Ana Francisca Correia Morais

Relatórios de Estágio e Monografia intitulada "Nanotechnology & Cosmetics" referentes à Unidade Curricular "Estágio", sob orientação do Dr. João Maia, da Dra. Ana Sofia Silva e da Professora Doutora Ana Cláudia Santos e apresentados à Faculdade de Farmácia da Universidade de Coimbra, para apreciação na prestação de provas públicas de Mestrado Integrado em Ciências Farmacêuticas

Setembro 2018

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Universidade de Coimbra

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UNIVERSIDADE DE COIMBRA

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Coimbra, 07 de setembro de 2018.

Ana Francisca Correia Morais

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A Coimbra - para sempre saudade no meu coração.

Chegou ao fim a viagem mais bonita da minha vida– mas haverão, certamente,
outros mares por cruzar.

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Pelo sacrifício e apoio incondicional.
No final do dia saberei sempre o caminho para nossa casa.

Índice

Parte I

Relatório de Estágio em Farmácia Comunitária

Abreviaturas

CHUC	Centro Hospitalar da Universidade de Coimbra
DCI	Denominação Comum Internacional
EC	Estágio Curricular
IFASF	Intervenção Farmacêutica em Auto-cuidados de Saúde e Fitoterapia
IPO	Instituto Português de Oncologia
MG	Medicamento Genérico
MICF	Mestrado Integrado em Ciências Farmacêuticas
MNSRM	Medicamento Não Sujeito a Receita Médica
MSRM	Medicamento Sujeito a Receita Médica
PVP	Preço de Venda ao Público
REM	Receita Eletrónica Materializada
RM	Receita Manual
RSP	Receita Sem Papel
SWOT	*Strengths, Weaknesses, Opportunities and Threats*

1. Introdução

O farmacêutico é um profissional de saúde cuja formação lhe permite aceder a um vasto leque de oportunidades profissionais. Durante nove semestres, é oferecido ao estudante do Mestrado Integrado em Ciências Farmacêuticas (MICF) um conjunto de conhecimentos "em banda larga", isto é, das mais diferentes áreas, que o especializam e tornam um profissional singular. Este percurso académico culmina no Estágio Curricular (EC), que se propõe a ser o desafio prático final no qual o estudante aplica os conhecimentos técnico-científicos apreendidos previamente.

Na farmácia comunitária, o farmacêutico desempenha mais que um mero papel de dispensa de medicamentos. Atualmente, a farmácia comunitária é vista como um local imprescindível de apoio às populações, oferendo serviços que colocam em destaque a saúde dos cidadãos. Neste sentido, o papel do farmacêutico centra-se, além da ponte que revela ser entre o medicamento dispensado e o utente que o recebe, uma peça fulcral no aconselhamento e um prestador de serviços e cuidados que ambicionam o bem-estar da sociedade. O EC permite, pois, o contacto com a farmácia comunitária e a assimilação de competências que privilegiam o farmacêutico na interação com utentes, nomeadamente no que ao uso racional do medicamento e promoção para a saúde concerne.

O meu EC iniciou-se a 8 de janeiro de 2018, tendo findado a 24 de abril de 2018, na Farmácia Machado, em Coimbra sob a orientação do Dr. João Maia, enquanto Diretor Técnico da mesma. O plano deste estágio estendeu-se às tarefas de armazém, como gestão de *stocks* e aprovisionamento de medicamentos, manutenção de receituário, preparação de lineares e atendimento ao balcão.

O presente relatório diz respeito ao estágio realizado, à execução das funções tendo por base os conhecimentos adquiridos no MICF, refletindo sobre o enquadramento do plano curricular do mesmo na realidade profissional, e apresenta-se sobre a forma de análise SWOT - *Strengths, Weaknesses, Opportunities and Threats* [1]. Nesta, através da descrição de fatores internos (Forças e Fraquezas) e externos (Oportunidades e Ameaças), pretendo demostrar a minha análise a este estágio, no que às competências adquiridas diz respeito, bem como à sua interligação com o plano curricular de MICF.

2. Análise SWOT

2.1. *Strenghts* (Forças)

2.1.1. Mudança de instalações

A Farmácia Machado é já uma farmácia centenária, que apresentava pouco espaço, tanto de atendimento como de *backoffice*. Assim, uma semana após o início do estágio, a farmácia foi transferida para um outro espaço, na mesma rua, remodelado e de maiores dimensões. Esta mudança representa um ponto forte na medida em que permitiu um maior contacto com uma quantidade superior de produtos e a organização de lineares, bem como um atendimento superior de utentes, já que apresenta um espaço convidativo, além de lhes proporcionar uma oferta maior de respostas aos seus pedidos. Dado que a distância geográfica entre os dois locais é extremamente reduzida, a presença de utentes habituais não foi comprometida, tendo mesmo reforçado as suas visitas à farmácia.

2.1.2. Localização e população abrangida

A Farmácia Machado encontra-se num local privilegiado em Coimbra, no centro de Celas, próxima ao Instituto Português de Oncologia (IPO), Centro Hospitalar da Universidade de Coimbra (CHUC), Centro de Saúde de Celas, bem como de vários consultórios médicos privados e escolas. A população que visita a farmácia é, portanto, bastante heterogénea no que se refere a classes socioeconómicas e etárias, abrangendo sobretudo idosos, mas também doentes oncológicos e jovens. Esta diversidade de utentes urge um atendimento diferenciado, o que permite desenvolver capacidades a nível da dispensa de medicamento e aconselhamento, contribuindo para um ganho de confiança nos diferentes casos que recorrem à farmácia.

2.1.3. Receção de encomendas, armazenamento e gestão de *stocks*

Nas semanas que sucederam ao início de estágio, desempenhei sobretudo funções de receção de encomendas, conferências das mesmas (produtos, data de validade e estado das embalagens) e armazenamento dos produtos nos locais respetivos. Estas dotam-se de extrema importância, na medida em que providenciam o contacto com os medicamentos e produtos comercializados pela farmácia, a familiarização com nomes comerciais, o seu local de armazenamento, bem como o conhecimento sobre o tipo de produtos mais requisitados. Por outro lado, possibilita a compreensão de conceitos referentes ao preço de venda ao público

(PVP) de acordo com a margem estipulada, relativamente aos medicamentos não sujeitos a receita médica (MNSRM).

Durante o estágio foi possível presenciar e auxiliar na realização de encomendas, tendo como base o *stock* presente de produtos, o número de vendas feitas relativas aos mesmos e o número médio de vendas por mês. Este exercício é de particular valor para o farmacêutico, dado que a rentabilização de *stocks* permite uma gestão mais eficaz da farmácia, assegurando a sua sustentabilidade financeira.

2.1.4. Atendimento ao balcão

O atendimento ao balcão representa a principal atividade de um farmacêutico numa farmácia comunitária. É, também, a atividade mais exigente e de maior responsabilidade, que possibilita às farmácias o protagonismo devido no seio da sociedade.

O atendimento do utente deve ser adequado a cada um, tendo em atenção as suas necessidades e questões. A linguagem utilizada deve ser simples e esclarecedora, advertindo o utente para todas as informações de uso correto e racional, não descurando a promoção da adesão à terapêutica e esclarecimento de possíveis dúvidas.

Inicialmente, limitei-me à observação do atendimento por parte dos membros da farmácia, tendo progressivamente participado no mesmo. O auxílio dos profissionais da farmácia foi essencial na assimilação de cuidados a ter na dispensa de medicamentos, na linguagem utilizada, no funcionamento de receitas sem papel (RSP), receitas eletrónicas materializadas (REM) e receitas manuais (RM) e ainda de regimes de comparticipação complementar. A prescrição por denominação comum internacional (DCI) revela-se, na maioria das vezes, um auxílio, pois permite a identificação das substâncias ativas e o seu nome comercial. Todos estes elementos permitiriam que executasse um atendimento mais correto e adequado ao utente, ultrapassando desafios diários e colocando a saúde da população como principal prioridade.

2.1.5. Plano curricular do MICF

O sucesso deste estágio não seria possível sem o forte *background* de conhecimentos científicos adquiridos na frequência do MICF. O plano curricular contempla áreas do saber que se revelam imprescindíveis na prática profissional numa farmácia comunitária, dado o seu âmbito abrangente que permite reunir todas as ferramentas necessárias. Destaco as unidades curriculares de "Farmacologia", "Intervenção Farmacêutica em Auto-cuidados de Saúde e

Fitoterapia" (IFASF), "Farmacoterapia" e "Farmácia Clínica" dado que o seu conteúdo programático é que o mais contribui para um correto aconselhamento farmacêutico.

2.2. *Weaknesses* (Fraquezas)

2.2.1. Nome comercial

Na maioria das situações de dispensa ao balcão, os medicamentos são requisitados segundo o nome comercial dos mesmos. Este fator revelou-se limitante na cedência mais adequada dos produtos, dado o desconhecimento inicial do nome comercial de grande parte dos produtos comercializados na farmácia, o que pode ter tido efeito na descredibilização da imagem do estagiário.

Os casos de maior dificuldade reportavam-se à cedência de MNSRM. Contudo, esta problemática é contrariada na prescrição por DCI no caso de medicamentos sujeitos a receita médica (MSRM), que permite disponibilizar ao utente todos medicamentos existentes na farmácia de acordo com o seu princípio ativo. Foi necessário uma dedicação e estudo profundo dos produtos existentes na Farmácia Machado, de modo a melhor contemplar os mesmos na sua cedência.

Para reverter esta situação, talvez a associação de nomes comerciais aos respetivos princípios ativos nos conteúdos lecionados nas unidades curriculares fosse uma solução que permitisse uma maior familiarização e evitasse o choque inicial aquando do estágio em farmácia comunitária.

2.2.2. Programa curricular do MICF

Apesar da excelência curricular disponibilizada na frequência do MICF que permite a formação de farmacêuticos exemplares e em alerta no exercício da sua profissão em âmbito comunitário, considero que existam algumas lacunas que podem limitar o aconselhamento farmacêutico.

A este respeito, reporto-me a unidades curriculares como "Dermofarmácia e Cosmética", "Preparações de Uso Veterinário" e "Dispositivos Médicos". No primeiro caso, considero que não é dado grande destaque ao aconselhamento farmacêutico. Há situações abrangidas em IFASF, contudo, o tempo dispensado a esta temática não se mostra suficiente. Assim, o aconselhamento farmacêutico de casos reportados à pele ou cabelo encontra-se grandemente limitado, o que condiciona a melhor prestação do estagiário face aos requerimentos dos utentes. Relativamente a "Preparações de Uso Veterinário", atento que o

seu programa curricular apresenta uma abordagem centrada na farmacodinâmica e farmacocinética de antiparasitários, no entanto, descura o aconselhamento farmacêutico, sobretudo em patologias mais comuns. Quanto à unidade curricular de "Dispositivos Médicos", dado ser uma unidade opcional, nem todos os estudantes têm oportunidade de aceder aos seus conteúdos, pelo que se revelou um entrave ao aconselhamento de tais produtos.

Saliento alguma dificuldade no aconselhamento farmacêutico de Suplementos Alimentares. Estes revelam uma grande procura por parte dos utentes, sendo que senti alguma retração na dispensa dos mesmos, por falta de algum conhecimento que poderia ter sido aprofundado em algumas unidades curriculares. Talvez uma solução fosse a separação de IFASF em duas unidades curriculares, permitindo abranger devidamente estes produtos e colmatar algumas falhas experienciadas ao longo do estágio curricular.

2.2.3. Receitas manuais

Ao longo do estágio curricular foram frequentes os atendimentos contendo RM. O usos desta é justificado por falência informática, inadaptação do prescritor, prescrição no domicílio ou outras situações, sendo que cada prescritor tem um máximo de quarentas RM por mês. Este tipo de receitas contempla um conjunto de dificuldades, muitas vezes associadas à caligrafia do prescritor que inviabiliza a leitura dos produtos prescritos. É ainda necessário atentar em alguns pormenores, como o prazo de validade da receita, a assinatura do prescritor e vinheta identificativa do mesmo, nome e número de utente, número de beneficiário caso seja aplicável, identificação da exceção que leva ao uso de uma RM e se a impressão no verso corresponde de facto à receita. Senti, nestas situações, algum nervosismo que levou a alguma cautela extra de modo a assegurar a dispensa da medicação correta, sem prejudicar de modo algum os utentes.

2.2.4. Visão do estagiário pela população

No decorrer do estágio curricular, pude sentir algum sentimento de desconfiança por parte dos utentes no atendimento. Nos utentes que mais frequentam a farmácia, a presença de um elemento desconhecido é alvo de desconfiança *a priori*, sendo muitas vezes solicitados outros profissionais da farmácia para efetuar o atendimento. Para os utentes de passagem, a presença de um estagiário é sinónimo de falta de experiência e conhecimento, solicitando estes também o atendimento por parte de outros elementos presentes na farmácia. Neste

sentido, um ponto fraco do meu estagiário baseou-se na dificuldade sentida em criar alguma empatia com os utentes, algo que foi sendo superado com o passar do tempo. Foi necessário algum esforço para que os utentes reconhecessem valor no meu atendimento, e me vissem como uma figura capaz de satisfazer os seus pedidos da melhor forma.

2.3. *Opportunities* (Oportunidades)

2.3.1. Formações e reuniões com Delegados de Informação Médica

A mudança de instalações da farmácia e consequente aquisição de novos produtos, nomeadamente de Dermofarmácia e Cosmética e Suplementos Alimentares, possibilitou a organização de formações das respetivas marcas comercializadas. Estas tinham em vista explicar o conceito de cada marca, a função de cada produto e o tipo de aconselhamento a ser feito na sua cedência. Além das formações marcadas, também as reuniões com Delegados de Informação Médica permitiam aumentar o leque de produtos disponibilizados, simultaneamente à revisão de conceitos-chave de cada produto. Destaco as formações da Lierac®, Vichie®, SkinCeuticals®, La Roche Posay® e MartiDerm®.

Considero estas formações uma oportunidade de aprendizagem, dado que possibilitaram preencher lacunas no que concerne ao conhecimento e aconselhamento deste tipo de produtos.

2.3.2. Consultas de nutrição

A Farmácia Machado associou-se à marca EasySlim®, tendo adquirido um conjunto de produtos de Suplementação Alimentar, além de disponibilizar consultas semanais de nutrição, com a presença de uma nutricionista que ajudaria os utentes num programa de perda de peso controlado.

Esta associação permitiu contactar com um leque maior de Suplementos Alimentares e, assim, responder melhor aos requisitos dos utentes, tanto no que concerne à suplementação nutricional nas situações de perda de peso, como também no que se refere à melhoria da qualidade de vida. A presença semanal de uma nutricionista mostrou-se igualmente como uma oportunidade para explorar mais conceitos e dicas relacionadas com a perda de peso, bem como indicações para a toma correta de certos produtos.

2.3.3. Aconselhamento farmacêutico

Como já referido, neste estágio pude contactar com um conjunto de utentes bastante heterogéneo. No entanto, a maioria representava sobretudo uma população mais envelhecida, espelhando bem a situação demográfica do nosso país. Uma boa parte deste conjunto de indivíduos apresenta uma situação de polimedicação, à qual o farmacêutico deve estar alerta. É, pois, necessário avaliar a medicação cedida a cada utente, no sentido de averiguar a sua relação risco-benefício, garantir que os mesmos são tomamos de acordo com a sua indicação, deixando sempre o utente elucidado acerca da utilização e adesão à terapêutica.

É o aconselhamento farmacêutico que distingue o farmacêutico dos demais profissionais de saúde. É este que visa o melhor estado de saúde e bem-estar do utente, assegurando a sua eficácia e prevenindo situações que ponham em risco a qualidade de vida de cada indivíduo (Anexo I e II).

Neste sentido, considero que o estágio proporcionou inúmeros casos de aprendizagem no que respeita ao aconselhamento farmacêutico, impulsionando melhorias nesta vertente, tendo em vista tanto o meu crescimento pessoal e profissional, como a saúde dos utentes.

2.3.4. Filosofia *Kaizen*

Durante a realização do estágio na Farmácia Machado, esta associou-se ao projeto de melhoria contínua implementado nas farmácias pela Glintt®, fundamentada na filosofia *Kaizen* [2]. Esta filosofia desenvolvida no Japão, apresenta como pressupostos o envolvimento de todos os colaboradores nas tarefas diárias da farmácia, discutindo ideias e modos de aperfeiçoar certas questões. Para isso, são incentivadas reuniões diárias entre os colaboradores para que todos possam estar a par da realidade diária que é vivida na farmácia, de modo a melhor compreender os aspetos onde é possível promover melhorias.

Considero o contacto com esta filosofia uma oportunidade, dado que evidenciou princípios de aplicação diária que têm impacto positivo na atividade da farmácia, seja na motivação dos seus colaboradores ou na gestão sustentável nos seus produtos.

2.4. *Threats* (Ameaças)

2.4.1. Parafarmácias e outros locais de dispensa

As parafarmácias e outros locais de dispensa de produtos de saúde revelam ser uma ameaça dado os preços competitivos que apresentam, colocando em desvantagem a maioria das farmácias. No entanto, atento que este ponto poderá ser revertido em virtude da diferença no aconselhamento farmacêutico prestado, sendo que muitas vezes este é praticado por indivíduos sem formação para tal, podendo representar um risco para o utente.

Neste sentido, considero haver um esforço na farmácia no sentido de deixar claro ao utente a qualidade do atendimento e que a sua saúde é o foco principal da atividade farmacêutica.

2.4.2. Prescrição por DCI e informação do preço nas RSP

A prescrição por DCI nas RSP tem em vista permitir ao utente fazer uso do seu livre-arbítrio na escolha do seu medicamento de preferência, seja este de referência ou MG, tendo em conta os encargos financeiros do mesmo. Contudo, considero este aspeto uma ameaça, dado que pude observar que uma grande maioria dos utentes não entendia a diferença entre os dois tipos de produtos, afirmando que queriam exatamente o que o médico lhes prescrevera, mesmo após todos os esclarecimentos efetuados. Caso o utente não fosse frequentador da farmácia, uma das soluções passaria por tentar adquirir uma descrição da embalagem. Se representasse um utente habitual, através da sua ficha pessoal no sistema informático da farmácia, neste caso Sifarma 2000® [3], era possível perceber o medicamente geralmente cedido.

Outro aspeto referente às RSP prende-se com o facto de possuírem, para cada linha de prescrição, uma indicação relativa ao preço máximo a pagar pelo medicamento genérico (MG) mais barato. No entanto, no momento da prescrição, esta informação pode não se encontrar atualizada, pelo que, mesmo adquirindo o MG mais barato, o encargo financeiro a ter pelo doente pode não corresponder ao indicado na receita. Além disso, o facto de o preço indicado ser do MG mais barato, que pode não ser o de preferência usual do utente, gera alguma confusão no atendimento.

3. Considerações Finais

Agora que findado, posso compreender a importância que o EC tem como etapa final do MICF. É, pois, o momento final para trazer à realidade todos os conhecimentos técnico-científicos adquiridos previamente, obtendo outros aos quais se somam competências humanas e sociais.

Considero ter vivido uma experiência por vezes extenuante, mas cujo desafio diário de melhorar a saúde e bem-estar da população é o que deixa maior recompensa. Pela excelente equipa técnica que me acompanhou e pelos conhecimentos adquiridos junto dos profissionais e dos utentes, este estágio deixará para sempre memórias e valores transmitidos. Cresci enquanto futura farmacêutica, mas estou certa que o crescimento pessoal enquanto ser humano foi também notório.

Compreendo mais do que nunca a nobreza da profissão farmacêutica, a riqueza que a compõe pela oportunidade de aprendizagem constante e sua contribuição evidente para a sociedade. Um farmacêutico é muito mais que um mero dispensador de medicação; é um verdadeiro porto-abrigo para os utentes, um profissional prezado e dedicado ao seu bem-estar. Apostar na sua formação e nas suas funções de aconselhamento e promoção para a saúde é apostar no seu reconhecimento que, espero, venha a ser maior dia após dia.

Anexo I

Uma senhora com cerca de 50 anos dirigiu-se à farmácia com queixas de queda de cabelo que perduravam há algumas semanas. A utente mostrava alguma preocupação não apenas com o aspeto estético, dado que notava o seu cabelo mais fino, referindo já ter iniciado a lavagem com um champô anti queda adquirido num supermercado.

Comecei por perguntar se o início da queda fora repentino, ao que a utente respondeu que foi algo gradual. Perguntei ainda se sentia comichão ou se tinha reparado em alguma zona avermelhada, sendo que a resposta foi negativa. Inquiri ainda sobre a toma de alguma medicação recente ou sobre alguma doença (anemia, diabetes, questões associadas à tiroide), sendo a resposta, uma vez mais, negativa. Esclareci que a queda de cabelo poderia ser algo sazonal dada a altura (abril), sendo que o tratamento passaria por promover o crescimento do cabelo através da estimulação do folículo piloso e diminuir a queda do cabelo.

Face a esta situação, aconselhei à utente dois produtos: champô estimulante Dercos® [4], dado que a sua formulação contendo aminexil previne a queda de cabelo, a utilizar em todas as lavagens. Indiquei ainda um suplemento alimentar, Ecophane® [5], dois comprimidos a tomar diariamente, devido à sua formulação contendo vitaminas B5, B6 e B8 e hidrolisado proteico de trigo e sésamo. Adverti ainda a utente para certos cuidados a ter com o cabelo como evitar lavagens muito frequentes, tratamentos muitos agressivos como colorações ou temperaturas elevadas (secadores ou placas) ou escovagens muito vigorosas.

Anexo II

Uma senhora apresentou-se na farmácia com os seguintes sintomas: espirros, congestão nasal com corrimento, sentindo-se mais incomodada com a comichão nos olhos.

Questionei pela existência de febre ou dores no corpo, sendo a resposta negativa. Perguntei então se tinha conhecimento de ter alguma alergia ou sensibilidade a algum produto, ao que a utente respondeu que tinha regressado de uma viagem ao Alentejo, ligando os sintomas ao aparecimento inicial de pólenes naquela altura.

Expliquei então que se poderia tratar de uma reação alérgica. Assim, indiquei Telfast 120® [6], um comprimido por dia, dado que o anti-histamínico que contém iria auxiliar na resolução dos sintomas alérgicos, sobretudo na rinorreia. Sob pedido do utente de algo que ajudasse na irritação ocular, questionei sobre medicação habitual ou uso de lentes oculares, tendo a resposta obtida sido negativa. Aconselhei então a aplicação de uma gota de manhã e outra à noite de Allergodil® [7] colírio

Parte II

Relatório de Estágio em Indústria Farmacêutica na Bluepharma – Indústria, S.A.

Abreviaturas

AR	Assuntos Regulamentares
MICF	Mestrado Integrado em Ciências Farmacêuticas
SWOT	*Strengths, Weaknesses, Opportunities and Threats*
RH	Recursos Humanos
EMA	*European Medicines Agency*
FDA	*Food and Drug Administration*
ICH	*International Conference on Harmonisation*
EC	Estágio Curricular

1. Introdução

Além do protagonismo notório em farmácia comunitária, o conteúdo programático do plano curricular do Mestrado Integrado em Ciências Farmacêuticas (MICF) dá oportunidade aos estudantes de enveredarem por outras áreas do ciclo do medicamento, nomeadamente a indústria farmacêutica. Neste ramo, o farmacêutico destaca-se nas suas variadas funções, desde a investigação, desenvolvimento galénico, fabrico, controlo de qualidade a assuntos regulamentares.

Assim, optei por realizar um segundo estágio, no meu Estágio Curricular (EC), em indústria farmacêutica. Na sequência de duas entrevistas, fui selecionada para o departamento de Assuntos Regulamentares e Farmacovigilância (AR) na Bluepharma®, em Coimbra, tendo iniciado a 7 de maio de 2018, com término a 27 de julho de 2018.

A Bluepharma® é uma empresa sediada em Coimbra, com nascimento em 2001, com reconhecidos valores a nível de investigação, desenvolvimento, fabrico, registo e comercialização de medicamentos [8]. Dada a importância que a exportação representa para esta empresa, o departamento de AR encontra-se estruturado em duas equipas - Europa e Internacional, sendo esta segunda aquela que me acolheu.

O departamento de AR reveste-se de uma relevância extrema para a atividade da empresa, dada a abrangência de conhecimento de todas as atividades praticadas de forma global sendo que a comunicação e articulação com todos os departamentos da empresa é essencial para a realização de todas as atividades regulamentares. Uma das principais funções da equipa Internacional é o registo de medicamentos no estrangeiro (fora da Europa) com base na legislação aplicável e cumprindo com os requisitos das Autoridades Competentes. Para isso, é imprescindível preparar e adaptar documentação regulamentar de suporte ao registo do medicamento, compreendendo o mecanismo e procedimentos internos da empresa, tendo sempre em foco a qualidade, eficácia e segurança do medicamento. Aqui, tive oportunidade de participar na preparação de *dossiers* de registo de medicamentos, sobretudo para países da América Latina e Médio Oriente, na composição de respostas a auditorias de cliente (*Due Diligences)* para suportar negócios de *Out-Licensing* ou Distribuição e ainda inteirar-me de todos os medicamentos atualmente em comercialização pela Bluepharma® participando da construção de bases de dados essenciais para as atividades do departamento. Todas estas funções foram orientadas e aperfeiçoadas por diversas formações específicas providenciadas pelos colaboradores da Bluepharma®, no sentido de melhor compreender aspetos intrínsecos à empresa e ao sector.

O presente relatório diz respeito ao estágio realizado, à execução das funções tendo por base o conteúdo técnico-científico adquirindo MICF, avaliando a sua adaptação à realidade profissional, e apresenta-se sobre a forma de análise SWOT - *Strengths, Weaknesses, Opportunities and Threats* [1]. Nesta, através da exposição de variáveis internas (Forças e Fraquezas) e externas (Oportunidades e Ameaças), pretendo demostrar a minha análise a este estágio, no que às competências adquiridas diz respeito, bem como à sua interligação com o plano curricular de MICF.

2. Análise SWOT

2.1. *Strengths* (Forças)

2.1.1. Equipa técnica do departamento de Assuntos Regulamentares

O estágio iniciou-se com a receção por parte do departamento de Recursos Humanos (RH) da Bluepharma®, como uma pequena visita às instalações e apresentação aos vários colaboradores de outros departamentos. Posteriormente, fui apresentada ao departamento de AR, tendo-me sido alocada uma tutora, responsável pelo acolhimento e introdução da missão e valores da empresa. Ao longo de todo o estágio, a equipa de AR, constituída por dez colaboradoras, mostrou esforços no sentido de me proporcionar uma excelente integração. É também de salientar a disponibilidade constante em esclarecer dúvidas e o cuidado em partilhar conhecimentos que considerassem de relevo para a minha evolução.

Este foi, claramente, um dos pontos mais fortes desta experiência. O contacto com profissionais dedicados e extremamente qualificados no exercício da sua função reforçou o meu interesse por esta área, desvendando um leque de desafios diários que é a área regulamentar.

2.1.2. Pesquisa e leitura de documentação oficial

Nas semanas que sucederam o início do estágio foram sobretudo preenchidas pela pesquisa de *Guidelines,* Diretivas e informação revelante para área regulamentar, sobretudo de Autoridades Competentes como a *Food and Drug Administration* (FDA) [9], *European Medicines Agency* (EMA) [10] e *International Conference on Harmonization* (ICH) [11]. Para além destas, seguiram-se outras referentes às Autoridades Competentes dos países alvo de exportação de produtos Bluepharma®.

Considero esta questão uma força, dado que permitiu adquirir um maior saber acerca dos processos realizados a nível industrial e procedimentos regulamentares a ter em conta, sejam estes harmonizados internacionalmente ou específicos para cada território. O objetivo não se centrou numa aprendizagem limitada ou estagnada, mas sim na promoção de hábitos constantes de pesquisa e leitura de informação atualizada, tendo em vista sempre os mais altos padrões de qualidade, segurança e eficácia dos medicamentos desenvolvidos, produzidos e comercializados.

2.1.3. Reuniões de Departamento

Ao longo do estágio pude assistir a várias reuniões no departamento AR, tanto de âmbito mais geral, como apenas direcionadas à equipa Internacional. Estas permitiram compreender as funções designadas a cada elemento do departamento e objetivos, a atualização de informação relativa à empresa, bem como metas a atingir. A nível internacional, estas reuniões possibilitaram inteirar-me acerca dos produtos exportados, procedimentos a efetuar de âmbito regulamentar e estratégias a adotar caso-a-caso.

2.1.4. Participação no Bluefun

No decorrer do estágio, tive a possibilidade de participar num evento de *team building* realizado anualmente pela Bluepharma® – Bluefun. Este teve lugar no Montebelo Aguieira Lake Resort e centrou-se na organização de um dia com atividades lúdicas com o objetivo de promover o contacto entre todos os colaboradores da empresa, tendo em vista a criação de laços entre todos os profissionais. Esta interação terá, eventualmente, o seu impacto na atividade diária da Bluepharma®. O lema deste ano foi *"Blue is green"* dadas as preocupações presentes com a saúde ambiental do planeta, situação da qual a Bluepharma® não é exceção.

Para mim, esta experiência foi extremamente frutífera, dado que pude interagir com profissionais dos diversos departamentos da Bluepharma®, perceber as suas funções e dinâmica das mesmas.

2.1.5. Programa curricular do MICF

Ao longo do percurso académico temos acesso a um conjunto de conhecimentos que de facto tornam o farmacêutico num profissional multifacetado. Unidades curriculares como "Assuntos Regulamentares do Medicamento", "Tecnologia Farmacêutica (I, II e III)" e "Garantia e Gestão da Qualidade" apresentam-se como uma mais valia na perceção de mecanismos e conceitos relacionados com a Indústria Farmacêutica.

Concretamente, Assuntos Regulamentares do Medicamento, uma unidade curricular da FFUC de caráter obrigatório, contrariamente ao verificado noutras faculdades e institutos superiores é, de facto, de particular importância para os que desejam prosseguir nesta área profissional, dado que possibilita uma formação e ganho de conhecimento nesta vertente, nomeadamente no que se refere à construção de um *dossier* de registo de medicamento de acordo com a legislação em vigor na União Europeia [12], e outros conceitos chave.

2.2 *Weaknesses* (Fraquezas)

2.2.1 Duração do Estágio

Apesar do tempo de estágio em indústria ser aquele que permite aos alunos conciliar com o estágio obrigatório em farmácia comunitária, dentro do tempo estipulado, considero este facto uma fraqueza.

De facto, três meses revelaram-se insuficientes para assimilar efetivamente todos os mecanismos, conceitos e processos a realizar. Por outro lado, os processos com os quais contactei e auxiliei no desenvolvimento de certas tarefas são, muitas vezes, morosos, pelo que não tive oportunidade de assistir ao seu desfecho final. Acrescento o facto de sentir maior confiança e facilidade no desempenho de certas funções na proximidade com o términus do estágio, pelo que, nesse sentido, não o considerei completamente proveitoso.

2.3 *Opportunities* (Oportunidades)

2.3.1 Formações

Durante a minha estadia na Bluepharma®, tive a oportunidade de assistir a formações presididas por colaboradores da empresa que contemplam o funcionamento geral desta, conceitos, procedimentos, etc. Estas, de caráter obrigatório que incluíram uma visita às instalações da fábrica, concentraram-se numa semana de intensa aprendizagem e abordaram temas como Ambiente, Saúde e Segurança no trabalho, Gestão de Qualidade, Assuntos Regulamentares, Farmacovigilância, Inovação, entre outros. Estas possibilitaram esclarecer algumas dúvidas, percecionar o funcionamento geral da empresa, familiarizar com fluxos de processos, etc.

Por outro lado, são organizadas na Bluepharma® formações de caráter facultativo, destinadas a todos os colaboradores, nas quais, de um modo geral, se pretende auxiliar os profissionais no desempenho das suas funções. Destas, destaco a formação destinada ao tema "Lean 6 sigma", uma metodologia de melhoria contínua instituída na Bluepharma®.

2.3.2 Presença numa avaliação de desenvolvimento de um medicamento genérico

Durante o estágio, pude presenciar a avaliação do possível desenvolvimento de um medicamento genérico após futura queda de patente do respetivo medicamento inovador. Estas avaliações são constituídas por elementos de diferentes departamentos que dão o seu parecer sobre as várias questões e situações relacionadas com a mesma, tendo em vista o desenvolvimento e produção de um produto de qualidade máxima assegurada.

Assim, foi-me possibilitado contactar com os diversos setores da empresa, e sobretudo compreender a interligação que os une no sentido de alcançar um produto final de qualidade, cumprindo com os objetivos da Bluepharma®.

2.3.3 Contacto com realidades internacionais

Sendo a exportação um fator importante para a atividade da Bluepharma® e com a minha integração na equipa Internacional do departamento de AR, tive a oportunidade de me familiarizar com regulamentos legais e processos próprios de cada território, preparando documentação de acordo com estes pressupostos. Adicionalmente, possibilitaram-me a participação em conferências com clientes para discussão de diversas situações, nomeadamente a definição da melhor estratégia regulamentar de forma a corresponder às expectativas do cliente e fazendo cumprir os requisitos locais aplicáveis. Desta forma, pude familiarizar-me com o tipo de contacto estabelecido com os clientes, bem como perceber que tipo de informação é trocada e como proceder na resolução de determinadas questões.

2.4 *Threats* (Ameaças)

2.4.1 Estágio não creditado

Segundo o artigo 44º, secção 7, capítulo III da Diretiva 2005/36/CE do Parlamento Europeu [13], a formação de um farmacêutico pressupõe, no mínimo, um ensino teórico e prático de quatro anos e seis meses de estágio em farmácia comunitária ou farmácia hospitalar para que possa ser reconhecido como tal. Contudo, a mesma diretiva descreve atividades da competência de um farmacêutico como aquelas desempenhadas numa indústria farmacêutica. Deste modo, os estudantes podem prosseguir a sua atividade em indústria, sem que para isso estejam preparados, pela não obrigatoriedade da sua passagem por esta realidade durante o

seu percurso académico. Neste sentido, considero esta situação uma ameaça, visto que poderá constituir um constrangimento na evolução e execução de determinadas atividades, num primeiro contacto com esta área. Posto isto, considero que estágios em indústria farmacêutica deveriam ser considerados de caráter obrigatório a par de farmácia comunitária e hospitalar, assegurando uma formação mais completa e abrangente dos estudantes.

De notar que não considero o facto do estágio em indústria farmacêutica não ser creditado como incapacitante na procura de emprego, quando na verdade se revela uma vantagem, pela experiência que proporciona.

2.4.2 Plano curricular do MICF

Uma das maiores dificuldades com a qual me deparei inicialmente no estágio foi perceber o elo que unia os diversos setores da indústria, como se desenrolavam certas atividades e, sobretudo, o fluxo de determinados processos. Acredito que isto se deva à abordagem que o plano curricular do MICF toma relativamente a determinadas unidades curriculares. De facto, as unidades curriculares acima mencionadas como pontos fortes apresentam planos curriculares de relevo para a compreensão de conceitos e execução de determinadas tarefas. No entanto, considero que não são lecionadas de modo a completarem-se, mas são antes apresentadas de modo algo isolado. As dificuldades referidas foram ultrapassadas com o contacto com as funções diárias, podendo ter sido minimizadas pelos argumentos descritos.

3. Conclusão

O farmacêutico é um profissional de saúde multifacetado, no entanto, por vezes as suas funções na realidade profissional podem parecer algo distantes e confusas aos olhos de um estudante que se encontre a frequentar o MICF. Por conseguinte, realizar parte do meu EC em indústria farmacêutica deu cores e forma a um futuro percurso.

Poder estagiar na Bluepharma® contribuiu para um crescimento pessoal e profissional, promovendo uma evolução que culminou numa formação académica que agora considero mais completa.

A oportunidade de ser incluída no departamento de AR abriu caminho à aprendizagem efetiva com profissionais dedicados e exemplares. Na verdade, tive oportunidade de ser acompanhada por pessoas que considero ser uma inspiração e que reforçaram o gosto pessoal que preservo por esta área.

Estagiar em áreas que vão além da farmácia comunitária e da farmácia hospitalar é um passo dado na construção de melhores futuros farmacêuticos. É algo que deve ser impulsionado e alargado a todos os estudantes. Estou certa de que esta oportunidade influenciará o rumo da minha futura vida profissional, e, por isso, mostro-me imensamente grata.

Parte III

Monografia

Nanotechnoly & Cosmetics

Resumo

A Nanotecnologia é uma área emergente pelas suas infindáveis aplicações e vantagens, sendo alvo de interesse em diversas áreas, particularmente em cosmética. A inclusão de nanosistemas irá permitir maior eficácia na penetração e libertação de substâncias ao nível da pele. As suas aplicações nesta área são diversas, desde cuidados antienvelhecimento, maquilhagem, cuidados para as unhas, desodorizantes, cuidados orais, protetores solares, entre outros. No entanto, só recentemente se iniciaram investigações no que respeita às suas desvantagens, nomeadamente no que se refere aos efeitos prejudiciais para a saúde e para o meio ambiente. Também a área regulamentar viu a sua adaptação no que respeita à utilização de formulações contendo tecnologias à escala nano. No geral, a nanotecnologia é uma área bastante promissora com vista à obtenção de novas formulações cosméticas.

Palavras-chave

Beleza, Cosmética, Nanocosmética, Nanotecnologia, Regulamentação, Toxicologia.

Abstract

Nanotechnology is an increasingly widespread area for its endless applications and advantages. In fact, nanotechnology has been a focus of investment in different areas of science, in particular, cosmetics. In cosmetics, nanoparticles (NPs) allow for a much more profit skin penetration and a very effective release of ingredients. Their applications in this area are several, from anti-aging care, make-up, nails, deodorants, oral care, sunscreens, among others. However, as an area of emerging knowledge, it has now begun to encourage investigations into its disadvantages, particularly as regards to health damage and environmental pollution. Also, the regulatory area saw its adaptation in what concerns to the use of formulations containing nanotechnology. Overall, the nanotechnology constitutes a highly promising area towards the obtainment of new cosmetic formulations.

Keywords

Beauty, Cosmetics, Nanocosmetics, Nanotechnology, Regulatory, Toxicological.

Abbreviations

ACI	Active Cosmetic Ingredient
AgNP	Silver Nanoparticle
AuNP	Golden Nanoparticle
BNP	Bioadhesive Nanoparticle
CdS	Cadmium Sulfide
CHX	Chlorohexidine
CoQ10	Coenzyme Q10
CPNP	Cosmetic Products Notification Portal
EC	European Commission
EDTA	Ethylenediaminetetraacetic acid
EU	European Union
EUON	European Union Observatory for Nanomaterials
FeO	Ferrous Oxide
Fe_2O_3	Ferric Oxide
GAC	Green Analytical Chemistry
H_2O_2	Hydrogen Peroxide
IL	Interleukine
JSH18	6-methyl-3-phenethyl-3,4-dihydro-1H-quinazoline-2-thione
MIC	Minimum Inhibitory Concentration
NaOCl	Sodium Hypochlorite
NLC	Nanostructured Lipid Carrier
NP	Nanoparticle
O/W	Oil-in-Water

PEG	Polyethylene Glycol
PLA	Poly-L-lactic Acid
PLGA	Poly (lactic-co-glycolic acid)
PVA	Poly (vinyl alcohol)
PVP	Polyvinyl Pyrrolidone
ROS	Reactive Oxygen Specie
SCCS	Scientific Committee on Consumer Safety
SLN	Solid Lipid Nanoparticle
TiO_2	Titanium Oxide
TNF-α	Tumor Necrosis Factor-α
UV	Ultraviolet
W/O	Water-in-Oil
ZnO	Zinc Oxide
ZnS	Zinc Sulfide

1. Introduction

Nanotechnology is an emerging area that has been extensively explored in the past decades. It is defined as any technology performed in the nanoscale, in the size range of about 1-1000 nm [14]. According to an inventory made by the project on Emerging Nanotechnologies, the global market has over 1800 consumer products based on nanotechnology, in a list with over 620 companies in 32 countries, with 42% of the total products regarding the Health and Fitness Category. At the time of this inventory, it was predicted that the nano-market could reach a value of 1 to 2.2 trillion dollars until 2015 [15]. This demonstrates the power that this kind of technology has been achieving in the largest fields of science and engineering.

The term "nanotechnology" is currently related to several areas of knowledge, and its applications can be found in electronics, healthcare, chemical or even food consumers [16]. In this respect, Cosmetics Industry is one of the strongest stimulating applications of nanotechnology. The growing interest of people in improving their appearance, concerning beauty, boosts the Cosmetics Industry, so there is a requirement to keep pace with the development of new technologies aiming to better meet consumer demands [17]. The different areas comprising nanotechnology in cosmetics formulations are illustrated in Fig. 1. Nanoparticles (NPs) are an open door for new products with improvements in formulation, active ingredients delivery, skin penetration or long-lasting effects. All these benefits may be achieved by nanoemulsions, liposomes, polymeric NPs, solid lipid nanoparticles (SLNs), among others [18], which will be thoroughly exposed in this review.

Nanomaterials have enhanced the different applications of cosmetics, with a diversified range of targets for interaction, such as the skin, the hair or even the teeth. These interactions may condition the safety of the product, so they must be taken into consideration. The growing interest in side effects of nanomaterials led to the development of an important area, nanotoxicology. Since this field was recently developed, there are still actions on the different targets that have not been completely elucidated. Therefore, it is necessary to promote the progress of test models that allow for an effective prediction of the nanocosmetics toxicological effect [19]. In this regard, it is also important to discuss the environmental impact that nanocosmetics may own. Therefore, efforts have been made to encourage green analytical chemistry (GAC), minimizing the impact of nanocosmetics production in the environment without compromising their performance [20]. Consequently, it is imperative to ensure the implementation of regulated methods and cosmetic ingredients to ensure their safety, always in accordance to the current legislation [21]. In this review, it will be made a general exposition

of the distinct nanosystems involved in the production of nanocosmetics formulations, followed by a brief description of the involved manufacturing methods and formulations, and by a discussion about nanocosmetic formulations. Afterwards, new insights and concerns into toxicological and regulatory aspects of nanocosmetics formulations will be discussed.

Figure 1 - Applications of nanotechnology in cosmetics formulations, including make-up, skin care, hair care, nails care, sun protection, lips care and dental care.

2. Manufacturing of nanotechnology-based cosmetics

Over the last years, the cosmetic industry has developed a striking interest by nanotechnology-based cosmetics. One of the many nanosystems applications is related to their ability to encapsulate formulation ingredients and cosmetic interest substances, such as ultraviolet (UV) filters [22]. In this sense, it is possible to assign advantages to the development of cosmetic formulations enclosing nanoparticles (NPs): enhance the stability and efficacy of these formulations; allow a more effective penetration of the ingredients into the skin, and act like UV filters with improved tolerance [23].

The nanomaterials used in cosmetics are divided into four large groups: lipid-based nanosystems, polymeric-based nanosystems, metal-based NPs and additional nanosystems (Table 1) [24].

2.1 Formulation parameters of nanotechnology-based cosmetics

The great number of advantages assigned to NPs makes them an important choice in formulating effective cosmetic products. The main goal is to develop NPs that increase the delivery of interest active cosmetic ingredients (ACIs) into the skin, with greater stability, lesser quantities and minor toxicological mechanisms. In this regard, some formulation parameters should be carefully analyzed, due to their direct impact in NPs performance. After NPs obtainment, important features are characterized, such as NPs shape, size, polydispersity index, zeta potential, entrapment efficiency, permeation behavior and retention time into the skin, ACI physicochemical properties and content, and vehicle rheological properties and pH (Fig. 2) [25-28].

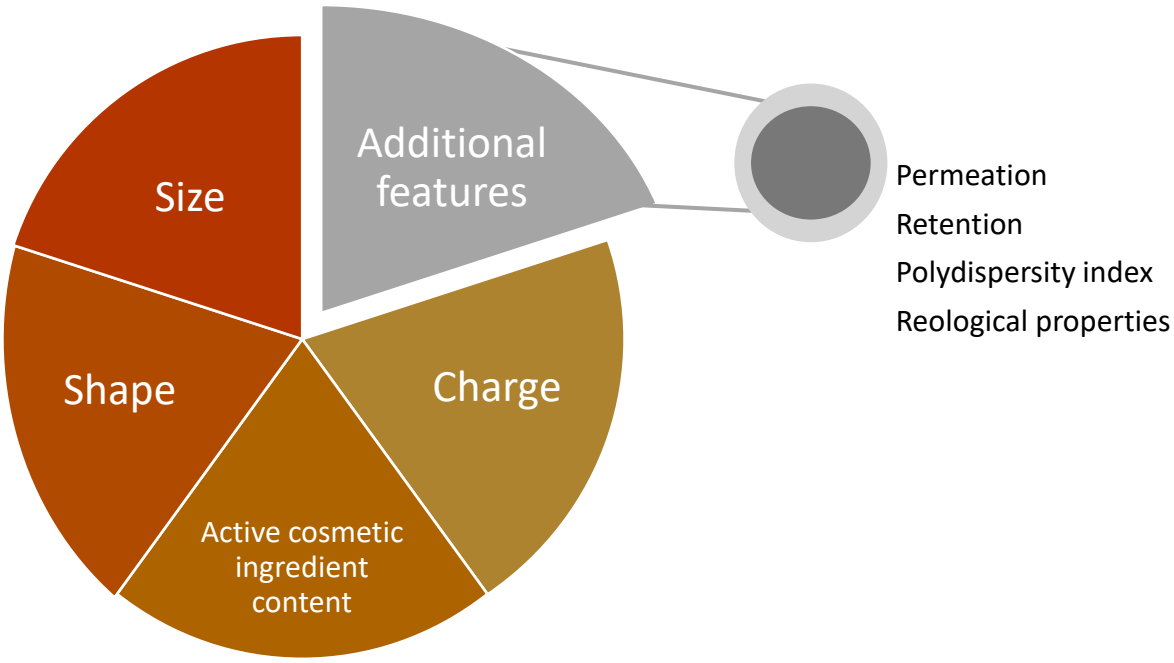

Figure 2 - Critical characteristics exhibited by NPs formulations.

2.2 Nanosystems

2.2.1 Lipid-based-nanosystems

Lipid-based NPs nanosystems comprising lipids in their composition and they show themselves to be a bet in terms of dermal carriers due to their effective active ingredient delivery and innovative dosage form. Their enhanced surface leads to an improved penetration of active ingredients into the skin tissues [29].

2.2.1.1 Lipid nanoparticles

i. Solid lipid nanoparticles and nanostructured lipid carriers

This group of nanosystems has received a growing attention since they show above mentioned attractive features. Solid Lipid Nanoparticles (SLNs) are the first generation of lipid-based NPs, mainly constituted by solid lipids, with attributes of controlled release and lower probability of skin damage due the lower quantity of active ingredient immediately released to the skin [30]. At room temperature, the used lipids are in the solid state, assisting the active ingredients encapsulation and release. The efficiency of SLNs strongly depends on different factors, such as the manufacturing method and physicochemical properties of the active ingredient, namely its lipophilicity [31]. The intimate contact among SLNs and the skin, results in their greater ability to penetrate into the *stratum corneum* [30]. During the SLNs storage, crystalline structure rearrangements, to a more ordered and stable form, reduces matrix imperfections and so the space to accommodate the interest active ingredient, leading to its loss or scape. To overcome this issue, a second generation of lipid-based NPs was developed, the Nanostructured Lipid Carriers (NLCs). NLCs are constituted by a combination of solid and liquid lipids, in which the active ingredients are entrapped. Their matrix of lipids is less organized which confers to NLCs stable properties, less possibility of active ingredients leaking and lower toxicity [32].

2.2.1.2 Vesicular systems

i. Liposomes, Ultrasomes, Photosomes and Nanosomes

Liposomes are organic NPs in which the aqueous core is surrounded by a phospholipid bilayer. Their external lipid bilayer enables hydrophobic active ingredients transport, while the hydrophilic active ingredients are confined in their core. This formulation entails a set of strategic advantages to the cosmetic products, like higher solubility of the ACI, higher biocompatibility towards the skin tissues, lower level of degradation and accumulation in the tissue, associated to a more controlled-release and lower doses use [33].

Ultrasomes are liposomes with a *Micrococcus luteus* endonuclease encapsulated. The incorporation of this enzyme allows the elimination the harmful effect of the UV radiation in skin DNA. It also inhibits the expression of pro-inflammatory cytokines, as tumor necrosis factor (TNF-α) and interleukines-1 (IL-I), IL-6 and IL-8. Similarly, photosomes are liposomes integrated in sunscreen products, where photolysis enzymes are encapsulated and released. These repair enzymes are able to prevent UV-induced DNA damages [34, 35].

Nanosomes are a smaller kind of liposomes with the ability to associate with larger molecules after penetration into tissues. This way, these nanosystems allow a more effective penetration into the skin. In addition, these NPs do not transport specific substances with insecure effects, as fragrances, chemical preservatives, among others [24].

ii. Niosomes

These NPs are very similar to liposomes in their structure. The difference lies with a nonionic surfactant insert in their bilayer, instead of some phospholipids. It is commonly incorporated with cholesterol or polyethylene glycol (PEG), which are responsible for the higher rigidity of its membrane, increased stability and mechanical properties [36]. Niosomes are composed by a hydrophilic core and a hydrophobic bilayer region. Thus, those nanosystems may carry both hydrophobic and hydrophilic ingredients, and are, for that reason, a great bet in active ingredient delivery applications [37].

Niosomes are used since the 80's, due to their capacity to incorporate biomacromolecules, like proteins, low toxicity and high compatibility towards the human tissues. These nanosystems have been highly used in chemotherapy treatments, for their lower cost and improved storage stability, compared with liposomes [38, 39].

iii. Ethosomes

Ethosomes, which size ranges between 30 nm to microns, are NPs with special features, as they can penetrate into the intact *stratum corneum*, allowing a profitable active ingredient delivery, whether it is a hydrophobic or a hydrophilic molecule. These vesicles, mostly made up of phospholipids, ethanol and water, are characterized for their deformable structure [40]. There are three types of ethosomes: classical, binary and transethosomes. The first ones consist of an improvement in liposomes design, introducing phospholipids and a high 45 % w/w of ethanol, revealing more entrapment capacity and better transdermal delivery. Binary ethosomes differ in the introduction of another alcohol, instead of ethanol. Finally, transethosomes are the ultimate generation of ethosomes. Their formulation includes a surfactant to improve vesicles penetration [41].

Their deep penetration and distribution are thought to be provided by phospholipids and high concentration of ethanol: the lipid bilayer is fluidized by ethanol, which, combined with alterations of the lipid structure in the skin, allows a release of the active ingredients in

the deeper layers. Their large applications are due to their simply manufacture, efficacy in the delivery associated with an increased level of safety [42].

iv. Transfersomes

Transfersomes are NPs composed by an aqueous core inside a lipid bilayer with edge activators incorporated. Those vesicles are recognized as deformable liposomes constituted by phospholipids, so they have the attribute of deformability throughout the tissues, penetrating the skin under the influence of the water gradient and accumulating in the subcutaneous tissue, promoting active ingredient deposition. Their increased flexibility through tissues is set by a number of edge activators as Tweens, sodium cholate, dipotassium glycyrrhizinate or Spans, which are surfactants with one chain, that acts by disrupting the lipid bilayer [43, 44].

These vesicles exhibit increased biocompatibility, additionally to their flexible features, that make transfersomes a valuable nanocarrier. Transfersomes have the possibility of delivery low as well as high molecular weight molecules, with the ability to protect them from degradation hurdles and control substance active delivery. Furthermore, their hydrophobic and hydrophilic features allow them to carry molecules with different levels of solubility. Transfersomes also present a relatively simple manufacturing, with the advantage of no need of additives [45, 46].

2.2.1.3 Cubosomes

Cubosomes are colloidal nanosystems whose lipids are organized into some 3D structured bi-continuous bilayers, as honeycombs architecture. They present, this way, an increased specific area, though preserving their sustained release feature. Their core is split into two aqueous canals, sustaining the interest substance to be carried.

These NPs present lower viscosity and their distinct structure seem to be responsible for the design of formulations with specific functions. In fact, due to their unique attributes, whether is sustained active ingredients release or targeting delivery, increased storage life and thermodynamic stability, cubosomes engineering is growing, as they appear to be a promising tool for pharmaceutical and cosmetic formulations [47, 48].

2.2.1.4 Nanoemulsions

This kind of nanosystems constitute a droplet size emulsion, on a range of 20 nm to 500 nm. These systems are thermodynamically unstable, requiring the use of a surfactant and cosurfactant. Nanoemulsions are unstable systems which need energy to be formed. This energy arises from low energy methods or condensation (internal sources), and from high energy methods or dispersion (external sources).

When compared to microemulsions, nanoemulsions are preferred due to the lower level of surfactant needed. These nanosystems have also become a strategy to the cosmetic industry because of the diminished level of toxicity and viscosity. The droplet size ensures a profit contact with the *stratum corneum* and thereby improves the efficacy of the active ingredients [49].

2.2.2 Polymeric-based nanoparticles

2.2.2.1 Polymeric nanoparticles

Polymeric NPs are constituted of a biocompatible polymer, evidencing a diameter between 200 to 300 nm. The encapsulation mechanism, the chemical and viscosity properties of ingredients, the size and active ingredient-release behavior seem to be the main responsible features affecting the extent of the active ingredients delivery. The interest of polymeric NPs is based on their ability to change the active ingredients physicochemical features, controlling, this way, their efficacy. These NPs presents themselves as "container of lipophilic drugs" and constitute a way of control their liberation mechanisms and retention time in skin [50, 51].

Several polymers can be applied in the formulation of polymeric NPs. Chitosan is widely used natural biopolymer used in nanotechnology, composed of β-(1-4)-linked D-glucosamine and N-acetyl D-glucosamine. Is it obtained from deacetylation of chitin, mostly found in crustaceans' skeleton [52]. Its interest rests in its renewability, biocompatibility and biodegradability properties, as well as in its wound-healing and antimicrobial features. This cationic polysaccharide can bound to proteins, lipids, nucleic acids, and metal ions and shows a great spectrum of antibacterial activity against bacteria, fungi and viruses, which depends on temperature, pH, level of deacetylation and molecular weight. The fact that is a weak base allows chitosan to bound to carboxylic groups, resulting in a salt formation. In this sense, it can bind to hyaluronic acid, a great notice to cosmetic products [53, 54].

i. Nanocapsules

Nanocapsules are capsules constituted of an oily or water core, surrounded by a polymeric wall. If presenting an oily core, it can be composed by a mixture of solid and liquid lipids or just liquid lipids. Nanocapsules are commonly produced as a colloidal suspension that can be incorporated into powders or gels in a way to promote physical stability. The structure of these NPs confers advantages to the cosmetic products. In this sense, their narrow size facilitates a better penetration into the target tissues and the surface changes encourages a longer effect, as well as leading to an improved recognition of the target site. The resulting nanostructure is responsible for the controlled release of the substance and lower adverse effects at the site of action [55].

ii. Nanospheres

Nanospheres are NPs specially designed to reach the deepest layers of skin. They are mainly made of a matrix, which entails great possibilities of application in the cosmetic field. In fact, they are reported to enhance the lipophilic substances delivery which, added to their singular structure containing interstitial space, implies a more effective action [56, 57].

2.2.2.2 Nanofibers

Nanofibers are NPs with potential cosmetics applications. Their diameter, reaching 500 nm, great surface area and porous structure make them a unique choice to deliver ACIs, whether hydrophobic or hydrophilic. Nanofibers can be produced from natural (collagen, silk, chitosan) or synthetic polymers like poly (lactic-co-glycolic acid) (PLGA), poly (vinyl alcohol) (PVA) or polyvinyl pyrrolidone (PVP) and their efficiency is dependent upon their porosity, morphology, polymer type and size [58].

2.2.2.3 Dendrimers

Dendrimers consist in an architecture composed of a core, from which symmetric units are built, typically, in a spherical form. This structure is the main responsible for dendrimers versatility. In fact, it is possible to manipulate their architecture and consequently their properties to obtain the desired features. The functional groups, linked to the periphery units, allow the changing of their characteristics [59].

The ACIs are entrapped in the dendrimer core, becoming the principal feature that makes dendrimers a good option for obtaining new formulations in cosmetics field. In fact, this mechanism enables molecules dissolution in water and the mix of both hydrophilic and hydrophobic ACIs. This is of value, since there is no need to add any dissolution promoting excipients or organic solvents and, at the same time, prevents the alleged water degradation. The entrapment capacity is also important to enhance the stability and dermal permeation of molecules [60].

2.2.3 Metal-based nanoparticles

NPs can integrate inorganic compounds, such as metals, nonmetals and metal oxides and their uses include, e.g., herbal products, sunscreens, hair cosmetics and make-up. The most used inorganic NPs in cosmetic compounds are detailed next [61].

2.2.3.1 Silver nanoparticles

Silver NPs (AgNPs) have been widely used in many consumer products, particularly due to its antimicrobial and antifungal spectrum of activity. Since antimicrobial resistance has been shown to be a great matter of discussion, AgNPs appear to be an effective alternative to this health issue. The antibacterial mechanism of action is based on a modification in the cell wall permeability associated to an assumed bactericidal activity. Inside the bacterial cell, the silver ions interact with the respiratory chain with an increase of reactive oxygen species (ROSs) production and, consequently, inhibition of growth; also, it can be seen a binding of AgNPs to the phosphorous and sulfur groups of DNA with consequent unwinding and loss of transcriptional and translation mechanisms. It is observed an inversional proportional behavior between the antimicrobial activity and AgNPs size: the effectiveness grows with the decrease of AgNPs size, since smaller NPs evidence higher contact surface.

AgNPs can be broadly found in different cosmetic products, as toothpastes, creams, soaps, lotions or deodorants [62, 63].

2.2.3.2 Gold nanoparticles

Gold NPs (AuNPs) are gaining the interest of the researchers due to their broad range of applications. In fact, AuNPs are associated to dermal substances delivery and biomedical

engineering, which is owned o AuNPs chemical and physical features, namely the manipulation of their size and form and the presumable nontoxicity.

The ability to deliver molecules through the skin makes AuNPs an attractive technology to the cosmetic industry. Their penetration into the *stratum corneum* strongly depends on their shape, chemical surface and compatibility with the skin lipids domains and size, as smaller NPs have a greater permeation through the tissues. Additionally, AuNPs present antioxidant and antimicrobial potentials, and proteasome inhibitory activity [64, 65].

2.2.3.3 Titanium oxide and zinc oxide nanoparticles

Titanium oxide (TiO_2) and zinc oxide (ZnO) NPs have been successfully incorporated in various cosmetic products as UV filters. In fact, TiO_2 is responsible for reflecting UVB radiation, whereas ZnO has the capacity of reflecting UVA radiation. The combined use of these two oxides reveals a more profit protection against sun radiation, alongside with optimal characteristics, like the transparency, the spreadability and better texture, without skin irritation, which is normally a consequence of chemical UV filters [66, 67]. ZnO has also proved to be an attractive option to the cosmetic and pharmaceutical industries, due to its antimicrobial property. Its antimicrobial activity is owed to the production of ROSs, followed by the release of Zn^{2+}, cytotoxic to the bacteria, and destabilization of the cell walls. This way, the association with TiO_2 shows a synergistic activity. However, ZnO NPs effectiveness is largely dependent on the ingredients used in topical formulations, since they can interact and minimize the ZnO antimicrobial activity, like antioxidants or EDTA [68].

2.2.3.4 Silica nanoparticles

The incorporation of silica in cosmetics through the use of NPs has seen a tremendous growth. Silica NPs present low levels of toxicity, pleasant touch and capacity to deliver lipophilic and hydrophilic substances to their site of action, by encapsulation [69].Silica NPs can be found in toothpaste, makeup products, hair styling, deodorants and skin care. They present functions as emulsifiers, emollients and water barriers, having the particularity of improving sun protection since they enhance the spread ability of sunscreen products and minimize their phototoxicity or degradation [35, 70].

2.2.4 Additional nanosystems

2.2.4.1 Nanocrystals

Nanocrystals are a promising type of NPs due to their unique characteristics. They are made uniquely by the active ingredient and a stabilizer, in a process of milling bulk material until it reaches sizes in the nano scale. The increased size and enhanced solubility, typical of these NPs, leads to a greater dissolution velocity and improved concentration gradient. This latter is responsible for a more profit diffusion of the active ingredients through the tissues. The greater surface promotes a bigger adhesiveness with consequently superior retention time at the site of action [71, 72].

2.2.4.2 Fullerenes

Fullerene is a spherical molecule, in which the disposition of its 60 atoms of carbon resembles a soccer ball. Although other types of fullerene (C_{70}, C_{76}, C_{84}, C_{90}, C_{28} and C_{36}) can be pointed in the various fields of science, the most used is C60, mainly due to its stability.

Fullerene presents itself as an electron acceptor and so its power to bound to free radicals makes it a powerful antioxidant. It has been the object in several of studies where its presence, in skin whitening products and sunscreens, was evaluated. In this sense, fullerene can minimize morphological alterations in cells, apoptosis and melanogenesis. Additionally, it can act like a skin protector since it inhibits keratinocyte differentiation. Its antioxidant effect can also reportedly be used as a hair grow promoter once hair loss may be caused by oxidative stress. Fullerene has also the ability to penetrate the epidermis. Thus, it can be used as a carrier for ACIs, namely, in the treatment of acne, since it also can reduce the sebum production and has antimicrobial properties against *Propionibacterium acne* [73, 74].

2.2.4.3 Nanodiamonds

Nanodiamonds consist of a diamond core with functional groups in the surface, and its medium size reaches 5 nm. Nanodiamonds are specially recognized by their biocompatibility and stability, mostly achieved by the oxygen groups bounded to the surface.

Nanodiamonds can act like nanosystems of ACIs since they promote a better permeation into the skin tissues, which is mainly achieved by their particle size. Additionally, they can function like a pool for the active ingredients, allowing a higher skin penetration.

These NPs apparently have UV filter activity through scattering and radiation absorbing, and antioxidant properties [75, 76].

2.2.4.4 Cyclodextrins

Cyclodextrins belong to the cyclic oligosaccharides class which contains glucopyranose units linked by α-(1,4) bonds. It can be pointed 3 types of cyclodextrins of natural origin: with 6, 7 and 8 glucopyranose units, respectively, α, β or ∂-cyclodextrins. Their structure is composed by a lipophilic central cavity and a hydrophilic outer surface due to the presence of hydrogen and oxygen bridges. Cyclodextrins are characterized by their ability to form complexes with various active ingredients, involving the active ingredient in the lipophilic center.

Their use in cosmetics products is related with the prevention of oxidation mechanisms and its harmful effects to the skin. The complex limits the production of degradation products and promotes the stability of volatile compounds. This latter feature is useful in perfumes, since it extends their effects. These complexes also act in the removal of odor and, thus, can be used in deodorants. The production of hydroxyacetone from the complexes is utilized as a tanning product, promoting a good-looking tanning [77].

Table I - Schematic representation of the different nanosystems types used in nanocosmetic formulations

Nanoparticles in cosmetics	Lipid-based nanoparticles	Vesicular systems	Liposomes Ultrasomes Photosomes Nanosomes Niosomes Ethosomes Transfersomes
		Cubosomes	
		Nanoemulsions	
		Lipid nanoparticles	Solid lipid nanoparticles Nanostructured lipid carriers
	Polymeric-based nanoparticles	Polymeric nanoparticles	Nanocapsules Nanospheres
		Nanofibers	
		Dendrimers	
	Metal-based nanoparticles	Silver nanoparticles Gold nanoparticles Zinc Oxide nanoparticles and Titanium Oxide nanoparticles	
	Additional nanosystems	Nanocrystals Fullerenes Nanodiamonds Cyclodextrins	

2.3 Preparation Methods

Generally, preparation methods of nanosystems are often classified in two groups, bottom-up and top-down techniques. The latter consists of a process in which the nanostructures are produced from particles with higher proportions, scaling back them into nanosized dimensions, with the desired features. The technique requires, thus, a vast amount of energy to exceed the internal forces. Top-down methods can be either physical, as photolithography, interference lithography, electron beam lithography, nano stencil lithography, nanoimprint lithography and nanosphere lithography, high-pressure

homogenization, milling; or chemical, which consists of employing input of energy of chemical reactions [78, 79].

Contrary, bottom-up techniques consist in the production of nanosized assembly molecules, from atomic or molecular compounds, allowing no waste of materials, and modest energy input is required. Examples of this method are atomic layer deposition, sol-gel nanofabrication, evaporative precipitation, molecular self-assembly [80], sonoprecipitation and spray drying [81]. Some of these techniques are summarized in Fig. 3. Other methods include thin-film hydration, reverse-phase evaporation, transmembrane pH-gradient [41] and rotary evaporation-sonication method [82].

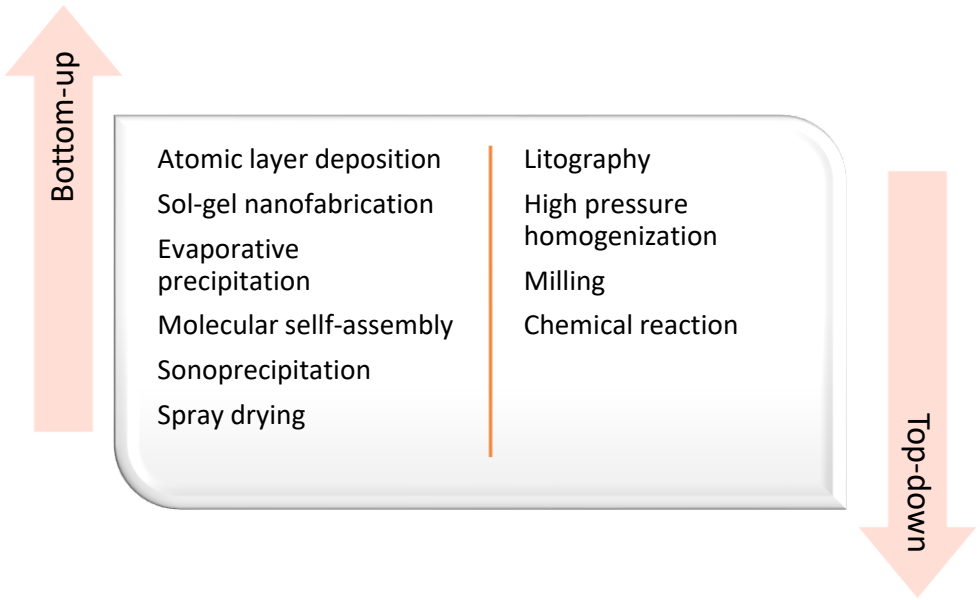

Figure 3 - Bottom-up and Top-down manufacturing approaches used in the manufacturing of nanosystems

Both methods have their advantages and disadvantages. For example, bottom-up approaches allow an improved control over the desire features, like morphology or size, in Both methods have their advantages and disadvantages. For example, bottom-up approaches allow an improved control over the desire features, like morphology or size, in comparison with top-down approaches, however, those can present low income. On the other hand, top-down methods like milling are easier to scale-up but others like high-pressure homogenization can lead to operational issues due to the enormous temperature and pressure required. It should be noticed that the selected method may have impact in the final formulation, and likely issues as active ingredients degradation [75]. High pressure homogenization method has been described as the most advantageous in NPs manufacturing, namely regarding SLNs and NLCs.

This technique is widely used in pharmaceutical industries, so it does not present regulatory issues in its use, beyond the escaping from organic solvents and the ease to scale-up [76].

3. Nanotechnology-based cosmetic formulations

In this section the applications of nanomaterials in cosmetics are described, having in mind their function in the different presented formulations. These nanostructures are present in a great number of cosmetic products, enhancing the penetration of anti-aging or skin-whitening ACIs, promoting make-up long last effects, as carriers for antibacterial ACIs in deodorants or even being part of UV protection products.

In Fig. 4 the opportunities and challenges of NPs incorporation in cosmetic formulations are described. Industries with cosmetic patents containing NPs are represented in Table 2.

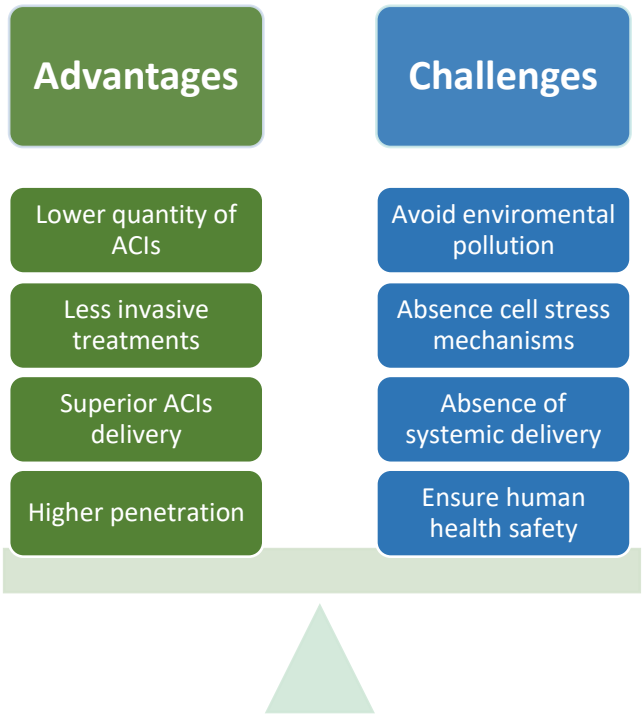

Figure 4 - Advantages and challenges of nanocosmetics formulations

3.1 Beautifying effect

So *et al.* described the use of SLNs in whitening skin cosmetics. 6-methyl-3-phenethyl-3,4-dihydro-1H-quinazoline-2-thione (JSH18) is a tyrosinase inhibitor with recognized depigmentation properties. In this sense, a molecule of this compound was incorporated in

SLNs to evaluate the inhibition of melanin synthesis and its application in topical formulations. After 7 days of UV radiation exposure and application of the formulation described during 4 days, the skin was evaluated by using reflectance spectrophotometry, showing a total recover of sun induced pigments [83]. Jiménez *et al.* also studied the effects of NPs with *Panax ginseng* extract incorporated in whitening cosmetic products. This plant is known for its antioxidant and antiaging properties and it was incorporated in synthetized AuNPs. Then, the whitening properties were investigated, and tyrosinase activity and melanin synthesis of skin melanoma cells have shown meaningfully reduced levels [84], proposing their use in cosmetic applications.

Other studies suggest the use of arbutin carried by chitosan NPs [85]. α and β-arbutin are known for their skin-whitening properties, through the inhibition of extreme melanin production. Chitosan NPs revealed themselves to be promising nanosystems for arbutin molecules in topical formulations, with great stability capabilities. Ethosomes and transfersomes [86] were also the subject of a skin-whitening formulation investigation entrapping linoleic acid. The lipid composition of both NPs allowed a good permeation and accumulation in the *stratum corneum* of the ACI, traveling through corneocytes channels. Although the higher delivery ability of the ethosomes, both NPs are found as capable nanosystems for linoleic acid for hyperpigmentation skin disorders.

NPs have also become an interesting technology approach on makeup products. Avon® [87] has launched a gel formulation containing TiO_2 NPs and color pigments which, when applied into the skin, forms a film with space filling and optical properties. It changes the refraction and diffusion of the light on the skin, becoming a tool to conceal wrinkles and skin spots, while presenting a natural looking. Guangzhou Jujike Green Chemical Common Tech Institute [88] has patented an eye mascara containing NPs with Fe_2O_3 core, presenting lipophilic and hydrophobic properties, which has showed water and sweat proof desired ends, promoting a long-lasting effect.

Hiroyuki *et al.* [89] described a solution to minimize the skin sebum production increasing make-up effects. A biocompatible polymeric NP containing a sebum production inhibitor was developed, so that this ACI could reach the skin pores. In this sense, glycyrrhetinic acid was encapsulated in chitosan NPs surface treated with silicone as a hydrophobic agent. As the biocompatible polymer is degraded, the ACI is continuously liberated, and the sebum production inhibition is prolonged. The use of a hydrophobic agent is extremely important to increase the affinity with the skin. This composition, integrated in skin foundations, prevents the collapse of make-up.

The use of nanotechnology in lip care has also been patented. Hyun *et al.* [90] reported a solution to lip care issues related to toxic pigments originally used. Cosmetic pigments

including Au e AgNPs used in lipstick show a broad spectrum of colors, innocuous to the skin. In this invention, AgNPs exhibited yellow color and AuNPs exhibited red color. The mixture of both NPs, depending on the ratio of each, can form a wide variety of colors according to the visible light spectrum.

Researches have been made to access the application of nanotechnology in nail care. Lau *et al.* [91] defined NPs generated by laser as a method to color traditional nail vanish. This method allows the incorporation of metal NPs in viscous environment like nail polish. This way, metal NPs properties can be applied in cosmetic product, conferring optical effects, durability of color, hardness and resistance to harm, or even antibacterial effects.

3.2 Dental care

NPs can be used in dental care formulations, so that the invasive procedures can be minimized. Malarkodi *et al.* [92] described the synthesis of zinc sulfide (ZnS) and cadmium sulfide (CdS) NPs with antimicrobial activity to pathogens responsible for dental disorders like *Candida albicans, Streptococcus sp., Lactobacillus sp., and Staphylococcus sp.* The synthesis of these NPs used a reducing agent, *K. pneumoniae*, which reduced sulphate into sulphide and was also responsible for NPs stabilization. This finding suggested the incorporation of these NPs in dental devices, mainly due to its biocompatibility, green manufacturing methods and non-toxicity.

Nanotechnology has been presented as an alternative to the invasive treatments of diseased pulp in teeth [93]. The original procedure has shown great limitations, especially due to reinfection by Gutta percha, the main filler material utilized so far. Nanodiamonds revealed to be a great solution to overcome the issue mentioned above. Lee *et al.* have described the development of Gutta percha embedded in nanodiamonds containing amoxicillin, a commonly applied antibiotic in endodontic infection. This formulation has demonstrated to be effective, with bacterial inhibition, and promising to be implemented in teeth treatments.

A liquid disinfectant containing AgNPs with different surface charges was synthesized and its antibacterial properties were compared with chlorohexidine (CHX) and sodium hypochlorite (NaOCl) [94]. minimum inhibitory concentrations (MIC) against *Enterococcus faecalis* were determined. The study revealed that positively charged of AgNPs evidenced the lowest MIC and presented less toxicity to fibroblasts, being a promising tool to be incorporated in teeth protector liquids, in a near future.

Hyun *et al.* [95] described a liquid formulation containing ferrous oxide (FeO) NPs for biofilm prevention and treatment. Since the traditional biofilms treatments are mainly made

by bactericides like CHX, those are not very effective for daily use. In fact, those have some disadvantages associated, such as teeth discoloration, pain, toxicity and stone formation. In this sense, FeONPs emerge as a substitute of CHX formulations without the limitations associated to some metal-based NPs, like bacterial resistance. FeONPs, found in elixirs, are intended to prevent the biofilm formation, inhibit bacterial growth, preventing teeth demineralization. Thus, this formulation can be the choice to oral diseases treatment, like dental caries, and it can be conjugated with hydrogen peroxide and enzymes.

NPs with whitening effect can also be added to dental care products. A toothpaste was synthesized enclosing activated carbon NPs as whitening agent [96]. The incorporation of these NPs overcome the disadvantages of peroxide and high friction, and the ones associated with traditional whitening methods utilized, as poor performance and enamel damage. The activated carbon NPs are responsible for adsorption of dental plaque.

3.3 Hair care

Studies have been developed to assess the uses of polymeric NPs as ACIs-loaded nanosystems designed towards hair follicles. Glówka *et al.* [97] described the development of polymeric NPs containing roxithromycin due to its role as hair restoring agent. These NPs were marked with a fluorescent dye to evaluate their penetration into hair follicles. The encapsulation revealed successful results, with distinctive penetration values. In fact, the roxithromycin NPs were able to achieve the hair bulb, suggesting their application in hair loss.

Because of the importance of hair presentation to self-esteem, anti-hair loss formulations have been patented [98]. It has been described the use of AuNP as hair growth promoter and its applications in hair formulations. In this invention, AuNPs are dispersed in an oil, forming a plate. These NPs promote blood circulation, stimulating the scalp, but also hormone secretion and cell division. This way, hair growth is stimulated, and its loss is prevented. This development is of great value since baldness is many times owned to a stressful way of life, besides its genetic complement. By promoting the hair growth, the new hair becomes stronger and so, the loss, due to the hair thickness, can be prevented. Other patented invention relates to a NP containing fermented extract, in a calcium alginate hydrogel, with hair growth properties [99]. These properties are enhanced by its biological permeability. The extract is constituted by natural products such as ginger and vinegar, ginger root and coconut oil.

Substances like silicone have major lubrification and preservation attributes, applicable to hair. However, they find some difficulties related to their absorption, due to its

hydrophobicity. Nanotechnology has the power to overcome these issues. Hu *et al.* reported [100] a study in which silicone oil was entrapped in stable O/W nanoemulsions, prepared with Tween 80 and Span 80 as surfactants. After the application of shampoo, with and without silicone nanoemulsions, the hair was analyzed. It was possible to observe that the weight percentage of silicone was enhanced in the hair treated with silicone nanoemulsions and this quantity increased with decrease of the nanoemulsions particle size. The decrease of particle size allows a greater interaction between nanoemulsions droplets, leading to an improve silicone oil disposal. Moreover, this disposal was not affected by temperature and time of storage, which proves the stability conferred by the nanoemulsions, which was not verified in control groups, experiencing decreases in silicone oil absorption.

3.4 Skin care

Chen *et al.* [101] studied the delivery into *stratum corneum* of vitamin E, resveratrol and epigallocatechin gallate, encapsulated in SLNs and NLCs. The delivery of these antioxidants can be challenging due to their restricted skin permeability, photodegradation and low water solubility.The investigation falls on establishing if these NPs are adequate carriers for these actives, overcoming traditional delivery issues. In fact, in traditional carriers there is not a controlled release of the ACIs, making them to be released practically at once, causing skin irritation with low effectiveness, and the product must be used few times a day. SLNs and NLCs were found to present increased encapsulation levels as well as improved protection of the ACIs. The formulations exhibited high levels of stability and uniformity, and the penetration showed improved levels. The release study presented a controlled release of 70% after 24 h for resveratrol, suggesting these NPs as suitable carriers for skin care antiaging ACIs.

Other investigations took place to ascertain the power of nanoemulsions in skin care products. El-Leithy *et al.* [102] suggested the use of Coenzyme Q10 (CoQ10) delivered by nanoemulsions to verify its influence as an antiaging product. Since CoQ10 presents low permeability levels, being an insoluble antioxidant, but with excellent anti-wrinkles properties, its penetration in *stratum corneum* was investigated in an O/W nanoemulsion formulation. An animal model was used to assess the antiwrinkle efficiency and the studies showed high release levels of the ACI in 24 h. The later analyses revealed a decrease in skin wrinkles and less hyperkeratosis and parakeratosis in the epidermis as well as inexistence of hyalinization in collagen fibers. These findings suggest the nanoemulsions as potential carriers of CoQ10 in topical formulations for antiaging care, improving its permeability and solubility.

Another study was based on the assessment of use of transfersomes as carriers for hyaluronic acid and epigallocatechin gallate in anti-aging skin formulations [103]. Thus, transfersomes were synthetized using high-pressure homogenization and were then characterized. Human keratinocytes were chosen to assess ROSs levels, lipid peroxidation, cell viability and matrix metalloproteinases 2 and 9, responsible for collagen degradation. All these features were found to be minimized with the use of transfersomes, along with the enhancement of skin permeation and deposition of the mentioned ACIs.

3.5 Deodorant

Deodorant products have seen their development comprising nanotechnology. There is an invention containing carbon-based NPs, to substitute the traditional odor removals, whether chemical, physico-chemical, biochemical and sensory. This method is able to sterilize the bacteria action, with great odor masking [104]. Another invention relates to a deodorant composed by Ag-TiO_2 NPs with antibacterial and deodorant activity [105]. This invention makes use of the features of inorganic antibacterial agents, as good dispersibility, heat resistance and stability. These NPs consist of a shell structure containing Ag and TiO_2, because the latter antibacterial activity is suspended without light exposure, as happens with coats, though coating of AgNPs increases its stability. Thus, there were synthesized AgNPs coated by TiO_2 that shows great antibacterial deodorizing features.

A method to release fragrances in cosmetics products, such as deodorants, was studied by Hosseinkhani *et al.* [106]. Fragrance molecules usual present low aqueous solubility and stability, which limits their use. To overcome this issue, an encapsulation strategy as a release system was developed to minimize the evaporation of the volatile fragrances molecules and, consequently, greater duration of their sensatory features. In this sense, the perfume molecules were entrapped in polymeric NPs and its applicability in the axillary microbiome was evaluated. The polymer chosen was poly-L-lactic acid (PLA) and the nanocapsules were prepared with about 115 nm of diameter. Chlorobenzene and fluorescein were the hydrophobic compounds used as model. The study revealed no harm to the axillary microbiome and a sustained release of the perfume molecules, which suggests the application of polymeric nanocapsules as an excellent alternative to apply in fragrances products as deodorants.

3.6 Sunscreen

Sunscreen belongs to a vast field of cosmetics in which the development of nanotechnology has seen a tremendous growth. Many studies have been published to evaluate nanosystems applicability in this type of product. In this respect, Shetty *et al.* [107] described the incorporation of morin polymeric NPs into sunscreen. Morin is a natural flavonoid with antioxidant and UV-protection activity. In this sense, PLGA polymeric NPs comprising morin were developed. The NPs were found to be spherical, with about 100 nm of diameter. They showed great *in vitro* results related to antioxidant activity and skin deposition and permeation, when compared to morin plain form. The creams comprising these NPs were produced and their evaluation indicated marked UV protection values, along with great deposition of morin, without cytotoxicity to the cells. These outstanding results confirm the value of these optimized NPs in sunscreens formulations.

Borase *et al.* studied [108] the potential use of phytolatex AuNPs in sunscreens as a way to improve the protection factor. The phytolatex derived from *Jatropha gossypifolia* were used in the synthesis of AuNPs, to substitute chemical reducers, and these were then characterized, including the UV protection factor. The NPs were incorporated in commercialized sunscreen without metal NPs in their original formula and their use was evaluated. The NPs incorporation increased more than 20% the sun protection factor. The mechanism beyond rests in the scattering and reflection of sun radiation by AuNPs. This research allows to conclude that AuNPs revealed themselves to be a remarkable technology to use in sunscreens formulations, as an alternative to chemical agents and their associated hazards effects.

Other research discusses the encapsulation of *padimate-O* in bioadhesive NPs (BNPs) to improve sun protection [109]. Many of the hazards associated to sunscreens are related to their ability to reach the epidermal cells and follicles. In this research, this deposition is preventable by the bioadhesive properties of the referred NPs. BNPs ease adherence to the skin but avoid the penetration into the hair follicles and prevents ROS toxicity, while holding water resistance. When compared to commercial models in two murine models, the UV protection was higher, along with decline in DNA chain breaks, preventing the sun induced damage.

Nanotechnology-based sunscreens have been patented. This invention relates to a polymeric NP comprising an organic UV blocker. The polymeric NP increases its stability and dispersibility; at the same time, it prevents the penetration of the UV blocker into the *stratum corneum* and, consequently, skin irritation [110].

Table 2 *- Commercialized nanocosmetic products.*

Nanotechnology-based cosmetic formulations				
Cosmetic action	Nanotechnology	Active Cosmetic Ingredient	Cosmetic Application	Brand & Reference
Beautifying				
	Niosomes	Panax ginseng	Skin-whitening	*Laome Cosmetics*®[111]
	Nanocapsules	Vitamin E	Lip treatment	*Lâncome*® [112]
	Polymeric NPs	-	Nail lacquer	*ARTDECO*®[112]
Hair care				
	Niosomes	-	Hair mask	*Identik*® [112]
	Nanoemulsions	Red Vine polyphenols	Hair protector	*Korres*® [111]
Skin Care				
	Carbon-based NPs	Fullerenes	Anti-aging cream	*Bella pelle*® [18]
	Nanocapsules	α-linoleic acid	Anti-aging cream	*Lâncome*® [113]
	Nanosomes	Pro-retinol A	Anti-wrinkle cream	*L'Oreal*® [113]
Deodorant				
	-	Benzalkonium chloride	Roll-on	*Lion Corporation*® [112]
Sunscreen				
	-	UV-filters	Makeup base	*Dior*® [113]
	Inorganic NPs	TiO_2/ZnO	Powder sunscreen	*Innovative*® *Skincare* [112]

4. Toxicological aspects

4.1. Human safety issues

The use of nanotechnology in cosmetic products is recognized as a tremendous strategy due to all its advantages described above. However, there are some toxicological aspects towards human health that need to be considered.

Borowska *et al.* [61] have reviewed the risk factors associated to the use of metal-based NPs in cosmetics products. Even though the presence of several advantages, the potential risks exist and those are related to the exhibited small size that allows them to better penetrate the skin and reach the blood stream. Here, the threat effects come from the NP path to the various organs. Cosmetic preparations enter in the organism through topical

formulations, but they can also be inhaled, as it happens with sprays. Metal-based NPs, like the TiO_2 NPs, reportedly induce cytokine secretion, leading to inflammatory processes and possible necrosis, which mainly depends on their concentration in cosmetics.

A research seeking the biological effects of AgNPs took place [114]. The hazard effect of 15 nm of AgNPs coated by PVP, on epidermal keratinocytes, was evaluated. After the exposure to different concentrations of these NPs, the metabolic activity and cell viability were characterized, and a diminished effect of these biological activities was observed, apart from a migratory effect. Furthermore, it was concluded that the continuous exposure could lead to DNA damage and caspase-3 and 7 activation.

TiO_2 NPs applicability has seen an extensive growth in cosmetics products, especially due to their biologically inert activity, which makes them a target to many toxicological studies [115]. This kind of NP has reportedly been part of oxidative stress induced processes, although the exact mechanisms remain unclear. In this sense, the negative effects of TiO_2NPs were assessed in human keratinocyte. It became clear that, although these NPs have no effect on cell death mechanism, they might alter the mitochondrial function. In about 268 metabolites identified, 85 associated to cellular stress were changed. It must be taken into account that this exposure only had the duration of 24 h, which may not be enough to properly evaluate this issue. Due to the significant metabolic results, extensive studies should be made in this matter.

ZnO NPs toxicity has also been the subject of many studies. Their toxicity mechanisms in sunscreens have been reviewed by Hackenberg *et al.* [116]. ZnO NPs show genotoxic potential to epidermal cells at low concentrations (0,8 μg/ml) and are responsible for changes in mitochondrial processes, cell cycle and cell morphology in concentrations of about 10 μg/ml. The toxic effects can also be seen in skin fibroblasts and cells belonging to nasal mucosa. It was found that cytotoxicity effects of ZnO NPs were increased in carcinoma cells exposed to UV radiation.

Another study concerning ZnO NPs was conducted by Ilves *et al.* [117]. ZnO NPs and bulk-sized ZnO were put in contact with injured skin in an atopic dermatitis prototype. As predicted, ZnO NPs might access the deep layers of skin, contrary to bulk-sized ZnO, and are found to encourage production of IgE antibodies, systemically, which shows that formulations containing these NPs promotes allergic effects on skin, although they suppress inflammatory activities.

Although all the negatives effects, ways exist to overcome these concerns. For example, Chang *et al.* reported a study contemplating the cytotoxicity of TiO_2 NPs comprising fatty acids usually incorporated in cosmetics, as palmitic acid, palmitoleic acid, oleic acid and

stearic acid [118]. As NPs may contact human organism through dermal or nasal exposure, human fibroblasts and adenocarcinoma cells were put in contact with the NPs. After 48 h, it was observed that the fatty acids remained intact and cytotoxicity decreased in comparison with bare TiO_2 NPs. This suggests that fatty acids play a major role in cells protection from the hazard effects of NPs.

4.2 Environmental safety issues

The toxicological effects of nanotechnology incorporated in cosmetics products have been reviewed by Sajid *et al.* [119]. The particle size, surface charge and chemical reactivity of the NPs are in the origin of toxic pathways, with ROSs production, consequently with damage to DNA and cell organelles.

The incorporation of nanotechnology in sunscreen has been a major step towards skin protection, but it entails unsafe mechanisms for aquatic environments [120]. TiO_2 and ZnO NPs, the most commonly NPs used in sunscreens, are reportedly the source of hydrogen peroxide (H_2O_2) under photoexcitation. H_2O_2 is a stress inductor in phytoplankton. According to the research, 463 nM/h of H_2O_2 can be generated by 1 g of commercial sunscreens and about 4 kg of TiO_2 NPs can be released in a summer day in a Mediterranean beach, which corresponds to 270 nM/day of H_2O_2. This study complains that TiO_2 NPs are, apparently, the more important oxidizing agent in beaches.

Botta *et al.* studied the evolution of TiO_2 NPs of four sunscreens in water [121]. The concentration of this compound was analyzed and the obtained were characterized. It was possible to observe that a significant part of these NPs was released from the respective sunscreens, forming aggregates which containing about one third of the original NPs concentration. These aggregates raise environmental questions, due to the sediment formed by them, which potentially threat the subaquatic species.

Besides TiO2, AgNPs are also incorporated in cosmetics products, In this sense, the toxicity of coated AgNPs and TiO2 NPs, with and without coating, were assessed towards *Daphnia magna* [122]. Two studies were performed in parallel: a 48 h investigation was conducted to evaluate coated AgNPs, and coated and uncoated TiO_2 NPs toxicity to the specie. A 24 days study was then conducted to assess the chronic toxicity of uncoated TiO_2 NPs. In the first study, no death organism was observed with coated TiO_2 NPs, in contrast to the other NPs. Also, the reproduction and growth of *D. magna* were reduced with uncoated TiO_2 NPs, in values of about 93%, at the higher concentration. In the second study, it was

verified a delay of two or three days in the first reproduction, and the size of the broods decreased.

To evaluate the effect of sunscreens NPs in aquatic species, TiO_2 and ZnO NPs, at concentrations about 700 mg/l and 70 mg/l, respectively, were put in river water, combined and separately [123]. Only the combined addition of NPs or ZnO NPs alone provoked changes in the microbial species – the NPs aggregated and formed bigger particles, and the genus distribution was altered.

Toxicologic mechanisms of ZnO NPs have also been reviewed [124]. This NP may be a significant threat to the environment since low concentrations such 1mg/l can cause dangerous pathways. The lack of knowledge in this matter seems to be the biggest risk to assess the hazard effects of this NP on ecosystems, namely in long time exposure and bioaccumulation. ZnO NPs mechanism of action should be clarified in order to predict its toxicological steps and interactions, and impact on the environment.

Asharani *et al.* carried a toxicological study to evaluate the effects of Au, Ag and Pt-based NPs in zebrafish embryos [125]. AgNPs lead to circulatory defects with changes in cardiac morphology and ultimately, death. Both Ag and PtNPs cause hatching delays. The accumulation of AuNPs did not show any harmful results. The accumulation of these NPs and the alarming effects, as a consequence of their exposure, claims further investigations on these matters.

5. Regulatory aspects

Consumer's health should be a top issue concerning legislation. Cosmetic products have to obey Regulation European Commission (EC) n.º1223/2009 [14] to be commercialized on the European Union (EU) market. This regulation is a safeguard for consumers that cosmetic products follow restricted rules related to their quality and safety. In this sense, manufactures must follow specific requirements to develop these products and a "responsible person", a legal person chosen within the EU, guarantees the cosmetics placement on the market. The responsible person, among others, has the duty to notify, via online, the products to be marketed in the EU Cosmetic Products Notification Portal (CPNP) [126]. In this portal it is possible to find all information related to cosmetic products and it is accessible for Competent Authorities, Poison Centers, responsible persons and cosmetic distributors. Also, the responsible person must notify undesirable effects to the competent authorities. All the preservatives, colorants and UV-filters need an authorization to be used. This is also extensible

to nanomaterials. In this matter, the nanomaterials not restricted by the Cosmetic Regulation need a complete safety assessment and their presence requires the suffix "nano" in brackets labelled in the list of ingredients, following the name of the ingredient.

According to Commission Recommendation of 18 October 2011 on the definition of nanomaterial, these are defined as "natural, incidental or manufactured material containing particles in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm-100 nm". The register in the CPNP must notify the use of nanomaterials. In this sense, all nanomaterials beyond preservatives, colorants and UV-filters require a 6 months previous notification to the Portal, before putting on the market. If the EC founds concerns related to the nanomaterials safety, a risk assessment may be required by the Scientific Committee on Consumer Safety (SCCS) [127]. The posterior approval is preceded by a SCCS opinion concerning the toxicological data. In the EU, only three UV-filters containing NPs are marketed: ZnO, TiO_2 and tris-biphenyl triazine. Nano carbon black can be used as colorant.

According to the Regulation previously mentioned there is a Catalogue of Nanomaterials [128] published by the EU, containing all the nanomaterials used in cosmetic products. It is organized by sections and cosmetic categories and indicates likely exposure conditions. This Catalogue is based on the information provided in the CPNP.

The European Union Observatory for Nanomaterials (EUON) has developed two databases, accessible to consumers. NanoData [129] comprises updated information's regarding nanomaterials, their uses in the different sectors, statistics and safety concerns. eNanoMapper [130] contains toxicological data of the nanomaterials.

FDA is the responsible agency, monitoring the use of nanotechnology in cosmetic in USA. Although this agency does not have a proper definition for nanomaterials, scientist refers NPs as the particles in a size range of 1 to 100 nm. Contrarily to EU market, cosmetic ingredients do not need the FDA approval to be marketed, with the exception of colorants.

FDA Nanotechnology Task Force reported, in 2007, an assessment, concerning the regulatory and scientific aspects of products enclosing nanomaterials and made a number of recommendations on this matter [131]. As a consequence, FDA launched a guidance document "Guidance for Industry: Safety of Nanomaterials in Cosmetic Products" [132]. In this document may be seen the FDA's opinion about the use of nanomaterials in cosmetic products. This guidance is destiny to manufactures and stakeholders, so they can predict potential safety occurrences and develop solutions to overcome them.

6. Concluding remarks and future perspectives

Nanotechnology has become the major tool in the growth of the different field of science in recent years. Its application has been extended to the development of cosmetic products. In fact, pharmaceutical industry is at the forefront in what concerns patented nanotechnology due to all its advantages, namely the ease to manufacture and low costs associated.

The manufactured NPs are mainly suggested to be used as ACIs or as nanocarriers. This way distinct classifications exist for NPs: lipid-based nanosystems, polymeric-based nanosystems, metal-based nanosystems and additional nanosystems. The number of NPs currently under research clearly depict the weight that this science has on the powerful and marked cosmetic market.

NPs allow a superior penetration into the skin and a reliable delivery of ACIs, along with their biocompatibility, stability and antioxidant properties. These nanostructures can be integrated into beautifying products, anti-aging creams, skin-whitening products, make-up, nail care, dental care, products like elixirs and toothpaste, as well as deodorants and hair care. Nanosystems have been also extensively incorporated in sunscreens, improving sun protection and preventing skin damage. It is possible to associate a number of functions to NPs, whether odor masking or removing ROS from the skin.

The tremendous use of nanosystems in cosmetics lead to concerns related to their safety. Investigations have been accessed the toxicological impact for human health and environment. In fact, nanomaterials are not free from harmless, inducing dangerous mechanisms, whether in humans or ecosystems, and long-term studies should be encouraged to gather more awareness in this field.

The toxicological aspects of NPs have led to the development of regulatory procedures in Europe and US. All the ACIs used in the cosmetics manufacturing, including nanomaterials, should be reported to the competent authorities, and information regarding NPs being accessible to consumers. The tendency is to warn manufacturers and stakeholders to safety issues associated to nanomaterials, but also to create a wise society, alerted about the marketed cosmetics products.

Overall, nanosystems represent a viable and promising technology towards the obtainment of the finest formulations, as required by the demanding cosmetic industry.

7. References

1. SEARCHCIO. - **SWOT analysis (strengths, weaknesses, opportunities and threats analysis)**. [Accessed on 2018-08-15]; Available from: https://searchcio.techtarget.com/definition/SWOT-analysis-strengths-weaknesses-opportunities-and-threats-analysis
2. GLINTT. - **Consultoria de Projeto**. [Accessed on 2018-04-01]; Available from: https://www.glintt.com/pt/o-que-fazemos/ofertas/BusinessConsulting/Paginas/Consultoria-de-Projeto.aspx
3. GLINTT. - **Sifarma**. [Accessed on 2018-04-20]; Available from: https://www.glintt.com/pt/o-que-fazemos/ofertas/SoftwareSolutions/Paginas/Sifarma.aspx
4. VICHY. - **DERCOS Champô Complemento Para Tratamentos Antiqueda Estimulante**. [Accessed on 2018-04-21]; Available from: https://www.vichy.pt/capilares/champo-complemento-para-tratamentos-antiqueda-estimulante-dercos/p19206.aspx
5. SKIN. - **Ecophane Suplemento Fortificante**. [Accessed on 2018-04-21]; Available from: https://skin.pt/ecophane-suplemento-fortificante-comprimidos-60unid
6. INFARMED, I.P. - **Resumo das Características do Medicamento, Telfast 120** [Accessed on 2018-04-22]; Available from: http://app7.infarmed.pt/infomed/
7. INFARMED, I.P. - **Resumo das Característica do Medicamento, Allergodil Colírio**. [Accessed on 2018-04-21]; Available from: http://app7.infarmed.pt/infomed/.
8. BLUEPHARMA®. - **Missão, Visão e Valores**. [[Accessed on 2018-08-15]; Available from: https://www.bluepharma.pt/about-mvv.php
9. FDA. - **Food and Drug Administration**. [Accessed on 2018-08-16]; Available from: https://www.fda.gov/
10. EMA. - **European Medicines Agency**. [Accessed on 2018-08-16]; Available from: http://www.ema.europa.eu/ema/
11. ICH. - **International Conference on Harmonisation**. [Accessed on 2018-08-16]; Available from: http://www.ich.org/home.html
12. EUDRALEX. - ***Volume 2B - Presentation and content of the dossier***. [[Accessed on 2018-08-15]; Available from: https://ec.europa.eu/health/documents/eudralex/vol-2_en

13. EUR-LEX. - **Directiva 2005/36/CE do Parlamento Europeu e do Conselho**. [2018-08-16]; Available from: https://eur-lex.europa.eu/legal-content/pt/TXT/?uri=celex%3A32005L0036
14. EUR-LEX. - **Regulation (EC) No 1223/2009 of the European Parlament and of the Council of 30 November 2009 on cosmetic products**. [Accessed on 2018-01-18]; Available from: https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32009R1223
15. VANCE, M.E., KUIKEN, T., VEJERANO, E.P., MCGINNIS, S.P., HOCHELLA, M.F., JR., REKESKI, D., and HULL, M.S., - **Nanotechnology in the real world: Redeveloping the nanomaterial consumer products inventory**. Beilstein J Nanotechnol, (2015): p. 1769-80
16. BUSHAN, B., - **Governance, policy, and legislation of nanotechnology: a perspective**. Springer-Verlag, (2015): p. 1137-1155
17. SINGH, P. and NANDA, A., - **Nanotechnology in cosmetics: a boon or a bane?** Toxicological & Environmental Chemistry, 8 (2012): p. 1467-1479
18. RAJ, S., JOSE, S., SUMOD, U.S., and SABITHA, M., - **Nanotechnology in cosmetics: Opportunities and challenges**. J Pharm Bioallied Sci, 3 (2012): p. 186-93
19. OWEN, R. and HANDY, R., - **Viewpoint: formulating the problems for environmental risk assessment of nanomaterials**. 16 (2007): p. 5582-5588
20. MOHAMED, H., - **Green, environment-friendly, analytical tools give insights in pharmaceuticals and cosmetics analysis**. TrAC Trends in Analytical Chemistry, (2015): p. 176-192
21. LORES, M., LLOMPART, M., ALVAREZ-RIVERA, G., GUERRA, E., VILA, M., CELEIRO, M., LAMAS, J.P., and GARCIA-JARES, C., - **Positive lists of cosmetic ingredients: Analytical methodology for regulatory and safety controls - A review**. Anal Chim Acta, (2016): p. 1-26
22. MORGANTI, P., - **Use and potential of nanotechnology in cosmetic dermatology**. Clin Cosmet Investig Dermatol, (2010): p. 5-13.
23. MU, L. and SPRANDO, R.L., - **Application of nanotechnology in cosmetics**. Pharm Res, 8 (2010): p. 1746-9
24. SAKAMOTO, K., LOCHHEAD, R.Y., MAIBACH, H.I., and YAMASHITA, Y., **Nanotechnology in Cosmetics**, in *Cosmetic Science and Technology: Theoretical Principles and Applications*, K. Marinakis, Editor. 2017, Elsevier: Cambridge. p. 337-369.

25. GARG, V. and SINGH, H., - **Systematic Development of Transethosomal Gel System of Piroxicam: Formulation Optimization, In Vitro Evaluation, and Ex Vivo Assessment**. 1 (2017): p. 58-71
26. AHAD, A., AL-SALEH, A.A., AL-MOHIZEA, A.M., AL-JENOOBI, F.I., RAISH, M., YASSIN, A.E.B., and ALAM, M.A., - **Formulation and characterization of Phospholipon 90 G and tween 80 based transfersomes for transdermal delivery of eprosartan mesylate**. Pharm Dev Technol, (2017): p. 1-7.
27. RAKESH, R. and ANOOP, K.R., - **Formulation and optimization of nano-sized ethosomes for enhanced transdermal delivery of cromolyn sodium**. J Pharm Bioallied Sci, 4 (2012): p. 333-40
28. ABDULBAQI, I.M., DARWIS, Y., ASSI, R.A., and KHAN, N.A.K., - **Transethosomal gels as carriers for the transdermal delivery of colchicine: statistical optimization, characterization, and ex vivo evaluation**. Drug Des Devel Ther, (2018): p. 795-813
29. CHAROENPUTTAKUN, P., PAMORNPATHOMKUL, B., OPANASOPIT, P., ROJANARATA, T., and NGAWHIRUNPAT, T., - **Terpene composited lipid nanoparticles for enhanced dermal delivery of all-trans-retinoic acids**. Biol Pharm Bull, 7 (2014): p. 1139-48
30. FANG, J.Y., FANG, C.L., LIU, C.H., and SU, Y.H., - **Lipid nanoparticles as vehicles for topical psoralen delivery: solid lipid nanoparticles (SLN) versus nanostructured lipid carriers (NLC)**. Eur J Pharm Biopharm, 2 (2008): p. 633-40.
31. JENSEN, L.B., MAGNUSSSON, E., GUNNARSSON, L., VERMEHREN, C., NIELSEN, H.M., and PETERSSON, K., - **Corticosteroid solubility and lipid polarity control release from solid lipid nanoparticles**. Int J Pharm, 1 (2010): p. 53-60
32. POPLE, P.V. and SINGH, K.K., - **Development and evaluation of colloidal modified nanolipid carrier: application to topical delivery of tacrolimus**. Eur J Pharm Biopharm, 1 (2011): p. 82-94
33. TIWARI, A. and NORDIN, A.N., **Recent Advances with Liposomes as Drug Carriers**, in *Advanced Biomaterials and Biodevices* A. Tiwari and A.N. Nordin, Editors. 2014, Scrivener Publishing LLC. p. 79-119
34. H, A., P, B., N, L., A, N.M., and S, Z., - **Liposomes in Cosmetics**. Journal of Skin and Steem Cell, (2016)
35. HOUGEIR, F.G. and KIRCIK, L., - **A review of delivery systems in cosmetics**. Dermatol Ther, 3 (2012): p. 234-7

36. RITWISET, A., KRONGSUK, S., and JOHNS, J.R., - **Molecular structure and dynamical properties of niosome bilayers with and without cholesterol incorporation: A molecular dynamics simulation study**. Applied Surface Science, (2016): p. 23-31
37. MONDAL, T., GHOSH, S., DAS, A.K., MANDAL, A.K., and BHATTACHARYYA, K., - **Salt effect on the ultrafast proton transfer in niosome**. J Phys Chem B, 28 (2012): p. 8105-12
38. MOGHASSEMI, S., HADJIZADEH, A., and OMIDFAR, K., - **Formulation and Characterization of Bovine Serum Albumin-Loaded Niosome**. AAPS PharmSciTech, 1 (2017): p. 27-33
39. PURAS, G., MASHAL, M., ZARATE, J., AGIRRE, M., OJEDA, E., GRIJALVO, S., ERITJA, R., DIAZ-TAHOCES, A., MARTINEZ NAVARRETE, G., AVILES-TRIGUEROS, M., FERNANDEZ, E., and PEDRAZ, J.L., - **A novel cationic niosome formulation for gene delivery to the retina**. J Control Release, (2014): p. 27-36
40. SHUMILOV, M., BERCOVICH, R., DUCHI, S., AINBINDER, D., and TOUITOU, E., - **Ibuprofen transdermal ethosomal gel: characterization and efficiency in animal models**. J Biomed Nanotechnol, 5 (2010): p. 569-76
41. ABDULBAQI, I.M., DARWIS, Y., KHAN, N.A., ASSI, R.A., and KHAN, A.A., - **Ethosomal nanocarriers: the impact of constituents and formulation techniques on ethosomal properties, in vivo studies, and clinical trials**. Int J Nanomedicine, (2016): p. 2279-304
42. BODADE, S.S., SHAIKH, K.S., KAMBLE, M.S., and CHAUDHARI, P.D., - **A study on ethosomes as mode for transdermal delivery of an antidiabetic drug**. Drug Deliv, 1 (2013): p. 40-6
43. SONG, C.K., BALAKRISHNAN, P., SHIM, C.K., CHUNG, S.J., CHONG, S., and KIM, D.D., - **A novel vesicular carrier, transethosome, for enhanced skin delivery of voriconazole: characterization and in vitro/in vivo evaluation**. Colloids Surf B Biointerfaces, (2012): p. 299-304
44. AL SHUWAILI, A.H., RASOOL, B.K., and ABDULRASOOL, A.A., - **Optimization of elastic transfersomes formulations for transdermal delivery of pentoxifylline**. Eur J Pharm Biopharm, (2016): p. 101-14
45. KASSEM, M.A., ABOUL-EINIEN, M.H., and EL TAWEEL, M.M., - **Dry Gel Containing Optimized Felodipine-Loaded Transferosomes: a Promising Transdermal Delivery System to Enhance Drug Bioavailability**. AAPS PharmSciTech, 5 (2018): p. 2155-2173

46. REDDY, Y., SRAVANI, A.B., RAVISANKAR, V., PRAKASH, P.R., and BHASKAR, N.V., - **Transferosomes A Novel Vesicular Carrier for Transdermal Drug Delivery System**. Journal of Innovations in Pharmaceuticals and Biological Sciences, (2015): p. 193-208

47. AZMI, I.D., MOGHIMI, S.M., and YAGHMUR, A., - **Cubosomes and hexosomes as versatile platforms for drug delivery**. Ther Deliv, 12 (2015): p. 1347-64

48. PAN, X., HAN, K., PENG, X., YANG, Z., QIN, L., ZHU, C., HUANG, X., SHI, X., DIAN, L., LU, M., and WU, C., - **Nanostructured cubosomes as advanced drug delivery system**. Curr Pharm Des, 35 (2013): p. 6290-7

49. SAKAMOTO, K., LOCHHEAD, R.Y., MAIBACH, H.I., and YAMASHITA, Y., **Microemulsions and Nano-emulsions for Cosmetic Applications**, in *Cosmetic Science and Technology: Theoretical Principles and Applications*, K. Marinakis, Editor. 2017, Elsevier: Cambridge. p. 507-518

50. DE BRUM, T.L., FIEL, L.A., CONTRI, R.V., GUTERRES, S.S., and POHLMANN, A.R., - **Polymeric Nanocapsules and Lipid-Core Nanocapsules Have Diverse Skin Penetration**. J Nanosci Nanotechnol, 1 (2015): p. 773-80

51. GUTERRES, S.S., ALVES, M.P., and POHLMANN, A.R., - **Polymeric nanoparticles, nanospheres and nanocapsules, for cutaneous applications**. Drug Target Insights, (2007): p. 147-57

52. JIMTAISONG, A. and SAEWAN, N., - **Utilization of carboxymethyl chitosan in cosmetics**. Int J Cosmet Sci, 1 (2014): p. 12-21

53. GUTHA, Y., PATHAK, J.L., ZHANG, W., ZHANG, Y., and JIAO, X., - **Antibacterial and wound healing properties of chitosan/poly(vinyl alcohol)/zinc oxide beads (CS/PVA/ZnO)**. Int J Biol Macromol, (2017): p. 234-241

54. CHAOUAT, C., BALAYSSAC, S., MALET-MARTINO, M., BELAUBRE, F., QUESTEL, E., SCHMITT, A.M., POIGNY, S., FRANCESCHI, S., and PEREZ, E., - **Green microparticles based on a chitosan/lactobionic acid/linoleic acid association. Characterisation and evaluation as a new carrier system for cosmetics**. J Microencapsul, 2 (2017): p. 162-170

55. FRANK, L.A., CONTRI, R.V., BECK, R.C., POHLMANN, A.R., and GUTERRES, S.S., - **Improving drug biological effects by encapsulation into polymeric nanocapsules**. Wiley Interdiscip Rev Nanomed Nanobiotechnol, 5 (2015): p. 623-39.

56. BATHEJA, P., SHEIHET, L., KOHN, J., SINGER, A.J., and MICHNIAK-KOHN, B., - **Topical drug delivery by a polymeric nanosphere gel: Formulation**

optimization and in vitro and in vivo skin distribution studies. J Control Release, 2 (2011): p. 159-67

57. BAKRUDEEN, H.B., SUGUNALAKSHMI, M., and REDDY, B.S., - **Auto-fluorescent mesoporous ZnO nanospheres for drug delivery carrier application**. Mater Sci Eng C Mater Biol Appl, (2015): p. 335-40
58. KAMBLE, P., SADARANI, B., MAJUMDAR, A., and BHULLAR, S., - **Nanofiber based drug delivery systems for skin: A promising therapeutic approach**. Journal of Drug Delivery Science and Technology, (2017): p. 124-133
59. ABBASI, E., AVAL, S.F., AKBARZADEH, A., MILANI, M., NASRABADI, H.T., JOO, S.W., HANIFEHPOUR, Y., NEJATI-KOSHKI, K., and PASHAEI-ASL, R., - **Dendrimers: synthesis, applications, and properties**. Nanoscale Res Lett, 1 (2014): p. 247
60. PENTEK, T., NEWENHOUSE, E., O'BRIEN, B., and CHAUHAN, A.S., - **Development of a Topical Resveratrol Formulation for Commercial Applications Using Dendrimer Nanotechnology**. Molecules, 1 (2017).
61. BOROWSKA, S. and BRZOSKA, M.M., - **Metals in cosmetics: implications for human health**. J Appl Toxicol, 6 (2015): p. 551-72
62. ULLAH KHAN, S., SALEH, T.A., WAHAB, A., KHAN, M.H.U., KHAN, D., ULLAH KHAN, W., RAHIM, A., KAMAL, S., ULLAH KHAN, F., and FAHAD, S., - **Nanosilver: new ageless and versatile biomedical therapeutic scaffold**. Int J Nanomedicine, (2018): p. 733-762
63. PULIT-PROCIAK, J., CHEWASTOWSKI, J., SIUDEK, M., and BANACH, M., - **Incorporation of Metallic Nanoparticles into Cosmetic Preparations and Assessment of Their Physicochemical and Utility Properties**. Journal of Surfactants and Detergents, 4 (2018): p. 575-591
64. GUPTA, R. and RAI, B., - **Effect of Size and Surface Charge of Gold Nanoparticles on their Skin Permeability: A Molecular Dynamics Study**. Sci Rep, (2017): p. 45292
65. JIMENEZ-PEREZ, Z.E., SINGH, P., KIM, Y.J., MATHIYALAGAN, R., KIM, D.H., LEE, M.H., and YANG, D.C., - **Applications of Panax ginseng leaves-mediated gold nanoparticles in cosmetics relation to antioxidant, moisture retention, and whitening effect on B16BL6 cells**. J Ginseng Res, 3 (2018): p. 327-333
66. LU, P.J., HUANG, S.C., CHEN, Y.P., CHIUEH, L.C., and SHIH, D.Y., - **Analysis of titanium dioxide and zinc oxide nanoparticles in cosmetics**. J Food Drug Anal, 3 (2015): p. 587-594

67. LU, P.J., FANG, S.W., CHENG, W.L., HUANG, S.C., HUANG, M.C., and CHENG, H.F., - **Characterization of titanium dioxide and zinc oxide nanoparticles in sunscreen powder by comparing different measurement methods**. J Food Drug Anal, 3 (2018): p. 1192-1200

68. PASQUET, J., CHEVALIER, Y., COUVAL, E., BOUVIER, D., and BOLZINGER, M.A., - **Zinc oxide as a new antimicrobial preservative of topical products: interactions with common formulation ingredients**. Int J Pharm, 1 (2015): p. 88-95

69. NAFISI, S., SCHAFER-KORTING, M., and MAIBACH, H.I., - **Perspectives on percutaneous penetration: Silica nanoparticles**. Nanotoxicology, 5 (2015): p. 643-57

70. MEBERT, A.M., BAGLOLE, C.J., DESIMONE, M.F., and MAYSINGER, D., - **Nanoengineered silica: Properties, applications and toxicity**. Food Chem Toxicol, Pt 1 (2017): p. 753-770

71. ZHAI, X., LADEMANN, J., KECK, C.M., and MULLER, R.H., - **Nanocrystals of medium soluble actives--novel concept for improved dermal delivery and production strategy**. Int J Pharm, 1-2 (2014): p. 141-50

72. COLOMBO, M., STAUFENBIEL, S., RUHL, E., and BODMEIER, R., - **In situ determination of the saturation solubility of nanocrystals of poorly soluble drugs for dermal application**. Int J Pharm, 1-2 (2017): p. 156-166

73. MOUSAVI, S.Z., NAFISI, S., and MAIBACH, H.I., - **Fullerene nanoparticle in dermatological and cosmetic applications**. Nanomedicine, 3 (2017): p. 1071-1087

74. LENS, M., - **Recent progresses in application of fullerenes in cosmetics**. Recent Pat Biotechnol, 2 (2011): p. 67-73

75. VAN DER LAAN, K., HASANI, M., ZHENG, T., and SCHIRHAGL, R., - **Nanodiamonds for In Vivo Applications**. 19 (2018): p. e1703838

76. LIM, D.G., KIM, K.H., KANG, E., LIM, S.H., RICCI, J., SUNG, S.K., KWON, M.T., and JEONG, S.H., - **Comprehensive evaluation of carboxylated nanodiamond as a topical drug delivery system**. Int J Nanomedicine, (2016): p. 2381-95

77. SHARMA, N. and BALDI, A., - **Exploring versatile applications of cyclodextrins: an overview**. Drug Deliv, 3 (2016): p. 739-57

78. FU, X., CAI, J., ZHANG, X., LI, W.D., GE, H., and HU, Y., - **Top-down fabrication of shape-controlled, monodisperse nanoparticles for biomedical applications**. Adv Drug Deliv Rev, (2018)

79. YU, H.D., REGULACIO, M.D., YE, E., and HAN, M.Y., - **Chemical routes to top-down nanofabrication**. Chem Soc Rev, 14 (2013): p. 6006-18
80. BISWAS, A., BAYER, I.S., BIRIS, A.S., WANG, T., DERVISHI, E., and FAUPEL, F., - **Advances in top-down and bottom-up surface nanofabrication: techniques, applications & future prospects**. Adv Colloid Interface Sci, 1-2 (2012): p. 2-27
81. CHAN, H.K. and KWOK, P.C., - **Production methods for nanodrug particles using the bottom-up approach**. Adv Drug Deliv Rev, 6 (2011): p. 406-16
82. JAIN, S., PATEL, N., MADAN, P., and LIN, S., - **Quality by design approach for formulation, evaluation and statistical optimization of diclofenac-loaded ethosomes via transdermal route**. Pharm Dev Technol, 4 (2015): p. 473-89
83. SO, J.W., KIM, S., PARK, J.S., KIM, B.H., JUNG, S.H., SHIN, S.C., and CHO, C.W., - **Preparation and evaluation of solid lipid nanoparticles with JSH18 for skin-whitening efficacy**. Pharm Dev Technol, 4 (2010): p. 415-20
84. JIMENEZ, Z., KIM, Y.J., MATHIYALAGAN, R., SEO, K.H., MOHANAN, P., AHN, J.C., KIM, Y.J., and YANG, D.C., - **Assessment of radical scavenging, whitening and moisture retention activities of Panax ginseng berry mediated gold nanoparticles as safe and efficient novel cosmetic material**. Artif Cells Nanomed Biotechnol, 2 (2018): p. 333-340
85. AYUMI, N.S., SAHUDIN, S., HUSSAIN, Z., HUSSAIN, M., and SAMAH, N.H.A., - **Polymeric nanoparticles for topical delivery of alpha and beta arbutin: preparation and characterization**. Drug Deliv Transl Res, (2018)
86. CELIA, C., CILURZO, F., TRAPASSO, E., COSCO, D., FRESTA, M., and PAOLINO, D., - **Ethosomes® and transfersomes® containing linoleic acid: physicochemical and technological features of topical drug delivery carriers for the potential treatment of melasma disorders**. Biomedical Microdevices, 1 (2012): p. 119-130
87. DINGLEY, G., FAIR, J., GLYNN, J., and SANDSTROM, A., **Optical Blurring Pigment Composition Suitable For Use In Cosmetics** AVON, Editor. 2010.
88. **Mascara cream**, G.J.G. CHEMICAL, Editor. 2017
89. HIROYUKI, T. and TAKESUKE, T., **COSMETIC** H. MICRON, Editor. 2010
90. HYUN, C., TAIK, Y., KYEONG, K., YOUNG, J., and HWAN, H., **COSMETIC PIGMENT COMPOSITION CONTAINING GOLD OR SILVER NANO-PARTICLES** K.R.I.O. BIOSCIENCE, Editor. 2009

91. LAU, M., WAAG, F., and BARCIKOWSKI, S., - **Direct Integration of Laser-Generated Nanoparticles into Transparent Nail Polish: The Plasmonic "Goldfinger"**. Industrial & Engineering Chemistry Research, 12 (2017): p. 3291-3296
92. MALARKODI, C., RAJESHKUMAR, S., PAULKUMAR, K., VANAJA, M., GNANAJOBITHA, G., and ANNADURAI, G., - **Biosynthesis and Antimicrobial Activity of Semiconductor Nanoparticles against Oral Pathogens**. Bioinorg Chem Appl, (2014): p. 347167
93. LEE, D.K., KIM, S.V., LIMANSUBROTO, A.N., YEN, A., SOUNDIA, A., WANG, C.Y., SHI, W., HONG, C., TETRADIS, S., KIM, Y., PARK, N.H., KANG, M.K., and HO, D., - **Nanodiamond-Gutta Percha Composite Biomaterials for Root Canal Therapy**. ACS Nano, 11 (2015): p. 11490-501
94. ABBASZADEGAN, A., NABAVIZADEH, M., GHOLAMI, A., ALEYASIN, Z.S., DOROSTKAR, S., SALIMINASAB, M., GHASEMI, Y., HEMMATEENEJAD, B., and SHARGHI, H., - **Positively charged imidazolium-based ionic liquid-protected silver nanoparticles: a promising disinfectant in root canal treatment**. Int Endod J, 8 (2015): p. 790-800
95. HYUN, K., LIZENG, G., DAVID, C., and PRATAP, N., **Iron oxide nanoparticles and methods of use thereof** U. PENNSYLVANIA, Editor. 2018
96. XIUYING, J., **Toothpaste** Q.Y.D. CHEMICAL, Editor. 2017
97. GLOWKA, E., WOSICKA-FRACKOWIAK, H., HYLA, K., STEFANOWSKA, J., JASTRZEBSKA, K., KLAPISZEWSKI, L., JESIONOWSKI, T., and CAL, K., - **Polymeric nanoparticles-embedded organogel for roxithromycin delivery to hair follicles**. Eur J Pharm Biopharm, 1 (2014): p. 75-84
98. YUN, Y., HYUN, K., WON, K., and HEE, H., **COMPOSITION FOR THE PREVENTING LOSS OF HAIR AND PROMOTING GROWTH OF HAIR WITH DISPERSED GOLD NANO PARTICLES AND MANUFACTURING METHOD THEREOF** I.C. LTD, Editor. 2018
99. KI, P., JIN, P., IL, K., and HYUN, K., **Fermented Extract Promoting Hair Growth-Hydrogel Nanoparticle Hybrid and Method for Preparing the Same** C.A.R.I. LTD, Editor. 2017
100. HU, Z., LIAO, M., CHEN, Y., CAI, Y., MENG, L., LIU, Y., LV, N., LIU, Z., and YUAN, W., - **A novel preparation method for silicone oil nanoemulsions and its application for coating hair with silicone**. Int J Nanomedicine, (2012): p. 5719-24
101. CHEN, J., WEI, N., LOPEZ-GARCIA, M., AMBROSE, D., LEE, J., ANNELIN, C., and PETERSON, T., - **Development and evaluation of resveratrol, Vitamin E, and**

epigallocatechin gallate loaded lipid nanoparticles for skin care applications. Eur J Pharm Biopharm, (2017): p. 286-291

102. EL-LEITHY, E.S., MAKKY, A.M., KHATTAB, A.M., and HUSSEIN, D.G., - **Optimization of nutraceutical coenzyme Q10 nanoemulsion with improved skin permeability and anti-wrinkle efficiency**. Drug Dev Ind Pharm, 2 (2018): p. 316-328
103. AVADHANI, K.S., MANIKKATH, J., TIWARI, M., CHANDRASEKHAR, M., GODAVARTHI, A., VIDYA, S.M., HARIHARAPURA, R.C., KALTHUR, G., UDUPA, N., and MUTALIK, S., - **Skin delivery of epigallocatechin-3-gallate (EGCG) and hyaluronic acid loaded nano-transfersomes for antioxidant and anti-aging effects in UV radiation induced skin damage**. Drug Deliv, 1 (2017): p. 61-74
104. IL, C., **AN DEODOREANT COMPOSITION COMPRISING CARBON GROUP NON-OXIDE NANOPARTICLES** S.C. LTD, Editor. 2018
105. SOO, K., **SYNTHESIS OF AG AND AG-TIO2 NANOPARTICLE CONTAINING ANTIBIOTIC AND DEODORANT PROPERTY** K.Y. SOO, Editor. 2006
106. HOSSEINKHANI, B., CALLEWAERT, C., VANBEVEREN, N., and BOON, N., - **Novel biocompatible nanocapsules for slow release of fragrances on the human skin**. N Biotechnol, 1 (2015): p. 40-6
107. SHETTY, P.K., VENUVANKA, V., JAGANI, H.V., CHETHAN, G.H., LIGADE, V.S., MUSMADE, P.B., NAYAK, U.Y., REDDY, M.S., KALTHUR, G., UDUPA, N., RAO, C.M., and MUTALIK, S., - **Development and evaluation of sunscreen creams containing morin-encapsulated nanoparticles for enhanced UV radiation protection and antioxidant activity**. Int J Nanomedicine, (2015): p. 6477-91
108. BORASE, H.P., PATIL, C.D., SALUNKHE, R.B., SURYAWANSHI, R.K., SALUNKE, B.K., and PATIL, S.V., - **Phytolatex synthesized gold nanoparticles as novel agent to enhance sun protection factor of commercial sunscreens**. Int J Cosmet Sci, 6 (2014): p. 571-8
109. DENG, Y., EDIRIWICKREMA, A., YANG, F., LEWIS, J., GIRARDI, M., and SALTZMAN, W.M., - **A sunblock based on bioadhesive nanoparticles**. Nat Mater, 12 (2015): p. 1278-85
110. HWA, L., SUN, S., JIN, B., MIN, H., and GYU, K., **Stably-suspended polymer composite nanoparticles containing organic sunscreen agents and preparing method thereof** L.H.H. CARE, Editor. 2018

111. KAUL, S., GULATI, N., VERMA, D., MUKHERJEE, S., and NAGAICH, U., - **Role of Nanotechnology in Cosmeceuticals: A Review of Recent Advances**. (2018): p. 3420204

112. NANOTECHPROJECT. - **The Project on Emerging Nanotechnologies**. [Accessed on 2018-08-15]; Available from: http://www.nanotechproject.org/

113. COSTA, R. and SANTOS, L., - **Delivery systems for cosmetics - From manufacturing to the skin of natural antioxidants**. Powder Technology, (2017): p. 402-416

114. SZMYD, R., GORALCZYK, A.G., SKALNIAK, L., CIERNIAK, A., LIPERT, B., FILON, F.L., CROSERA, M., BOROWCZYK, J., LACZNA, E., DRUKALA, J., KLEIN, A., and JURA, J., - **Effect of silver nanoparticles on human primary keratinocytes**. Biol Chem, 1 (2013): p. 113-23

115. TUCCI, P., PORTA, G., AGOSTINI, M., DINSDALE, D., IAVICOLI, I., CAIN, K., FINAZZI-AGRO, A., MELINO, G., and WILLIS, A., - **Metabolic effects of TiO2 nanoparticles, a common component of sunscreens and cosmetics, on human keratinocytes**. Cell Death Dis, (2013): p. e549

116. HACKENBERG, S. and KLEINSASSER, N., - **Dermal toxicity of ZnO nanoparticles: a worrying feature of sunscreen?** Nanomedicine (Lond), 4 (2012): p. 461-463

117. ILVES, M., PALOMAKI, J., VIPPOLA, M., LEHTO, M., SAVOLAINEN, K., SAVINKO, T., and ALENIUS, H., - **Topically applied ZnO nanoparticles suppress allergen induced skin inflammation but induce vigorous IgE production in the atopic dermatitis mouse model**. Part Fibre Toxicol, (2014): p. 38

118. CHANG, J., LEE, C.W., ALSULIMANI, H.H., CHOI, J.E., LEE, J.K., KIM, A., PARK, B.H., KIM, J., and LEE, H., - **Role of fatty acid composites in the toxicity of titanium dioxide nanoparticles used in cosmetic products**. J Toxicol Sci, 4 (2016): p. 533-42

119. SAJID, M., ILYAS, M., BASHEER, C., TARIQ, M., DAUD, M., BAIG, N., and SHEHZAD, F., - **Impact of nanoparticles on human and environment: review of toxicity factors, exposures, control strategies, and future prospects**. Environ Sci Pollut Res Int, 6 (2015): p. 4122-4143

120. SANCHEZ-QUILES, D. and TOVAR-SANCHEZ, A., - **Sunscreens as a source of hydrogen peroxide production in coastal waters**. Environ Sci Technol, 16 (2014): p. 9037-42

121. BOTTA, C., LABILLE, J., AUFFAN, M., BORSCHNECK, D., MICHE, H., CABIE, M., MASION, A., ROSE, J., and BOTTERO, J.Y., - **TiO(2)-based nanoparticles released in water from commercialized sunscreens in a life-cycle perspective: structures and quantities**. Environ Pollut, 6 (2011): p. 1543-50

122. DAS, P., XENOPOULOS, M.A., and METCALFE, C.D., - **Toxicity of silver and titanium dioxide nanoparticle suspensions to the aquatic invertebrate, Daphnia magna**. Bull Environ Contam Toxicol, 1 (2013): p. 76-82

123. LONDONO, N., DONOVAN, A.R., SHI, H., GEISLER, M., and LIANG, Y., - **Impact of TiO2 and ZnO nanoparticles on an aquatic microbial community: effect at environmentally relevant concentrations**. 9-10 (2017): p. 1140-1156

124. MA, H., WILLIAMS, P.L., and DIAMOND, S.A., - **Ecotoxicity of manufactured ZnO nanoparticles--a review**. Environ Pollut, (2013): p. 76-85

125. ASHARANI, P.V., LIANWU, Y., GONG, Z., and VALIYAVEETTIL, S., - **Comparison of the toxicity of silver, gold and platinum nanoparticles in developing zebrafish embryos**. Nanotoxicology, 1 (2011): p. 43-54

126. EC. - **Cosmetic Product Notification Portal**. [Accessed on 2018/08/18]; Available from: https://ec.europa.eu/growth/sectors/cosmetics/cpnp

127. EC. - **Nanomaterials**. [Accessed on 2018-08-18]; Available from: https://ec.europa.eu/growth/sectors/cosmetics/products/nanomaterials_en

128. EC. - **Catalogue of nanomaterials used in cosmetic products placed on the EU market**. [Accessed on 2018-08-15]; Available from: http://ec.europa.eu/docsroom/documents/24521

129. EUON. - **NanoData**. [Accessed on 2018-08-19]; Available from: https://nanodata.echa.europa.eu/

130. EUON. - **eNanoMapper**. [Accessed on 2018-08-15]; Available from: https://euon.echa.europa.eu/enanomapper

131. FDA. - **Nanotechnology**. [Accessed on 2018-08-19]; Available from: https://www.fda.gov/cosmetics/scienceresearch/nanotech/

132. FDA. - **Guidance for Industry: Safety of Nanomaterials in Cosmetic Products**. [Accessed on 2018-08-19]; Available from: https://www.fda.gov/cosmetics/guidanceregulation/guidancedocuments/ucm300886.htm