UNIVERSIDADE D
COIMBRA

Sofia Gonçalves Pires Peito

Relatórios de Estágio e Monografia intitulada "Nano- and microparticle-stabilized Pickering emulsions designed for therapeutic and cosmetic applications" referente à Unidade Curricular "Estágio", sob a orientação do Dr. Daniel Ribeiro, do Dr. João Pinto e do Professor Doutor Francisco Veiga, apresentados à Faculdade de Farmácia da Universidade de Coimbra, para apreciação na prestação de provas públicas de Mestrado Integrado em Ciências Farmacêuticas.

Outubro de 2020

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Eu, Sofia Gonçalves Pires Peito, estudante do Mestrado Integrado em Ciências Farmacêuticas, com o n.º 2015229301, declaro assumir toda a responsabilidade pelo conteúdo do Documento Relatórios de Estágio e Monografia intitulada de "Nano- and microparticle-stabilized Pickering emulsions designed for therapeutic and cosmetic applications" 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 2020.

Sofia Gonçalves Pires Peito

(Sofia Gonçalves Pires Peito)

Agradecimentos

À minha mãe,

Por me incentivar sempre a ser cada vez melhor e me ajudar a ultrapassar todos obstáculos. Pelo sacrifício que fez para me garantir um futuro melhor.

Ao meu pai,

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PARTE I

Relatório de Estágio em Indústria Farmacêutica

Pharmilab

Lista de Abreviaturas

CE – Conselho Europeu

CIR – *Cosmetic Ingredient Review*

CosIng – *Cosmetic Ingredient Database*

CPNP – Portal de Notificação de Produtos Cosméticos

ECHA – *European Chemical Agency*

EMA – *European Medicines Agency*

EU – *European Union*

FIP – Ficheiro de Informação do Produto

MICF – Mestrado Integrado em Ciências Farmacêuticas

NICNAS – *National Industrial Chemicals Notification and Assessment Scheme*

PR – Pessoa Responsável

RAS – Relatório de Avaliação de Segurança

SCCS – *Scientific Committee on Consumer Safety*

SWOT – *Strenghts, Weaknesses, Opportunities, Threats*

TOXNET – *Toxicology Data Network*

UE – União Europeia

1. Introdução

O plano curricular no MICF permite adquirir um vasto conhecimento e aptidão para desempenhar as mais variadas vertentes da área farmacêutica.

O estágio curricular consiste no primeiro momento em que o estudante contacta com o exercício da sua profissão. É, portanto, uma oportunidade única, com a possibilidade de não só exercer estágio em Farmácia Comunitária, mas também em Farmácia Hospitalar ou em Indústria Farmacêutica.

Neste sentido, o estágio possibilita consolidar os conteúdos programáticos lecionados ao longo dos cinco anos do MICF, bem como colocá-los em prática.

Sendo do meu interesse ganhar experiência noutra área, para além da de Farmácia Comunitária, optei por realizar um estágio em Industria Farmacêutica. Tendo em consideração que a área que mais me aliciava era a Cosmética, escolhi a empresa de consultoria regulamentar e controlo de qualidade para o setor de dispositivos médicos, cosméticos, biocidas, suplementos alimentares e químicos, a Pharmilab.

Assim, enquanto consultora regulamentar, a Pharmilab tem a capacidade de apoiar os seus clientes no registo de marcas, *design* de rótulos e embalagens, no cumprimento regulamentar europeu e ainda representa estas entidades, assumindo o papel de Pessoa Responsável (PR). Como empresa de controlo de qualidade, realiza ainda testes laboratoriais, como testes de microbiologia, de performance, de estabilidade e compatibilidade e challenge test. [1]

Esta pequena empresa, em expansão e desenvolvimento, está inserida no Instituto Pedro Nunes (IPN). Assim, foi possível um contacto mais direto com os colaboradores-e um apoio mais individualizado. Através de desafios e oportunidades adquiri novas capacidades para um melhor desenvolvimento pessoal e profissional. Também permitiu ter uma perspetiva mais realista do que o farmacêutico pode exercer na área regulamentar.

Foi com grande entusiasmo e dedicação que trabalhei na Pharmilab, desde o dia 6 de janeiro até ao dia 11 de março de 2020, sob orientação do Dr. Daniel Ribeiro.

Por fim, e de modo a descrever a minha experiência ao longo do estágio, será apresentada uma análise SWOT (*Strenghts, Weaknesses, Opportunities* e *Threats*), onde serão analisados os pontos fortes e pontos fracos numa avaliação interna e as oportunidades e ameaças numa avaliação externa.

2. Análise SWOT

Tabela 1 – Análise SWOT relativa ao estágio em Industria Farmacêutica

Avaliação Interna

Pontos Fortes	Pontos Fracos
✓ Aprendizagem de novas plataformas e bases de dados científicas ✓ Regulamentação ✓ Tarefas executadas ✓ Autonomia / Espírito crítico ✓ Ambiente agradável	× Elaboração de um FIP × Avaliação de rotulagem

Avaliação Externa

Oportunidades	Ameaças
✓ Língua inglesa ✓ Pesquisa de informação científica ✓ Conhecimentos de cosméticos e regulamentação	× Informação sobre os ingredientes × Plano curricular do MICF × Dependência dos dados fornecidos pelos clientes

2.1. Pontos Fortes

2.1.1. Aprendizagem de novas plataformas e bases de dados científicas

Durante o tempo de estágio tive acesso a plataformas específicas para os cosméticos, nomeadamente o *Cosmedesk* e o Portal de Notificação de Produtos Cosméticos (CPNP), onde pude aprender a sua aplicação e como utilizá-las. O *Cosmedesk* é uma plataforma direcionada para a indústria cosmética que contempla a informação de cada ingrediente, *raw* material e produto, permitindo uma maior facilidade de preparação e execução do Relatório de Avaliação de Segurança (RAS) e Ficheiro de Informação do Produto (FIP). Estes últimos dois documentos são essenciais no processo de introdução de novos produtos cosméticos no mercado da União Europeia (UE). [2] O CPNP é um portal europeu onde são notificados todos os produtos cosméticos que pretendem ser colocado no mercado da UE. Este sistema de notificação tem a vantagem de não ser necessária uma nova notificação quando o produto cosmético se encontra noutro estado membro da UE. [3]

Adicionalmente, também tive acesso a várias bases de dados cientificas, nomeadamente *Cosmetic Ingredient Review* (CIR), *Cosmetic Ingredient Database* (CosIng), *CosmeticInfo, European Chemical Agency* (ECHA), *European Medicines Agency* (EMA), *Environmental Working Group* (EWG), *National Industrial Chemicals Notification and Assessment Scheme* (NICAS), *Pubmed, Pubchem*, *Scientific Committee on Consumer Safety* (SCCS) and *Toxicology Data Network* (ToxNet).

Não só aprendi o funcionamento destas plataformas e bases de dados, como também foram as minhas ferramentas diárias de trabalho. Esta descoberta de novas plataformas e base

de dados alargou os meus horizontes, no conhecimento que adquiri e na forma de pesquisar informação, o que muitas das vezes se revelava uma tarefa árdua.

2.1.2. Regulamentação

No início do meu estágio, tive acesso desde logo à regulamentação necessária para aprovação dos produtos cosméticos no mercado. Isto revelou-se bastante importante e útil, visto ser a base do trabalho que exerci e era uma regulamentação com que eu não estava familiarizada. Saliento o Regulamento (CE) n.º 1223/2009, o Regulamento (EU) n.º 655/2013 e *Technical Document on cosmetic claims*. [4]

O Regulamento (CE) n.º 1223/2009 institui normas que cosméticos devem cumprir, quando colocados no mercado da UE, para garantir o cumprimento de especificações que asseguram a qualidade, segurança, eficácia do produto a ser utilizado.

O Regulamento (EU) n.º 655/2013 é uma extensão do Regulamento (CE) n.º 1223/2009 que explicita critérios comuns a utilizar para corroboração das alegações referentes a produtos cosméticos.

O *Technical Document on cosmetic claims* tem como objetivo orientar a aplicação do Regulamento (EU) n.º 655/2013, estabelecendo critérios comuns para a justificação das alegações utilizadas aos produtos cosméticos.

Esta regulamentação é fundamental para todo o tipo de atividades que uma PR tem de exercer. A PR garante o cumprimento da segurança, das boas práticas de fabrico, dos requisitos do RAS, FIP, da notificação do produto cosmético, dos ensaios em modelos animais, rotulagem e alegações do produto, de restrições às substâncias assim como a não utilização de substâncias proibidas ou vestígios das mesmas e ainda a divulgação ao público das informações relevantes do produto cosmético. [5]

2.1.3. Tarefas Executadas

As tarefas que realizei no estágio consistiram na elaboração do perfil toxicológico de ingredientes, notificação no CPNP e comprovação de alegações.

O perfil toxicológico de ingredientes resume-se na pesquisa de informação toxicológica relativa ao ingrediente e descrever no *Cosmedesk* os estudos toxicológicos bem como a sua classificação. Este perfil toxicológico é feito para cada ingrediente presente na formulação de cada cosmético. O objetivo deste perfil toxicológico é garantir que nenhum ingrediente da formulação é prejudicial para o ser humano e que é utilizado nas concentrações indicadas.

Embora seja uma tarefa morosa, é essencial para a garantir a segurança do cosmético sem abdicar da sua eficácia.

A notificação no CPNP foi outra atividade que realizei com o intuito de atualizar a plataforma de cosméticos dos novos produtos e das atualizações feitas nos produtos já existentes. Esta tarefa é executada pela PR a pedido do cliente que representa, no caso de serem atualizações o motivo pode ser mudança de rotulagem, de composição ou quantidade de ingredientes presentes.

A notificação de alegações foi também uma das minhas funções. Esta é realizada após a avaliação de rotulagem. É composta por um documento que expõe a razão pela qual a rotulagem do produto alega que este tem uma determinada função ou é indicado para um determinado fim. As alegações podem ser as mais variadas e podem ser justificadas através dos ingredientes que compõem a formulação ou pelas matérias-primas utilizadas. A quantidade presente nos cosméticos também se revela um fator decisivo, visto que a função do ingrediente ou matéria-prima pode ser diferente ou não representar importância caso esta seja muito reduzida. Mas, na generalidade das alegações, é fundamental uma pesquisa científica para a sua comprovação.

2.1.4. Autonomia/ Espirito crítico

Ao longo do estágio foi me concedida liberdade para executar as tarefas propostas de forma autónoma e responsável. Deste modo, consegui desenvolver espírito crítico e poder de decisão, sem que me fosse negado qualquer tipo de ajuda, quando necessário, ou esclarecimento de dúvidas. Sem dúvida que é uma mais-valia para mim como pessoa, mas também como futura farmacêutica, pois ajuda a que tenha uma maior capacidade de analisar a situação e conseguir responder de forma mais rápida e eficaz ao problema.

2.1.5. Ambiente agradável

Desde o primeiro dia, fui bem-recebida e integrada na equipa. O ambiente foi sempre agradável o que fez com que esta experiência se revelasse ainda mais profícua.

A interação interpessoal era com informal, o que permitiu conhecer pessoalmente todos os colaboradores. Também proporcionou uma maior facilidade de comunicação, uma vez que há uma maior proximidade, o que se traduz numa maior abertura para expressar as minhas dúvidas.

Outra vantagem decorrente deste ponto forte foi ter oportunidade de trabalhar em equipa e existir um espírito de entreajuda. Mais uma vez, é algo que me faz evoluir pessoalmente e como profissional de saúde.

2.2. Pontos Fracos

2.2.1. Elaboração de um FIP

Durante o período de estágio, não me foi possível realizar um FIP devido à sua extensão e exigência requerida. O FIP é um documento que contém toda a informação relativa a um produto cosmético. Um FIP contém a descrição do produto, o RAS, o processo de fabrico, informações relativas aos ensaios em animais e justificações de alegações. A elaboração deste documento é efetuada para cada produto cosmético produzido e vendido na UE, sendo consequentemente um ficheiro exclusivo daquele produto. Com a contínua expansão no mundo dos cosméticos são cada vez mais os FIPs realizados. É, portanto, indispensável a existência de uma estrutura fixa e uniforme na UE, para tal o Regulamento (CE) n.º 1223/2009 contempla as normas que têm de ser cumpridas. [5]

2.2.2. Avaliação de rotulagem

Durante o estágio não tive oportunidade de fazer uma avaliação de rotulagem. No entanto, foi-me explicado como se efetua a mesma, os critérios a ter em conta e em que legislação me devo basear. Esta avaliação de rotulagem tem como objetivo verificar se os componentes que estão presentes na rotulagem estão corretos, se obedece a todos os critérios de rotulagem e se não contém alegações, outro tipo de informação discriminatória ou que possa induzir o consumidor final em erro. Tais normas e critérios estão presentes no Regulamento (CE) n.º 1223/2009, Regulamento (EU) n.º 655/2013 e *Technical Document on cosmetic claims* e baseiam-se na conformidade legal, veracidade, sustentação de prova, honestidade, imparcialidade e tomada de decisão, de modo a proteger e providenciar uma maior segurança ao consumidor final. [6]

2.3. Oportunidades

2.3.1. Língua Inglesa

Na área Regulamentar, todos os documentos têm de ser redigidos na língua inglesa, para que todos os países sejam capazes de os compreender. O mesmo acontece com as

plataformas e bases de dados utilizadas nos produtos cosméticos, que também se encontram na língua inglesa.

Consequentemente, estive em contacto constante com a língua inglesa na execução das tarefas que exerci, desde a pesquisa de dados e informação científica até à realização de perfis toxicológicos e comprovação de alegações.

Através deste contacto pude desenvolver e aperfeiçoar a minha escrita e compreensão nesta língua.

2.3.2. Pesquisa de informação científica

Tal como já foi referido, o meu estágio passou por muita pesquisa de informação científica. Esta pesquisa era fundamental e decisiva nos dados recolhidos e apresentados nos documentados elaborados. Devido a uma certa dificuldade em encontrar a informação pretendida, desenvolvi uma maior capacidade de pesquisa. Este desenvolvimento passou pela descoberta de novas bases de dados científicas e aprimoramento das minhas técnicas de pesquisa, tanto na eficácia como no rigor aplicado.

2.3.3. Conhecimentos de cosméticos e regulamentação

Durante o curso de ciências farmacêuticas, e através das unidades curriculares Dermofarmácia e Cosmética e Assuntos Regulamentares do Medicamento, adquiri conhecimentos gerais relativos a cosméticos e assuntos regulamentares do medicamento. Estes ajudaram-me a compreender melhor determinados conceitos com que me deparei no decorrer do estágio. Foram, portanto, bases importantes para o conhecimento mais específico que adquiri. Através do estágio, tive oportunidade de obter novos conhecimentos relacionados com os cosméticos e aprender a área regulamentar do produto cosmético, algo que não tinha tido acesso anteriormente. Permitiu-me assim, aprofundar mais um tema que sempre despertou o meu interesse e vontade de aprender.

2.4. Ameaças

2.4.1. Informação sobre os ingredientes

Durante as tarefas que desempenhei no estágio, apercebi-me de que a falta de informação específica para alguns dos ingredientes se revelava um obstáculo. Muitas das vezes a informação era agrupada em classes de ingredientes, sendo demasiado generalizada ou não fazendo referência à sua função e aplicação em cosméticos, apenas referindo as suas aplicações terapêuticas ou nutricionais. Como consequência, havia uma constante necessidade de

extrapolar informação. Para além disto, nem sempre existiam estudos e testes toxicológicos, sendo que em alguns casos, estes se encontravam incompletos, obrigando mais uma vez à extrapolação de dados.

Esta falta de dados e de informação específica para cada ingrediente representa uma ameaça para o mundo da cosmética e da regulamentação a ela associada, pois expõe a falta de segurança, bem como o trabalho que ainda tem de ser feito.

A área da Cosmética é uma área em expansão e devido às exigências do consumidor em que os produtos sejam mais "naturais" possíveis, ou seja, à base de plantas. É de salientar que os ingredientes que apresentam maior falta de estudos toxicológicos e que comprovem a sua eficácia, segurança e qualidade são os de origem natural, nomeadamente os provenientes de extratos de plantas e óleos essenciais e que, portanto, são estes os ingredientes que apresentam maior risco à segurança, logo uma maior ameaça.

2.4.2. Plano curricular do MICF

O plano curricular do MICF é um plano abrangente que serve para nos qualificar nas várias áreas que um farmacêutico pode vir a desempenhar. Pode, então, ser considerado como um curso completo, na medida em que integra diferentes áreas essenciais para a aprendizagem do farmacêutico. No entanto, devido à extensão de áreas abrangidas dificulta o aprofundar de certas matérias. O farmacêutico é, não só responsável pelo medicamento, mas também pelos suplementos alimentares, cosméticos e dispositivos médicos. Como tal, deveria existir uma maior aprendizagem nestes setores, e na parte regulamentar associada. Durante o meu estágio, apercebi-me da falta de conhecimento que tinha na área regulamentar relativamente aos cosméticos.

2.4.3. Dependência dos dados fornecidos pelos clientes

Numa consultoria regulamentar de cosméticos existe uma elevada dependência pelos clientes. Esta dependência existe porque é através do cliente que são obtidas quase todas as informações necessárias relativamente ao produto cosmético, desde informação relativa à composição do cosmético, ao material da embalagem até testes de estabilidade e de segurança. Como tal, o trabalho exercido pela RP será sempre condicionado pela entrega correta e atempada dos documentos necessários.

3. Conclusão

O estágio em Assuntos Regulamentares permitiu-me experimentar uma área distinta do estágio obrigatório em Farmácia Comunitária e, como resultado, explorar outro setor da atividade farmacêutica.

Num mercado de trabalho cada vez mais competitivo, a distinção entre os profissionais revela-se um ponto fulcral. Para tal, a formação e a experiência em diferentes áreas podem constituir uma vantagem.

A oportunidade de estagiar na Pharmilab possibilitou também o desenvolvimento das minhas competências profissionais, como o sentido de responsabilidade, autonomia, espírito crítico, bem como a ampliação do meu conhecimento no manuseamento de diversos sistemas informáticos, na área de Assuntos Regulamentares e no domínio da língua inglesa, e ainda competências pessoais, como a capacidade de trabalhar em equipa e espírito de entreajuda.

Gostaria de deixar o meu mais sincero agradecimento a todos os colaboradores, que desde do primeiro dia me fizeram sentir integrada na equipa, que me ajudaram sempre que precisei e me ensinaram as particularidades do trabalho na vertente cosmética de Assuntos Regulamentares.

No final do período de estágio posso concluir que se tratou de uma experiência enriquecedora, que contribuiu para o meu crescimento enquanto farmacêutica e que, no futuro, traduzir-se-á numa mais valia.

4. Referências Bibliográficas

1. PHARMILAB. [Acedido a 2 de março de 2020]. Disponível em: https://www.pharmilab.eu/
2. COSMEDESK. [Acedido a 2 de março de 2020]. Disponível em: https://www.cosmedesk.com/
3. EUROPEAN COMMISSION - **Guia de utilização do CPNP - Portal de Notificação de Produtos Cosméticos.** [Acedido a 1 de março de 2020]. Disponível em:https://www.infarmed.pt/documents/15786/1440983/Manual+de+instrucoes+CPNP+PT/6304df68-0e3a-49e9-b521-b3fea06d44af
4. EUR-LEX. [Acedido a 1 de março de 2020]. Disponível em: https://eur-lex.europa.eu/homepage.html?locale=pt
5. UNIÃO EUROPEIA - **Regulamento (CE) n.º 1223/2009 do Parlamento Europeu e do Conselho de 30 de novembro de 2009 relativo aos produtos cosméticos**. Jornal Oficial da União Europeia.
6. UNIÃO EUROPEIA - **Regulamento (UE) n.º 655/2013 da Comissão de 10 de julho de 2013 que estabelece critérios comuns para justificação das alegações relativas a produtos cosméticos.** Jornal Oficial da União Europeia.

PARTE II

Relatório de Estágio em Farmácia Comunitária

Farmácia São Sebastião

Lista de Abreviaturas

FFUC – Faculdade de Farmácia da Universidade de Coimbra

MICF – Mestrado Integrado em Ciências Farmacêuticas

MNSRM – Medicamento Não Sujeito a Receita Médica

MSRM – Medicamento Sujeito a Receita Médica

PA – Princípio Ativo

PVF – Preço de Venda à Farmácia

PVP – Preço de Venda ao Publico

SWOT – *Strenghts, Weaknessess, Opportunities, Threats*

1. Introdução

A farmácia comunitária representa, muita das vezes, o local de primeira escolha para resolução dos problemas de saúde da comunidade. A ampla cobertura geográfica no nosso país e a elevada competência técnico-científica dos seus recursos humanos, constituem pilares do Serviço Nacional da Saúde. A preferência dos cidadãos por este espaço de fácil acesso geográfico e o reduzido tempo de espera, em comparação com os centros de saúde e hospitais, evidenciam o papel preponderante do farmacêutico, evitando deslocações desnecessárias a outros serviços por problemas de saúde menores. [1]

A atividade primordial do farmacêutico é a promoção do uso responsável do medicamento, em articulação com os restantes profissionais de saúde. O farmacêutico tem um papel fundamental junto da população, em aconselhar o utente em situações de automedicação, sugerindo a terapêutica adequada, minimizando interações medicamentosas e reações adversas. Não é só o especialista do medicamento, é também um profissional de saúde, e como tal contribui de diversas formas para o bem-estar e estilos de vida mais saudáveis dos cidadãos.

O aconselhamento farmacêutico, monitorização da terapêutica, preparação de medicamentos manipulados e determinação de parâmetros bioquímicos são alguns dos serviços prestados pelo farmacêutico, podendo este último contribuir para identificação de pessoas de risco e deteção precoce de diversas doenças.

Frequentemente o contato direto e pessoal com o utente permite conhecer as situações sociais, económicas e familiares pelo que se pode considerar que o farmacêutico estabelece relações humanas.

O estágio curricular em farmácia comunitária promoveu o contato com a realidade profissional permitindo consolidar e pôr em prática os conhecimentos teóricos, adquiridos ao longo do Mestrado Integrado em Ciências Farmacêuticas (MICF) e desenvolver competências necessárias para o desempenho de funções numa farmácia comunitária. Conferiu uma oportunidade de conhecer o funcionamento de uma farmácia, de desenvolver a capacidade de trabalhar em equipa, de exercer com zelo, responsabilidade e dever ético a saúde pública. [2] A realização do estágio na Farmácia São Sebastião, em Coimbra, efetuou-se no período de 1 de junho a 24 de setembro de 2020, sob orientação do Dr. João Pinto, em conjunto com restante equipa, constituída pela diretora técnica Dra. Ana Pimentel, e pelas farmacêuticas Dra. Cidália Roxo e Dra. Beatriz Póvoa.

O presente relatório é apresentado sob a forma de uma análise SWOT (*Strenghts, Weaknessess, Opportunities* e *Threats*), onde se expõem os pontos fortes, pontos fracos

oportunidade e ameaças com que me deparei durante o estágio curricular, finalizando com a explanação de dois casos clínicos.

2. Farmácia São Sebastião

A Farmácia São Sebastião localiza-se atualmente na Rua Vitorino Nemésio, número 420, na freguesia de Santo António dos Olivais, em Coimbra, tendo mudado de instalações desde de maio do presente ano. Esta nova localização permite uma maior acessibilidade dos utentes que se desloquem de carro ou de transporte público, uma vez que existem zonas para estacionamento de viaturas e três paragens de autocarros muito próximas. Em termos de visibilidade a farmácia destaca-se junto da rotunda do Tovim, no cimo da Av. Dr. Elisio de Moura (Figura 1).

A equipa da farmácia é constituída por quatro elementos, todos farmacêuticos, sendo a proprietária e diretora técnica a Dra. Ana Pimentel.

A farmácia está aberta ao público de segunda a sexta das 9h até às 20h e sábado das 9h às 14h.

Figura 1 – Fachada da Farmácia São Sebastião

3. Análise SWOT

Uma análise SWOT engloba duas vertentes, a avaliação interna e a externa que permitem analisar de forma crítica a integração e aprendizagem teórica à realidade profissional do estágio na Farmácia São Sebastião.

Tabela 1 – Análise SWOT relativa ao Estágio em Farmácia Comunitária

Avaliação Interna

Pontos fortes	Pontos fracos
✓ Equipa de Trabalho e a sua Integração ✓ Preparação de Medicamentos Manipulados ✓ Tarefas desempenhadas ✓ Metodologia *Kaizen* ✓ Utentes Fidelizados	× Plano de Estudos do MICF × Associação do nome comercial ao PA

Avaliação Externa

Oportunidades	Ameaças
✓ SIFARMA 2000® e novo SIFARMA® ✓ Dermocosmética, Veterinária e Suplementos Alimentares	× Receitas Manuais × Informação de Preços nas Guias de Tratamento × Medicamentos esgotados × Plano de contingência de COVID-19

3.1. Pontos Fortes

3.1.1. Equipa de trabalho e a sua integração

Um dos pontos fortes da Farmácia São Sebastião é a sua equipa de trabalho. Uma equipa de excelência, com elevado conhecimento e profissionalismo que tem como objetivo primordial a máxima qualidade de serviços prestados à população, em que se privilegia o aconselhamento farmacêutico em detrimento apenas da comercialização dos medicamentos.

Desde o primeiro dia que fui muito bem acolhida por todos, num ambiente familiar e de boa disposição, em que me senti muito bem integrada.

A equipa sempre se mostrou disponível para esclarecer todas as minhas dúvidas e foram um exemplo a seguir para desenvolver competências de realizar tarefas de forma autónoma e responsável. Em todas as funções que desempenhei tive sempre a colaboração e supervisão.

Sem dúvida que a equipa da farmácia São Sebastião contribuiu para o meu crescimento profissional e processo de aprendizagem.

3.1.2. Preparação de Medicamentos Manipulados

Um dos pontos fortes da Farmácia São Sebastião é a preparação de medicamentos manipulados. Um medicamento manipulado é, segundo a Portaria n.º 594/2004, de 2 de junho, "qualquer fórmula magistral ou preparado oficinal preparado e dispensado sob a responsabilidade de um farmacêutico". [3]

A preparação de medicamentos manipulados ocorre quando um medicamento para determinada patologia não se encontra em comercialização, na dosagem, formulação ou associação de substâncias ativas necessária.

A farmácia possui um laboratório equipado, de acordo com as normas exigidas pelo INFARMED, com material e matérias-primas necessário para execução dos medicamentos manipulados eficientes, seguros e de qualidade.

As prescrições de medicamentos manipulados solicitadas nesta farmácia são essencialmente de cariz dermatológico.

Neste estágio, tive oportunidade de assistir à preparação de vários medicamentos manipulados como as cápsulas de ivermectina, dapsona e sulfato de zinco, pomadas com ácido salicílico, enxofre, solução de trimetropim e creme de hidroquinona, dexametasona e ácido retinóico.

No último mês do estágio, sob orientação e supervisão de um elemento da equipa, tive a possibilidade de realizar algumas preparações de medicamentos manipulados, nomeadamente as cápsulas de dapsona e sulfato de zinco (Anexo 1) e ainda a solução desinfetante de álcool gel. A execução desta tarefa de elevada responsabilidade contribuiu para a minha realização a nível profissional e pessoal.

Neste âmbito, procedi ainda ao preenchimento de documentação relativa aos movimentos de matérias-primas decorrente do uso das mesmas na preparação dos medicamentos manipulados (Anexo 2).

3.1.3. Tarefas desempenhadas

Ao longo do estágio na Farmácia São Sebastião pude desempenhar várias tarefas. No primeiro mês, foi-me permitido fazer o armazenamento e receção de encomendas e gestão de *stocks*.

O armazenamento de medicamentos não sujeitos a receita médica (MNSRM) é divido por classes e de acordo com a indicação terapêutica. A farmácia divide-se em zonas quentes, locais com maior visibilidade, e zonas frias, áreas de menor visibilidade para os utentes, e por isso a disposição dos produtos de venda livre nestas zonas altera consoante a rotatividade,

margem e a época do ano. A constante dinamização dos lineares realizada pela Farmácia São Sebastião pretendia promover a atenção prestada pelo utente e a compra por impulso.

O armazenamento dos medicamentos sujeitos a receita médica (MSRM) é efetuado por ordem alfabética e forma farmacêutica, separando os medicamentos com condições especiais de armazenamento, como as insulinas e vacinas, e antibióticos, devido às especiais restrições envolvidas na sua dispensa, dos restantes MSRM.

Na primeira fase, esta tarefa revelou-se de extrema importância para me permitir memorizar os locais de armazenamento e as particularidades dos diferentes produtos e assim facilitar o posterior atendimento.

Numa receção de encomendas procede-se à verificação de *stocks* dos produtos, prazo de validade, preço de venda à farmácia (PVF), preço de venda ao público (PVP) e margens a aplicar nas diferentes categorias de produtos. A receção de encomendas permitiu-me conhecer as diferentes classes de medicamentos e produtos de venda livre e familiarizar com as embalagens, formas farmacêuticas, nomes comerciais, princípios ativos e correlacionar com a indicação farmacêutica. Foi a partir da receção de encomendas que tive o primeiro contacto com os suplementos alimentares, cosméticos e produtos veterinários.

A partir do segundo mês de estágio, procedi ao atendimento ao público, onde fui confrontada com casos clínicos reais, nos quais aprendi e coloquei em prática o conhecimento adquirido nas várias unidades curriculares do MICF e no primeiro mês de estágio. O aparecimento de novas problemáticas em diferentes áreas traduziu-se numa aprendizagem mais abrangente.

Durante o meu estágio também procedi à preparação individual da medicação, que também é um serviço de grande importância prestado pela farmácia, pois cada vez mais a população idosa é polimedicada, o que aumenta o risco de confusão, esquecimento ou toma inadequada da medicação. A preparação individual da medicação surge como uma solução para colmatar esta toma inadequada da medicação por parte dos utentes, permitindo também fazer uma monitorização da terapêutica do utente (Anexo 3). [4]

Numa população em que patologias como a hipertensão, diabetes *mellitus* e hipercolesterolemia são muito prevalentes, a determinação de parâmetros bioquímicos como a pressão arterial, a glicémia, o colesterol total e os triglicerídeos é um serviço essencial em farmácia comunitária, pois pode ser realizado de forma simples e rápida, permitindo um aconselhamento e monitorização personalizado. Enquanto estagiária, tive oportunidade de aprender e efetuar em contexto real a avaliação destes parâmetros. Com este serviço, senti que contribuí para a identificação de algumas destas doenças silenciosas, exercendo um papel fundamental na promoção da saúde do utente.

A forma progressiva com que me foi permitido desempenhar as várias funções, aumentando a responsabilidade, possibilitaram o contacto com todas as vertentes de um farmacêutico.

3.1.4. Metodologia *Kaizen*

A Farmácia São Sebastião segue uma metodologia de organização e gestão *Kaizen*. Esta metodologia tem como premissa a melhoria contínua da farmácia através do estabelecimento de objetivos e tarefas que devem ser alcançados por toda a equipa. O *Kaizen* é único, na medida em que confere estratégias específicas e adequadas a cada farmácia, resultando numa otimização das várias etapas executadas, desde a receção de encomendas até ao atendimento. Do meu ponto de vista, a aplicação da metodologia *Kaizen* permite, de uma forma simplificada, compreender quais as tarefas a aprimorar para que o trabalho na farmácia seja mais eficiente e com uma gestão mais eficaz.

3.1.5. Utentes fidelizados

A Farmácia São Sebastião conta, na sua maioria, com residentes locais e clientes habituais, de diferentes faixas etárias, sendo maioritariamente idosos, que tem por hábito se dirigem frequentemente a esta instalação.

A fidelização dos utentes é a criação de um vínculo entre o utente e a farmácia, no qual permite ao farmacêutico atuar e aconselhar de forma mais personalizada, de acordo com as preferências e terapêutica do utente. Esta operação é rápida e simples de executar, que permite que o registo da medicação do utente seja mantido pelo Sifarma®. Este registo auxilia a prática de atendimento ao público porque possibilita uma dispensa do medicamento mais célere, contribuindo assim para a satisfação do utente. Esta ferramenta do Sifarma® é especialmente útil em utentes com doenças crónicas e polimedicados.

O histórico da medicação dos utentes fidelizados também se revela fulcral em casos de prescrição de fármacos que não fazem parte da terapêutica atual do utente ou de dosagens incorretas.

3.2. Pontos Fracos

3.2.1. Plano de Estudos do MICF

O plano curricular do MICF abrange diversas áreas científicas fundamentais na formação de farmacêuticos versáteis e capazes de ingressar em qualquer vertente do mundo farmacêutico. Os conhecimentos adquiridos, ao longo do MICF, revelaram-se indispensáveis

na minha formação e proporcionaram-me uma forte componente teórica fulcral para desempenhar com sucesso as tarefas propostas durante o estágio. As unidades curriculares que, na minha opinião, se revelaram preponderantes para o exercício da profissão em farmácia comunitária, foram Indicação Farmacêutica, Farmacologia e Dermofarmácia e cosmética.

O Plano de estudos do MICF, embora seja abrangente e permita que um aluno obtenha diversas valências, apresenta algumas lacunas que facilmente podem ser superadas.

Durante o meu estágio na farmácia São Sebastião, encontrei alguma dificuldade no aconselhamento, particularmente quando este se tratava de suplementos alimentares, preparações para uso veterinário, produtos de cosmética e dispositivos médicos.

Ao longo dos cinco anos do MICF, seria vantajoso reforçar aulas em que fosse possível adquirir maior conhecimento acerca das propriedades e aconselhamento terapêutico destes MNSRM e produtos de venda livre.

3.2.2. Associação do nome comercial ao Princípio Ativo

Nos atendimentos aos cidadãos, em múltiplas ocasiões, senti dificuldade entre os princípios ativos e os nomes comerciais dos MSRM, que eram solicitados.

Esta falta de conhecimento deveu-se principalmente ao facto de, ao longo do MICF, apenas nos ser ensinada a substância ativa e não haver correspondência com os nomes comerciais. A ausência de conhecimentos na correspondência foi uma dificuldade que, em primeira instância, condicionou a prática de atendimento ao público, tornando-a mais morosa. Este condicionamento deveu-se à necessidade de pesquisar entre os princípios ativos presentes em cada receita, com o intuito de descobrir qual seria o princípio ativo correspondente ao nome requerido pelo utente.

3.3. Oportunidades

3.3.1. SIFARMA 2000® e novo SIFARMA®

A Farmácia São Sebastião dispõe do Sifarma 2000® como programa base para todas as operações necessárias numa farmácia. O estágio possibilitou um contacto direto e diário com esta ferramenta de trabalho, nas mais variadas funções que desempenhei, como a receção de encomendas, gestão de *stocks*, venda de MSRM e MNSRM, devoluções e também na obtenção de informação científica sobre os produtos e o historial da terapêutica do utente.

Para além do Sifarma 2000®, a farmácia também possui o novo Módulo de Atendimento do Sifarma®. Este novo Sifarma® apresenta um *design* gráfico mais apelativo, interativo e funcional

que permite simplificar algumas das tarefas decorrentes do atendimento ao público, traduzindo-se num atendimento mais rápido.

Apesar das suas evidentes vantagens, este novo módulo, revela algumas limitações nomeadamente, a falta de cruzamento de informação relativa ao historial de medicação do utente e, portanto, num atendimento ser necessário utilizar os dois sistemas em simultâneo e a impossibilidade de realizar vendas suspensas de MSRM.

O contacto com o novo Módulo de Atendimento do Sifarma® revelou-se uma mais-valia, enquanto estagiária, na medida em que adquiri mais competências para utilizar este novo sistema.

3.3.2. Dermocosmética, Veterinária e Suplementos Alimentares

Com cada vez maior frequência, a farmácia é o local onde o utente procura obter aconselhamento sobre outras áreas que não a do medicamento, pelo que a Farmácia São Sebastião dispõe de produtos cosméticos, veterinários e suplementos alimentares para colmatar essa procura.

Este tipo de produtos são produtos de venda livre e, como tal, o aconselhamento do farmacêutico na decisão da compra por parte do utente é de extrema importância.

No entanto, esta tarefa revelou ter alguma complexidade, devido à existência no mercado de vários produtos para o mesmo fim, marcas com as quais nunca tinha contactado, o que aliado à minha falta de experiência e a dificuldade em identificar alguns dos problemas apresentados pelos utentes se traduziu num obstáculo.

Um bom aconselhamento passa por conhecer bem os produtos, fazer as perguntas certas ao utente para poder identificar qual o produto mais indicado às suas preferências e necessidades.

Felizmente, com o acompanhamento, colaboração e orientação prestado diariamente por toda a equipa da Farmácia São Sebastião, que esclareceram todas as minhas dúvidas, familiarizei-me com os diferentes MNSRM e adquiri confiança na sua seleção e recomendação durante o aconselhamento farmacêutico.

Adicionalmente, assisti a formações de marcas de produtos cosméticos, como a *Caudalie* e o grupo *Pierre Fabre*, que me possibilitaram aprofundar o meu conhecimento sobre as suas filosofias, respetivos produtos e formulações. Em última análise, estas formações contribuíram para um maior domínio de competências no atendimento e aconselhamento aos utentes.

3.4. Ameaças

3.4.1. Receitas Manuais

Durante o estágio tive oportunidade de contactar com os três tipos de receitas: eletrónicas materializadas, eletrónicas desmaterializadas e manuais. O procedimento a ter é diferente em cada um dos tipos de receita. Contudo, o processamento de receitas manuais apresenta singular dificuldade devido à presença de particularidades adicionais, como por exemplo, ser da responsabilidade do farmacêutico a introdução no Sifarma® de cada medicamento prescrito na receita, do plano de comparticipação do utente e também da verificação de todos os dados necessários à validação da receita. A validação final obrigatória dos medicamentos cedidos não é totalmente eficaz a detetar erros na cedência, dado que é o farmacêutico que introduz a linha do produto, e este pode ter colocado incorretamente. A dispensa única dos medicamentos é também uma desvantagem desta tipologia de receita, que condiciona o levantamento dos medicamentos pelo utente e a sua dispensa pelo farmacêutico. As receitas manuais têm um passo adicional que é realizado após a faturação de cada mês que implica enviar uma cópia da receita para a entidade comparticipadora.

3.4.2. Informação de Preços nas Guias de Tratamento

Numa guia de tratamento consta o fármaco na dosagem a dispensar, a quantidade de embalagens, a validade e o preço máximo a pagar pelo utente, caso o medicamento seja MSRM. Este montante refere-se sempre ao preço máximo do medicamento genérico mais dispendioso pertencente ao grupo homogéneo dos cinco medicamentos mais baratos, atualmente comercializado, que pode ou não existir na farmácia ou inclusivamente estar ou não disponível no mercado, e que induz muitas vezes o utente ao erro, relativamente ao valor a pagar.

Em diversas situações aquando o atendimento, fui confrontada com utentes que me questionavam sobre o preço a pagar pelo MSRM, que se apresentava superior ao indicado na guia de tratamento.

Estes acontecimentos potenciam alguma desconfiança e descontentamento que podem prejudicar a relação que deve ser estabelecida entre o farmacêutico e o utente.

3.4.3. Medicamentos esgotados

Durante o tempo em que estagiei na farmácia São Sebastião, em diversas ocasiões, deparei-me com o esgotamento de determinados medicamentos, como por exemplo, o Victan®, Serenal® e Xanax XR® ou o difícil acesso a outros, como Victoza®, Prevenar 13®, ou Broncho-Vaxom®. Diariamente, era necessário verificar no Sifarma® se estes medicamentos já

se encontravam disponíveis no mercado. A falta de *stock* ou o número reduzido destes medicamentos, traduz-se num enorme inconveniente para os utentes.

O inconveniente causado é uma consequência direta da deslocação à farmácia sem obtenção da totalidade da medicação pretendida, mas também em determinadas circunstâncias, como a falta de genéricos ou de recetividade dos utentes aos genéricos, a única solução ser a substituição da terapêutica por outro medicamento.

3.4.4. Plano de Contingência de COVID-19

Devido à pandemia do COVID-19, Portugal ficou em estado de emergência em meados de março. Consequentemente, o meu estágio, que deveria ter começado em abril apenas se iniciou em junho. Este adiamento do estágio foi importante para as farmácias que não tinham possibilidade de receber devidamente os estagiários e para salvaguardar a saúde dos estudantes da Faculdade de Farmácia da Universidade de Coimbra. Em junho, já eram várias as medidas do plano de contingência que tinham sido implementadas o que contribuiu para uma melhor integração dos estagiários. Rapidamente me habituei à realidade de utilizar a máscara durante horas seguidas, desinfetar rotineiramente as mãos e os balcões de atendimento e a ter um acrílico e máscaras entre mim e o utente, que constituíam uma barreira adicional e que frequentemente dificultavam a comunicação.

No entanto, pelo facto de o período em que estive na farmácia se estender entre junho e setembro, tive dois fatores que pesaram na pouca afluência de utentes à farmácia, sendo o primeiro de que estes meses são na sua maioria meses de férias de verão e o segundo o receio inerente a um possível contágio pelo vírus SARS-CoV-2, que condicionavam as deslocações que os utentes faziam à farmácia. Esta diminuição conduziu, por sua vez, à redução do número e heterogeneidade de atendimentos. Adicionalmente, devido ao período em que realizei o estágio, não tive oportunidade de aprender e aconselhar MNSRM comuns em outras épocas do ano, como os xaropes para a tosse e os descongestionantes do outono/inverno.

4. Casos Clínicos

Caso Clínico 1

Um senhor dirige-se à farmácia e solicita Aerius®.

Como este medicamento é um MSRM, perguntei se possuía receita para o dispensar, tendo-me respondido que não. Após ter questionado sobre os sintomas que o utente apresentava, percebi que se tratava de uma rinite alérgica e que o utente desconhecia as alternativas não sujeitas a receita médica. Optei por lhe aconselhar MNSRM como Telfast®

120mg ou Cetix®, que embora sejam três moléculas diferentes pertencem à mesma classe de anti-histamínicos, H1 não sedativos, e, portanto, terão uma ação muito similar. O utente selecionou o Telfast® 120mg, por conter mais comprimidos na sua embalagem e poder ser utilizado em ocasiões futuras ou durante um maior período de tempo. Caso os sintomas permanecessem ou agravassem, aconselhei a consultar um médico.

Caso Clínico 2

Uma senhora desloca-se à farmácia queixando-se de prurido, ardor e vermelhidão em várias zonas do corpo.

Após ter feito determinadas questões, a utente referiu que não tinha ingerido ou aplicado produtos diferentes do habitual e exibiu algumas das áreas sintomáticas. Perante esta observação percebi que os sintomas seriam uma consequência de uma pele seca e desidratada. Optei por, em primeira instância, aconselhar a utente a evitar banhos prolongados e com água muito quente, usar produtos para pele sensível e aplicar diariamente um hidratante. Devido às medidas implementadas pela pandemia, o aumento de higienização das mãos e o uso do álcool gel são fatores agravantes neste tipo de patologias, por isso reforcei a ideia de aplicar creme nas mãos várias vezes ao dia. Nas zonas da pele que estavam mais secas e de maior prurido, aconselhei uma pomada de hidrocortisona, um MNSRM, que reduziria a sintomatologia apresentada e o desconforto associado. Embora seja um corticoide, este é aplicado em afeções da pele de sintomatologia leve e aguda. A aplicação da pomada é indicada durante um curto período, de apenas dois dias, com aplicação de duas vezes por dia.

5. Conclusão

Após quatro meses de estágio na farmácia São Sebastião, senti que foi uma experiência bastante enriquecedora, que me permitiu consolidar os conhecimentos, desenvolver competências profissionais, relacionais e pessoais importantes.

Durante o estágio, tive oportunidade de me familiarizar com a profissão farmacêutica, onde aprendi a executar tarefas no Sifarma®, aconselhar os utentes de forma autónoma e a ultrapassar os receios de errar, sem perder o sentido de responsabilidade.

O estágio na Farmácia São Sebastião permitiu-me ainda contactar com diversas situações que fizeram com que o meu desenvolvimento fosse mais abrangente, tanto a nível de aconselhamento na área da cosmética, veterinária e suplementação alimentar, como na preparação de medicamentos manipulados.

Neste período de aprendizagem, tive uma visão mais real do papel do farmacêutico comunitário como sendo o profissional que zela pela saúde da população, que pode em diversas situações ajudar os utentes na resolução dos seus problemas de saúde e preservação do seu bem-estar.

Cada atendimento, que tive oportunidade de vivenciar, representou uma mais-valia repleta de experiências enriquecedoras e compensadoras, tanto a nível profissional como pessoal.

Agradeço à Farmácia São Sebastião o seu acolhimento, ensinamentos e a demonstração diária de forma exemplar da prestação de serviços e aconselhamento farmacêutico.

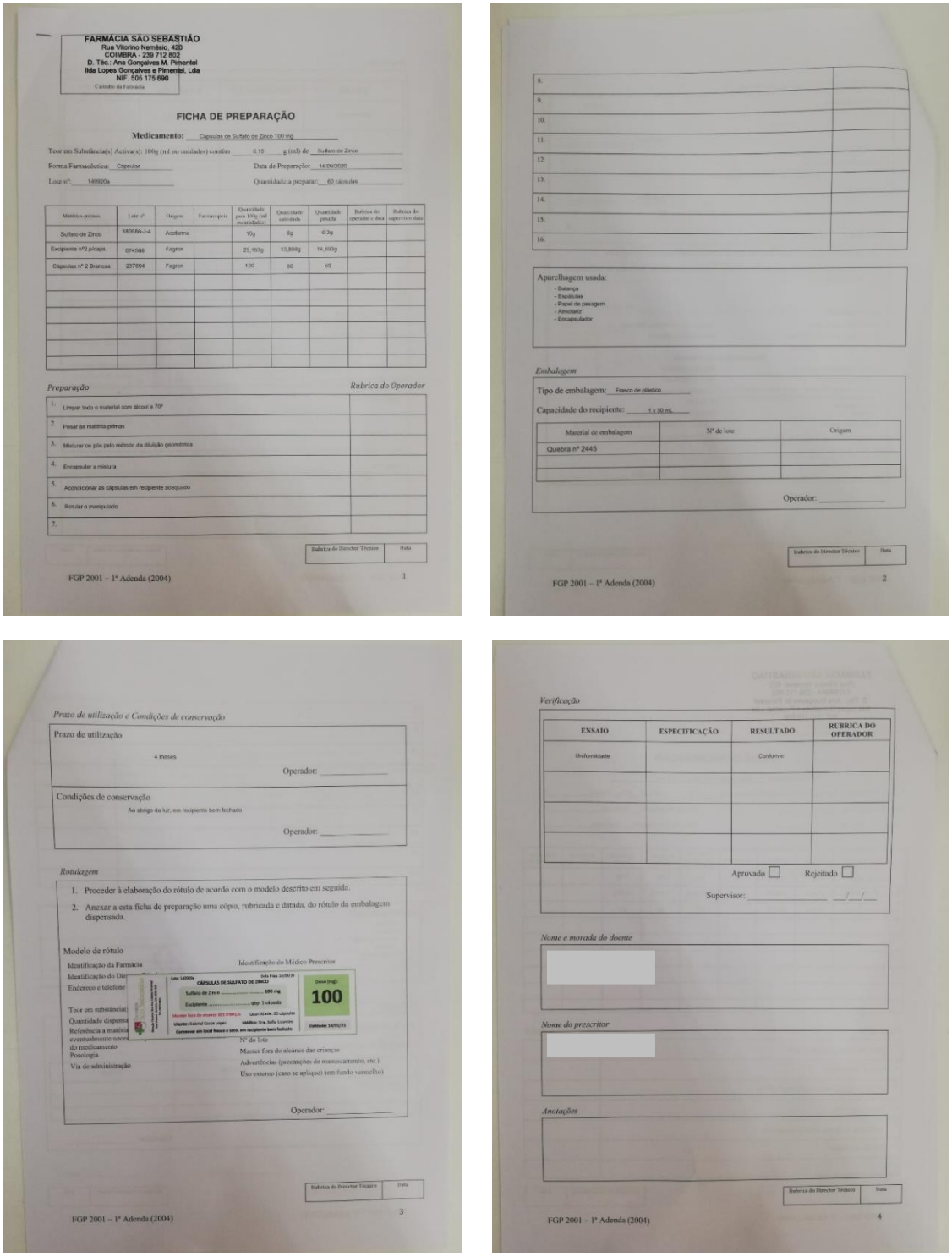
Por fim, concluo esta etapa com uma enorme satisfação de quem acredita que evoluiu, mas que ainda tem tanto para aprender.

6. Referências Bibliográficas

1. ORDEM DOS FARMACÊUTICOS – **A Farmácia Comunitária** [Acedido a 5 de Outubro de 2020]. Disponível em: https://www.ordemfarmaceuticos.pt/pt/areas-profissionais/farmacia-comunitaria/a-farmacia-comunitaria/
2. ORDEM DOS FARMACÊUTICOS – **Código Deontológico da Ordem dos Farmacêuticos** [Acedido a 5 de outubro de 2020]. Disponível em: https://www.ordemfarmaceuticos.pt/fotos/documentos/codigo_deontologico_da_of_44366676175988472c14020.pdf
3. INFARMED – **Portaria n.º 594/2004, de 2 de junho - Aprova as boas práticas a observar na preparação de medicamentos manipulados em farmácia de oficina e hospitalar** [Acedido a 6 de outubro de 2020]. Disponível em: https://www.infarmed.pt/documents/15786/17838/portaria_594-2004.pdf/d8b8cac3-3250-4d05-b44b-51c5f43b601a
4. ORDEM DOS FARMACÊUTICOS – **Norma Geral – Preparação Individualizada da Medicação (PIM)** [Acedido a 6 de outubro de 2020]. Disponível em: https://www.ordemfarmaceuticos.pt/fotos/documentos/norma_pim_vfinal_30_nge_00_010_02_1834827175bf58d479434f.pdf

7. Anexos

Anexo I – Ficha de preparação de um medicamento manipulado



FARMÁCIA SÃO SEBASTIÃO
Rua Vitorino Nemésio, 42D
COIMBRA - 239 712 802
D. Téc.: Ana Gonçalves M. Pimentel
Ilda Lopes Gonçalves e Pimentel, Lda
NIF. 505 175 690

FICHA DE PREPARAÇÃO

Medicamento: Cápsulas de Sulfato de Zinco 100 mg

Teor em Substância(s) Activa(s): 100g (ml ou unidades) contém 0.10 g (ml) de Sulfato de Zinco

Forma Farmacêutica: Cápsulas — Data de Preparação: 14/09/2020

Lote nº: 140920a — Quantidade a preparar: 60 cápsulas

Matérias-primas	Lote nº	Origem	Farmacopeia	Quantidade para 100g (ml ou unidades)	Quantidade calculada	Quantidade pesada	Rubrica do operador e data	Rubrica do supervisor data
Sulfato de Zinco	180980-J-4	Acofarma		10g	6g	6,3g		
Excipiente nº2 pilogia	074568	Fagron		23,163g	13,898g	14,593g		
Cápsulas nº 2 Brancas	237894	Fagron		100	60	60		

Preparação — *Rubrica do Operador*

1. Limpar todo o material com álcool a 70º
2. Pesar as matéria-primas
3. Misturar os pós pelo método da diluição geométrica
4. Encapsular a mistura
5. Acondicionar as cápsulas em recipiente adequado
6. Rotular o manipulado
7.

Rubrica do Director Técnico | Data

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8.
9.
10.
11.
12.
13.
14.
15.
16.

Aparelhagem usada:
- Balança
- Espátulas
- Papel de pesagem
- Almofariz
- Encapsulador

Embalagem

Tipo de embalagem: Frasco de plástico

Capacidade do recipiente: 1 x 50 mL

Material de embalagem	Nº de lote	Origem
Quebra nº 2445		

Operador:

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Prazo de utilização e Condições de conservação

Prazo de utilização

4 meses

Operador:

Condições de conservação

Ao abrigo da luz, em recipiente bem fechado

Operador:

Rotulagem

1. Proceder à elaboração do rótulo de acordo com o modelo descrito em seguida.
2. Anexar a esta ficha de preparação uma cópia, rubricada e datada, do rótulo da embalagem dispensada.

Modelo de rótulo

Identificação da Farmácia
Identificação do Médico Prescritor
Identificação do Di
Endereço e telefone
Teor em substância(
Quantidade dispens
Referência a matéria
eventualmente neces
do medicamento
Posologia
Via de administração

CÁPSULAS DE SULFATO DE ZINCO
Sulfato de Zinco ..... 100 mg
Excipiente ..... qbp. 1 cápsula
Dose (mg): 100
Nº do lote
Manter fora do alcance das crianças
Advertências (precauções de manuseamento, etc.)
Uso externo (caso se aplique) (em fundo vermelho)

Operador:

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Verificação

ENSAIO	ESPECIFICAÇÃO	RESULTADO	RUBRICA DO OPERADOR
Uniformidade		Conforme	

Aprovado ☐ Rejeitado ☐

Supervisor: _____ __/__/__

Nome e morada do doente

Nome do prescritor

Anotações

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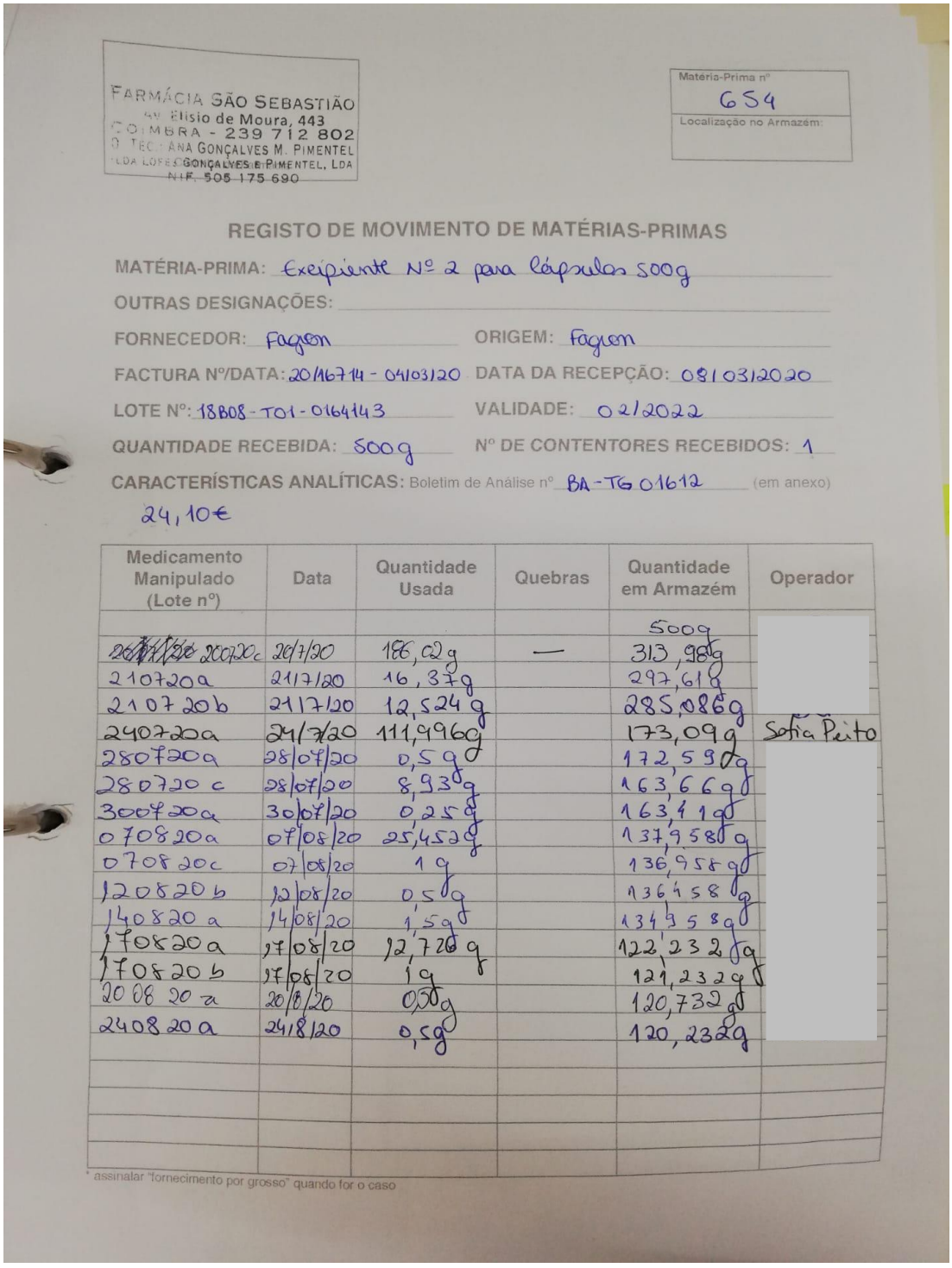
Figura 2 – Ficha de preparação de um medicamento manipulado de cápsulas de sulfato de zinco.
Na primeira página é colocada a informação relativa a forma farmacêutica, quantidade a preparar, identificação de que medicamento manipulado se trata, dos componentes que o constituem e as suas respetivas dosagens.
Na primeira e segunda página são descritas as etapas da preparação. Ainda na segunda página é mencionado o material a utilizar e a embalagem de acondicionamento.
Na terceira página é referido o prazo de validade, condições de armazenamento e a rotulagem.
A quarta página contempla a verificação e a informação do utente e do médico.

Anexo 2 – Registo de movimento de matérias-primas



FARMÁCIA SÃO SEBASTIÃO
Av. Elísio de Moura, 443
COIMBRA - 239 712 802
O TEC.: ANA GONÇALVES M. PIMENTEL
GONÇALVES E PIMENTEL, LDA
NIF. 505 175 690

Matéria-Prima nº 654
Localização no Armazém:

REGISTO DE MOVIMENTO DE MATÉRIAS-PRIMAS

MATÉRIA-PRIMA: Excipiente Nº 2 para cápsulas 500g
OUTRAS DESIGNAÇÕES:
FORNECEDOR: Fagron ORIGEM: Fagron
FACTURA Nº/DATA: 20/16714 - 04103120 DATA DA RECEPÇÃO: 08103/2020
LOTE Nº: 18808-T01-0164143 VALIDADE: 02/2022
QUANTIDADE RECEBIDA: 500g Nº DE CONTENTORES RECEBIDOS: 1
CARACTERÍSTICAS ANALÍTICAS: Boletim de Análise nº BA-TG 01612 (em anexo)
24,10€

Medicamento Manipulado (Lote nº)	Data	Quantidade Usada	Quebras	Quantidade em Armazém	Operador
				500g	
~~200720c~~	20/7/20	186,02g	—	313,98g	
210720a	21/7/20	16,37g		297,618g	
210720b	21/7/20	12,524g		285,086g	
240720a	24/7/20	111,996g		173,09g	Sofia Peito
280720a	28/07/20	0,5g		172,590g	
280720c	28/07/20	8,93g		163,66g	
300720a	30/07/20	0,25g		163,41g	
070820a	07/08/20	25,452g		137,958g	
070820c	07/08/20	1g		136,958g	
120820b	12/08/20	0,5g		136,458g	
140820a	14/08/20	1,5g		134,958g	
170820a	17/08/20	12,726g		122,232g	
170820b	17/08/20	1g		121,232g	
200820a	20/8/20	0,50g		120,732g	
240820a	24/8/20	0,5g		120,232g	

* assinalar "fornecimento por grosso" quando for o caso

Figura 3 – Ficha de registo de movimentos de matérias-primas. Documento destinado a cada matéria-prima presente no laboratório da Farmácia São Sebastião onde se indicam todos os dados relativos à matéria-prima e se regista todas as suas utilizações. Este registo permite saber quando é necessário repor *stock* bem como rastrear em que manipulados a matéria-prima foi utilizada.

Anexo 3 – Caixa semanal de medicação

Figura 4 – Caixa semanal de medicação. No exterior da caixa são preenchidos os dados referentes ao utente e à farmácia.

Figura 5 – Parte interior de uma caixa de medicação semanal. No interior são colocados os medicamentos conforme a sua posologia, bem como uma tabela resumo da posologia, de forma a facilitar a administração pelo utente.

PARTE III

"Nano- and microparticle-stabilized Pickering emulsions designed for therapeutic and cosmetic applications"

List of Abbreviations

5′-AMP – 5′-Adenosine monophosphate

5′-ATP – 5′-Adenosine triphosphate

ADME – Absorption, distribution, metabolism and excretion

AONB – Acridine orange 10-nonyl bromide

ASt – Aluminum atarch octenylsuccinate

CA – Carminic acid

CAA – Cellular antioxidant activity

CAT – Catalase

CD – Cyclodextrin

CFU – Colony-forming unit

CGTase – Cyclodextrin glycosyltransferase

CNC – Cellulose nanocrystal

Col I – Collagen Type I

CSSNP – Solid core-mesoporous shell silica nanoparticles

EC – European Commission

EC50 – Median effective concentration

EYP – Egg yolk peptide

FE – Fuller's Earth

GA – Gum Arabic

GSH – Reduced glutathione

HA – Hyaluronic acid

HAp – Hydroxyapatite

HNT – Halloysite nanotube

HRIPT – Human repeat insult patch test

MDA – Malondialdehyde

MEC10 – Minimum effective concentration

MFC – Minimum fungicidal concentration

MH – Minocycline hydrochloride

MIC90 – Minimum inhibitory concentration

MIP – Molecularly imprinted polymer

NIP – Non-imprinted polymer

MMT – Montmorillonite

O/O – Oil-in-Oil

O/O/W – Oil-in-Oil-in-Water

O/W – Oil-in-Water

OMC – Octyl methoxycinnamate

OSA – Octenyl succinic anhydride

PCL – Poly(ε-caprolactone)

PCL-b-PEG – Poly(ε-caprolactone)-block-Poly(ethylene glycol) copolymer

PE – Pickering emulsion

PEG – Poly(ethylene glycol)

PGA – Poly(glycolic acid)

PLA – Poly(lactic acid)

PLA-b-PEG – Poly(glycolic acid)-block-Poly(ethylene glycol) copolymer

PLGA – Poly(lactic-co-glycolic acid)

PLGA/PSS – Poly(styrene-co-4-styrene-sulfonate) coated Poly(lactic-co-glycolic acid)

PLLA – Poly(L-lactic acid)

PSS – Poly(styrene-co-4-styrene-sulfonate)

PVA – Poly(vinyl alcohol)

PVA/PLGA – Poly(vinyl alcohol) coated Poly(styrene-co-4-styrene-sulfonate)

QSB – Quercus suber bark

ROS – Reactive oxygen species

SACP – Self-aggregated chitosan particle

SC – *Stratum corneum*

SLG – Short linear glucan

SPF – Sun protection factor

TA – Tocopheryl acetate

TiO2 – Titanium dioxide

UV – Ultraviolet

VED – Viable epidermis and dermis

W/O – Water-in-oil

W/W – Water-in-water

WPI – Whey protein isolate

Resumo

As emulsões Pickering são sistemas compostos por dois fluídos imiscíveis, estabilizados por partículas sólidas orgânicas ou inorgânicas. Uma maior resistência à coalescência e menor toxicidade tornam estas emulsões candidatas apropriadas para inúmeras aplicações, como catálise, cosmética, alimentação, recuperação de óleo e terapêutica. Uma ampla gama de partículas pode ser usada para estabilizar emulsões de Pickering. Nesta monografia, é apresentada uma visão geral das emulsões Pickering, com foco em aplicações tópicas. Numa primeira fase, são referidos os parâmetros que influenciam a estabilização das emulsões Pickering. Em segunda instância, são discutidas algumas das aplicações tópicas já investigadas de nano e micropartículas usadas para estabilizar emulsões de Pickering. Posteriormente, são descritos alguns dos estabilizadores mais promissores das emulsões Pickering para aplicações tópicas. Por fim, realiza-se uma breve análise da toxicidade e avanços nas perspetivas futuras.

Palavras-chave: emulsão de Pickering, nanopartículas, micropartículas, aplicação tópica, aplicação terapêutica, aplicação cosmética.

Abstract

Pickering emulsions are systems composed of two immiscible fluids stabilized by solid organic or inorganic particles. A greater resistance against coalescence and lower toxicity make these emulsions suitable candidates for numerous applications such as catalysis, cosmetic, food, oil recovery and therapeutic. A broad range of particles can be used to stabilize Pickering emulsions. In this monograph, we give an overview of Pickering emulsions, focusing on topical applications. First, we reference the parameters that influence the stabilization of Pickering emulsions. Second, we discuss some of the already investigated topical applications of nano- and microparticles used to stabilize Pickering emulsions. Afterwards, we consider some of the most promising stabilizers of Pickering emulsions for topical applications. Ultimately, we carried out a brief analysis of toxicity and advances in future perspectives.

Keywords: Pickering emulsion, nanoparticles, microparticles, topical applications, therapeutic applications, cosmetic applications.

1. Introduction

The skin, the largest organ in the human body, has the main function of protecting the internal environment against external damage. It is formed by three layers, epidermis, dermis and hypodermis. The epidermis can be further divided into four different layers, with *stratum corneum* (SC) being the outermost layer. The SC is very important because it regulates absorption into the skin, making it a barrier that needs to be crossed by cosmetics and therapeutic formulations. Molecules of topical formulations can permeate through the skin by three possible routes: intercellular, transcellular or appendageal. The first route is the most used but it is slow because molecules cross through intercellular spaces. In the second route, the molecules pass through the phospholipid membranes and the cytoplasm of the dead keratinocytes. In the last route, the molecules pass through hair follicles and eccrine glands, which may be an advantage for drug delivery, especially involving nanoparticles. Thus, the penetration of molecules into the skin can be challenging and, in most situations, it is necessary to combine multiple strategies to achieve a significant penetration. Other factors need to be considered to make sure molecular permeation occurs, such as the vehicle used, the substance's physical properties and the substance-vehicle interactions. The vehicle used in topical formulations is very important since it remains in the area of application and can increase drug release. Additionally, chemical enhancers may be employed to further increase permeation through skin. [1]

Cosmetic and pharmaceutical formulations such as creams, lotions and gels are emulsions. [2] Emulsions are defined as systems comprised of two immiscible liquids, dispersed into one another in the form of droplets. [1] The topical application of emulsions has several advantages, such as enhanced drug release and permanence on the skin. [1] One of the problems of using conventional emulsions is that they usually contain surfactants, which is are emulsifiers that can cause environmental and toxicity concerns [3], such as skin reactions like contact dermatitis or inflammation [4], cell damage [5] and carcinogenicity. [6] The irritating potential is generally higher for cationic surfactants when compared to non-ionic or anionic surfactants, and decreases when the surfactant concentration decreases as well. Emulsions are promising formulation for the treatment of skin disorders such as atopic dermatitis or eczema however, due to the presence of surfactants, they may also cause or even aggravate the symptoms. [4] Thus, developing new approaches to reduce toxicity and stabilize emulsions is very attractive to the cosmetic and pharmaceutic industries. Recent studies have been focusing on "surfactant-free" emulsions, where these compounds are substituted with other emulsifiers such as polymers and solid particles. [2,3]

A Pickering emulsion is an emulsion stabilized with colloidal solid particles at the interface of the two immiscible fluids. The emulsion stabilization is based on an irreversible and effective adsorption which leads to the creation of a mechanical barrier around the droplets against coalescence. [7]

The growing interest in Pickering emulsions is due to the higher stabilization achieved by irreversible adsorption, that occurs when particles cover homogeneously the droplet, avoiding coalescence and even restricting Ostwald ripening. [8] Other advantages are good biocompatibility and low cytotoxicity, which cannot be achieved when using surfactants. [9] Several different particles can be used due to their useful intrinsic properties, which make them suitable for several applications such as catalysis, cosmetic, food, oil recovery and therapeutic. [3,6] Additionally, solid particles can be low-cost stabilizers. [5] Concerning size, the particles can be divided into nano- and microparticles, while chemically they can be organic or inorganic particles. Nano- and microparticles have advantages over bigger particles such as higher surface energy, unique composition and architecture. [1]

Pickering emulsions are particularly useful in cosmetics, where the surfactants are unwanted, [5] as well as in the pharmaceutical field, where transdermal and/or dermal drug delivery is difficult to achieve and controlled drug release is desired. [10]

2. Stabilization Parameters for Pickering emulsions

The effectiveness of Pickering emulsion stabilization depends on wettability, phase properties, phase ratio, adsorption, concentration, particle size and shape, roughness and charge of the surface particle, salt concentration and pH.

For many researchers, the key parameter for the stabilization is the particle wettability. [11] The solid particles have a dual wettability responsible for their spontaneous accumulation at the interface of oil and water phases. The wettability is calculated by the angle formed between the interface and the particle, known as contact angle (θ), and it determines which kind of emulsion will be formed. When θ is under 90°, the emulsion obtained is oil-in-water (O/W). Contrarily, when θ is above 90°, the emulsion obtained is water-in-oil (W/O). In order to achieve a strong stabilization, the particle wettability should be close to 90° (Figure 1). Pickering emulsions can be W/O, W/O, multiple emulsions or even water-in-water (W/W) or oil-in-oil (O/O) only when the two phases are immiscible. [3]

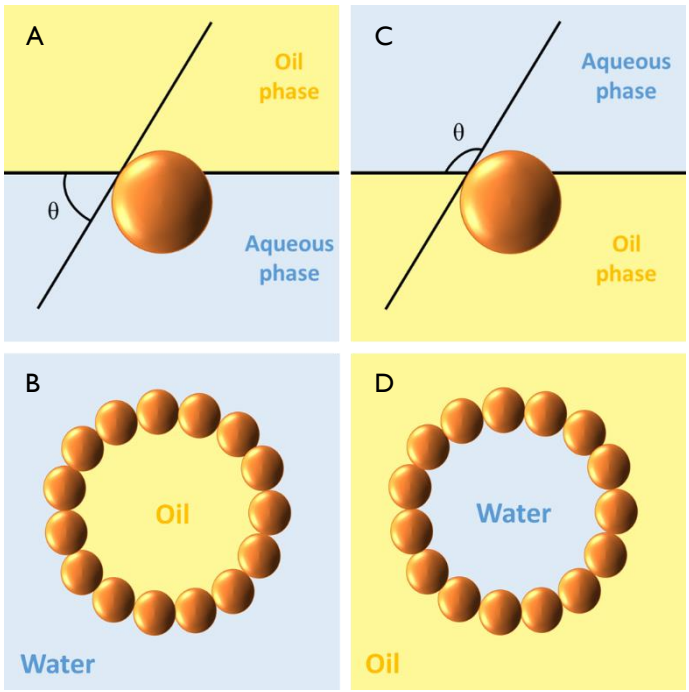


Figure 1 - Wettability mechanism in W/O and O/W Pickering emulsions. (A) The particle at the emulsion interface with θ <90°. (B) The type of emulsion obtained when θ <90° (O/W). (C) The particle at the emulsion interface with θ >90°. (D) The type of emulsion obtained when θ >90° (W/O). [11]

The characteristics of the oil phase such as polarity and viscosity can affect the contact angle and therefore compromise the stabilization, change the type of the emulsion or the droplet size. [3] A study by Binks and Lumsdon [12] showed the influence of the oil polarity in particles with intermediate contact angle, with polar oils forming W/O, whereas non-polar oils formed O/W.

The ratio of the phase can disturb the size of the droplets and the type of emulsions obtained. By increasing the phase that is dispersed, the size of droplets augments and the type of emulsion may change (for example from W/O to O/W or multiple). When the dispersed phase increases, the interfacial area also increases. The same amount of particles is not able to stabilize a greater interfacial area thus the droplets become larger. [3]

The phase where the particles were dispersed before the emulsification is also important because it can determine the kind of emulsion achieved. Particles with identical wettability may change this parameter due to the interactions established with the liquids where they were dispersed. If the particles were dispersed in oil, the emulsion achieved will preferentially be W/O. [3]

The stabilization of Pickering emulsion is predicated on the particle adsorption at the interface of the emulsion, as mentioned before. The adsorption free energy is the energy necessary to remove a solid particle with a spherical shape from the interface of the emulsion. [3] The adsorption of the particles is irreversible, due to the high energy required to remove

the particles, which can be up to 10^8-fold the thermal energy. [13] Therefore, the stabilization of Pickering emulsions is greater than that of conventional emulsions. [11] A specific radius, contact angle and interfacial tension are determinant to the adsorption energy. The highest adsorption energy is achieved when θ is 90°. Particles with larger size need higher adsorption energy, when compared to smaller particles with the same θ. The rate of particle adsorption is important as well because if it is not faster than the rate of coalescence, the droplets will coalesce rather than being stabilized. [3]

The particle concentration is correlated to the droplet size. When the particle concentration increases, the interfacial coverage improves and the size of the droplets decreases homogenously, a process called "limited coalescence". Nevertheless, when the particle concentration is too high, it enables a fast emulsification with heterogeneous droplet sizes or may even cause phase inversion. Conversely, at low particle concentration, the stabilization is not achieved because the particles are not sufficient to stabilize the droplets. [3]

The particle size also has an impact on the stabilization of the emulsion and the size of the droplet. [3] The size of the stabilizing particles can be in the nanoscale or in the microscale, thus the solid particles can be nanoparticles or microparticles. [1] The increase in the size of the particle is accompanied by an increase in the size of the droplet. [3] As mentioned before, the size of the particles influences the adsorption energy, which in turn, affects the stabilization. The larger particles have slower adsorption kinetics and, consequently, create barriers with high adsorption energy and weaker packing efficiency over the droplet surface. [11]

Particles of different shapes can be used to stabilize Pickering emulsions, including dumbbell, flake, ellipsoid, cylinder, wire, [6] tube, ribbon, [14] sheet, [15] rods, cubes, and deformable nanogel; the most used are spherical particles. [3] The particle shape affects the stabilization of the emulsion, with different shapes leading to different stabilization mechanisms. The particle arrangement, how they adsorbed at the interface and the aspect ratio play a role in the stabilization of non-spherical particles. The higher the aspect ratio the greater the stabilization. [3] In addition, features such as flexibility, conformation, multilayer creation at the interface or all atoms of the particle contribute to stabilization, allowing 2D structures to increase the coverage around the droplet. [16]

The roughness of the particle surface plays a significant role in the wettability. However, the effect of roughness in the stability of the emulsion needs further research, since it was observed that roughness may cause a decrease but also an increase of the contact surface of the particles with the interface. [3]

When the particles have weak adsorption at the interface, the charge of the particle surface, potential zeta, has an impact on the emulsion stability. This phenomenon occurs due to the creation of electrostatic repulsions between particles and between particles and droplets, which are against adsorption. As a consequence, the adsorption rate decreases, leading to system instability. [3]

Changes in salt concentration or pH also significantly affects the particles potential zeta and their contact angle. The variation of these parameters has been widely studied, in order to control the emulsion stability. The change of salt concentration or pH can convert repulsive into attractive interactions between particles. An increase of salt concentration can improve the efficiency of the emulsion and induce a pH change in pH-responsive particles, increasing their stability. [3] Additionally, pH changes can ionize the surface groups of the particles modifying their hydrophobicity. Therefore, the pH variations can tune the adsorption mechanism or even shift the emulsion type. [16]

In summary, it is crucial to select the right particle and the respective phases when developing Pickering emulsions.

3. Stabilizers of Pickering Emulsions for Topical Application

Topical application concerns the local application of formulations on external surfaces such as hair, mucosa or skin. This type of application is very attractive for the consumer because it is easy to perform and usually has less adverse effects compared to other routes, especially the systemic. [17]

3.1. Solid Particles

Several particles have been widely studied as emulsion stabilizers. [7] Nano- and microparticles are an excellent choice for topical applications because of their customizable size and surface polarity that enhance skin penetration. Also, they can create an occlusive layer and extend retention time, which is advantageous for drug delivery. [1]

In this section, solid nano- and microparticles used as stabilizers for topical Pickering emulsions are divided into organic or inorganic particles, according to their chemical structure. These solid particles are summarized in Table I. Table II presents interesting examples of topical applications of Pickering emulsions, summarizing challenges and discoveries made recently in the cosmetic and pharmaceutical fields.

3.1.1. Inorganic particles

3.1.1.1. Silica

Over the last few years, studies have been conducted on inorganic particles like silica. [18] Silica, another name for silicon dioxide, can be divided into three main categories: amorphous silica, synthesized amorphous silica and crystalline silica. The synthetic process of amorphous silica generates precipitated silica, silica gel, colloidal silica and fumed silica. Only fumed silica is obtained by a thermal method, the others are obtained via wet methods. Silica nanoparticles have well-defined shapes, in a range of sizes, with tight distribution. [18] These amorphous silica nanoparticles can also be surface modified [19] by physical or chemical processes. [20] Silica can be physically modified through adsorption of different compounds such as surfactants, polymers or salts, as well as polymers, pigments, natural polyphenols and other substances. Examples of chemical changes include the addition of chemical groups, such as dimethylsilyl or hydroxyl groups, in order to provide hydrophobicity or hydrophilicity, respectively. Silica can undergo modification during its synthesis process so that some properties of these nanoparticles can be improved. Modified silica particles are porous, allowing the incorporation of a great volume of drug, because of the large specific surface available. [20] Unmodified silica is most likely to stabilize O/W emulsions because of its hydrophobicity, due to the silanol groups. Modified silica acquires hydrophobic groups at its surface and, as a result, these particles will primarily stabilize W/O emulsion. [6,19]

Frelichowska *et al.* [21] described the modification of silica by addition of dimethylsilyl groups for hydrophobicity, and hydroxyl groups for surface hydrophilicity (Figure 2). This modification allowed silica particles to bind caffeine, a hydrophilic drug, via hydrogen bonding. The modified silica particles created a shell around the droplets containing caffeine, acting like a barrier, which resulted in a much slower caffeine release into the skin in comparison with conventional emulsions. This phenomenon is only possible if the amount of silica particles is enough to cover all the droplets. Additionally, the modification permits interactions between surface hydrophobic groups from silica and lipids from the outermost layer of the skin, promoting an easier skin penetration and caffeine transport. The physicochemical characteristics of the silica particles used in this study (20 nm of size, 9.7±0.5 μm droplet size, 151.4±1.3° wettability in a W/O Pickering emulsion with 550±50 mPa.s at 20°C), allowed a sustained release behaviour. As a result, the emulsion skin permeation was increased 3-fold and there were 2-fold more caffeine accumulated in the receptor fluid when compared to a conventional emulsion, which proves that this hydrophilic drug permeates properly through the epidermis and dermis. [21]

In a subsequent study, Frelichowska *et al.* [22] used fumed silica nanoparticles ranging from 15 to 20 nm to stabilize O/W emulsions with 6±2 mPa.s at 20°C, with the aim to deliver the lipophilic *all-trans* retinol to the skin. The silica was hydrophobized by the addition of dichloro dimethyl silane grafts, to provide partial wetting in oil and water phases. A large amount of silica was employed in this formulation which led to a full coverage of oil droplets by silica aggregates. This phenomenon occurs because the silica nanoparticles have a strong affinity for the interface of the emulsion. The rigid shell that the modified silica creates around the droplets stabilizes the emulsion even when it is applied to the skin. Moreover, the improved stability enables the intact droplets to cross the SC, like microcapsules of 3±1 μm, in size. The penetration of retinol from Pickering emulsions and conventional emulsions was similar but increased approximately 5-fold in both emulsions, in comparison with the retinol solution. Retinol present in the Pickering emulsion was mostly distributed and retained in the outermost layer of the skin, 5-fold more than with the conventional emulsion. Therefore, the Pickering emulsion provided an improvement in active ingredient retention in the SC, as well as sustained release behaviour. [22]

Eskandar *et al.* [23,24] also showed that Pickering emulsions can be stabilized by fumed silica particles. In two different works, fumed silica was used to cover oleylamine or lecithin, two surfactants, in order to achieve a synergistic effect in the O/W emulsion stabilization as well as in the emulsification efficiency. The interactions between fumed silica and oil charged droplets led to a partial coverage of the negatively charged lecithin, and a strong coverage of the positively charged oleylamine. In these two studies, the fumed silica had a mean diameter of 7 nm. In the first study, the droplet size ranged from 166.5 to 261.6 nm, while the zeta potential was between -49.9 and -52 mV for the lecithin emulsion, and between +32 and +35.6 mV for the oleylamine emulsion. [22] In the second study the droplet size range was from 166.5 to 361.5 nm, while the zeta potentials varied between -39.5 and -40.6 mV, or from +48.1to +52.2 mV, for the lecithin and oleylamine emulsions, respectively. [23,24] In the first study the skin delivery of *all-trans* retinol was evaluated. The retinol skin retention in Pickering emulsion with lecithin was 12.6 times higher than the control emulsion of lecithin, while the Pickering emulsion with oleylamine provided a 3 to 4-fold higher retinol skin retention, compared to the lecithin Pickering emulsion. The use of fumed silica nanoparticles enabled a sustained release of the drug from both Pickering emulsions, in the Pickering emulsion with lecithin the release decreased 3.6 times and with oleylamine reduced 1.28 times. Also, this inorganic particle-stabilized the emulsions in the long-term and had an impact on the skin hydration. [23]

In the second study, the Pickering emulsions were used to deliver acridine orange 10-nonyl bromide (AONB), a fluorescent probe. The contact angle was 159±1° for lecithin and 162±3.4° for oleylamine. These results oppose the statement that only particles with contact angle less than 90° stabilize O/W emulsion. The results also showed an improvement of AONB skin retention, 2-fold higher for lecithin and oleylamine compared to their controls, and 5- to 10-fold higher for oleylamine when compared to lecithin. Furthermore, when fumed silica particles were used, the skin penetration was enhanced 2-fold in lecithin and 1.18 times in oleylamine. [24]

Wang *et al.* [25] investigated the skin permeation of rutin using an oil-in-oil-in-water (O/O/W) Pickering emulsion. Rutin, also called vitamin P, is a natural flavonoid with a high antioxidant activity. Due to its properties, rutin has a protective function against ultraviolet (UV) radiation, having a role in anti-ageing and enhancing skin condition. The formulation was stabilized by fumed silica nanoparticles and nonionic surfactants (Tween 20, 40, 60 and 80 and PEG-40 hydrogenated castor oil). The results showed that the O/O/W emulsion provided a more sustained rutin release, which was 1.2 times slower, in comparison with the ethanol solution. Additionally, the skin permeation of rutin in the emulsion formulation was 2.394-fold higher, when compared to an aqueous solution with the active ingredient. [25]

Azizoglu *et al.* [26] used silica nanoparticles to stabilize an O/W Pickering emulsion with melatonin as the active component, to be used as a sunscreen. [26] UV radiation, especially the UVB type, can modify or induce dermal cells (e.g., keratinocytes, melanocytes and fibroblasts) to synthesize melatonin. This substance has anti-inflammatory, immunomodulatory and antioxidant action. It is also a scavenger of reactive oxygen species (ROS), radicals that may induce mutagenicity and carcinogenicity. The addition of melatonin to the sunscreen provides therapeutic properties to this product. [27] The formulation developed was composed by a Pickering emulsion with octyl methoxycinnamate (OMC), a UV filter, and silica as a stabilizer, to which melatonin-loaded niosomes were added. The beneficial properties of melatonin are achieved when it reaches the deeper layers of the epidermis, while OMC should remain in the epidermis outer layers. *Ex vivo* studies showed a 5.57-fold increase in melatonin penetration and 1.7-fold increase of skin accumulation in comparison with the formulation composed only by niosomes and melatonin. The antioxidant activity of melatonin in Pickering emulsions was similar to that of the melatonin solution dispersed in ethanol, both significantly high. [26]

Ayari *et al.*, [28] developed an anti-ageing formulation using molecularly imprinted polymers (MIPs) in a W/O Pickering emulsion to regulate the release of 5′-adenosine monophosphate (5′-AMP). This nucleotide is widely distributed in the human body and, when

released in the epidermal layer, it accelerates its turnover. This turnover is linked to the increased amount in 5′-adenosine triphosphate (5′-ATP), required for cell division and renovation, which are processes that slow as skin ages. Through a process of derivatization, silica dioxide acquires hydrophobic properties, allowing the preparation of the Pickering emulsion by inverse polymerization. Trials were performed to evaluate MIPs activity and the results showed that Pickering emulsions with these polymers had a 4.7-fold higher maximum adsorbed capacity, and a 5.18-fold increased binding constant, compared to the formulation with non-imprinted polymers (NIPs). The high value of the binding constant suggests a possible controlled release. The bioactive compound release was studied, and it was confirmed that the MIPs retained the 5′-AMP in their cavities allowing a controlled release by diffusion. This sustained-release prevented the burst phenomenon, which occurred with the NIPs. [28]

Arriagada *et al.* [20] developed solid core-mesoporous shell silica nanoparticles (CSSNPs) to stabilize Pickering emulsions. First, the silica nanoparticles formed dense cores, which were coated by mesoporous silica. Then, the CSSNPs obtained were functionalized by (3-aminopropyl)triethoxysilane, and then carminic acid (CA) was linked to the CSSNPs shell. CA is a known pigment commonly used in the food, cosmetic and pharmaceutical fields, that confers different shades of red to the formulation by changing pH. In addition, this compound has an antioxidant activity. The synthesis of mesoporous shell and dense cores of silica enables obtaining an ideal particle density for adsorption at the O/W emulsion interface because these cores have the area required to incorporate a large number of molecules. The antioxidant activity was evaluated by the quenching rate of singlet oxygen and the results showed that CA linked to CSSNPs had a 2-fold increased quenching rate compared to free CA, when in acetone. Furthermore, when in deuterium oxide, the quenching rate improved 11-fold. The Pickering emulsion stabilized with CSSNPs and CA also showed a superior protective effect on vitamin E, decreasing its oxidation 2.59 times in comparison with a conventional emulsion. [20]

A study by Das *et al.* [29] described the stabilizing effect of modified silica nanoparticles on an O/W Pickering emulsion with chamomile essential oil. Essential oils have antifungal and antibacterial activity, so the aim of this study was to study the effect of the stabilization on the antimicrobial activity of the Pickering emulsions. This activity was evaluated by the minimum effective concentration (MEC10) and minimum inhibitory concentration (MIC90). The MIC90 results showed a 14-fold lower concentration of chamomile oil in Pickering emulsion in comparison with chamomile oil in ethanolic solution, and from 1.5 to 2.36 times less concentration for bacteria and 1.85 to 3.67 times less concentration for fungi when compared to a conventional emulsion. The MEC10 results showed that a 1.04 to 2.64 times lower

concentration of chamomile oil in Pickering emulsion was needed to achieve the same antibacterial action of the oil in the conventional emulsion. The same antifungal activity was obtained with a 1.79 to 4-fold lower concentration of chamomile oil in Pickering emulsion, compared to the conventional emulsion. Therefore, chamomile oil Pickering emulsion had an effective antimicrobial activity, predicting an interesting application for this formulation. However, *in vitro* and *in vivo* trials should be done in order to prove their efficiency as a therapeutic formulation. [29]

Silica was also studied to be a stimuli-responsive stabilizer. Stimuli-response Pickering emulsions are stable emulsions in certain conditions and unstable in others, simplifying demulsification processes and enabling the control of these formulations. In a study by Zhang *et al.*, [30] the silica particles were functionalized by selenium-containing 11-(benzylselanyl)-N,N-dimethylundecan-1-amine, in order to be redox- and CO_2-responsive. In the absence of CO_2, the oil phase was not emulsified into the water phase, while in the presence of CO_2 an O/W Pickering emulsion was formed. Additionally, when CO_2 was removed the formulation was demulsified and after CO_2 replacement it emulsified again. The same phenomenon was observed for the redox stimulus: in the presence of H_2O_2, a very stable Pickering emulsion was obtained. These stimuli-responsive silica nanoparticles represent a very interesting and potential application for the cosmetics and pharmaceutical fields. [30]

3.1.1.2. Titanium dioxide

Titanium dioxide (TiO_2) contains hydroxyl groups which confer hydrophilicity to its surface. [31] TiO_2 comprises three polymorphic forms named rutile, anatase and brookite. One of the parameters that may affect the physicochemical properties of the particles, hence their activity, is the variation in surface characteristics. Anatase is one of the crystal forms of TiO_2, chemically more reactive than rutile and brookite and generating more ROS than rutile, which is also a crystalline form of TiO_2. Anatase also presents a higher toxicity potential, when compared to rutile. [1] TiO_2 has been a common ingredient in sunscreens for over 25 years, due to its safety and effectiveness. It is included in formulations with SPF and used by people with a high tendency to present skin irritation. Thus, using TiO_2 as a stabilizer of Pickering emulsions, will add SPF properties to the formulation. [1] The modification of TiO_2 particles further improves their performance and compatibility. Two main modifications are used in cosmetic applications: the inclusion of aluminium oxide graft, and the inclusion of silane, stearic acid or dimethicone. The first modification decreases the production of ROS and

photocatalytic activity by TiO_2, while the second one allows the incorporation of hydrophobic groups into the surface. [31]

Marto *et al.* [32] used triethoxycaprylylsilane TiO_2 as a stabilizer in a Pickering emulsion (Figure 2). This formulation was composed by triethoxycaprylylsilane TiO_2, zinc oxide, aluminum starch octenylsuccinate (ASt) and green coffee oil. The TiO_2 was modified by triethoxycaprylylsilane, in order to stabilize the W/O emulsion. Once incorporated in an emulsion, the stabilization with TiO_2 particles occurs by adsorption of these particles at droplet's surface. The corresponding to 90% percentile of the size distribution of the particles was 7.1±0.3 μm and the corresponding to 50% percentile for the droplets' size was 6.2±4.1 μm for the emulsion without (ASt), and 5.7±4.3 μm for the emulsion with ASt. The contact angle of TiO_2 for this emulsion was 106.5±0.7° and the formulation acquired a non-Newtonian behaviour. A non-Newtonian fluid is characterized by having a viscosity dependent on the shear rate. The TiO_2 also showed a UVB filter action, while the zinc oxide present in the formulation protected more against UVA radiation. *In vivo* and *in vitro* studies demonstrated that this sunscreen formulation improved the protection against both UV radiations, in particular when the antioxidant green coffee oil and ASt were added. In this case, ASt only acted as a promoter and not as a stabilizer. The SPF value of the formulation with ASt increased about 2-fold. Moreover, ASt ensures skin spreadability of the formulation, which further contributes to better protection against the harmful effects of UV radiation. The formulations with and without ASt were considered water-resistant and proved to be safe and stable for topical application. [32]

Marto *et al.* [27] also developed a sunscreen formulation with melatonin. This W/O Pickering emulsion was stabilized by triethoxycaprylylsilane TiO_2, like in the previously described study. The formulation with melatonin enhances sunscreen photoprotection by eliminating ROS from the skin cells, which prevents cell damage, stopping skin cancer induced by UV radiation. *In vitro* and *in vivo* studies showed that melatonin delivery was accomplished with a high protection against UV radiations (UVA and UVB) and ROS. Thus, this active molecule might be advantageous for sun protection. [27]

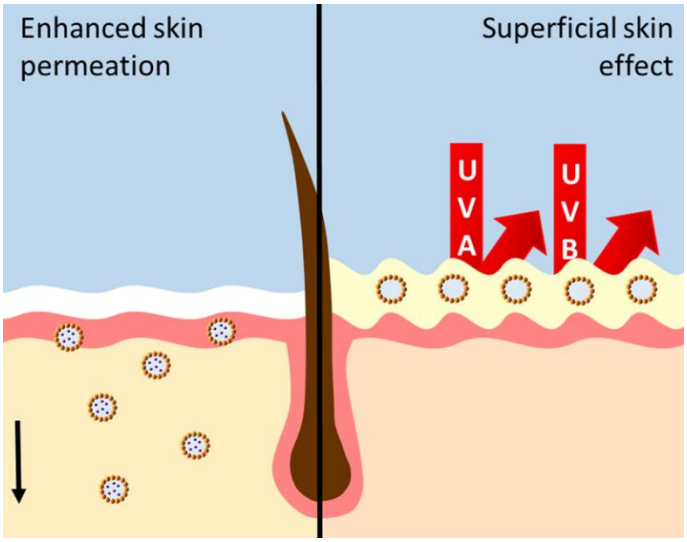


Figure 2 - Comparative scheme of an enhanced skin permeation (left) and a superficial skin effect (right) application based on Pickering emulsions. The left side of the illustration shows a dermal deep action of Pickering emulsions, such as a W/O emulsion stabilized by silica nanoparticles (orange spheres) to deliver caffeine (purple spheres). [21] The right side of the figure exemplifies a dermal superficial action like, for example, the mechanism of the protective action of physical sunscreens, in which the W/O emulsion is stabilized by triethoxycaprylylsilane titanium dioxide (orange spheres). [32]

3.1.1.3. Clay

Clay is another popular solid particle used for the stabilization of Pickering emulsions. The use of clay presents several advantages, such as being non-pollutant, having low-cost, and being easily accessible. However, its strong surface hydrophilicity demands a surface modification, in order to adsorb properly the two phases at the interface. [6]

In a study by Salerno *et al.* [15], the solid particles used as stabilizers were fumed silica nanoparticles and Fuller's earth (FE), which is mainly composed of montmorillonite (MMT). [15] MMT is a clay particle characterized by environmental sustainability, a high specificity in surface area and good dispersibility. MMT is composed of two sheets of tetrahedral silica with an octahedral sheet of aluminum hydroxide or magnesium hydroxide in between. [33] The FE particles used in this study had a size ranging from 10 to15 μm and formed O/W Pickering emulsions with a viscosity of 13 mPa·s at 35°C and a droplet diameter of 58 μm, when the 50% percentile was applied. Fumed silica nanoparticles had 20 nm size, with 26 mPa·s at 35°C and 2.7 μm, respectively. The aim was to use the formulation as an efficient skin decontaminating agent of the highly toxic chemical warfare nerve agent VX. In this study, two water suspensions and two O/W Pickering emulsions were tested. Both solid particles adsorbed at the oil-water interface in order to stabilize the emulsion. Additionally, these particles were used as decontaminant systems due to their ability to adsorb the contaminant. The results showed that all formulations decreased the VX amount in the skin. Pickering

emulsions stabilized by FE enhanced the decontamination efficiency by decreasing the contaminant by 2-fold, comparatively to the use of the suspension, and 3.8-fold when compared to the nontreated skin. However, Pickering emulsion stabilized by silica showed a decontamination efficiency equivalent to that of the water suspension. [15]

In a study by Wang *et al.* [33] the MMT was also used as a Pickering emulsion stabilizer in combination with alginate. MMT is extremely hydrophilic, and cannot be used as an effective emulsion stabilizer, unless it is modified. The modification of MMTs surface wettability by physical adsorption of the surfactant or chemical reaction with a hydrophobic molecule increases the adsorption at the oil-water interface. However, the substances used for the modification can be toxic, environmentally hazardous and/or expensive, preventing the application on a large scale. To overcome this difficulty, salt or polymers can be added in order to increase viscosity and create a network composed of clay particles in water. Since alginate is biocompatible and its properties are a combination of salt and polymer, this substance is a good candidate for combination with MMT, as stabilizers of Pickering emulsions. Furthermore, alginate has a tunable rheological behaviour with salt and pH variations. Alginate is also adsorbed on the surface of MMT by hydrogen binding and through electrostatic interactions, adjusting MMT dispersibility, therefore promoting the stabilization of the emulsion. Moreover, alginate increases viscoelasticity, providing a gel-like consistent phase that hinders droplet coalescence. Thus, MMT and alginate are two promising compounds that can be easily combined to improve emulsion stability, with the advantages of being cost-efficient and biocompatible. [33]

Halloysite is another clay material that belongs to the family of aluminosilicates and presents a hollow structure with a tubular shape, being considered the safest clay. [34] The surface of halloysite clay nanotubes (HNTs) is composed of tetrahedral bonds between silica and oxygen, while the inner lumen is composed of octahedral bonds between alumina and oxygen. Due to its layered structure, halloysite preserves most of its hydroxyl groups on the inner surface. [35] When in contact with halloysite, water binds to the layered walls, functioning as glue. In Pickering emulsions, HNTs are stabilizing elements, positioning themselves laterally in the interface in order to reduce surface tension. The contact with the non-aqueous phase can be increased by hydrophobizing halloysite's surface. There are several different topical formulations containing HNT, such as creams, bandages and sprays. HNTs in creams are especially useful in cosmetics, allowing the sustained release of the active substances, which in turn enables controlled absorption by the skin. HNTs can also be used in sprays due to their high zeta potential. They are used, for example, in the development of antibacterial sprays by the formation of stable colloids, enabling loading of antiseptics. Another

potential topical application of HNTs is in bandages, where HNTs are loaded with antibacterial substances and embedded in a matrix of gel. [36] Despite their numerous applications in the cosmetic and therapeutic fields, these particles have yet to be thoroughly studied as Pickering emulsion stabilizers.

3.1.2. Organic particles

3.1.2.1. Synthetic polymeric particles

Synthetic polymers are derived from petrochemicals, but recently their biodegradable versions started being considered as stabilizers for Pickering emulsions. Despite their acceptance as stabilizers, their use is still limited for healthcare applications. [37] Some examples of biodegradable polymers are poly(lactic acid) (PLA), a glassy and solid material, and poly(ε-caprolactone) (PCL), an amorphic substance of soft consistency. [38] These polymers are only considered biodegradable under strict industrial composting, thenceforth the importance of their end of life conditions. [37] However, all synthetic polymers are biocompatible molecules and they have better stability than bioparticles. [39] Additionally, they have different chain conformations and behaviours, a feature that can be explored for the development of Pickering emulsions. [9]

3.1.2.1.1. PLA

PLA is a bio-based polymer with thermoplastic properties, which belongs to the alpha-hydroxy acid group. This polymer is manufactured by direct polycondensation of naturally extracted lactic acid or by a process of ring-opening polymerization of the lactide dimer, using an appropriate catalyst. Recently, an enzymatic process using lipase was developed for the manufacture of PLA, eliminating the need for metallic catalysts. However, the major process of synthesis is still the condensation technique. PLA is mainly used due to its multiple advantageous properties such as biodegradability, biocompatibility, processability and mechanical strength, which gives it the flexibility to fulfil multiple needs and a wide spectrum of possible applications. However, this compound has limitations, namely its hydrophobicity, degradation rate and impact toughness. To mitigate these disadvantages PLA can be combined with other polymers, in order to enhance some properties and/or generate new ones, to target applications without having to develop new materials. [40]

3.1.2.1.2. PCL

PCL is a synthetic polyester with adjustable biodegradable and tunable drug release behaviour, processability and good biocompatibility. However, PCL has low cell adhesion, low bioactivity [17] and high hydrophobicity. In spite of these disadvantages, PCL has a high permeability to hydrophobic and hydrophilic drugs, is hydrolytically more stable than PLA and poly(glycolic acid) (PGA), and is currently under investigation for possible applications in the synthesis of biomolecules to be employed in drug delivery to specific targets. Due to its small melting and glass transition temperatures, PCL eases drug integration without compromising properties such as the drug potency and chemical stability. Additionally, PCL is cheaper than other polymers. [41]

In a study performed by Laredj-Bourezg *et al.* [42], nanoparticles composed by PCL-poly(ethylene glycol) (PEG) block copolymer (PCL-b-PEG) or PLA-PEG block copolymer (PLA-b-PEG) were used as stabilizers of O/W Pickering emulsions, with triglycerides as an oil phase. [42] Pickering emulsions with excess of these copolymers can be combined to enhance the delivery of compounds with hydrophobic properties to the upper layers of the skin. [37] From a drug delivery perspective, block copolymers are attractive due to their small size, ranging from 20 to 100 nm, and tunable amphiphilicity. [9,38] The amphiphilic properties of block copolymers are similar to those of surfactant molecules because of the separation between hydrophilic and hydrophobic components in their chemical structure. Their core is made of the hydrophobic PLA or PCL, surrounded by a shell of the hydrophilic PEG, which can swell when in contact with water. Another reason for the use of block copolymers in drug delivery is the capacity of these particles to solubilize drugs with hydrophobic characteristics and deliver them to the skin while avoiding the penetration of nanoparticles into the skin. In classical emulsions, on the contrary, surfactants permeate the skin and interact with the components of the SC. [38] In the study by Laredj-Bourezg *et al.* [42], the Pickering emulsions with both copolymers were developed by two different methods, a classical process and spontaneous emulsification. The PCL-b-PEG nanoparticles had a size of 32 nm with a droplet size of 3±0.4 μm and the emulsion viscosity ranged between 15.2 and 15.3 mPa.s, while the PLA-b-PEG nanoparticles had a size of 50 nm, with a droplet size from 2 to 2.7 μm and an emulsion viscosity of 14.5 - 14.7 mPa.s. The differences in droplet size and viscosity are due to the use of the different preparation methods. The two block copolymers were used to encapsulate *all-trans* retinol in an O/W formulation. *In vitro* studies were conducted to compare the retinol absorption and distribution of the Pickering emulsions obtained by the two different preparation methods. The results showed that all Pickering emulsions enhanced retinol skin

penetration when compared to the conventional emulsion; the increase was 2.22-fold for the PLA-b-PEG Pickering emulsion and 1.77-fold for the one using PCL-b-PEG copolymer. The retinol distribution was mainly observed in the outermost skin layer for all formulations, showing a 1.4-fold increase when PLA-b-PEG was used and 1.27-fold increase for PCL-b-PEG, compared to the conventional emulsion. [42]

3.1.2.1.3. PLGA

Poly(lactic-co-glycolic acid) (PLGA) is a frequently used polymer, manufactured using PLA and glycolic acid. Lactic acid and glycolic acid have different hydrophobicities and crystallinities, allowing the synthesis of particles with characteristics that can be adjusted to different applications, depending on the synthesis process. This adjustment is made by varying the composition of the copolymer, the ratio of the components or by modification of the surface of the polymer. Yet another advantage is that lactic acid and glycolic acid are not toxic, which is important when these compounds decompose through enzymatic reactions and hydrolysis. [43] PLGA has been used in the medical field for many years, as a polymer for biodegradable sutures, and has potential application in different targeting, therapy and imaging technologies. This polymer is a great candidate as a nano-stabilizer due to its biodegradability, biocompatibility, FDA and EMA approval as a viable delivery system, possibility of designing the molecule in order to provide sustained release as well as surface modification to grant new properties like stealthiness and biological interactions. It also protects the drug from possible degradation and has a well-described of preparation synthesis, with different kinds of drugs. PLGA also offers the opportunity to target different cells and organs. Among a wide variety of biomaterials available to be used as nanoparticles, PLGA is well-known and widely studied, and can be used in many different applications.[44]

Wei *et al.* [39] developed a PLGA/poly(styrene-co-4-styrene-sulfonate) (PSS) polymer to stabilize an O/W Pickering emulsion and to encapsulate the lipophilic component tocopheryl acetate (TA), a form of vitamin E with antioxidant activity. [39] PSS is a polystyrene partially sulfonated with sulfonic acids. When added to PLGA, PSS has the function of charged density modification, allowing the design of a nanocarrier with a negative charge and adjustable charged density. To prepare the PLGA/PSS nanoparticles, the polymers were first dissolved in an organic solvent and afterwards in water. PSS and PLGA created a polymer film, after organic solvent evaporation. Moreover, the use of different amounts of PSS showed that this polymer increased the particle diameter due to its swelling properties. [45] The PLGA/PSS nanoparticles developed by Wei *et al.* [39] showed sizes ranging from 105 to 115 nm and a

zeta potential ranging from -57.5 to -30 mV, both physicochemical parameters dependent on the pH value, which was varied between 2.52 and 10.14. When the nanoparticles were set in the emulsion with 5% of the oil phase, their size increased up to 425 nm. This phenomenon suggests that the nanoparticles were adsorbed at the interface of the emulsion. The droplets formed in this emulsion had a shell/shaped structure with approximately 2 μm of diameter. The stability of the Pickering emulsion was achieved at pH 4.29 to 7.07, due to the decreased electrostatic repulsion, which led to a better adsorption of the nanoparticles. In addition, this pH range is also suitable for the pH of the skin, which is nearly 5.5. The stability of TA was evaluated using the DPPH assay and calculating the median effective concentration (EC50) of free TA and TA encapsulated in the Pickering emulsion, by UV irradiation of both Pickering and conventional emulsion. The EC50 values obtained for both samples were similar, suggesting that TA, when encapsulated in Pickering emulsions, preserves its activity. The retention of antioxidant activity decreased with increasing UV irradiation time but it was higher for the Pickering emulsion, compared with the conventional one. Thus, the Pickering emulsion enhanced TA stability. The cellular antioxidant activity (CAA) results showed a 1.18-fold decrease of cellular fluorescence intensity when using the Pickering emulsion compared to free TA, indicating a greater antioxidant activity of TA in the emulsion. Overall, the results suggest that the utilization of Pickering emulsion to encapsulate TA can be beneficial in cosmetic products. [39]

PLGA, as a tunable particle, can also be combined with poly(vinyl alcohol) (PVA), which is a non-toxic polymer with stabilizing properties. PVA/PLGA has potential in a wide variety of applications in pharmaceutical and cosmetic fields. [46] Moreover, polymers can be designed at molecular levels and synthesised by different methods, improving the control over the emulsion compared with inorganic emulsifiers. Among different polymeric particles, polymeric self-assembled micelles are recognized as holding great potential due to their architectural tailorability. In some studies, self-assembled polymeric micelles using amphiphilic copolymers showed great emulsifying performance and proved surface active. However, further studies need to be performed. [47]

3.1.2.2. Bioparticles

Nowadays, consumer demands, legal requirements and corporative sustainability aims are pressuring the market in the direction of sustainable, environmentally friendly and natural products with natural ingredients instead of synthetic components, with plant-based formulations also preferred over animal-based ones. These products are also known as "clean

label" products. [2] Substituting synthetic surfactants for renewable emulsifiers such as biosurfactants, amphiphilic proteins, phospholipids, polysaccharides and bioparticles [48], can also provide low toxicity, specific activity and high selectivity at high temperature, salinity, and pH. For these reasons, cosmetic, food and pharmaceutical industries have been investing in research to identify natural alternatives, from microorganisms and plants. [2] Pickering emulsions using bioparticles as stabilizers are a very promising sustainable and environmental-friendly approach. [49]

3.1.2.2.1. Polysaccharides

Polysaccharides are polymers of monomers called monosaccharides. They can be found in natural sources such as plants, algae, crustacean shells and bacteria. The use of polysaccharides is an alternative to some synthetic or inorganic particles because they are biodegradable and biocompatible, making these particles valuable candidates as Pickering emulsions stabilizers. [3]

3.1.2.2.1.1 *Starch*

Starch is one of the most used polysaccharides to stabilize Pickering emulsions. It can be obtained from several plants such as rice, potato, corn or wheat. This polysaccharide is extracted from different parts of the plant like roots, tubers, seeds and fruits. Starch presents several advantages that make it an attractive option for food, pharmaceutical and cosmetic applications. [1,3] Like other polysaccharides, it is biocompatible and biodegradable, it is inexpensive, edible, non-irritant and non-toxic. The wide range of starch sources allows obtaining particles with different physicochemical characteristics, such as the size range, that will affect the emulsion stabilization. Frequently, it is necessary to modify the starch granulates, by physical or chemical methods, in order to increase their hydrophobicity. [6, 50]

Innovative studies showed that starch modified with octenyl succinic anhydride (OSA) is an adequate candidate to be used as a stabilizer in Pickering emulsions. [51] Marto *et al.* [50] exploited the effect of OSA-modified starch particles, ASt, on the stabilization of W/O emulsions. The addition of OSA to starch granulates conferred hydrophobicity properties to the particles because of their hydrocarbon chains length and coverage density. ASt particles are intensely adsorbed at the interface of the emulsion and constitute a barrier against instability. The ASt granules used in this formulation had 20.85±0.02 μm size when the 90% percentile was applied and formed a W/O emulsion with droplets of 150 μm in diameter and with a contact angle of 109.0±0.4°. The emulsion showed a non-Newtonian behaviour, with

the viscosity dependent on shear rate, and an increase in ASt resulted in increased formulation viscosity. Additionally, this system exhibited viscoelastic behaviour. The change of external phase or ASt concentration also had an impact on skin adhesion and drug release. [50]

In a subsequent study, the use of ASt particles was tested in antibiotic topical delivery. The antibiotic used in this W/O Pickering emulsion was minocycline hydrochloride (MH), which has an action against Gram-positive bacteria such as *Staphylococcus aureus* (*S. aureus*). *In vitro* studies showed that Pickering emulsions stabilized by ASt particles led to a significant accumulation of MH in the outermost skin layer, and a skin penetration with a slow-release of the antibiotic. MH did not reach the innermost layers, which suggests a reduced effect by systemic antibiotic absorption. The antibacterial activity was evaluated *in vitro* by determining the MIC and *in vivo* by Tape-Stripping Infection Model, both on *S. aureus*. The Pickering emulsions with MH increased the inhibition zone up to 1.7-fold in comparison with MH in solution and significantly decreased the colony-forming units (CFU)/mL when compared with untreated skin. In addition, ASt particles showed enhanced wound healing properties in a scratch test. The skin histology evaluation showed epidermis re-epithelization and decreased inflammatory activity by all Pickering emulsions, which was more accentuated in the presence of MH. Thus, this work emphasized the potential therapeutic application of starch as a stabilizer and an external bacterial infection treatment. [52]

Marku *et al.* [53] developed an OSA-modified quinoa starch, with a small size of 1 to 2 μm, to stabilize an O/W Pickering emulsion. The formulation had a droplet size of 30 to 75 μm and a contact angle of 4.9 to 13°. The range of these results depends on the type of oil used (paraffin oil, Miglyol and sheanut oil). The stabilization by starch particles occurred mainly by monolayer adsorption on the surface of the droplet, but starch aggregates could also be formed. Methyl salicylate was incorporated in all formulations and the skin penetration was investigated *in vitro* and showed that the steady state fluxes were 2-fold higher than that of methyl salicylate in buffer solutions. There were no significant skin penetration differences between the Pickering emulsions with the three different oils, thus it was considered that all systems allowed a high skin penetration. [53]

In a study performed by Cossu *et al.* [54], modified starch was used in an O/W emulsion, with the aim of developing an antifungal topical treatment for oral candidiasis. Topical oral treatments have the disadvantage of reduced drug bioavailability in the oral cavity, due to the potential for drug digestion, making it challenging to design formulations with adequate drug release. In this study, a Pickering emulsion with starch nanoparticles was designed with the objective of inducing the controlled release of hydrophobic antifungal substances, such as thymol oil. The flat disc shape of starch particles allows them to stack

above each other and around the droplet, preventing coalescence and providing stability. The oral α-amylase enzyme can then enhance the release of amphotericin B and thymol, contributing to a higher bioavailability of these compounds to eradicate *Candida albicans*. The amphotericin B and thymol antifungal activity was evaluated in *C. albicans*, using the minimum fungicidal concentration (MFC) as a parameter. The addition of α-amylase to the emulsion only affected the MFC of both substances when a concentration of 100 U/mL was used. The decrease of MFC was up to 0.5 for thymol and 0.8 for amphotericin B. These findings indicate that the antifungal activity of these substances can be greater and controlled by the concentration of the enzyme. Additionally, *C. albicans* growth inhibition was measured and, for both components, the enzyme did not modify the effective concentration of inhibition but decreased the inhibition zone. Thus, these starch particles exert a stabilizing action and have the potential to deliver hydrophobic drugs in the oral cavity. [54]

Some studies suggest that starch can be used to encapsulate tea polyphenols in Pickering emulsions stabilized by nanoparticles of taro starch. Starch nanoparticles can also be used as thermo-responsive stabilizers, however, none have been tested for topical applications. [51]

3.1.2.2.1.2 *Chitosan*

Chitosan is another considerably abundant polysaccharide, obtained by deacetylation of the natural polysaccharide chitin. Chitin is abundant and can be extracted from shrimps, crabs, insects and microorganisms. The amine groups in the polysaccharide confer a pH dependency to chitosan. This compound is biodegradable, biocompatible, non-toxic, non-irritant and has antibacterial properties. In Pickering emulsions, chitosan can form complexes with other particles or self-aggregate. [3,6,18]

In a study by Asfour *et al.* [55], chitosan was used as self-aggregated chitosan particles (SACP). In an acidic environment, chitosan possesses a cationic amine and hydroxide groups that induce a polycationic behaviour. This generates a poor surface activity, leading to a suboptimal emulsifier performance. However, at pH higher than the chitosan pKa, amine groups are deprotonated and become more hydrophobic by the increase of the intermolecular attraction. This phenomenon creates gel nanoparticles that can stabilize O/W emulsions. These nanoparticles had an average diameter of 287.3 nm, with a contact angle of 42.47±1.19° and a zeta potential between -48.1±4.7 and -78.4±4.1 mV. The oil droplets formed had a diameter of 5.8±1.1 to 18.7±3.4 μm with three different viscosities at 25°C, 2.07, 7.81 and 37.2 mPa.s, depending on the chitosan percentage, 0.2%, 0.3% and 0.4%, respectively (all having

the same 20% of oil). Additionally, chitosan proved to have bioadhesiveness which was beneficial for the aim of the formulation as well as for drug release efficiency. [55] The aim of the formulation was to deliver rutin for wound healing. Chitosan was chosen not only for its stabilization attributes but also for its bactericidal activity and tissue regeneration properties, which contribute to the wound healing process. *In vitro* studies showed that drug release efficiency of the three Pickering emulsions with different chitosan concentration improved 1.45 to 1.6 times compared with rutin in suspension. *In vivo* studies were performed only with Pickering emulsion with 0.4% chitosan because it showed enhanced healing properties and higher wounded tissue adhesion. After 10 days of treatment, the Pickering emulsion with rutin significantly enhanced wound healing 1.17 times when compared with Pickering emulsion without rutin, and 2-fold compared to the untreated wound. However, despite the significant efficacy of Pickering emulsion with rutin in wound healing treatment, the Pickering emulsion without rutin also showed the ability to improve the healing process, with an increase of 1.7-fold when compared to the untreated wound at day 10. This result indicates that the formulation itself plays an active role in the therapeutic properties of this Pickering emulsion. Moreover, the oxidative stress markers such as malondialdehyde (MDA), catalase (CAT) and reduced glutathione (GSH) were evaluated. The presence of MDA is due to the reaction of ROS with fatty acids, that occurs at high levels of oxidative stress, while CAT and GSH are free radical scavengers. The results showed that Pickering emulsion decreased the amount of MDA by 1.2-fold and increased 1.6 times the levels of GSH and 35 times the levels of CAT. The evaluation of collagen type I (Col I) and hyaluronic acid (HA) was also considered in this study due to activity of these two substances in the wound healing process, in particular connective tissue formation. The concentration of HA increased 1.46-fold and Col I improved 1.2-fold in comparison with the untreated wound. These results suggest that Pickering emulsions stabilized by chitosan are promising formulations for wound healing. [55]

3.1.2.2.1.3 *Gum Arabic*

Gum Arabic (GA) is a dried exudate extracted from *Acacia* tree, mainly composed by branched polysaccharides, [56] and it is biodegradable and biocompatible. At an approximately neutral pH, carboxyl groups dissociate, leading to an expanded structure and highly charged molecule. This conformation provides a better surface activity and viscoelastic behaviour with the formation of a film. In comparison with other polysaccharides, GA presents more interactions sites as well as a negative charge, which is beneficial to establish electrostatic

interactions with chitosan, since it is a polycationic molecule. [57] GA has applications in food, cosmetic, pharmaceutical, textile and biomedical industries. [56]

The use of GA to stabilize an O/W Pickering emulsion to be topically applied was explored by Sharkawy *et al.*. [58] In this work, chitosan was used in association with GA to make Pickering emulsion stabilizers. The chitosan/GA nanoparticles had a mean size of 109 nm with a zeta potential of +56.3 mV. The oil droplet generated had a mean diameter of 17.11 μm for 0.5% of nanoparticles and 23.98 μm for 1.5% of nanoparticles. [58] In a previous work by the same authors, the chitosan/GA nanoparticles showed a contact angle of 89.2±0.94° for the same weight ratio (1:1). The viscosity of the formulation with 1.5% of nanoparticles was measured and exhibited a non-Newtonian fluid and a shear-thinning performance. The nanoparticles create a well-defined layer over the oil droplet interface, restricting their free movement and avoiding the formation of separate phases, which ensures the stability. [56] The aim of the developed formulation was to increase the topical delivery and photostability of *trans*-resveratrol, to enhance its anti-ageing effect. In cosmetic, *trans*-resveratrol induces the production of elastin and collagen, improving skin thickness and elasticity and minimising wrinkles. *In vitro* release studies of *trans*-resveratrol showed a slow release for Pickering emulsion in comparison with the component in the solution. Furthermore, *ex vivo* experiments were performed to evaluate the skin permeation and retention of resveratrol. The resveratrol retention was higher in the viable epidermis and dermis (VED), instead of in the SC, with an increase of 3.76-fold compared to the solution, while permeation decreased up to 5.28-fold when compared with the solution. The photostability of *trans*-resveratrol was also tested, because its photosensitive properties decrease its effectiveness. The photodegradation of Pickering emulsion after 4 h was zero, while the remaining ingredients in the control solution decreased 1.47-fold. In summary, the results showed an increase of the *trans*-resveratrol skin delivery and photoprotection by Pickering emulsion, which makes this formulation more effective and stable for longer periods of time. [58]

3.1.2.2.2. Cyclodextrin

Cyclodextrin (CD) is a cyclic oligosaccharide in a cone shape form, composed by glucose hydroxyl groups that provide hydrophilic properties on the outside and a hydrophobic cavity on the inside. [59] It is obtained by starch hydrolysis carried out by cyclodextrin glycosyltransferase (CGTase), a bacterial enzyme. Native CDs can be α-CD, a CD with six glucose units, β-CD with seven and γ-CD with eight. [3] The amphiphilic properties of CD make them suitable for drug delivery due to their ability to encapsulate hydrophobic molecules in their cavity by non-covalent interactions. [1,3] These nano-stabilizers are characterized for

being biocompatible, biodegradable and non-toxic, which makes them a suitable candidate for skincare and pharmaceutical applications. [6,59] In topical therapeutic applications, CDs enhance drug delivery by improving the availability of the drug at the SC and have the ability to modify the pharmacokinetics and physicochemical properties of the drug.

The development of CDs as Pickering emulsion stabilizers was studied by Leclercq and Nardello-Rataj. [59] The mechanism of stabilization of the Pickering emulsion with CDs was different from that of other particles used as stabilizers. Before stabilizing the emulsion, CDs form a complex with the oil, which acts as a surfactant on the emulsion interface, with polar and nonpolar parts, and with properties similar to conventional emulsions. An increase in CDs concentration causes the clustering of the complexes in particles, thus creating a Pickering emulsion. The Pickering emulsion was stabilized by CDs with particle diameters between 30 and 250 nm, which originated an O/W emulsion with a droplet diameter range from 9.2 to 16.1 μm, resulting in a Non-Newtonian fluid. Furthermore, the Pickering emulsions obtained with CDs showed thixotropy, the phenomenon of changing viscosity, where the emulsion has high viscosity in storage and has low viscosity when it is applied. The formation of this Pickering emulsion aimed to encapsulate econazole nitrate, an antifungal drug which also has *in vitro* antibacterial activity, particularly on *S. aureus*. The *in vitro* antibacterial and antifungal (*C. albicans*) studies showed microbial growth inhibition by econazole nitrate. Three types of Pickering emulsions were prepared, each stabilized by a different type of CD (α, β and γ) and the antimicrobial activity was tested. The results obtained with the econazole nitrate commercial formulation, and the Pickering emulsions stabilized by α-CD and β-CD, were identical meaning that the formulations have, at the very least, the same biocidal effectiveness as the commercial formulation. However, the Pickering emulsions with γ-CD as stabilizer exhibit minimal or no biocidal activity, because econazole nitrate cannot diffuse from the CD. In summary, Pickering emulsions stabilized by α- and β-CD can be a great alternative to the commercially available formulations. [59]

In a recent study from the previously referred authors, another azole-based drug, miconazoctylium bromide, was encapsulated in the O/W Pickering emulsion stabilized by CDs. [60] The drug was used in association with two phytochemical oils, carvacrol and terpinen-4-ol, to achieve a synergy between antibiofilm and antimicrobial activities. The formulation with miconazoctylium bromide and carvacrol was 2-fold more effective against *C. albicans* and methicillin-resistant *S. aureus* than the marketed formulations and had high activity against *E. coli*, in contrast to the commercial formulation which was inactive against this bacterium. This type of formulation may be beneficial for clinical purposes because it is more effective in killing

the pathogens in a shorter time, which results in decreased proliferation of resistant pathogens.

In a different study, the CD was modified by a short linear glucan (SLG) to achieve a hybrid CD/SLG, in order to enhance the native CD properties as a stabilizer. The hybrid with a 1:1 ratio provided better adsorption, with an improved film at the interface and enhanced stability. However, the physicochemical parameters, such as wettability, did not match the stability standards, since the contact angle was not close to 90°, suggesting that a different stabilization mechanism was involved. This needs further investigation but can provide a different perspective for the development of improved stabilizers with accurate mechanisms. [61]

3.1.2.2.3. Quercus suber Bark

Quercus suber Bark (QSB) also known as cork is extracted from *Quercus suber* L. bark, predominantly found in the Mediterranean region. QSB is mostly composed by cellulose, lignin and suberin. Additionally, it has saccharides, terpenes, fatty acids and aliphatic compounds, in small amounts. Due to its complex composition, it has multiple functions such as anti-inflammatory, antioxidant, antimicrobial, antifungal, anti-ageing and radical scavenger actions. In a study by Carriço *et al.* [62], this organic material was used to stabilize a W/O Pickering emulsion. The QSB particles used in this study had a particle size of 91.4±0.3 μm and a droplet size of 182±1.3 μm, both when the 90% percentile was applied. The contact angle of these particles was 97.3±0.3° and the formulation acquired a thixotropic, as well as a non-Newtonian behaviour. In order to assess the antioxidant activity of the formulation, *in vitro* studies were carried out, and the results showed that the percentage of ROS reduction was slightly lower, in comparison to ascorbic acid, a potent antioxidant. Besides, the formulation exhibited anti-elastase activity in *in vitro* studies, which prevents elastin degradation. In a sensorial study, the formulation was characterized as cosmetically appealing during and after application. [62]

In summary, these studies described a wide diversity of Pickering emulsions used on topical application, which have been developed in the past few years. The results clearly suggest that Pickering emulsions improve drug skin stability and permeation and provide better topical application for skin decontamination, antimicrobial treatments, sunscreens and anti-ageing formulations. Additionally, Pickering emulsions proved to be a beneficial alternative to conventional emulsions in therapeutic and cosmetic applications.

3.2. Other Promising Stabilizers

Pickering emulsions are the subject of several research studies and have several applications in different fields. Thus, in addition to the use of solid particles as stabilizers of Pickering emulsions, other particles have been researched and revealed as potential stabilizers for topical applications, as well as different approaches for the formation of Pickering emulsions.

Proteins are stabilizers widely used in food formulations as biocompatible biopolymers and have also been studied as stabilizers of cosmetic formulations. [3] They have several advantages such as biodegradability, biocompatibility, simple structure, sustainability, cost-effectiveness, easy access and chemical diversity. [14] In addition, protein nanoparticles have several shapes, such as tubes, spherical micelles, vesicles or even ribbons, and are characterized by unique binding through non-covalent forces, such as hydrogen bridges, electrostatic and hydrophobic bonding. [14] Numerous proteins present a great balance between hydrophilicity and hydrophobicity [3] but several others have a heterogeneous charge surface and are considered vulnerable to high temperatures or pH changes. [63] The main disadvantages of organic particles is their polydispersity and the need for surface modification in order to increase the activity. Environmental conditions, namely temperature, ionic strength, storage conditions and pH can easily change the surface activity of organic particles [64], which can be a challenge in the emulsion preparation process. In order to overcome these adversities, a few different approaches have been considered. One example is the use of protein nanobarrels from *E. coli*, which have robust structure and stabilization efficiency. These nanobarrels are characterized by high chemical denaturation or thermal resistance. In addition, this structure has a hydrophobic cavity which provides binding sites for hydrophobic molecules or surfaces. This is a promising approach to achieve enhanced protein stability as well as a bioactive compound carrier functionality. [63] Another strategy is the use of whey protein isolate (WPI) as a heat-resistant particle. This protein has significant surface activity and amphiphilic properties, which makes it an excellent stabilizer. Therefore, WPI could be a feasible option in applications that require heat treatment. [65] Another alternative is the use of E2 pyruvate dehydrogenase multienzyme complex, a protein extracted from the thermophilic bacterium *Geobacillus stearothermophilus*. The E2 protein unit has a dodecahedron cage framework, which can encapsulate drugs, dyes and oils. This protein induced emulsion stability even at different ionic strength, storage temperatures and pH. [64] Egg yolk peptides (EYPs) were also used as stabilizers of Pickering emulsions, with promising results. These particles are characterized by having an acceptable surface activity and an intermediate

wettability, which improve the emulsion stabilization. These features, alongside the versatility of the emulsion, can be an advantage for cosmetic, pharmaceutical and food applications. [14]

Cellulose nanocrystals (CNC) are promising Pickering emulsion stabilizers, due to their size and rod-like morphology. [66] These are regarded as an ideal material due to reduced carbon footprint and density, environmental, sustainability and low cost. Their main applications are in the pharmaceutical, medical and cosmetic fields [67], as drug carriers, emulsifiers for Pickering emulsions and nanofillers. [68] Additionally, they are biocompatible and biodegradable. [69] Cellulose is a highly adaptable molecule that can undergo multiple modifications. These potential modifications occur due to the presence of anhydrous glucose groups and numerous functional groups, such as hydroxyl and aldehyde groups, which can be easily modified. [68] Materials derived from cellulose have the capacity to aggregate in water due to electrostatic interactions, namely repulsions between hydrochloride acid and cellulose nanocrystals resulting from its hydrolysis. This limitation can be surpassed by cellulose oxidation, which grants these particles a larger charge density, keeping them stable when in contact with water. This versatile biomaterial can also be a stabilizer in stimuli-response Pickering emulsions. These are emulsions with manageable stability through a directed response to different stimuli, with a more precise response being obtained when multiple stimuli are applied. Wettability is the main factor in stability control and, since wettability is altered when an external stimulus is applied, there is a possibility of controlling the Pickering emulsion through its stabilizer. [69]

Hydroxyapatite (HAp) is a mineral that exists in the human body. This mineral has been exploited as a stabilizer of Pickering emulsions in many applications, due to its excellent adsorbability, biocompatibility and osteoinductivity [70], as well as a simple synthesis procedure. [6] Recently, a study described the concomitant use of HAp and a surfactant, in order to create a synergetic effect and maximize the stabilization of the emulsion. The surfactant changed the HAp physicochemical characteristics, improving its hydrophobicity and stabilizing the emulsion. Additionally, the increasing amount of surfactant led to an inversion of the emulsion type, which changed from O/W to W/O. The coating of HAp with poly(L-lactic acid) (PLLA) also enhanced the emulsion stabilization. [70]

Calcium carbonate (CC) is an inorganic particle obtained from mineral rocks, such as limestone and marble, used in the cosmetic formulations as absorbent agent, bulking, opacifying, buffer or abrasive. This ingredient can be found in oil-free moisturizers, foundations, exfoliants and toothpastes. It is characterized by its biocompatible and eco-friendly properties. In a recent study, CC was exploited as a stabilizer in an O/W Pickering emulsion. The formulation showed in *in vitro* trials to be safe as well as to have great stability and spreadability

into the skin, which suggests that CC can be a promising stabilizer for topical formulations. [71]

4. Toxicity issues

Many studies using Pickering emulsions are currently at lab research stages or under experimental trials. [11] However, the safety of these formulations must also be considered and evaluated before being used in humans. The toxicity tests are crucial in any ingredient or formulation to ensure human safety.

Dermatotoxicology is the field which evaluates the toxicity of ingredients and formulations for topical applications. Many tests are required in order to classify a substance as toxic or non-toxic. *In vitro* and *in vivo* studies are performed to assess the pharmacokinetic parameters (absorption, distribution, metabolism and excretion: ADME). In the cosmetic and pharmaceutical industries, the evaluation of the eye and skin irritation potential is crucial to ensure human safety of topical applications. [72]

The sunscreen formulation stabilized by TiO_2 previously discussed was assessed by *in vitro* (EpiSkin® model) and *in vivo* studies (Human Repeat Insult Patch Test (HRIPT)). The results showed that no skin reactions occurred, thus the formulation was classified as non-irritating and non-sensitizing. [32] The sunscreen containing melatonin was also tested by HRIPT, and the same classification was achieved. [27] The sunscreen with melatonin stabilized by silica nanoparticles was tested using cell viability and cell proliferation as parameters to assess toxicity and showed no negative outcomes. [26]

The Pickering emulsion stabilized by PLGA / PSS was evaluated by cellular uptake and cytotoxicity. [39] The cellular uptake was similar in Pickering emulsion and free TA, thus the encapsulation by Pickering emulsion did not affect this parameter. The cytotoxicity was assessed in human keratinocyte HaCaT cells, and the results showed that the cells exposed to the Pickering emulsion had a survival rate higher than 90%, therefore it was considered non-toxic for these cells.

In vitro cytotoxicity studies were also performed on the antibiotic (MH) formulation stabilized by ASt particles. [52] The cells exposed to the Pickering emulsion had a viability percentage higher than 50% thus the formulation was considered non-irritating. Furthermore, the literature mentions that starch up to 30.5% of concentration is non-irritating and non-sensitizing.

The formulation stabilized by QSB was evaluated by *in vitro* cytotoxicity and *in vivo* studies (HRIPT). In the cytotoxicity assay, the cell viability was greater than 50% therefore,

the formulation was considered non-irritating. The QSB concentration in the Pickering emulsion can be claimed safe. In HRIPT, the formulation did not cause reactions or even skin sensitization/irritation. [62]

The toxicity of nanoparticles is also an important subject in Pickering emulsion due to the nanoscale of some of the particles. In nanotoxicology, three main parameters must be considered: size, biodegradability and biocompatibility. The size of the nanoparticles is a very important parameter for their toxicity. Particles larger than 100 nm are most likely less toxic, because they must enter the cell by phagocytosis. On the other hand, particles smaller than 100 nm can enter by endocytosis, which renders these particles more toxic. The biodegradability is characterized by the disappearance of the material in the human body. A biodegradable material has reduced toxicity because the potential activation of the immune system will be brief, due to the faster disappearance of the particles. The last important parameter is biocompatibility, i.e., the capacity of the particle to be compatible with living systems, not producing a toxic or immune responses. [73]

Inorganic particles have a narrow size distribution and defined shape, but they present low biocompatibility and low biodegradability. [64] Silica nanoparticles are of synthetic origin, thus there are concerns about their topical application and their effects on the environment. [1] In addition, inorganic substances can accumulate after crossing different biological barriers and lead to adverse effects. [3] Thus, inorganic particles present some limitations [18] that may limit possible applications in pharmaceutical and cosmetic fields. [65]

For this reason, natural particles that are biodegradable and biocompatible are ideal candidates. [49] Beyond their biocompatibility and biodegradability, these particles are also desirable because of their environmentally friendly characteristics. [65] The attractive characteristics of these biomaterials are causing a shift from using inorganic particles to using bioparticles, (e.g., modified starch, chitosan, cellulose, among others) as stabilizers of Pickering emulsions. [64]

The solid particles mentioned in section 3.1 were all biocompatible, but only the organic particles were biodegradable. A few of the stabilizer particles have a size below 100 nm, in particular silica nanoparticles, PCL-b-PEG and PLA-b-PEG. Additionally, cyclodextrin has a size ranging from 30 to 250 nm, thus cyclodextrin nanoparticles may also be toxic.

There are only a few reports on cytotoxicity, distribution or *in vivo* metabolic concerns in Pickering emulsions. Currently, most of the research is still focused on the design and *in vitro* evaluation of new formulations. [11]

5. Conclusions and future perspectives

The high stability, biocompatibility and ease of preparation are some of the advantages of Pickering emulsions, making these highly promising in a wide range of fields. [6] Inorganic and organic particles are able to stabilize Pickering emulsions, in different approaches and applications. The particle size, wettability, zeta potential, pH, salt concentration and particle adsorption were some of the physicochemical characteristics addressed as main parameters for Pickering emulsion preparation. All these factors are interconnected thus changing one of them may also change the others. [3] Stabilizers such as silica, titanium dioxide, clay, polymers (PCL, PLA and PLGA), starch, chitosan, gum arabic and cyclodextrin have all been researched for topical applications. Additionally, different promising stabilizers, such as proteins, cellulose nanocrystals and hydroxyapatite have also been researched, with the aim of stabilizing cosmetic and/or pharmaceutical formulations.

New approaches for the stabilization of Pickering emulsions are being pursued and different techniques for the preparation of these emulsions are being studied. Moreover, the use of particles with tunable characteristics or stimuli-responsive, the association of different solid particles or solid particles with other emulsifiers in the same emulsion, open way for new applications. The development of these methodologies in Pickering emulsions plays an important role in unravelling further possible stabilizers for numerous applications, as well as in fully and accurately understanding the emulsification mechanism. [6]

6. Bibliography

1. MARTO, J., ASCENSO, A., SIMOES, S., ALMEIDA, A.J., RIBEIRO, H.M. - ***Pickering emulsions: challenges and opportunities in topical delivery***. Expert Opin Drug Deliv. 13, 8 (2016) 1093-107.
2. COSTA, C., MEDRONHO, B., FILIPE, A., MIRA, I., LINDMAN, B., EDLUND, H., NORGREN, M. - ***Emulsion Formation and Stabilization by Biomolecules: The Leading Role of Cellulose***. Polymers (Basel). 11, 10 (2019).
3. ALBERT, C., BELADJINE, M., TSAPIS, N., FATTAL, E., AGNELY, F., HUANG, N. - ***Pickering emulsions: Preparation processes, key parameters governing their properties and potential for pharmaceutical applications***. J Control Release. 309, (2019) 302-332.
4. LÉMERY, E., BRIANCON, S., CHEVALIER, Y., BORDES, C., ODDOS, T., GOHIER, A., BOLZINGER, M.A. - ***Skin toxicity of surfactants: Structure/toxicity relationships***. Colloids and Surfaces a-Physicochemical and Engineering Aspects. 469, (2015) 166-179.
5. LOW, L.E., TEY, B.T., ONG, B.H., CHAN, E.S., TANG, S.Y. - ***Palm olein-in-water Pickering emulsion stabilized by Fe3O4-cellulose nanocrystal nanocomposites and their responses to pH***. Carbohydr Polym. 155, (2017) 391-399.
6. YANG, Y., FANG, Z., CHEN, X., ZHANG, W., XIE, Y., CHEN, Y., LIU, Z., YUAN, W. - ***An Overview of Pickering Emulsions: Solid-Particle Materials, Classification, Morphology, and Applications***. Front Pharmacol. 8, (2017) 287.
7. WINUPRASITH, T.,SUPHANTHARIKA, M. - ***Properties and stability of oil-in-water emulsions stabilized by microfibrillated cellulose from mangosteen rind***. Food Hydrocoll. 43, (2015) 690-699.
8. KANG, D.J., BARARNIA, H., ANAND, S. - ***Synthesizing Pickering Nanoemulsions by Vapor Condensation***. Acs Applied Materials & Interfaces. 10, 25 (2018) 21746-21754.
9. WANG, Z.,WANG, Y. - ***Tuning Amphiphilicity of Particles for Controllable Pickering Emulsion***. Materials (Basel). 9, 11 (2016).
10. CHEVALIER, Y., BOLZINGER, M.-A., BRIANÇON, S. - ***Pickering Emulsions for Controlled Drug Delivery to the Skin.*** In: DRAGICEVIC, N.,MAIBACH, H.I. Percutaneous Penetration Enhancers Chemical Methods in Penetration Enhancement: Drug Manipulation Strategies and Vehicle Effects. Berlin, Heidelberg: Springer Berlin Heidelberg, 2015. 978-3-662-45013-0 p. 267-281.
11. WU, J.,MA, G.-H. - ***Recent Studies of Pickering Emulsions: Particles Make the Difference***. Small. 12, 34 (2016) 4633-4648.

12. BINKS, B.P.,LUMSDON, S.O. - ***Effects of oil type and aqueous phase composition on oil-water mixtures containing particles of intermediate hydrophobicity***. Physical Chemistry Chemical Physics. 2, 13 (2000) 2959-2967.
13. BENHAMOU, M.,EL-MOUDNY, S. - ***Review on Pickering emulsions stabilized by adsorbed nanoparticles: Structure, Thermodynamics, Cage Effect and Subdiffusion***. International Journal of Nanomaterials, Nanotechnology and Nanomedicine. (2017).
14. DU, Z., LI, Q., LI, J., SU, E., LIU, X., WAN, Z., YANG, X. - ***Self-Assembled Egg Yolk Peptide Micellar Nanoparticles as a Versatile Emulsifier for Food-Grade Oil-in-Water Pickering Nanoemulsions***. J Agric Food Chem. 67, 42 (2019) 11728-11740.
15. SALERNO, A., BOLZINGER, M.A., ROLLAND, P., CHEVALIER, Y., JOSSE, D., BRIANCON, S. - ***Pickering emulsions for skin decontamination***. Toxicology in Vitro. 34, (2016) 45-54.
16. GONZALEZ ORTIZ, D., POCHAT-BOHATIER, C., CAMBEDOUZOU, J., BECHELANY, M., MIELE, P. - ***Current Trends in Pickering Emulsions: Particle Morphology and Applications***. Engineering. 6, 4 (2020) 468-482.
17. HU, Y., LIU, S., LI, X., YUAN, T., ZOU, X., HE, Y., DONG, X., ZHOU, W., YANG, Z. - ***Facile preparation of biocompatible poly(l-lactic acid)-modified halloysite nanotubes/poly(ε-caprolactone) porous scaffolds by solvent evaporation of Pickering emulsion templates***. Journal of Materials Science. 53, 20 (2018) 14774-14788.
18. LAM, S., VELIKOV, K.P., VELEV, O.D. - ***Pickering stabilization of foams and emulsions with particles of biological origin***. Current Opinion in Colloid & Interface Science. 19, 5 (2014) 490-500.
19. FRUIJTIER-PÖLLOTH, C. - ***The toxicological mode of action and the safety of synthetic amorphous silica—A nanostructured material***. Toxicology. 294, 2 (2012) 61-79.
20. ARRIAGADA, F., UGARTE, C., GUNTHER, G., LARRAÍN, M.A., GUARNIZO-HERRERO, V., NONELL, S., MORALES, J. - ***Carminic Acid Linked to Silica Nanoparticles as Pigment/Antioxidant Bifunctional Excipient for Pharmaceutical Emulsions***. Pharmaceutics. 12, (2020) 376.
21. FRELICHOWSKA, J., BOLZINGER, M.A., VALOUR, J.P., MOUAZIZ, H., PELLETIER, J., CHEVALIER, Y. - ***Pickering w/o emulsions: drug release and topical delivery***. Int J Pharm. 368, 1-2 (2009) 7-15.

22. FRELICHOWSKA, J., BOLZINGER, M.A., PELLETIER, J., VALOUR, J.P., CHEVALIER, Y. - ***Topical delivery of lipophilic drugs from o/w Pickering emulsions***. Int J Pharm. 371, 1-2 (2009) 56-63.
23. GHOUCHI ESKANDAR, N., SIMOVIC, S., PRESTIDGE, C.A. - ***Nanoparticle Coated Submicron Emulsions: Sustained In-vitro Release and Improved Dermal Delivery of All-trans-retinol***. Pharmaceutical Research. 26, 7 (2009) 1764-1775.
24. ESKANDAR, N.G., SIMOVIC, S., PRESTIDGE, C.A. - ***Mechanistic insight into the dermal delivery from nanoparticle-coated submicron O/W emulsions***. Journal of Pharmaceutical Sciences. 99, 2 (2010) 890-904.
25. WANG, Q., HU, C., ZOGHBI, A., HUANG, J., XIA, Q. - ***Oil-in-oil-in-water pre-double emulsions stabilized by nonionic surfactants and silica particles: A new approach for topical application of rutin***. Colloids and Surfaces A: Physicochemical and Engineering Aspects. 522, (2017) 399-407.
26. ARSLAN AZIZOGLU, G., TUNCAY TANRIVERDI, S., AYDIN KOSE, F., BALLAR KIRMIZIBAYRAK, P., OZER, O. - ***Dual-Prevention for UV-Induced Skin Damage: Incorporation of Melatonin-Loaded Elastic Niosomes into Octyl Methoxycinnamate Pickering Emulsions***. AAPS PharmSciTech. 18, 8 (2017) 2987-2998.
27. MARTO, J., ASCENSO, A., GONÇALVES, L.M., GOUVEIA, L.F., MANTEIGAS, P., PINTO, P., OLIVEIRA, E., ALMEIDA, A.J., RIBEIRO, H.M. - ***Melatonin-based pickering emulsion for skin's photoprotection***. Drug Delivery. 23, 5 (2016) 1594-1607.
28. AYARI, M.G., KADHIRVEL, P., FAVETTA, P., PLANO, B., DEJOUS, C., CARBONNIER, B., AGROFOGLIO, L.A. - ***Synthesis of imprinted hydrogel microbeads by inverse Pickering emulsion to controlled release of adenosine 5'-monophosphate***. Materials Science and Engineering: C. 101, (2019) 254-263.
29. DAS, S., HORVÁTH, B., ŠAFRANKO, S., JOKIĆ, S., SZÉCHENYI, A., KŐSZEGI, T. - ***Antimicrobial Activity of Chamomile Essential Oil: Effect of Different Formulations***. Molecules (Basel, Switzerland). 24, 23 (2019) 4321.
30. ZHANG, Y., GUO, S., REN, X., LIU, X., FANG, Y. - ***CO2 and Redox Dual Responsive Pickering Emulsion***. Langmuir. 33, 45 (2017) 12973-12981.
31. ROSSANO, M., HUCHER, N., PICARD, C., COLLETTA, D., LE FOLL, F., GRISEL, M. - ***Effects of aging on structure and stability of TiO2 nanoparticle-containing oil-in-water emulsions***. Int J Pharm. 461, 1 (2014) 89-96.
32. MARTO, J., GOUVEIA, L.F., GONÇALVES, L., CHIARI-ANDRÉO, B.G., ISAAC, V., PINTO, P., OLIVEIRA, E., ALMEIDA, A.J., RIBEIRO, H.M. - ***Design of novel starch-***

based Pickering emulsions as platforms for skin photoprotection. Journal of Photochemistry and Photobiology B: Biology. 162, (2016) 56-64.

33. WANG, J., DENG, H., SUN, Y., YANG, C. - ***Montmorillonite and alginate co-stabilized biocompatible Pickering emulsions with multiple-stimulus tunable rheology***. J Colloid Interface Sci. 562, (2020) 529-539.
34. LVOV, Y., PANCHAL, A., FU, Y., FAKHRULLIN, R., KRYUCHKOVA, M., BATASHEVA, S., STAVITSKAYA, A., GLOTOV, A., VINOKUROV, V. - ***Interfacial Self-Assembly in Halloysite Nanotube Composites***. Langmuir. 35, 26 (2019) 8646-8657.
35. LISUZZO, L., CAVALLARO, G., PARISI, F., MILIOTO, S., LAZZARA, G. - ***Colloidal stability of halloysite clay nanotubes***. Ceramics International. 45, 2, Part B (2019) 2858-2865.
36. SANTOS, A.C., FERREIRA, C., VEIGA, F., RIBEIRO, A.J., PANCHAL, A., LVOV, Y., AGARWAL, A. - ***Halloysite clay nanotubes for life sciences applications: From drug encapsulation to bioscaffold***. Adv Colloid Interface Sci. 257, (2018) 58-70.
37. CALABRESE, V., COURTENAY, J.C., EDLER, K.J., SCOTT, J.L. - ***Pickering emulsions stabilized by naturally derived or biodegradable particles***. Current Opinion in Green and Sustainable Chemistry. 12, (2018) 83-90.
38. LAREDJ-BOUREZG, F., BOLZINGER, M.A., PELLETIER, J., VALOUR, J.P., ROVERE, M.R., SMATTI, B., CHEVALIER, Y. - ***Skin delivery by block copolymer nanoparticles (block copolymer micelles)***. Int J Pharm. 496, 2 (2015) 1034-1046.
39. WEI, Y.-S., NIU, Z.-C., WANG, F.-Q., FENG, K., ZONG, M.-H., WU, H. - ***A novel Pickering emulsion system as the carrier of tocopheryl acetate for its application in cosmetics***. Materials Science and Engineering: C. 109, (2020) 110503.
40. SAINI, P., ARORA, M., KUMAR, M.N.V.R. - ***Poly(lactic acid) blends in biomedical applications***. Advanced Drug Delivery Reviews. 107, (2016) 47-59.
41. IVANOVA, E., BAZAKA, K., CRAWFORD, R. - ***Advanced synthetic polymer biomaterials derived from organic sources.*** (2014). 9781782422655 p. 71-99.
42. LAREDJ-BOUREZG, F., BOLZINGER, M.A., PELLETIER, J., CHEVALIER, Y. - ***Pickering emulsions stabilized by biodegradable block copolymer micelles for controlled topical drug delivery***. Int J Pharm. 531, 1 (2017) 134-142.
43. WHITBY, C.P., LIM, L.H., GHOUCHI ESKANDAR, N., SIMOVIC, S., PRESTIDGE, C.A. - ***Poly(lactic-co-glycolic acid) as a particulate emulsifier***. J Colloid Interface Sci. 375, 1 (2012) 142-147.

44. MIR, M., AHMED, N., REHMAN, A.U. - ***Recent applications of PLGA based nanostructures in drug delivery***. Colloids and Surfaces B: Biointerfaces. 159, (2017) 217-231.

45. CAI, C., BAKOWSKY, U., RYTTING, E., SCHAPER, A.K., KISSEL, T. - ***Charged nanoparticles as protein delivery systems: A feasibility study using lysozyme as model protein***. European Journal of Pharmaceutics and Biopharmaceutics. 69, 1 (2008) 31-42.

46. ALBERT, C., HUANG, N., TSAPIS, N., GEIGER, S., ROSILIO, V., MEKHLOUFI, G., CHAPRON, D., ROBIN, B., BELADJINE, M., NICOLAS, V., FATTAL, E., AGNELY, F. - ***Bare and Sterically Stabilized PLGA Nanoparticles for the Stabilization of Pickering Emulsions***. Langmuir. 34, 46 (2018) 13935-13945.

47. ZHU, Y., SUN, J., YI, C., WEI, W., LIU, X. - ***One-step formation of multiple Pickering emulsions stabilized by self-assembled poly(dodecyl acrylate-co-acrylic acid) nanoparticles***. Soft Matter. 12, 36 (2016) 7577-7584.

48. MCCLEMENTS, D.J.,GUMUS, C.E. - ***Natural emulsifiers — Biosurfactants, phospholipids, biopolymers, and colloidal particles: Molecular and physicochemical basis of functional performance***. Adv Colloid Interface Sci. 234, (2016) 3-26.

49. BAI, L., HUAN, S., XIANG, W., LIU, L., YANG, Y., NUGROHO, R.W.N., FAN, Y., ROJAS, O.J. - ***Self-Assembled Networks of Short and Long Chitin Nanoparticles for Oil/Water Interfacial Superstabilization***. ACS Sustainable Chemistry & Engineering. 7, 7 (2019) 6497-6511.

50. MARTO, J., GOUVEIA, L., JORGE, I.M., DUARTE, A., GONÇALVES, L.M., SILVA, S.M.C., ANTUNES, F., PAIS, A.A.C.C., OLIVEIRA, E., ALMEIDA, A.J., RIBEIRO, H.M. - ***Starch-based Pickering emulsions for topical drug delivery: A QbD approach***. Colloids and Surfaces B: Biointerfaces. 135, (2015) 183-192.

51. ZHAI, K., PEI, X., WANG, C., DENG, Y., TAN, Y., BAI, Y., ZHANG, B., XU, K., WANG, P. - ***Water-in-oil Pickering emulsion polymerization of N-isopropyl acrylamide using starch-based nanoparticles as emulsifier***. Int J Biol Macromol. 131, (2019) 1032-1037.

52. MARTO, J., DUARTE, A., SIMÕES, S., GONÇALVES, L., LUÍS, F., GOUVEIA, L., ALMEIDA, A., RIBEIRO, H. - ***Starch-Based Pickering Emulsions as Platforms for Topical Antibiotic Delivery: In Vitro and In Vivo Studies***. Polymers (Basel). 11, (2019)

53. MARKU, D., WAHLGREN, M., RAYNER, M., SJÖÖ, M., TIMGREN, A. - ***Characterization of starch Pickering emulsions for potential applications in topical formulations***. Int J Pharm. 428, 1 (2012) 1-7.

54. COSSU, A., WANG, M.S., CHAUDHARI, A., NITIN, N. - ***Antifungal activity against Candida albicans of starch Pickering emulsion with thymol or amphotericin B in suspension and calcium alginate films***. Int J Pharm. 493, 1 (2015) 233-242.

55. ASFOUR, M.H., ELMOTASEM, H., MOSTAFA, D.M., SALAMA, A.A.A. - ***Chitosan based Pickering emulsion as a promising approach for topical application of rutin in a solubilized form intended for wound healing: In vitro and in vivo study***. Int J Pharm. 534, 1 (2017) 325-338.

56. SHARKAWY, A., BARREIRO, M.F., RODRIGUES, A.E. - ***Preparation of chitosan/gum Arabic nanoparticles and their use as novel stabilizers in oil/water Pickering emulsions***. Carbohydr Polym. 224, (2019) 115190.

57. TAN, C., XIE, J., ZHANG, X., CAI, J., XIA, S. - ***Polysaccharide-based nanoparticles by chitosan and gum arabic polyelectrolyte complexation as carriers for curcumin***. Food Hydrocoll. 57, (2016) 236-245.

58. SHARKAWY, A., CASIMIRO, F.M., BARREIRO, M.F., RODRIGUES, A.E. - ***Enhancing trans-resveratrol topical delivery and photostability through entrapment in chitosan/gum Arabic Pickering emulsions***. Int J Biol Macromol. 147, (2020) 150-159.

59. LECLERCQ, L.,NARDELLO-RATAJ, V. - ***Pickering emulsions based on cyclodextrins: A smart solution for antifungal azole derivatives topical delivery***. Eur J Pharm Sci. 82, (2016) 126-37.

60. LECLERCQ, L., TESSIER, J., DOUYERE, G., NARDELLO-RATAJ, V., SCHMITZER, A.R. - ***Phytochemical- and Cyclodextrin-Based Pickering Emulsions: Natural Potentiators of Antibacterial, Antifungal, and Antibiofilm Activity***. Langmuir. 36, 16 (2020) 4317-4323.

61. HU, Y., QIU, C., JIN, Z., QIN, Y., ZHAN, C., XU, X., WANG, J. - ***Pickering emulsions with enhanced storage stabilities by using hybrid β-cyclodextrin/short linear glucan nanoparticles as stabilizers***. Carbohydr Polym. 229, (2020) 115418.

62. CARRICO, C., PINTO, P., GRACA, A., GONCALVES, L.M., RIBEIRO, H.M., MARTO, J. - ***Design and Characterization of a New Quercus Suber-Based Pickering Emulsion for Topical Application***. Pharmaceutics. 11, 3 (2019).

63. XU, B., LIU, C., SUN, H., WANG, X., HUANG, F. - ***Highly Surface-Active Chaperonin Nanobarrels for Oil-in-Water Pickering Emulsions and Delivery of Lipophilic Compounds***. J Agric Food Chem. 67, 36 (2019) 10155-10164.

64. SARKER, M., TOMCZAK, N., LIM, S. - ***Protein Nanocage as a pH-Switchable Pickering Emulsifier***. Acs Applied Materials & Interfaces. 9, 12 (2017) 11193-11201.
65. WU, J., SHI, M., LI, W., ZHAO, L., WANG, Z., YAN, X., NORDE, W., LI, Y. - ***Pickering emulsions stabilized by whey protein nanoparticles prepared by thermal cross-linking***. Colloids and Surfaces B: Biointerfaces. 127, (2015) 96-104.
66. GONG, X., WANG, Y., CHEN, L. - ***Enhanced emulsifying properties of wood-based cellulose nanocrystals as Pickering emulsion stabilizer***. Carbohydr Polym. 169, (2017) 295-303.
67. XIE, J., LUO, Y., CHEN, Y., LIU, Y., MA, Y., ZHENG, Q., YUE, P., YANG, M. - ***Redispersible Pickering emulsion powder stabilized by nanocrystalline cellulose combining with cellulosic derivatives***. Carbohydr Polym. 213, (2019) 128-137.
68. TANG, C., SPINNEY, S., SHI, Z., TANG, J., PENG, B., LUO, J., TAM, K.C. - ***Amphiphilic Cellulose Nanocrystals for Enhanced Pickering Emulsion Stabilization***. Langmuir. 34, 43 (2018) 12897-12905.
69. REN, G., ZHENG, X., GU, H., DI, W., WANG, Z., GUO, Y., XU, Z., SUN, D. - ***Temperature and CO2 Dual-Responsive Pickering Emulsions Using Jeffamine M2005-Modified Cellulose Nanocrystals***. Langmuir. 35, 42 (2019) 13663-13670.
70. SONG, N., WANG, A.-J., LI, J.-M., ZHU, Z., SHI, H., MA, X.-L., SUN, D. - ***Study on influencing factors of Pickering emulsions stabilized by hydroxyapatite nanoparticles with nonionic surfactants***. Soft Matter. 14, 19 (2018) 3889-3901.
71. MARTO, J., NUNES, A., MARTINS, A., CARVALHEIRA, J., PRAZERES, P., GONÇALVES, L., MARQUES, A., LUCAS, A., RIBEIRO, H. - ***Pickering Emulsions Stabilized by Calcium Carbonate Particles: A New Topical Formulation***. Cosmetics. 7, (2020) 62.
72. NGO, M.A.,MAIBACH, H.I. - ***Dermatotoxicology: Historical perspective and advances***. Toxicology and Applied Pharmacology. 243, 2 (2010) 225-238.
73. KECK, C.M.,MÜLLER, R.H. - ***Nanotoxicological classification system (NCS) – A guide for the risk-benefit assessment of nanoparticulate drug delivery systems***. European Journal of Pharmaceutics and Biopharmaceutics. 84, 3 (2013) 445-448.

7. Annexes

Table I - Nano-stabilizers for topical application.

Particle	Type of PE	Particle Size (nm)	Droplet size	Viscosity (mPa.s)	Potential zeta (mV)	Wettability θ(º)	Mechanism	Reference
Inorganic								
Silica dimethyl silylate	W/O	~20 nm	9.7±0.5 µm	550±50 (at 20°C)	–	151.4±1.3	Hydrogen bonds are formed between the hydrophilic drug and silica; silica creates a shell around water droplets.	[20]
Fumed silica nanoparticles	O/W	15-20 nm	3±1 µm	6±2 (at 20°C)	–	–	Formation of silica aggregates and creation of a shell around oil droplets.	[21]
		~7 nm	166.5-261.6 nm	–	−49.9-52 or +32-35.6	–	Fumed silica nanoparticles coat oleylamine or lecithin to adsorb to the emulsion interface.	[22]
		~7 nm	166.5-361.5 nm	–	−39.5-40.6 or +48.1-52.2	159±1 or 162±3.4		[23]
		20 nm	2.7 µm	26 (at 35°C)	–	–	Fumed silica nanoparticles adsorb at the oil-water interface and adsorb the decontaminant.	[15]
Triethoxycaprylylsilane titanium dioxide	W/O	d(90)= 7.1±0.3 µm	d(50)= 6.2±4.1 µm or 5.7±4.3 µm	non-Newtonian fluid	–	106.5±0.7	Triethoxycaprylylsilane modifies TiO_2 to make it hydrophobic in order to adsorb at droplets surface.	[31]
Fuller's Earth	O/W	10-15 µm	d(50)= 58 µm	13 (at 35°C)	–	–	FE adsorbs at the oil-water interface and adsorbs the decontaminant	[15]

(continued on next page)

Table I - Nano-stabilizers for topical application. (continued)

Particle	Type of PE	Particle Size (nm)	Droplet size	Viscosity (mPa.s)	Potential zeta (mV)	Wettability θ(º)	Mechanism	Reference
Organic								
PCL-b-PEG	O/W	32 nm	3±0.4 µm	15.2-15.3 (at 20°C)	–	–	PEG provides hydrophobic properties to polymer in the core (PCL or PLA).	[41]
PLA-b-PEG		50 nm	2-2.7 µm	14.5-14.7 (at 20°C)	–	–		
PLGA/PSS	O/W	105-115 nm Up to 425 nm	~2 µm	–	− 30-57.5	–	PSS modifies the charge density of PLGA to adsorb and create a shell around the droplet.	[38]
Aluminium starch octenylsuccinate	W/O	d(90)= 20.85±0.02 µm	150 µm	non-Newtonian fluid	–	109.0±0.4	Aluminium octenylsuccinate confers hydrophobicity to the starch.	[49]
Starch modified by OSA	O/W	1-2 µm	30-75 µm	–	–	4.9-13	Droplet adsorption by starch monolayer or starch aggregates	[52]
Self-aggregated chitosan particles	O/W	287.3 nm	5.8±1.1 to 18.7±3.4 µm	2.07, 7.81 and 37.2 (at 25°C)	−48.1±4.7 to −78.4±4.1	42.47±1.19	At pH>pKa chitosan deprotonates and become more hydrophobic	[54]
Chitosan and Gum Arabic	O/W	~109 nm [57]	17.11 and 23.98 µm [57]	non-Newtonian fluid [55]	+56.3 [55], [57]	89.2±0.94 [55]	Chitosan/GA nanoparticles create a well-defined layer over the oil droplet. [55]	[55,57]
Cyclodextrin	O/W	30-250 nm	9.2 - 16.1 µm	non-Newtonian fluid	–	–	CD/oil complex aggregates to adsorb the emulsion interface.	[58]
Quercus Suber Bark	W/O	d(90)= 91.4±0.3 µm	d(90)= 182±1.3 µm	non-Newtonian fluid	–	97.3±0.3°	–	[61]

PE – Pickering Emulsion; OSA – Octenyl Succinic Anhydride; W/O – water in oil emulsion; O/W – oil in water emulsion; TiO2 – titanium dioxide PCL-b-PEG – poly(ε-caprolactone)-block-poly(ethylene glyco)l; FE – Fuller's Earth; PLA-b-PEG – poly(lactic acid)-block-poly(ethylene glycol); PEG – poly(ethylene glycol); PCL – poly(ε-caprolactone); PLA – poly(lactic acid); PLGA/PSS – polymer poly(lactide-coglycolide)/ poly(styrene-co-4-styrene-sulfonate); PSS – poly(styrene-co-4-styrene-sulfonate); PLGA – poly(lactide-coglycolide); GA – Gum Arabic; CD – Cyclodextrin

Table II - Pickering emulsions for topical application.

Therapeutic application	Nano-stabilizer	Type of PE	Active ingredient	Output	Reference
Active ingredient delivery	Silica dimethyl silylate	W/O	Caffeine	PE increased skin permeation 3-fold; caffeine accumulated twice more in receptor fluid when in PE; caffeine had good skin permeation.	[20]
	Fumed silica nanoparticles	O/W	AONB	Lecithin and oleylamine PEs increased 2-fold when compared to their controls; oleylamine PE was 5 to 10-fold higher in comparison with lecithin PE.	[23]
		O/W	*all-trans* retinol	Retinol penetration in PE was 5-fold higher when compared to retinol in solution; PE retinol distribution was 5-fold higher in the *stratum corneum* when compared to conventional emulsion.	[21]
		O/W	*all-trans* retinol	Retinol skin retention in PE with lecithin was 12.6 times higher than the control emulsion of lecithin; PE with oleylamine had 3-fold to 4-fold higher retinol skin retention compared with lecithin PE; lecithin PE drug release was 3.6 times slower; oleylamine PE drug release 1.28 times slower.	[22]
	PCL-b-PEG	O/W	*all-trans* retinol	PE enhanced retinol skin penetration 1.77-fold when compared to the conventional emulsion; retinol distribution in the second method was 1.27-fold higher than conventional emulsion.	[41]
	PLA-b-PEG			PE enhanced retinol skin penetration 2.22-fold when compared to the conventional emulsion; retinol distribution in the second method was 1.4-fold higher than conventional emulsion.	

Skin decontamination	Fumed silica Nanoparticles	O/W	Fumed silica nanoparticles	PE showed equivalent decontamination efficiency in comparison to water suspension.	[15]
	Fuller's Earth		Fuller's Earth	PE decreased the contaminant amount by 2-fold when compared to the suspension; PE decreased 3.8-fold when compared with the skin without treatment.	
Skin penetration vehicle	OSA quinoa starch	O/W	Paraffin Oil Miglyol Sheanut Oil	The skin penetration in PEs with methyl salicylate was 2-fold higher when compared to methyl salicylate in buffer solutions.	[52]
Wound healing	Self-aggregated chitosan particles	O/W	Rutin	PE drug release efficiency improved between 1.45 - 1.6 times compared with rutin in suspension; PE with rutin enhanced wound healing 1.17 times when compared with PE without rutin and 2-fold compared to the untreated wound; PE without rutin increased the wound healing process 1.7-fold when compared to the untreated wound; PE decreased 1.2-fold the MDA amount and increased 1.6 times the GSH levels and 35 times the CAT levels; HA concentration increased 1.46-fold, and Col I increased 1.2-fold in comparison with untreated wound.	[54]
Antibacterial	Aluminium starch octenylsuccinate	W/O	Minocycline hydrochloride	The PE with MH increased the inhibition zone up to 1.7-fold in comparison with MH in solution and significantly decreased the colony-forming units (CFU)/mL when compared with untreated skin; ASt particles proved an enhanced of wound healing; all PE led to epidermis re-epithelization and decreased inflammatory activity, but this are more accentuated in PE with MH.	[51]
Antifungal	Modified starch	O/W	Thymol oil	α-amylase enhanced the amphotericin B and thymol release; MFC decreased up to 0.5 for thymol and 0.8 for amphotericin B, when α-amilase was 100 U/mL.	[53]

Antifungal and antibacterial	Cyclodextrin	O/W	Econazole nitrate	The commercial formulation with econazole nitrate and PE stabilized by α-CD and β-CD had identical action; PE with γ-CD as stabilizer exhibit minimal or no biocidal activity, due to inability of econazole nitrate to diffuse from the CD.	[58]
			Miconazoctylium bromide	PE was 2-fold more effective against *C. albicans* and methicillin-resistant *S. aureus* than the commercial formulation; PE had high activity on *E. coli*, in contrast to the commercial one that is inactive for this bacterium.	[59]
	Silica nanoparticles	O/W	Chamomile oil	PE MIC90 results showed a mean of 14 times lower concentration in comparison with ethanolic solution; PE MIC90 results showed a range from 1.5 to 2.36 times of lower concentration in bacteria and from 1.85 to 3.67 times of lower concentration in fungi when compared to conventional emulsion: the MEC10 outcome exhibited 1.04 - 2.64 times lower concentration in bacteria and 1.79 - 4-fold in fungi when compared to conventional emulsion.	[28]
Sunscreen	Triethoxycaprylylsilane titanium dioxide	W/O	Triethoxycaprylylsilane titanium dioxide Zinc oxide Aluminum starch octenylsuccinate Green coffee oil	Formulation with starch increased the SPF value about 2-fold; both formulations were water resistant.	[31]
			Triethoxycaprylylsilane titanium dioxide Zinc oxide Aluminum starch octenylsuccinate Green coffee oil Melatonin	Formulation with melatonin had a 1.09-times lower SPF value; melatonin potentiated photoprotection by eliminating ROS from cells.	[26]
	Silica Nanoparticles	O/W	Melatonin Octyl methoxycinnamate	PE enhanced 5.57 times the melatonin penetration when compared to melatonin in niosomes; PE improved the skin accumulation 1.7 times compared to melatonin in niosomes; melatonin in PE had high antioxidant activity.	[25]

Antioxidant activity	PLGA/PSS	O/W	Tocopheryl acetate	The EC50 of free TA or in the PE were similar, thus, the TA in PE preserves its activity; the antioxidant activity retention was higher for PE when compared to conventional emulsion; PE decreased 1.18-fold the intensity of cellular fluorescence in comparison with free TA, indicating a greater antioxidant activity.	[38]
	Solid core-mesoporous shell silica nanoparticles		Carminic acid Tocopheryl acetate	In acetone CA linked to CSSNPs increased the antioxidant activity over free CA by 2-fold; in deuterium oxide CA linked to CSSNPs improved the antioxidant activity over free CA by 11-fold. PE stabilized with CSSNPs and CA had a 2.59 times lower vitamin E oxidation when compared to a conventional emulsion.	[19]
	Quercus Suber Bark	W/O	Quercus Suber Bark	The percentage of reduction of ROS was slightly lower, in comparison to ascorbic acid; the formulation exhibited anti-elastase activity.	[61]
Anti-ageing	Chitosan and Gum Arabic	O/W	*Trans*-resveratrol	The resveratrol retention increased up to 3.76-fold and permeation decreased up to 5.28-fold when compared with the solution; PE photodegradation was zero while the remaining ingredients in the control solution decreased 1.47-fold	[57]
	Modified silica dioxide	W/O	5′-AMP	MIPs had a maximum adsorbed capacity 4.7-fold higher and a binding constant 5.18 times higher than NIPs; MIPs retained the 5′-AMP allowing a sustained release by diffusion.	[27]
	Fumed silica nanoparticles	O/O/W	Rutin	Sustained release 1.2 times lower than from the ethanol solution; skin permeation increased 2.394-fold in comparison with aqueous solution.	[24]

PE – Pickering Emulsion; PCL-b-PEG – poly(ε-caprolactone)-block-polyethyleneglycol; PLA-b-PEG – poly(lactic acid)-block-polyethyleneglycol; PLGA/PSS – polymer poly(lactide-coglycolide)/ poly(styrene-co-4-styrene-sulfonate); OSA – Octenyl Succinic Anhydride; W/O – water in oil emulsion; O/W – oil in water emulsion; O/O/W – Oil-in-Oil-in-Water; AONB – acridine orange 10-nonyl bromide; 5′-AMP - 5′-Adenosine Monophosphate; MDA – Malondialdehyde; GSH – Reduced Glutathione; CAT – Catalase; HA – Hyaluronic Acid; Col I – Collagen Type I; MH – Minocycline Hydrochloride; CFU – Colony-Forming Unit; ASt – Aluminum Starch Octenylsuccinate; MFC – Minimum Fungicidal Concentration; CD – Cyclodextrin; MIC90 – Minimum Inhibitory Concentration; MEC10 – Minimum Effective Concentration; SPF – Sun Protection Factor; ROS – Reactive Oxygen Species; EC50 – Median Effective Concentration; TA – Tocopheryl Acetate; CA – Carminic Acid; CSSNPs – Solid core-mesoporous shell silica nanoparticles; NIP – Non-Imprinted Polymer