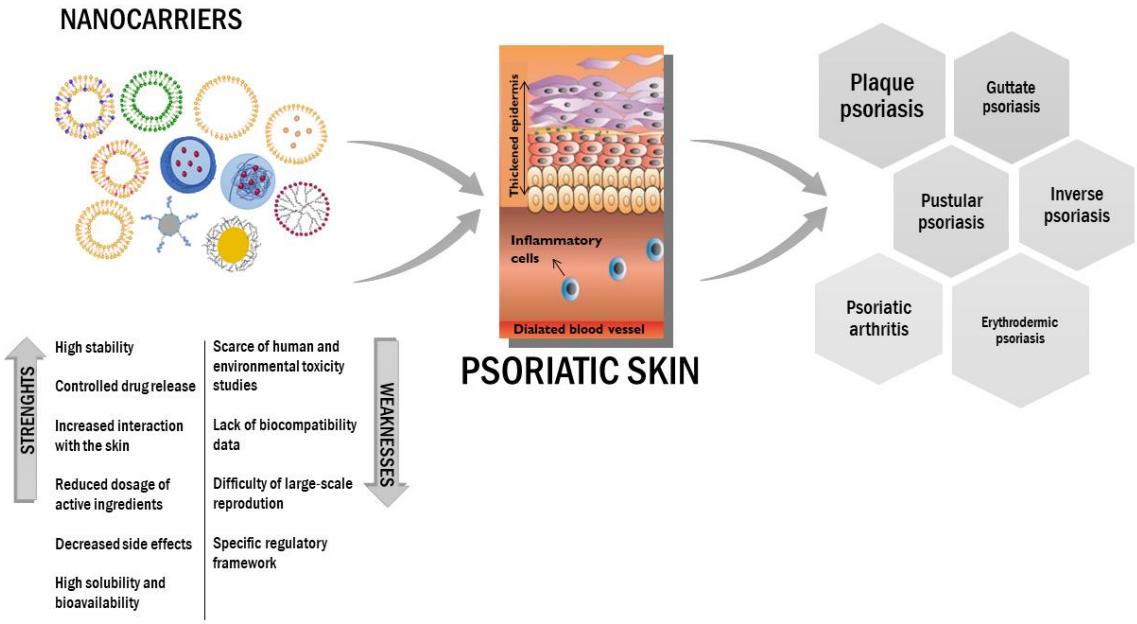
The investigation of nanocarriers occurs due to the obstacles that conventional treatments place. Nanotechnology started receiving much attention regarding the better solubility nanocarriers offer, better drug delivery, and the limited side effects they provoke.

Thus, a lot more studies are necessary, inclusively about toxicological aspects and long-term safeness, both for the user and the environment.

Besides psoriasis pathophysiology and its conventional treatments, this paper will also be presented and discussed nanotechnological strategies for topical application that intend to increase the effectiveness of treatment, as well as its regulatory and toxicological context.

Keywords: Conventional treatment; Inflammatory disease; Nanocarriers; Nanotechnology; Psoriasis.

Graphical Abstract



List of Abbreviations

2G-NN16 – Second generation of ammonium terminated carbosilane dendrimer

AG – Antigen

AgNP – Silver nanoparticle

ALA-PDT – 5-aminolevulinic acid-photodynamic therapy

APC – Antigen-presenting cell

Au-3MPS – Sodium 3-mercapto-1-propane sulfonate

AuNP – Gold nanoparticle

BSA – Body Surface Area

CAP – Capsaicin

DLQI – Dermatology Life Quality Index

EMA – European Medicines Agency

ETO – Ethosome

LIP – Liposome

MHC – Major histocompatibility complex

MTX – Methotrexate

NC – Nanocapsule

NIO – Niosome

NLC – Nanostructured lipid carrier

NS – Nanosphere

PAMAM – Poly(amido) amine

PASI – Psoriasis Area Severity Index

PE – Phosphatidylethanolamine

PEG-DSPE – Lipopolymer poly(ethylene glycol)-distearoyl phosphoethanolamine

PUVA – Psoralen + UVA radiation

REACH – Registration, Evaluation, Authorization and restriction of Chemical Substances

SA – Salicylic acid

SCCS – Scientific Committee on Consumer Safety

SLN – Solid lipid nanoparticle

TEM – Transmission electron microscopy

TEWL – Transepidermal water loss

TRA – Transfersome

UV – Ultraviolet radiation

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1. Introduction

Psoriasis is a chronic and progressive illness with a significant impact on the lives of those who suffer from it, regardless of its severity and form. In recent years, an increase in the incidence of dermatosis has been observed. The immune system of the population is more and more deregulated and, consequently, the rate of autoimmune diseases is also increasing. Different forms of psoriasis will be addressed along with this paper.

Based on several studies, the prevalence of psoriasis in the global population varies according to gender, age, and geographical area, and also by ethnicity since caucasian people are the population with the higher rate of psoriasis.[1] The incidence of this disease in children is lower but may develop with age.[2] Due to this high prevalence, the search for effective treatments became urgent.

Psoriasis is a disease that has no cure. Therefore, an early diagnosis is crucial for therapeutic success, although many patients tend to isolate themselves out of stigma for the disease. However, there are multiple treatment options to cope and deal with this disease according to its severity and based on its signs and symptoms regardless of its form.

Initially is necessary a clinical check background of the patient and a clinical examination. Being an erythematous squamous disease, due to its reddish lesions with scaling this dermatosis could easily be mistaken with other skin diseases, such as seborrheic dermatitis (at the level of the scalp, face, and chest), atopic dermatitis, and contact dermatitis pityriasis, mycosis or even allergies.

Innovations are being studied for the treatment of psoriasis, but still, topical agents are the first therapeutic step used in most patients.

The stigma associated with this disease, which affects more than 200 thousand people in Portugal and 2-5% of the global population, has been decreasing progressively due to the effectiveness of the therapeutic and demystification of the patient's fears.[3]

The biggest goal in the treatment of psoriasis is to relieve the symptoms of the disease and improve the skin lesions, nails, and joints to, indirectly, promote a better quality of life.[4] Therefore, some non-pharmacological measures could be taken such as lifestyle changes, reduced consumption of alcohol, and smoking, among others.[5]

Therapeutically speaking, topical treatments are the first line of treatment. If the disease is considered moderate to severe, and the topical treatments are no longer effective, it is usually used phototherapy and conventional systemic drugs.[6,7,8]

The chosen therapeutic approach should always be discussed between doctor and patient and be appropriate accordingly to the type of patient and the symptoms they present, as well as the presentation and severity of the disease.[7,9]

Some of the topical agents used in the treatment of psoriasis are topical corticosteroids, vitamin D3 analogues, topical retinoids, calcineurin inhibitors, or even the combination between two or more agents is also used.[10,11] The problem with these drugs, although they are highly effective, they also have unwanted secondary effects such as cutaneous irritations, burning sensation, namely with the calcineurin inhibitors and topical retinoids, or rebound effect.

Systemic therapeutic approaches can include methotrexate, ciclosporin, and acitretin. Despite being economically viable and efficient, their side effects can provoke nausea, hepatotoxicity, a higher risk of infections, and others.[12] Thus, it becomes necessary to find new, safer, and more effective therapeutic alternatives for the treatment and control of psoriasis, with a focus on skin application.

Nanocarrier-based strategies have been studied for the topical delivery of different drugs for several skin diseases.[13]

This new technology-based in nanoencapsulation brings more benefits like reduction of ingredient active dosage to achieve its biological activity, a decrease in the side effects presented by conventional treatments, higher solubility and bioavailability, and a reduction of toxicity.[14]

2. Pathophysiology

The skin is the largest organ of the human body and is in constant contact with the exterior. The skin barrier works as a shield at the same time as ensures a normal function of the skin by restraining the loss of water and avoiding the entrance of pathogens.[15]

Among the various routes of administration using nanocarriers, the topical route is of utmost importance when addressing skin diseases. As the biggest organ of the body must be taken with great consideration since it has many crucial functions such as protection, maintenance of homeostasis, metabolism, and deposition.

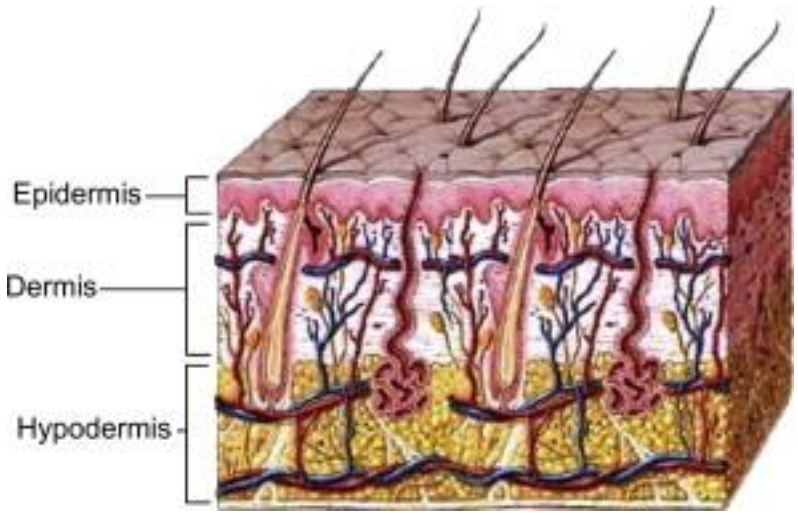


Figure 1: Anatomical structure of the skin.[16]

The skin is made up of three different layers: the epidermis, dermis, and hypodermis as shown in Figure 1.[16] Any interference in these layers may cause inflammation and irritation of the skin. Within the epidermis, there is the *stratum corneum* that is highly affected in psoriasis. According to studies made, temperature and erythema are also more expressed in psoriatic skin.[17]

Psoriasis besides being known as a chronic, inflammatory, immune disease that affects the skin, is also a result of the combination of genetic and environmental factors that will cause hyperproliferation and abnormal inflammation of the skin.[18,19]

It is normally characterized by a multisystemic inflammation with reddish plaques and withish scales with greater incidence in the knees, feet, and hands, elbow, scalp, and sacral areas. It is not contagious in either its stage or form and there are effective treatments able to maintain clean skin.[3] Can cause itching, swelling, and pain becoming incredibly uncomfortable and negatively affecting the patient's quality of life.[20,21]

Psoriasis progresses accordingly to the susceptibility of each individual to the disease and the aggressiveness of the triggering factors. If the area of the skin affected is less than 5% we are facing mild psoriasis. If the area affected is between 5-10% it's considered moderated psoriasis and above 10% it's a more severe form and very commonly associated with other comorbidities.[3] The different types of psoriasis differ in the form and severity in which they occur.

Plaque psoriasis it's the most common form of psoriasis, or as it's called, common psoriasis. It's characterized by raised, red lesions and the extension and dimension of these lesions are variable among individuals. It can affect any part of the body however, the more

affected skin areas are the elbows, knees, lumbar region, and scalp. It's responsible for approximately 85-90% of psoriasis cases.[3]

Guttate psoriasis is a less frequent form of psoriasis, although it affects especially children and adolescents and appears suddenly. The psoriatic lesions are small (2-10 mm) and presented in a drop shape. They normally have a centripetal distribution but can evolve to more chronic plaque psoriasis.[22] A lot often is associated with streptococcal infection.

Inverse Psoriasis is a form of psoriasis characterized by reddish, shinning, and well delimited psoriatic lesions mainly on the skin fold, for example, armpits, groin, and infra-mammary region.[3]

Erythrodermic psoriasis it's a form that affects all corporal area, and it can occur due to a progression of plaque psoriasis or by a manifestation of unstable psoriasis caused by an infection, other drugs or from discontinuing the use of corticosteroids.[9]

Pustular psoriasis appears with pustules, bubbles fill with pus. The most frequent one is the palmoplantar pustulosis which is characterized by pustules initially yellow and then in a later stage they turn brownish, the most affected areas are the palms of the hands and soles.[23] This type of psoriasis is also normally associated with nail involvement.[22] Generalized pustular psoriasis has a rapid development and it's a rare and unstable form of this disease. It's more common among patients who stopped abruptly the treatment with oral or systemic corticosteroids.[23]

Acrodermatitis continua of Hallopeau is a rare, chronic, pustular psoriasis of the fingers and toes.[24] The pustules develop in the fingers and toes with proximal extension, involvement, and nail destruction.[9]

Psoriatic nail disease is a type where once the fingers and nails are affected, the patient loses function and this loss generates pain and emotional stress, affecting their quality of life. The nails grow abnormally, thicken and start to scale and in some cases, it forms yellow areas beneath the nail plate called oil-spots. The nail may also get detached, known as onycholysis.[23]

Psoriatic arthritis affects particularly the hands and toes, as well as the spine causing pain, hardness, and inflammation of the joints. Between 10-30% of people suffer from this form of psoriasis which is associated, besides the pain, to deformation of the affected areas. It can manifest at any point, but the higher prevalence is between 30 and 50 years.[3] It's considered a severe form of psoriasis and if it's not properly treated can lead to permanent damage and deformation of joints.[25]

In normal skin, usually, the keratinocytes take 35-40 days to mature and move to the epidermis, however, in psoriatic skin this process is accelerated and only takes about a week. The keratinocytes accumulate in the epidermis and start causing lesions.[26]

The immuno-pathogenesis of psoriasis is considerably complex and involves inflammatory processes where the mechanisms of the immune system are activated which imply recruitment of T cells, macrophages, dendritic cells to the focus of the psoriatic lesion. Due to the rapid and uncontrolled proliferation, vascular alterations and dilation of the blood vessels occur causing scaling and skin thickening.[7,27] The main structural differences between normal and psoriatic skin can be shown in Figure 2.

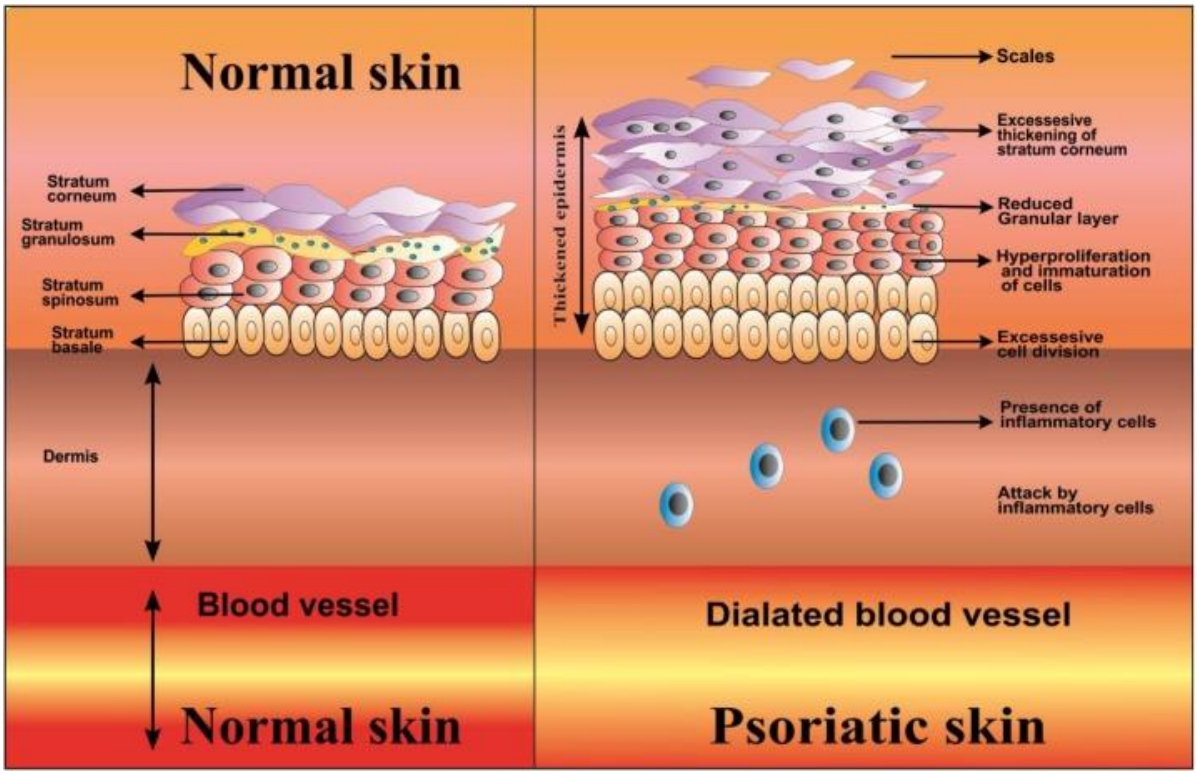


Figure 2: Main structural differences between normal skin and psoriatic skin.[26]

Exogenous factors such as other infections, some medication or trauma, can trigger the development of the disease, even more in people who are already genetically predisposed.[25]

Different types of cells and cytokines are involved in the mechanism of psoriasis. The hyperproliferation of keratinocytes secret autoantigens and occurs an inflammatory cascade.[28] The activation of T lymphocytes develops when the antigen (AG) binds to the major histocompatibility complex (MHC) which in turn is located at the top of dendritic cells, which

are considered antigen-presenting cells (APC).[19] These cells migrate to lymphatic nodes involving interaction with T lymphocytes and the first sign of activation occurs. The T lymphocytes, now active, will expand and recognize the AG penetrating the blood circulation until they reach the inflammatory spot.

In the dermis, T lymphocytes reacting to APC and macrophages will induce the production of cytokines. IL-12 and IL-23 will, respectively, enhance the production of lymphocytes Th1 and Th17 that not only proliferate but also will generate particular cytokines.[19,29,30]

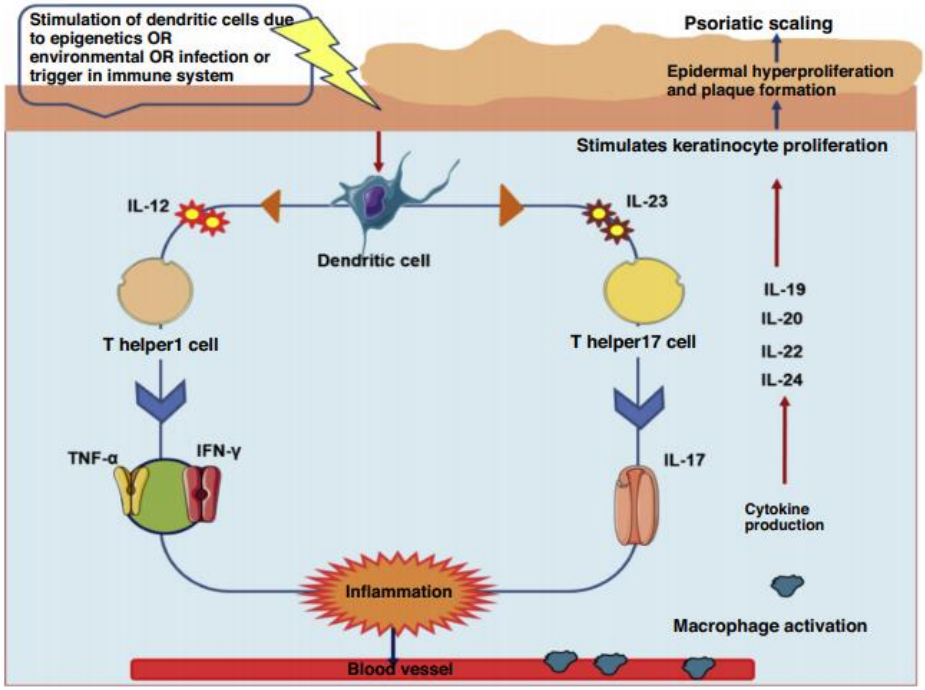


Figure 3: Pathophysiological mechanism of psoriasis.[31]

This immunological deregulation turns this illness into a systemic inflammatory disease by correlating the increased number of cells in the skin lesion and the immune system cells, which are continuously being produced.[18] The pathophysiological mechanism of psoriasis is schematized in Figure 3.

Through the years, many scoring systems were developed to measure the percentage of the skin surface (*BSA – Body Surface Area*)[18] affected by the psoriatic lesions, being the PASI (*Psoriasis Area Severity Index*) system the most used. Calculations are made before, during, and after the treatment in four different parts of the body being them the head, upper limb, chest, and lower limb. The severity is then determined based on three characteristics, erythema, peeling, and infiltration of the lesions and the score is between 0-4. The extension of the

lesions is scored between 0-6, with being 6 the highest affected area between 90-100%. The lower the classification, the lesser the lesions and severity of the disease.[9]

The impact of this disease in the life of the patients who suffer from it is enormous, therefore is also essential to evaluate the impact that psoriasis has on the quality of life of its patients. Having that said, a new method emerged called DLQI (*Dermatology Life Quality Index*) that consists of a simple questionary of 10 questions answered by the patient (Annex 1).

3. Conventional treatment for psoriasis

Topical therapies are, by far, the most used in the treatment of psoriasis. Nowadays, it is based on topical corticosteroids, vitamin D analogues, topical retinoids, and calcineurin inhibitors.[10,11] Some examples are calcitriol and calcipotriol (or calcipotriene) as vitamin D analogues, tazarotene as a topic retinoid and tacrolimus as a calcineurin inhibitor.

The need for a systemic treatment occurs when the topic therapy is no longer working, or because the extension and severity of the lesions have worsened or in cases of discomfort for the patient. In these cases, the methotrexate is the most commonly used systemic agent.[12]

Methotrexate has been used in the treatment of psoriasis for over 50 years.[12] It's an analogue of folic acid and its mechanism of action it's based on the competitive inhibition of the dihydrofolate reductase enzyme. Therefore, it's going to inhibit the synthesis of cofactors that are necessary to produce nucleic acids, and consequently, the synthesis of T lymphocytes and keratinocytes is compromised.

Initially used as an immunosuppressant to avoid rejection of transplanted organs, ciclosporin proved to be quite effective as an antipsoriatic drug. Its effect is due to the inhibition of calcineurin blocking the production of inflammatory cytokines and inhibiting the activation of T lymphocytes.[13] On the other hand, the side effects caused by ciclosporin are nephrotoxicity, hypertension, and elevated immunosuppression forcing the necessity of close monitoring.[32] The use of ciclosporin is contraindicated in patients with deregulated and unstable hypertension, kidney failure, and cancer. The use of this agent cannot be taken while taking other drugs metabolized by cytochrome P450.[12]

Acitretin is the only systemic retinoid approved for the treatment of psoriasis. It's very effective, especially in the erythrodermic and pustular forms of psoriasis. Exerts its psoriatic effect by modulation of the differentiation and proliferation of epidermis. The treatment begins with a lower dosage, and then slowly increases the dose. Despite being contraindicated in

pregnancy and women of childbearing potential and having side effects, such as xerosis, nail and hair break, and being dose-dependent, acitretin is the most used treatment for the most severe forms of psoriasis.[33]

Phototherapy is a very ancient method used in the treatment of dermatosis. Consists of controlled and repetitive solar expositions to ultraviolet radiation (UV) through artificial sources, which is absorbed by endogenous chromophores localized in the skin. The radiation used can be UVA or UVB.[34] UVA radiation (320-400nm), when used in monotherapy, is ineffective but associated with photosensitizing agents, systemic or topic (psoralen) is quite effective, and the treatment is called PUVA (psoralen + UVA radiation). This therapy decreases epidermic proliferation and depresses the secretion of cytokines.[32,34] UVB radiation (290-320 nm) has a higher biological effect, altering cellular mechanisms. The beams emitted can be broadband or narrowband, and it is estimated that beams with a narrowband are more effective with longer periods of remission and lesser cutaneous reactions (less number of treatments that cause burns and erythema) than the UVB broadband emissions.[34]

These therapies, PUVA, and UVB can be associated with other topical agents, or systemic ones, to obtain better treatment results and maximum effectiveness.[34]

However, although they are extensively used, these treatment options have a lot of bad side effects, so it became urgent to formulate other treatment options with lesser side effects and more effective results, such as nanotechnology-based strategies.

4. Nanotechnology-based strategies for the topical treatment of psoriasis

Nanocarriers are a class of innovating formulations with less than 100 nm and have been considered for the treatment of skin diseases.[35] The use of nanotechnology has been showing great interest and offering numerous advantages in comparison to conventional treatments.[26,36] A lot of nanocarriers have been studied cautiously by researchers for dermatological applications.[26] The major advantage of these nano-based formulations is the reduction of adverse effects that are caused by traditional treatments, but also better drug penetration and greater profiles of drug release to achieve the therapeutic target.[37] However, some disadvantages need to be addressed.[38,39] We will address individually the nanotechnology-based strategies understudy for topical application in psoriasis (Figure 4), and in Table 1 we will present a summary of their main advantages and disadvantages, allowing an easier and faster reference for the reader.

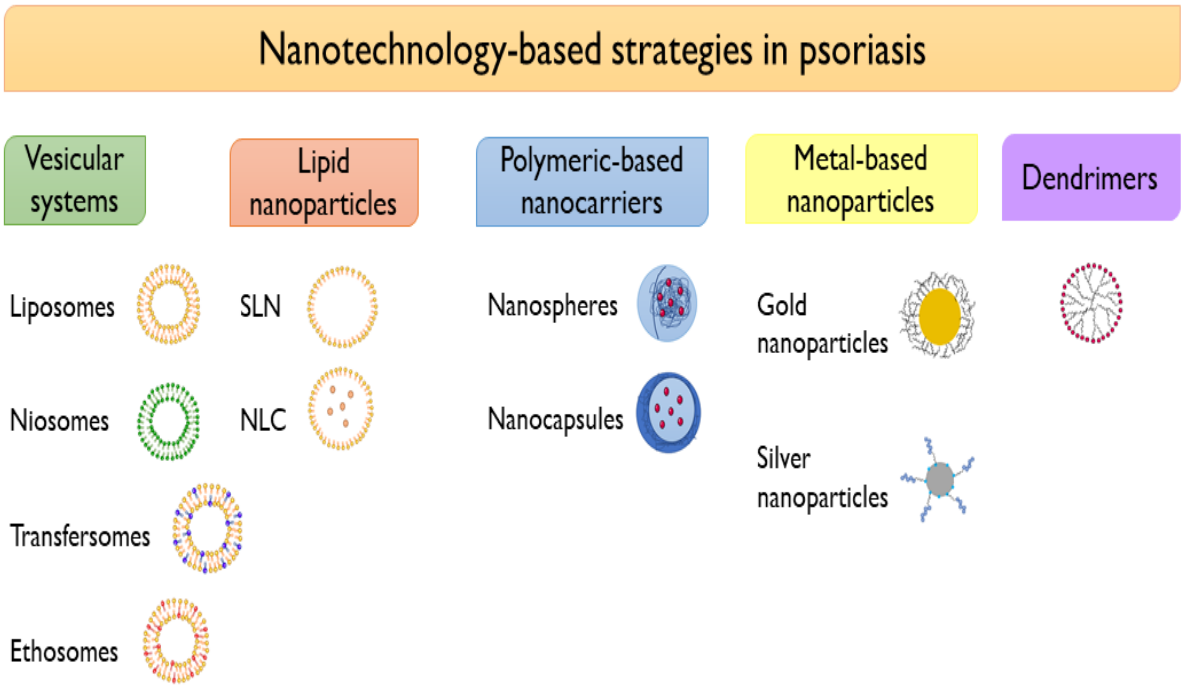


Figure 4: Different nanotechnology-based strategies for the topical treatment of psoriasis.

4.1 Lipid-based nanocarriers

4.1.1 Vesicular systems

4.1.1.1 Liposomes

Liposomes (LIPs) are small vesicles, unilamellar or multilamellar, that are originated from phospholipids, cholesterol, and long-chain fatty acids.[40] This nano-system consists of the core of vesicles surrounded by a hydrophilic environment and between the layers of phospholipids we have a lipophilic environment.[41] LIPs were particularly designed for the control of inflammatory diseases, including psoriasis as they have hydrating properties, with the purpose of better drug delivery. Their use has been successfully associated with an improvement of drug penetration and permeation through the skin, and it can incorporate either lipophilic as well as hydrophilic substances.[15,41]

A study was conducted regarding LIPs and their stabilizing efficacy with the lipopolymer poly(ethylene glycol)-distearoyl phosphoethanolamine (PEG-DSPE) and their capacity to deliver calcipotriol through the skin.[42] They came to the conclusion that the higher stabilization of the formulation was due to the stabilizing effect that the polymer provides and the concentration of calcipotriol into the skin was not compromised and calcipotriol loaded-LIPs had even reached a higher amount of calcipotriol in the skin.[42]

The use of MTX has been narrow as a result of its hydrophobicity and high molecular weight. A study with MTX entrapped in oleic acid-containing LIPs processed by hydration heightened the permeability through the skin. Additionally, the oleic acid activates calmodulin-dependent protein kinase that will enhance the Ca^{2+} influx resulting in even higher skin permeability.[43]

Fusidic acid-loaded LIPs were prepared to be topically delivered for the treatment of psoriasis. Four different treatment groups were analyzed, using mouse tail as a model, a control group, fusidic acid 2% commercial cream, fusidic acid 2% liposomal gel, and fusidic acid 2% plain hydrogel. In skin permeation and retention studies, the fusidic acid liposomal gel showed both better permeation and retention in comparison to the other groups since this liposomal system can integrate skin cells. Regarding anti-psoriatic activity, all groups containing fusidic acid, except the control group, showed a decrease in the cell population. Therefore, fusidic acid itself in addition to being a good treatment option for psoriasis, conjugated with LIPs is also a promising line of treatment for this disease.[44]

All in all, some of the main LIPs advantages are the ability to pass through the skin both lipophilic and hydrophilic drugs[45,46], have better controlled drug release[47], preventing systemic drug absorption by acting as a barrier and increased drug deposition into the skin layers.[39] On the other hand, some disadvantages encompass difficulties to produce large scale [39], high cost and the purity of phospholipids.[38]

4.1.1.2 Niosomes

Niosomes (NIOs) are structures obtained by hydration of non-ionic surfactants, cholesterol, and other lipids.[48] The NIO vesicle can contain either hydrophilic and/or hydrophobic drugs, and based on the capacity of this vesicle, NIOs can be divided into three groups: small unilamellar vesicles (SUV, size 0.025–0.05 mm), multilamellar vesicles (MLV, size 0.05 mm) and large unilamellar vesicles (LUV, size 0.10 mm).[48]

Such as LIPs, NIOs can be used through many routes of administration including topical administration. They can enhance drug release and their skin permeation. They don't require special storage conditions, as they are also biodegradable, biocompatible, and osmotically active.[48]

The potential of NIOs for the distribution of ammonium glycyrrhizinate was investigated and the results were very satisfying. The ammonium glycyrrhizinate salt is characterized by its anti-inflammatory effects by reducing edema, apoptosis, and tissue damage.

It was shown the ability to enhance the drug's anti-inflammatory activity, good tolerability and no toxicity from the ammonium glycyrrhizinate loaded vesicles.[49]

A study with MTX-loaded NIOs was also conducted for the treatment of psoriasis with the main goal of lowering MTX systemic toxicity (Figure 5).[50] Different solvents and different sonication times were used concluding that the mix methanol-chloroform was the one who produced the better film to forming materials and sonication time was stabilized at 1 minute since the encapsulation efficacy of NIOs diminished after 2 minutes. The other aim of this study was to determine the better particle size to avoid systemic absorption and it was documented that a larger sized vesicle was unable to reach deeper skin layers, therefore only reaching the *stratum corneum*.[50]

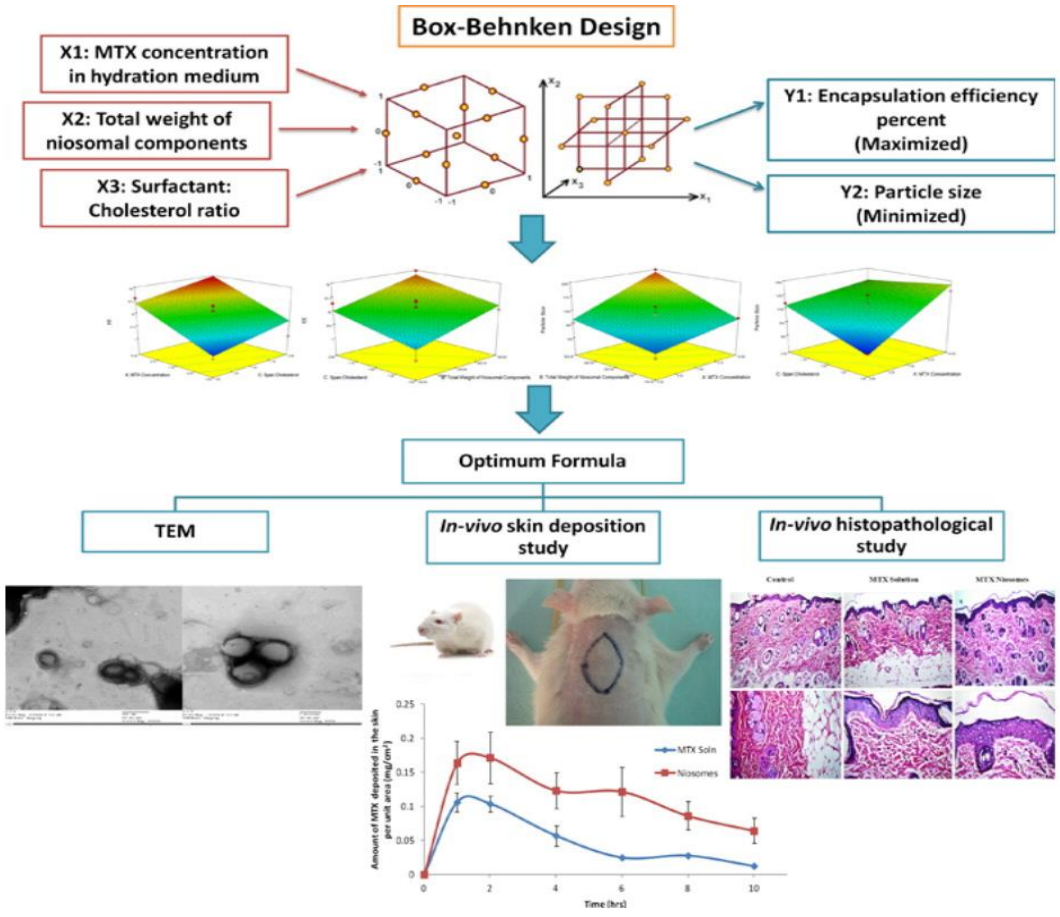


Figure 5: Graphical abstract illustrating the Box-Behnken Design used to test different variables and the response 3D plots; Transmission electron microscopy (TEM) micrographs of the MTX-loaded NIOs formulation; Graphic comparing the skin deposition between MTX-loaded NIOs and MTX solution and histopathological sections of untreated control rat skin (group I), skin treated with MTX solution (group II), and skin treated with MTX-loaded NIOs (group III).[50]

Box-Behnken design is a software that was used in this study to optimize the different variables, them being MTX concentration in hydration medium, weight of composing NIOs

and surfactant. The dependent variables were the particle size and encapsulation efficiency. TEM was used to determine the size and shape of NIOs, which presented a circular shape and an aqueous core.

The *in vivo* topical study showed that the percentage of MTX delivered to the skin was indeed higher with the use of NIOs as shown in Figure 5.[50]

Also, the in vivo histopathological analysis of this study was conducted to determine the irritating nature of the application of MTX niosomal formulation and was recorded no histopathological alteration confirming the lack of irritation when applying topical NIOs.[50]

In short, NIOs present higher stability[51], reduced transepidermal water loss[52] and lower cost.[38] However, also have lower skin permeation in comparison to liposomes and difficulties with high-scale production.[38]

4.1.1.3 Transfersomes

Transfersomes (TRAs) are carriers with an aqueous compartment enclosed by surfactants and lipids that can be deformable very easily. Their most remarkable advantage is the ability to be pass-through smaller pores due to their flexibility. Electrostatic and hydrophobic forces help to trap the drugs in the bilayered wall if they are lipophilic or in their aqueous core if they are hydrophilic.[53]

A study was conducted through the preparation of tacrolimus-loaded TRAs. Recent studies implied that the topical use of tacrolimus ointment can be effective in the treatment of acute skin diseases, however, could not pass through the skin barrier leading to the necessity of an innovative system.[54] In order to ease the dispersion for topical use, TRAs were mixed with Carbopol®940 and turned into a gel. The results showed a much higher release of the drug with the tacrolimus-loaded TRA gel to both epidermis and dermis than with the tacrolimus ointment.[54]

The histopathological analysis showed the number of inflammatory cells significantly reduced with the transfersomal gel, however in the ointment group the infectious cells were still quite evident.[54]

A different study using resveratrol, a non-flavonoid polyphenol, was prepared. Resveratrol's beneficial effects have been reported in many different studies for its use in skin cancer and psoriasis.[55] Resveratrol-loaded TRAs were then prepared using different surfactants such as Tw80, sodium cholate, and sodium deossicholate. Respecting encapsulation

efficiency, all formulations showed great efficiency, of which Tw80 and sodium deossicholate presented 100% efficiency and sodium cholate about 95%.[55]

In short, TRAs have the advantage of delivering both high or low molecular weight drugs to the skin[36] and have ultra-deformability capacity.[38] On the other hand, their high-scale production is difficult and they're high priced.[38]

4.1.1.4 Ethosomes

Ethosomes (ETOs) are mainly composed of phospholipids, water and alcohol. The size of the systems can be arranged to range from 30nm to microns. They can also be called elastic vesicles due to their high flexibility and their formulations along with TRAs can penetrate pores smaller than their diameter.[56] ETOs can encompass either amphiphilic, hydrophilic, or lipophilic molecules with distinguished characteristics. Heighten compliance and permeation of substances, non-toxic materials, and simpler drug delivery are some of the advantages of ethosomal carriers.[57]

These systems are suited from biotechnology, pharmaceutical, veterinary to cosmetic purposes.[58]

Phosphatidylethanolamine (PE) is a strong ethosomal carrier that was employed to study the penetration of 5-aminolevulinic acid-photodynamic therapy (ALA-PDT) in the rehabilitation of hyperproliferative skin. The ethosomal carrier showed a significant increase in the delivery of ALA and the expression of TNF-alfa decreased, meaning that the hyperproliferation was reduced in comparison with the plain ALA solution.[59]

A different study was conducted using ethosomal formulation with MTX and then later converted into a gel with salicylic acid (SA).[60] The three main objects of study were an *ex vivo* permeation study between the different solutions, a comparison between ethosomal gel and drug solution of skin permeation and retention, and an *in vivo* animal study for psoriatic lesions. The conclusions drawn were that the ETOs showed better skin penetration when compared to the plain MTX solution and the results with MTX-SA gel were even better. From the animal study, the treatment with MTX optimized gel showed normal skin and very slight keratosis.[60] The main results are shown in Figure 6.

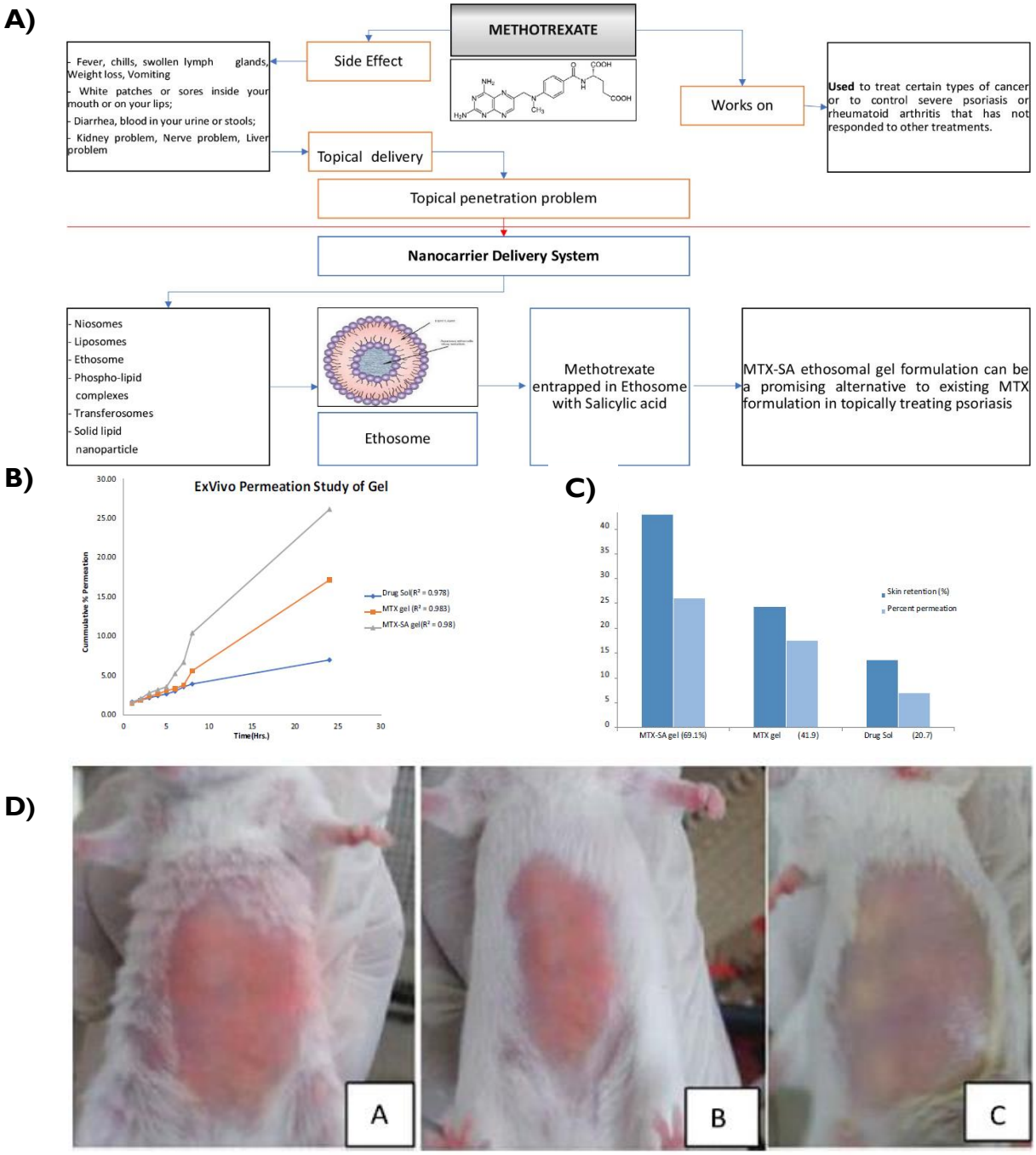


Figure 6: (A): Graphical abstract. **(B):** Comparison of the permeation percentage between drug solution, MTX gel and MTX-SA gel. **(C):** Comparison of the skin retention and permeation percentage of the ethosomal gel with the drug solution. **(D):** A) positive control animal; B) Vaseline treated animal; C) MTX gel treated animal.[60]

ETOs have the advantage to encapsulate both lipophilic and hydrophilic molecules, as well as malleability.[61] However, have a predisposition to degradation and a higher cost.[61]

4.1.2 Lipid nanoparticles

Lipid nanoparticles include solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs).

SLNs are colloidal systems constituted from a combination between physiological lipids and surfactants. They have a special interest in topical delivery.[26,62]

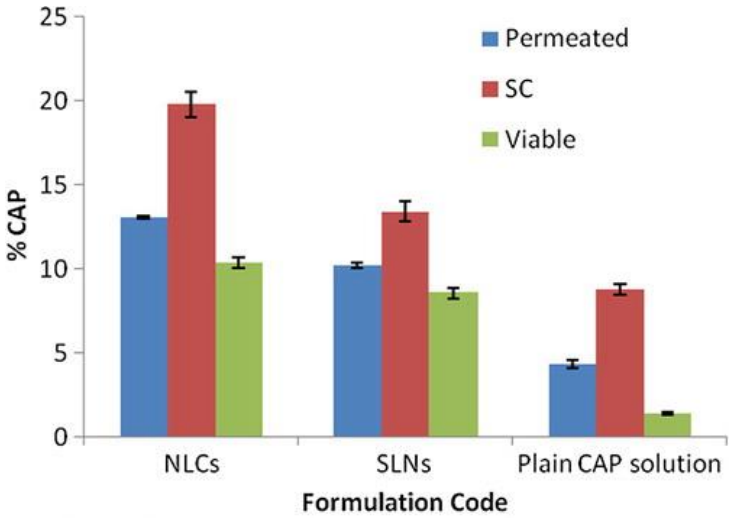
NLCs are constituted from a combination of solid lipids with unmatched liquid lipids. NLCs are a new form of lipid nanoparticles and offer increased compatibility as well as relevancy in the administration of drugs through many different routes.[63]

SLNs can carry both hydrophilic and lipophilic drugs, while NLCs only carry lipophilic drugs. Both systems improve drug permeation into the *stratum corneum* and prevent transepidermal water loss (TEWL).[64]

A study was conducted to develop SLNs and NLCs with better skin infiltration and controlled release characteristics for psoralens. The chosen liquid and solid cores were, respectively, squalene and Precirol ATO 5. Various emulsifiers were used in this study to prepare SLNs and NLCs, as well as different parameters such as polarity, zeta potential, loading capacity, among others, were investigated. The study showed that NLCs formulations had a better permeation and controlled liberation of psoralens than SLNs, and it was concluded that both systems are of great interest in terms of dermal application due to these characteristics.[62]

Capsaicin (CAP) is one of the option treatments for psoriasis, however, its topical use presents some undesirable effects such as the appearance of erythema followed by pain and burning sensations.[65] Therefore, a study was made with SLNs and NLCs to evaluate the level of permeation and skin retention, among other factors, of CAP into the damaged skin. The comparison between CAP-SLNs, CAP-NLCs, and plain CAP was conducted, and the results showed a higher permeation of CAP obtained from the lipid nanoparticles compared to the plain CAP solution.[66] The results are shown in Figure 7.

A)



B)

Formulation code	CAP permeated through the skin at 24 h (μg/cm²)	Flux (μg/cm²/h)	Total CAP accumulated in to skin (%)
CAP-NLCs	32.62 ± 2.34	27.45 ± 2.27	30.07
CAP-SLNs	18.97 ± 2.15	16.78 ± 1.14	21.91
Plain CAP solution	11.28 ± 1.92	10.80 ± 1.59	10.11

The data were expressed as percentage of dose applied per unit area. Each point represents the mean ± S.D. ($n = 3$).

Figure 7: (A): Percentage of CAP for CAP-SLNs, CAP-NLCs, and plain CAP solutions for permeation and skin retention studies. **(B):** Percentage of CAP accumulated in the skin between the different solutions.[66]

The possible explanation for the higher amount of CAP permeated and accumulated through the skin in the solutions with the lipid nanoparticles relies on their lipidic content and smaller size.

A skin irritation test was also conducted, and it showed that both SLNs and NLCs caused non or very minimum skin irritation and, as such, demonstrated to be safer and with no erythema compared to the plain solution.[66]

This study concluded that both systems are safe and efficient for the topical delivery of CAP. The slightly better results with NLCs may be explained by the fact that this nanocarrier has an amorphous core.[67,68]

SLNs have biocompatibility and good tolerability towards the drugs[69] and also present reduced skin irritation.[70] However, have lower skin penetration than NLCs[62] and limited

encapsulation of the drug.[71] Meanwhile, NLCs have better adhesion to the skin[38,62] and high entrapment efficiency, with the disadvantage of low viscosity.[62]

4.2 Polymeric-based nanocarriers

4.2.1 Nanospheres

Nanospheres (NSs) are particles with less than 1µm and with a matrix system in which we have a polymer matrix and the drug is homogeneously distributed in it. Polymers employed can be biodegradable or not. NSs provide more stability and enhanced solubility as well as better control of the drug release and improved absorption.[72]

NSs loaded with vitamin D3 were developed and its potential for the topical treatment of psoriasis was studied. Results reported that was a higher distribution of vitamin D3 into the epidermis in comparison to the control (Transcutol®). They also tested these NSs against photodegradation, and the results concluded that both hydrolysis and degradation were avoided. Therefore, vitamin D3 is eligible due to its proven stability to be used in a topical formulation.[73]

Erianin is a natural agent extracted from *Dendrobium chrysotoxum Lindl*[74] that has demonstrated the ability to inhibit hyperproliferation of the keratinocytes. However, has a low penetration capacity through the skin and it is poorly soluble in water so a nanosystem is required to improve erianin delivery into the skin to make it eligible to be used in the treatment of psoriasis.[74]

Some of NSs advantages go through better skin permeation of lipophilic drugs[72], being biocompatible and biodegradable[75], higher cutaneous penetration[38] and protection against degradation.[76] On the other hand, NSs are not suitable for transdermal use[72] and require purification processes.[38]

4.2.2 Nanocapsules

Equally to NSs, nanocapsules (NCs) are particles with less than 1µm and colloidal size but unlike NSs, NCs have a reservoir system where the drug core is coated by a polymeric membrane. They have gained popularity due to their exceptional skin permeation. They conserve the drug from degradation and are considered excellent materials for dermatological applications.[26]

NCs suspensions with a lipid core were obtained to determine the stability and safety of dithranol-loaded NCs. Dithranol is a drug used in psoriasis with its action on the inflammation and proliferation stages, however, it reacts very easily in the presence of light causing tissue damage and severe skin irritation. In the stability test was used dithranol-loaded NCs encompassing either EDTA or ascorbic acid. Both systems maintained their original characteristics.[77] Photodegradation was also one of the subjects studied in this research due to the fact the dithranol is quite an unstable drug in the presence of light, causing skin irritation.[78,79] This test was taken to determine if the encapsulation wouldn't degrade thanks to radiation. The two systems were then exposed to UV radiation and the results showed that both of them shield dithranol from the radiation in comparison to the drug solution.

Furthermore, it was conducted an *in vitro* irritation study showed no irritation from dithranol-loaded NCs unlike free drug solution evidencing the significance of nanoencapsulation.[77]

Quercetin is a flavonoid and can have potential use in the treatment of psoriasis due to its antioxidant and anti-inflammatory actions. However, quercetin is poorly soluble in water which makes it inactive when topically used. In order to solve this problem, three different formulations were tested: quercetin liposomes, quercetin smartCrystals® and quercetin nanocapsules and their effects on keratinocytes and monocytes cell lines were explored.[80]

With the aim of topical application, cellular toxicity was assessed through the comparison between the quercetin formulations and plain quercetin on the keratinocytes and monocytes cells. After 24 hours of exposure, neither quercetin formulations and plain quercetin showed cellular toxicity, and quercetin nanocapsules presented higher cellular viability of the keratinocytes and monocytes cells when compared to the plain quercetin formulation. Also, quercetin nanocapsules were demonstrated to be capable of delivering quercetin to deeper skin layers than the other formulations, therefore being a good strategy in psoriasis.[80]

Some of the advantages of NCs are minimized irritation effects[81] and increased permeation through the skin[82], however the disadvantages go through difficulties in scale-up manufacturing.[82]

4.3 Metal-based nanoparticles

Metallic nanoparticles have been showing great interest in drug delivery in skin diseases due to their small size, facility of modification, and high reactivity against living cells. They have

been a great subject of interest mainly due to their use in the treatment of tumors, but also more recently because of their application as anti-inflammatory agents in the treatment of dermatological pathologies.[83]

4.3.1 Gold nanoparticles

Gold nanoparticles (AuNPs) are inert and with low toxicity, which makes them useful in drug delivery.[84,85] They are becoming popular among scientists due to their advantages regarding a larger surface area, a smaller size along with the anti-inflammatory effect.[86]

In this context, AuNPs containing MTX were developed to treat psoriasis. It was used sodium 3-mercapto-1-propane sulfonate (Au-3MPS) to increase its distribution and stability. The results were effective, proving that the therapy with MTX associated with AuNPs was more effective than MTX by itself. It was also reported that this could be a safe, non-toxic, and effective topical option treatment for psoriasis.[86]

Gold and silver nanoparticles bearing polyphenol-rich extracts, *Cornus mas*, were developed since they have been showing growing potential in the treatment of psoriasis by their anti-inflammatory properties. Gold and silver nanoparticles containing *Cornus mas* extracts were applied in psoriatic lesions, including plaques, and the results obtained showed a decrease of IL-12 and TNF-α, both important pathogenic mediators in psoriasis, and recovery of psoriasis plaques with lesser scales. Also, comparing the effects of these nanoparticles containing *Cornus mas* ointment versus hydrocortisone ointment, metallic NPs were more effective regarding the suppression of macrophage activation. Additionally, no side effects were reported concerning the gold and silver nanoparticles ointment.[87]

AuNPs have the advantage of being able to be synthesized from chemical and organic materials[83], as well as biocompatible.[82] However, scale-up processes are also a disadvantage.[82]

4.3.2 Silver nanoparticles

Silver nanoparticles (AgNPs) are mostly used in the therapy and diagnosis of cancer, however, AgNPs have also been successfully studied as antipsoriatic drug options for the treatment of psoriasis. Their anti-inflammatory effects were studied by developing AgNPs containing an extract from blackberry fruit to characterize their activity in psoriatic lesions.[88] To do so, they proceed to a cream preparation based on a mix between petrolatum, vaseline oil, and cetyl alcohol with a hydrophilic surfactant and emulsified into an aqueous phase

containing AgNPs. This study was tested in 8 volunteers all correctly diagnosed for psoriasis and with the appropriate informed consent.

Each patient received twice a day the AgNPs cream and 1% hydrocortisone before and until 2 weeks of analysis. The data recollected proved that the AgNPs and their anti-inflammatory effects could be an effective approach to treat psoriasis, by reducing edema and lowering the levels of cytokines.[88]

Inflammation is one of the main features of psoriasis disease, therefore there is a need to find anti-inflammatory agents to fight this action. AgNPs have proven to have anti-inflammatory and antioxidant properties, so AgNPs containing polygalacturonic acid (PGA) were prepared. PGA is a natural polymer and in this study was used as a stabilizer for the AgNPs. The results showed a decrease in inflammatory cells when treated with the nanoparticles cream in comparison to the commercial cream, demonstrating the AgNPs anti-inflammatory properties and their potential use in psoriasis.[89]

In short, AgNPs have also the ability to be synthesize by both chemical and organic materials[83], as well as being biocompatible[82] and having antimicrobial activity.[90] However, they suffer difficulties in terms of high-scale processes.[82]

4.4 Dendrimers

Another possible structure for the incorporation of drugs or other active ingredients are dendrimers. Dendrimers are typically three-dimensional structures, multivalent and spheroidal macromolecules with a hyperbranched conformation and several active terminal groups.[36,91] Dendrimers can bear an encapsulated drug or their conjugated form. They also help to conquer numerous resistance mechanisms and facilitate the distribution of the active substance. These characteristics make them excellent carriers being able to be administrated via intravenous, oral, transdermal, pulmonary, and ocular.[92]

Beyond these advantages, they also showed increased solubility, better control at the release of the drug as well as the formation of pro-drugs (drug-polymer). According to these features, dendrimers have shown great use for antipsoriatic drugs.[92]

The potential use of the second generation of ammonium terminated carbosilane dendrimer (2G-NN16) to treat Th17 deregulations was evaluated. The results showed a decreased level of Th17 interleukins such as IL17, IL22, IL23, and others when the dendrimer was present. This concludes that 2G-NN16 could be an option for the treatment of psoriasis

since it's an autoimmune disease that contemplates IL17 as one of those responsible for this disease.[93]

A microsponge gel was developed to analyze the efficacy of poly(amido) amine (PAMAM) dendrimers in the topical application of dithranol for psoriatic disease.[94] The use of microsponges was beneficial since this drug delivery system has a chemical affinity for the skin and can stay in the skin for longer periods of time.[95]

As discussed above, dithranol is an antipsoriatic drug very used in psoriatic lesions, however, suffers very susceptible to oxidation. The results showed that dithranol encapsulated in PAMAM dendrimer reduced and control the oxidation problem as well as increased the drug permeability. Compatibility between dithranol and dendrimer was also comproved using UV-spectrophotometry as well as stability studies which were performed for 12 weeks and showed no changes in several parameters.[94]

Some advantages of dendrimers are increased skin permeation[96,97] and biocompatibility[98], however, they have a high production cost.[82]

Table I: Main advantages and disadvantages of the different nanocarriers used for topical treatment of psoriasis.

Nanocarriers-based strategies	Advantages	Disadvantages	References
LIPs	Ability to pass through skin both lipophilic and hydrophilic drugs; Better drug release; Increased drug deposition into skin layers	Difficult of large-scale production; High-cost production; Necessity of phospholipids purification	[38,39,45,46,47]
NIOs	Higher stability; Lower-cost production; Reduced transepidermal water loss	Lower permeation compared to liposomes; Difficult high-scale production	[38,51,52]
TRAs	Delivery of both high and low weight drugs to the skin; Ultra-deformability capacity	Difficult high-scale production; High-cost production	[36,38]
ETOs	Malleability; Encapsulation of both lipophilic and hydrophilic molecules	Predisposition to degradation; High-cost production	[61]
SLNs	Reduced skin irritation; Biocompatibility and tolerability	Lower skin penetration than NLC; Limited encapsulation of the drug	[62,69,70,71]
NLCs	Better adhesion to the skin; Higher entrapment efficiency	Low viscosity	[38,62]
NSs	Better skin permeation of lipophilic drugs; Biocompatible and biodegradable; Higher cutaneous penetration; Protect against premature degradation	Not suitable for transdermal use; Requirement of purification processes	[38,72,75,76]
NCs	Minimized irritation effect; Increased permeation through the skin; Biocompatible and biodegradable	Difficult in scale-up processes	[81,82]
AuNPs	Ability to be synthesized from chemical and organic materials; Biocompatiility	Difficult in scale-up processes	[82,83]
AgNPs	Biocompatibility; Antimicrobial activity	Difficult in scale-up processes	[82,83,90]
Dendrimers	Increased skin permeation; Biocompatible	High-cost production	[82,96,97,98]

5. Legal issues and toxicological concerns

EMA (European Medicines Agency) is the regulatory agency in charge of the evaluation and supervision of medicines for their use in the EU. In addition, EMA also monitors the safety and risk-benefit concerning the product.

All nanocarriers need a previous authorization and a complete risk assessment evaluation in order to be able to be used, and if there is any suspicion of lack of safety regarding the nanocarrier it must be reported to the Scientific Committee on Consumer Safety (SCCS).[99] Two databases were developed respecting updated information about nanocarriers, their uses in different subjects and safety interests (NanoData[100]) and toxicological information (eNanoMapper[101]). Thus, regulatory issues are an important factor for the safe use of nanocarriers.

Nanotoxicology is an evolving concept[102] and according to REACH (Registration, Evaluation, Authorization and restriction of Chemical Substances) the risk assessment of nanocarriers should be done according to conventional materials.[103] Nanocarriers' chemical and morphological characteristics have a great impact when it comes to the interaction with biological cells and nanotoxicology plays an important role by analyzing their toxicological effects.[104]

The enlarged use of nanocarriers in the health industry has translated into a growing concern about their possible toxicological issues regarding human health as well as the environment and therefore its control and risk assessment are essential requirements.[104]

Nanoecotoxicology is defined as the toxic effects that nanocarriers can induce on humans, plants, animals, and microorganisms[105] and when in contact with the environment, their effects on air, water, and soil, which are already ongoing studies to determine their potential toxicity.[106] Advances in the applications of nanocarriers have resulted in the liberation of these systems into aquatic environments, therefore the toxic effect of AuNPs was assessed in *Moina macrocopa*, an aquatic crustacean. The results showed gastric accumulation in the digestive tract of *M. macrocopa* that could clearly be distinguished from the control group, which interfered with their ingestion and could lead to transfers in the food chain. Enzymes activity were also reported and with higher concentrations of AuNPs oxidative stress was generated.[107]

In another environmental study, the effects of AgNPs in the soil and rice growth were studied. Rice seeds were exposed to different AgNPs concentrations, and the data recollected

demonstrated that the higher the concentration, the more the germination was inhibited. Equally, regardless of the concentrations, AgNPs tested in the soil heterotrophs aerobic microorganisms also showed inhibitory effects on their respiratory activities.[108]

Thus, in order to properly assess nanoecotoxicology, more research needs to be conducted. Nanocarriers that are biocompatible and biodegradable, such as polymeric nanocarriers as mentioned above, are a lesser concern. Nonetheless, other nanocarriers need to be evaluated.[109]

The fact that nanocarriers display so many advantages over conventional treatments in psoriatic disease, and not only, it is all the more reason for toxic effects to be investigated.

For the investigation of the toxicity of nanocarriers some criteria have to be taken into accounts such as the particle size, dose, distribution, solubility, morphology, surface area, and surface reactivity, among others.[110,111]

For example, one of the concerns about nanocarriers, which is also one of their advantages, is their small size. The smaller the particle, the more the volume ratio increases, and consequently the reactivity increases, because the surface area also increases. Thus, bigger attention must be taken towards the surface material rather than the core material, implying that not only the nanocarriers have to be studied for toxic features but also the environment they are set in.[112]

Three of the most possible routes for the nanocarriers entering the human body are air pathways, ingestion, or skin.[102,113] Dermal absorption is a particular route of high risk since the skin is the biggest human organ and has a very important barrier function.[102]

In one of the studies mentioned in this paper regarding dendrimers[94], a dermal toxicological study was made in order to determine either the existence or absence of toxicity from dithranol-dendrimer microsponge gel. The two groups of the study were treated with the dithranol-dendrimer gel and with commercial formulation and the results were observed within 14 days. The dithranol-dendrimer gel group did not show any toxicity signs, neither edema, skin irritation, or inflammation symptoms were observed.[94]

In other of the studies mentioned above[55], it was detected some cytotoxicity from the surfactants. The investigators concluded that the toxicity was most likely due to their detergent activity and plain Tw80 was the one who compromised the viability of the cells the most.

Other nanomaterials can be included in various products, such as clothing, medical devices, disinfectants, and others.[114]

As shown, the existing data concerning nanocarriers and skin penetration allied to toxicological concerns are contradictory. It's yet to be defined if they are a target issue.[102] At the moment, there aren't enough adequate studies to evaluate the risks that can be associated with nanocarriers.[115] Also, due to the lack of clinical trials in humans, it is not yet possible to measure accurately the toxicity these nanocarriers can bring to people and this means that the data gathered about safety and risk assessments may not be illustrative of what would really happen in clinical environment.

However, highlighting the most concordant points of the studies that have been carried out in this area, we summarize in Figure 8 the main strengths and weaknesses associated with nanocarriers presented in this work.

Therefore, it is noteworthy that many more studies need to be done with nanocarriers which, due to their nano size, compared to conventional materials, gives rise to many more challenges.

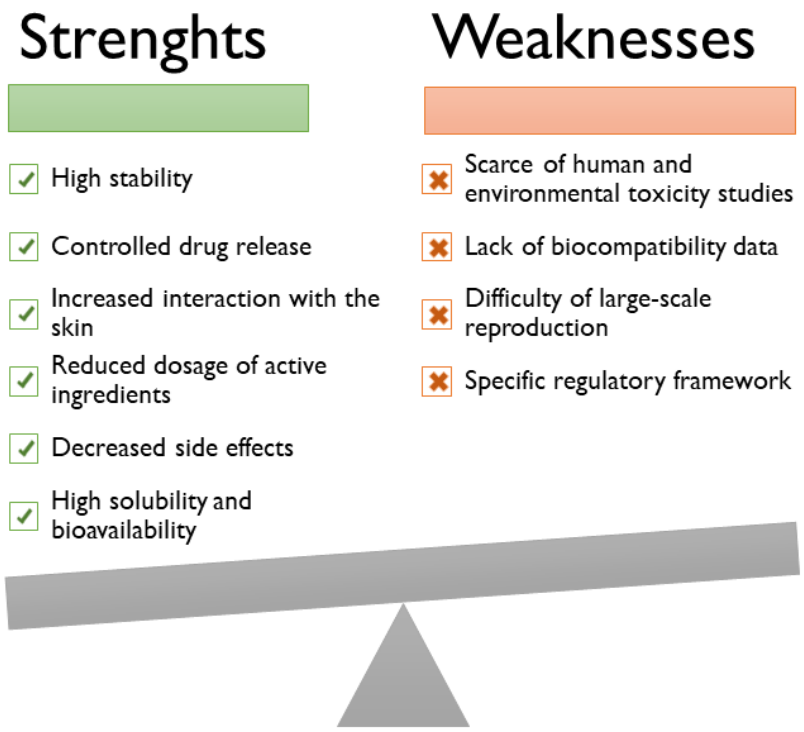


Figure 8: Main strengths and weaknesses of nanocarriers.

6. Conclusion and future challenges

The current topical treatment options to treat skin diseases, such as psoriasis, have a small drug penetration and a systemic absorption that can lead to undesirable reactions. Most of the *in vivo* studies with nanoformulations have shown greater skin permeability and showed non or very minimum cases of skin irritation or inflammatory effects.

Nanotechnology is one of the most promising technologies with various possibilities and great potential to contribute to innovative option treatments. Nevertheless, there are still many uncertainties ally to it and risks to be addressed.

While much research is underway and important discoveries have emerged regarding the topical application of nanotechnology as a treatment option for skin diseases, there is still much to understand. And while recent discoveries about psoriasis pathogenesis and treatment options have had a positive impact, this disease is still very ambiguous and quite challenging.[24]

A future prospect should be the transition from preclinical studies to clinical trials. Even though nanocarriers have been showing significant beneficial effects demonstrated by the many studies that have been made over the years, this clinical evolution is an important challenge towards nanoformulations starting to be widely introduced in the market and used in the clinic to be.[82]

Another interesting future challenge would be the determination of the best nanocarrier for each form of psoriasis in order to further increase the benefits of nanotechnology. That is, taking into account the different characteristics that each nanocarrier has to offer, and the type of active ingredient that is intended to be incorporated, which nanocarrier would be most beneficial for the different types of psoriasis.

Also, large-scale production is another conflict due to its higher cost and the difficulty in controlling reproducibility.

Nonetheless, major investigations still need to be made but it's safe to say that nano-based carriers are a promising alternative to conventional treatment and an improvement regarding safety and efficacy.[116]

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Annex

Annex I:

DERMATOLOGY LIFE QUALITY INDEX (DLQI) - INSTRUCTIONS FOR USE

The Dermatology Life Quality Index questionnaire is designed for use in adults, i.e. patients over the age of 16. It is self explanatory and can be simply handed to the patient who is asked to fill it in without the need for detailed explanation. It is usually completed in one or two minutes.

SCORING

The scoring of each question is as follows:

Very much	scored 3
A lot	scored 2
A little	scored 1
Not at all	scored 0
Not relevant	scored 0
Question 7, 'prevented work or studying'	scored 3

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

HOW TO INTERPRET MEANING OF DLQI SCORES

0 – 1	no effect at all on patient's life
2 – 5	small effect on patient's life
6 – 10	moderate effect on patient's life
11 – 20	very large effect on patient's life
21 – 30	extremely large effect on patient's life

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There is more information about the DLQI, including over 85 translations, at www.dermatology.org.uk. The DLQI is copyright but may be used without seeking permission by clinicians for routine clinical purposes. For other purposes, please contact the copyright owners.

DERMATOLOGY LIFE QUALITY INDEX (DLQI)

Hospital No: …… **Date:** ……..

Name: …… **Score:** ……

Address: …… **Diagnosis:** ……

……

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick (✓) one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒		
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒		
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	Not relevant	❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒		
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant	❒

Please check you have answered EVERY question. Thank you.