UNIVERSIDADE D
COIMBRA

Pedro Alexandre Rosa Baptista

Relatórios de Estágio e Monografia intitulada "Nanotechnology Approaches for the Topical Delivery of Minoxidil" referentes à Unidade Curricular "Estágio", sob a orientação, respetivamente, da Dra. Clementina Varela, do Dr. João Monteiro e da Professora Doutora Ana Cláudia Santos apresentados à Faculdade de Farmácia da Universidade de Coimbra, para apreciação na prestação de provas públicas de Mestrado Integrado em Ciências Farmacêuticas.

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Eu, Pedro Alexandre Rosa Baptista, estudante do Mestrado Integrado em Ciências Farmacêuticas, com o nº 2013138491, declaro assumir toda a responsabilidade pelo conteúdo do Documento Relatórios de Estágio e Monografia intitulada "Nanotechnology approaches for the topical delivery of minoxidil" apresentados à Faculdade de Farmácia da Universidade de Coimbra, no âmbito da unidade de Estágio Curricular.

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Coimbra, 07 de setembro de 2018

Pedro Alexandre Rosa Baptista

(Pedro Alexandre Rosa Baptista)

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A todos, muito obrigado!

INDICE

Parte I

Relatório de Estágio em Farmácia Hospitalar

(Instituto Português de Oncologia de Coimbra Francisco Gentil, E.P.E.)

Abreviaturas

CFT –Comissão de Farmácia e Terapêutica

DCI –Denominação Comum Internacional

FFUC –Faculdade de Farmácia da Universidade de Coimbra

FHNM –Formulário Hospitalar Nacional de Medicamentos

IPOCFG, E.P.E. –Instituto Português de Oncologia de Coimbra Francisco Gentil, E.P.E.

LASA – Look Alike, Sound Alike

MICF –Mestrado Integrado em Ciências Farmacêuticas

SNS –Serviço Nacional de Saúde

TDT – Técnico de Diagnóstico e Terapêutica

UPC –Unidade de Preparação de Citotóxicos

1.Introdução

No âmbito da unidade curricular, Estágio Curricular, do quinto ano do Mestrado Integrado em Ciências Farmacêuticas (MICF), da Faculdade de Farmácia da Universidade de Coimbra (FFUC), escolhi um estágio curricular nos Serviços Farmacêuticos do Instituto Português de Oncologia de Coimbra Francisco Gentil, E.P.E. (IPOCFG, E.P.E.), no período de 9 de janeiro a 9 de março, sob a orientação da Dr.ª Clementina Varela e restante equipa técnica. Aqui, o farmacêutico assume-se como o profissional de saúde mais especializado na área do medicamento e ao qual é imputado um papel preponderante em toda a dinâmica de funcionamento dos Serviços Farmacêuticos Hospitalares, sendo responsáveis por criar uma estrutura de máxima importância ao nível dos cuidados de saúde prestados em meio hospitalar. Face a isto, foi imensamente enriquecedor poder assistir de perto a qual é o papel do farmacêutico no seio de uma equipa multidisciplinar de saúde e o contexto diário daquilo que é a sua realidade profissional. Com este relatório pretendo evidenciar pormenores da experiência que foi a realização deste estágio, uma etapa que considero fundamental para o meu processo de formação. Após uma breve apresentação do IPOCFG, E.P.E. e dos seus Serviços Farmacêuticos, irei focar-me numa análise SWOT. Esta análise irá incidir sob os pontos fortes (*Strenghts*), os pontos fracos (*Weaknesses*), as oportunidades (*Opportunities*) e as ameaças (*Threats*) do estágio que realizei, no que diz respeito à frequência do estágio, à integração da aprendizagem teórica no contexto prático profissional e à adequação dos conhecimentos adquiridos durante o MICF, relativamente às exigências profissionais atuais do farmacêutico. Além disto, pretendo descrever quais os conhecimentos obtidos ao longo deste período, bem como todas as situações que considero relevantes e que contribuíram para a sua valorização.

2.Instituto Português de Oncologia de Coimbra Francisco Gentil, E.P.E.

De acordo com Regulamento Interno do IPOCFG, E.P.E., este hospital trata-se de uma pessoa coletiva de direito público de natureza empresarial dotada de autonomia administrativa, financeira e patrimonial [1]. Esta instituição é uma unidade hospitalar integrada na rede de unidades prestadoras de cuidados de saúde do Serviço Nacional de Saúde (SNS), com objetivo primordial o diagnóstico e tratamento de doenças oncológicas a todos os cidadãos em toda a Região Centro do país, sejam eles benificiários ou não do SNS. Outro dos seus objetivos, é a participação na formação de profissionais de saúde e o desenvolvimento de projetos e programas de investigação, ensino, formação e rastreio oncológico [1]. Desta forma, o IPOCFG, E.P.E. assume-se como um dos centros oncológicos de referência a nível nacional, destacando-se nas áreas do tratamento, investigação, ensino, diagnóstico, reabilitação e continuidade de cuidados e tendo inúmeras articulações com os Institutos de Porto e Lisboa, pela sua comissão coordenadora [1].

2.1. **Serviços Farmacêuticos do Instituto Português de Oncologia de Coimbra Francisco Gentil, E.P.E.**

Baseado no Regulamento Interno do IPOCFG, E.P.E., os Serviços Farmacêuticos são uma das áreas de suporte à prestação de cuidados de saúde, responsáveis por toda a gestão, circuito, manipulação e dispensa de medicamentos e produtos farmacêuticos. As suas funções passam por participar na seleção dos medicamentos e produtos farmacêuticos que estão disponíveis no hospital, pela sua distribuição aos doentes em regime de internamento e de ambulatório e produção de formulações adequadas a diversos fins específicos do hospital. Também possuem como função a garantia da boa utilização dos medicamentos e produtos farmacêuticos, através do fornecimento de informação adequada, do exercício da farmácia clínica, da participação em comissões técnicas e multidisciplinares, da colaboração em ensaios clínicos, da orientação de estágios e da formação contínua dos profissionais de saúde [1]. Estes serviços Farmacêuticos promovem um leque de atividades farmacêuticas, exercidas em organismos hospitalares ou serviços a estes ligados, que são designadas por "atividades de Farmácia Hospitalar". Desta forma, assumem-se como departamentos com autonomia técnica e científica, sujeitos à orientação geral dos Órgãos de Administração dos Hospitais, perante os quais respondem pelos resultados do seu exercício. Na prática, é o serviço hospitalar que assegura a terapêutica medicamentosa dos doentes, sendo responsáveis pela qualidade, eficácia e segurança dos medicamentos[2]. A sua direção é obrigatoriamente assegurada por um farmacêutico hospitalar com habilitações académicas e profissionais adequadas e nomeado pelo concelho de administração do hospital[1].

No IPOCFG, E.P.E., os Serviços Farmacêuticos situam-se no 1º piso do edifício dos Cuidados Paliativos, funcionando das 9h às 17h30, de segunda a sexta-feira, e das 9h às 13h, aos sábados. Após o encerramento dos serviços, situações especiais são asseguradas por uma farmacêutica de prevenção.

A equipa técnica destes serviços Farmacêuticos é constituída por 9 farmacêuticos e ainda um vasto leque de Técnicos de Diagnóstico e Terapêutica (TDTs). A direção desta equipa e de todo o serviço farmacêutico do IPOCFG, E.P.E., encontra-se a cargo da Dr.ª Clementina Varela, estando a subcoordenação a cargo da Dr.ª Ana Cristina Teles sendo o corpo farmacêutico, ainda, constituído pela Dr.ª Ana Costa, Dr.ª Andrea Silva, Dr.ª Cristina Baeta, Dr.ª Graça Rigueiro, Dr.ª Maria Inês Costa, Dr.ª Rita Lopes e pela Dr.ª Marina Sales. Os Técnicos de Diagnóstico e Terapêutica são coordenados por Prazeres Sacramento. Fazem parte dos recursos humanos deste serviço, também, um assistente técnico, auxiliares de ação médica e assistentes operacionais. Cada um deles possui tarefas individuais específicas, que são realizadas com o maior rigor, de forma a garantirem que o circuito do medicamento é o mais seguro, tanto no meio hospitalar, como no ato da sua dispensa ou administração.

Três dos farmacêuticos deste serviço fazem parte, ainda, da Comissão de Farmácia e terapêutica em conjunto com 3 profissionais da área da medicina, podendo existir ou não um profissional da área da gestão afim de potenciar a gestão dos recursos económicos do hospital. Esta comissão serve para

controlar o uso de psicotrópicos e estupefacientes, segundo a legislação que lhes é imputada, garantir o cumprimento do formulário nacional dos medicamentos e, se for caso disso, adicionar ou excluir informações de modo a criar um formulário próprio do IPOCFG, E.P.E.. A proposta de critérios de utilização de medicamentos, a ação de farmacovigilância e a correção da terapêutica, embora sempre com respeito às regras deontológicas são outras funções que esta comissão desempenha.

Fisicamente, os Serviços Farmacêuticos do IPOCFG, E.P.E. encontram-se compartimentados em seis áreas principais, nomeadamente a área de distribuição clássica ou tradicional e armazenamento de medicamentos, área de distribuição individualizada diária em dose unitária, área de distribuição de medicamentos em regime de ambulatório, radiofarmácia, Unidade de Preparação de Citotóxicos (UPC) e a área de reembalagem de medicamentos. Durante o estágio que realizei neste serviço tive a oportunidade de vivenciar as atividades de todos os setores.

3.Análise SWOT

Ferramenta de gestão muito utilizada, que permite avaliar qualitativamente uma dada atividade, quer numa vertente interna, em relação aos pontos fortes (*Strenghts*) e aos pontos fracos (*Weaknesses*), quer numa vertente mais externa, relativamente a oportunidades (*Opportunities*) e a ameaças (*Threats*). Vulgarmente, este tipo de análise é conhecido pelo acrónimo SWOT. Posto isto, apresento a minha análise SWOT relativa a este estágio, onde abordo os aspetos que considero que valorizaram o meu estágio, as dificuldades sentidas durante a realização do mesmo, mas também as oportunidades e as ameaças que reconheci.

Pontos fortes	Pontos Fracos	Oportunidades	Ameaças
Contacto com a área da oncologia e doente oncológico	Carácter Observacional do estágio	Controlo de *Stocks* dos serviços	Distância entre Farmacêuticos e Doentes
Organização do estágio e a Oportunidade de contacto com todos os Sectores	Falta de conhecimentos na área		Escolha e aquisição de medicamentos
Trabalhos de pesquisa			
Equipa Multidisciplinar			

Tabela 1: Análise SWOT do estágio em Farmácia Comunitária.

3.1.Pontos Fortes

3.1.1.Contacto com a área da oncologia e com o doente oncológico

O facto de o IPOCFG, E.P.E. ser um hospital especializado na área da oncologia foi um dos aspetos que me levou a optar por realizá-lo, na tentativa de perceber mais como funciona esta área e qual o papel de um farmacêutico numa área tão especifica. E acabou por revelar-se um dos pontos fortes deste estágio pelo intenso contacto com a área da oncologia e com o doente oncológico, um tipo de doentes que, a meu ver, é bastante especial. A oncologia era, até então, uma área clínica sobre a qual tinha poucos conhecimentos, quer em termos de terapêuticas, quer em relação aos cuidados de saúde que são prestados nesta área. Devido a este facto foi um estágio foi muito enriquecedor na medida em que me permitiu aumentar os conhecimentos desta área e, além de trabalhar com terapêuticas convencionais e comuns que também são utilizadas nestes doentes, permitiu-me o primeiro contacto com medicação antineoplásica que desconhecia. Desde medicamentos citotóxicos a fármacos que constituem protocolos de terapêutica hormonal contra o cancro, permitiu-me percecionar a complexidade que é o tratamento e o acompanhamento de um doente oncológico, uma área em relação à qual, inicialmente, não possuía muitos conhecimentos. Nesta área, o farmacêutico tem várias áreas de intervenção, desde a validação da prescrição médica de doentes em regime de internamento ou validação de protocolos de quimioterapia até à dispensa de fármacos em regime de ambulatório. Consegui, também, entender que a investigação científica mais atual se revela cada vez mais importante, permitindo explorar novas estratégias terapêuticas para o tratamento dos doentes. Assim, é uma área onde impera a atualização científica constante pois a cada dia podem surgir novos fármacos ou terapêuticas que podem ajudar na intervenção desta doença.

O tempo que estive na dispensa de medicamentos em Ambulatório associado a 2 visitas ocasionais que tive a oportunidade de fazer ao Hospital de Dia (local de Administração da Quimioterapia) e à Unidade cirurgia de Cabeça e Pescoço permitiram-me um contacto pessoal com doentes oncológicos e consegui, ainda mais, perceber que nestes casos cada doente se trata de um caso individual, com uma história de vida diferente. A área da dispensa em Ambulatório revela-se muito importante, uma vez que se trata de imunoterapia oral e, devido ao facto de alguns dos doentes serem população idosa que mora sozinha, é mais importante ainda o esclarecimento de todas as dúvidas que possam ter em relação à medicação que estão a levar. E aí, o corpo técnico responsável por esta área do Serviço revela-se uma grande ajuda a estes doentes, prestando-lhes toda a informação necessária para que estes consigam levar a bom porto a terapêutica prescrita.

3.1.2. Organização do estágio e a Oportunidade de contacto com todos os Sectores

A forma como o estágio foi planeado foi, também, um dos pontos fortes, na medida em que me proporcionou uma passagem por todos os setores dos Serviços Farmacêuticos do IPOCFG, E.P.E.

A primeira passagem foi pela área da distribuição tradicional de medicamentos e armazenamento e permitiu que contactasse com os processos utilizados na receção de encomendas, o seu armazenamento nos locais indicados, de acordo com a sua tipologia. Todos os medicamentos são armazenados segundo a Norma nº 020/2014, da Direção-Geral de Saúde, que define a lista de medicamentos LASA [3], por forma a evitar erros na dispensa de medicação. Também, todos eles são colocados nos locais devidos obedecendo ao princípio «*First In, First Out»,* por forma a garantir que se escoam primeiro os medicamentos mais antigos, evitando-se, assim, perdas por uso negligente. Nesta área, é também desenvolvido o armazenamento de materiais inflamáveis, gases medicinais e soros/injetáveis de grande volume, que, também, tive a oportunidade de presenciar e observar a maneira como é feito. Neste período, as tarefas além da receção de medicamentos e matérias passavam por auxiliar na dispensa dos medicamentos para os serviços dos hospitais e, ainda, a preparação de algumas formas magistrais como a Suspensão de Nistatina para bochechos (solução usada para evitar a xerose bocal provocada pela quimioterapia), no setor da farmacotecnia.

Numa segunda instância, passei para o setor da distribuição individualizada em dose unitária que visa a preparação de gavetas individualizadas para os serviços que possuem doentes em regime de internamento. Estive neste setor durante duas semanas onde acompanhei de perto a forma como o farmacêutico responsável por cada serviço de internamento do hospital faz a validação da medicação prescrita para cada doente em função de uma ficha onde constam todos os parâmetros que caracterizam o doente. Auxiliava também os TDTs na preparação dos volumes de gavetas que seguiam para os serviços. Este trabalho permitiu-me perceber como é feita a validação farmacêutica das terapêuticas instituídas pelos médicos e, ainda, contactar com quais os medicamentos que seguem para cada serviço e a sua razão.

Posteriormente, passei para o ambulatório onde se tem o maior contacto com os medicamentos antineoplásicos e onde tive a noção de quais os protocolos terapêuticos aplicados em cada caso de cancro. Como já referi, foi também o local onde o contato com os doentes foi mais constante. Após esta semana no ambulatório, passei uma semana pela unidade

de preparação de radiofármacos, onde presenciei a preparação das soluções utilizadas para diagnóstico de massas cancerígenas utilizando material radioativo como o tecnécio^{99}.

Por último, assisti à preparação dos protocolos de quimioterapia intravenosa que são preparados nos serviços farmacêuticos, no setor da Unidade de Preparação de Citostáticos (UPC), onde presenciei a forma como é feita a validação destes protocolos e a forma como estes envolvem médicos (prescrição), farmacêuticos (validação) e enfermeiros (administração) numa rede interligada em todos os momentos. Pude, ainda, neste setor auxiliar o trabalho dos TDTs na preparação dos citotóxicos nas camaras de segurança biológica.

Este estágio permitiu-me, nestes moldes, contactar com o medicamento em todas as fases do seu ciclo em meio hospitalar, desde a sua receção à sua dispensa e, ainda, verificar qual o papel do farmacêutico em cada uma dessas etapas.

3.1.3. Trabalhos de pesquisa

Foi me solicitado um trabalho de pesquisa, aquando da minha passagem pelo setor do ambulatório, onde tinha de reunir as informações mais úteis para o doente a partir do RCM do medicamento antineoplásico e coloca-las num documento de fácil consulta e intuitivo para os doentes consultarem. Neste documento constavam informações como o nome do medicamento, reações adversas mais frequentes, protocolos a seguir em caso de esquecer toma ou vomitar, interações com outros medicamentos e/ou alimentos, precauções a ter depois da toma como a condução, entre outras. Este documento servia para ficar no arquivo e ser entregue ao doente aquando da dispensa do medicamento em causa. Com este trabalho consegui aprofundar os meus conhecimentos sobre os fármacos em causa e ainda, prestar um serviço aos doentes, uma vez que, estas informações reunidas desta forma intuitiva permitem uma mais fácil compreensão de todos (Anexo 1).

3.1.4. Equipa Multidisciplinar

O contacto com uma vasta equipa de profissionais desde TDTs a farmacêuticos passando por auxiliares e assistentes revelou-se uma enorme vantagem no processo de integração e aprendizagem na medida em que pude perceber quais as tarefas de cada um incorporadas um mesmo serviço e a forma como cooperam de modo a satisfazer os doentes. Juntos, garantem uma gestão eficaz do medicamento garantindo o seu uso racional e responsável.

3.2. Pontos Fracos

3.2.1. Caracter observacional do estágio

Uma das coisas que me fez sentir mais reticente no final do estágio foi o facto de o contacto prático com cada uma das funções que observei ser próximo de nulo. Apesar de compreender que fruto da responsabilidade que é a farmácia de um hospital há tarefas que um estagiário não pode desempenhar embora ache que devia estar melhor organizado de modo a que pudéssemos contactar mais, de forma prática, com as funções que o farmacêutico desempenha.

3.2.2. Falta de conhecimentos na área

Existiram certos momentos, principalmente quando confrontado com terapêuticas, em que me senti um pouco perdido pelo facto de não possuir conhecimentos precisos de quais seriam e para que caso se aplicavam. Penso que isto acontece pelo facto de no MICF ser uma área pouco abordada ou, para bem dizer, abordada muito superficialmente. De realçar, também, que toda a equipa do IPOCFG,E.P.E. me ajudou muito nesta parte, esclarecendo todas as dúvidas que tivesse e dando-me materiais onde pudesse efetuar pesquisa por forma a ficar mais dentro do tema. Ainda assim, acho que o MICF devia tentar incluir nos seus conteúdos programáticos uma visão mais aprofundada deste tema, uma vez que é uma doença, infelizmente, cada vez mais do dia a dia e que é importante que um farmacêutico entenda quais são os protocolos utilizados no seu tratamento.

3.3. Oportunidades

3.3.1. Controlo de *Stocks* dos serviços

Neste hospital, apenas o Hospital de dia recebe, semanalmente, TDTs dos Serviços Farmacêuticos para controlo de *stocks* dos medicamentos que estão nos serviços com posterior envio dos medicamentos em falta. Isto é uma medida que impede medicamentos em excesso nos serviços. Nos outros serviços do hospital, o controlo é feito pelo enfermeiro-chefe, sendo que por vezes são solicitadas mais quantidades que as necessárias. Assim, para uma melhor gestão e controlo pelos serviços farmacêuticos das quantidades e de quais os medicamentos que estão em cada serviço, esta tarefa devia ser efetuada por membros deste serviço por forma a garantir uma gestão mais eficaz do medicamento.

3.4.Ameaças

3.4.1.Distância ente Farmacêuticos e Doentes

Face à conjuntura do Pais é muito difícil ter um farmacêutico à cabeceira de cada doente mas penso que devia existir um maior acompanhamento presencial por parte dos farmacêuticos dos doentes em regime de internamento. O facto de o farmacêutico apenas participar em visitas médicas em alguns dos serviços do IPOCFG, E.P.E., dificulta a sua prática profissional visto que lhe podem escapar parâmetros importantes para a validação da prescrição médica instituída. Assim, seria importante, para um melhor acompanhamento dos doentes, a presença de um farmacêutico junto do médico em todas as visitas médicas.

3.4.2.Escolha e aquisição de Medicamentos

O processo de escolha de medicamentos é feito segundo um concurso público, ao inicio de cada ano civil. É um processo que envolve muita demora e burocracias, o que pode comprometer o acesso à terapêutica e onde o único critério de seleção é, exclusivamente, o preço. Assim, todos os anos ocorrem mudanças de laboratórios e medicamentos, o que pode comprometer adesão à terapêutica ou, até mesmo, o comprometimento de algumas.

4.Conclusão

Esta passagem pelos Serviços Farmacêuticos do IPOCFG, E.P.E. foi, sem dúvida, uma experiência muito enriquecedora e que me permitiu um contacto com uma vertente farmacêutica diferente das que já tinha experienciado. No final, saio com a certeza firme de que o papel do farmacêutico hospitalar, embora por vezes na penumbra, é um suporte dos cuidados de saúde que são prestados nas instituições de saúde de Portugal. Apesar de ter sido um curto espaço de tempo, dois meses, foi uma enorme aprendizagem que não se centrou, apenas, em conhecimentos técnico-científicos, mas, também, num alargar de horizontes humanísticos pelo contacto com os doentes.

Considero, ainda, que esta é uma área que necessita de uma reestruturação onde seja potenciada a sua expressão e contacto com os doentes e onde seja mais fácil o ingresso. Espero, ainda, que os dois decretos de lei aprovados em 20 de julho de 2017 e onde se estabeleceu o regime legal da carreira especial farmacêutica na Administração Pública sejam o mote para este processo de reestruturação.

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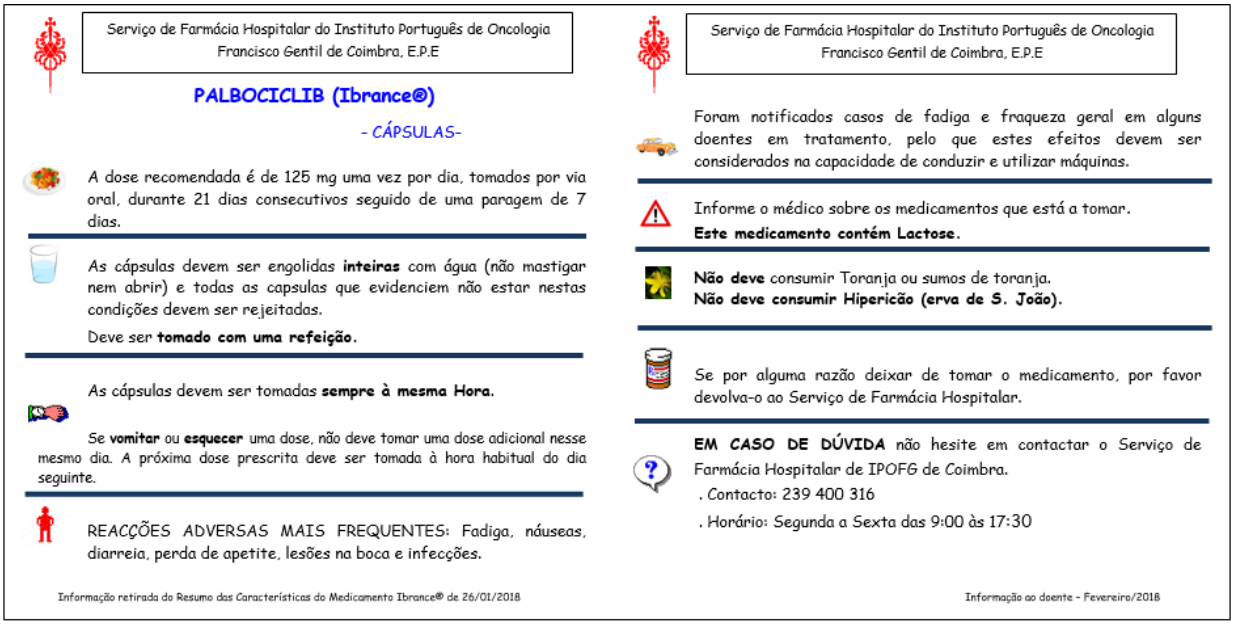
6.Anexo I

Na imagens seguintes encontram-se dois dos folhetos informativos cedidos no ambulatório do IPOCFG, E.P.E..



Serviço de Farmácia Hospitalar do Instituto Português de Oncologia Francisco Gentil de Coimbra, E.P.E

PALBOCICLIB (Ibrance®)

- CÁPSULAS-

A dose recomendada é de 125 mg uma vez por dia, tomados por via oral, durante 21 dias consecutivos seguido de uma paragem de 7 dias.

As cápsulas devem ser engolidas **inteiras** com água (não mastigar nem abrir) e todas as capsulas que evidenciem não estar nestas condições devem ser rejeitadas.

Deve ser **tomado com uma refeição.**

As cápsulas devem ser tomadas **sempre à mesma Hora.**

Se **vomitar** ou **esquecer** uma dose, não deve tomar uma dose adicional nesse mesmo dia. A próxima dose prescrita deve ser tomada à hora habitual do dia seguinte.

REACÇÕES ADVERSAS MAIS FREQUENTES: Fadiga, náuseas, diarreia, perda de apetite, lesões na boca e infecções.

Informação retirada do Resumo das Características do Medicamento Ibrance® de 26/01/2018

Serviço de Farmácia Hospitalar do Instituto Português de Oncologia Francisco Gentil de Coimbra, E.P.E

Foram notificados casos de fadiga e fraqueza geral em alguns doentes em tratamento, pelo que estes efeitos devem ser considerados na capacidade de conduzir e utilizar máquinas.

Informe o médico sobre os medicamentos que está a tomar.
Este medicamento contém Lactose.

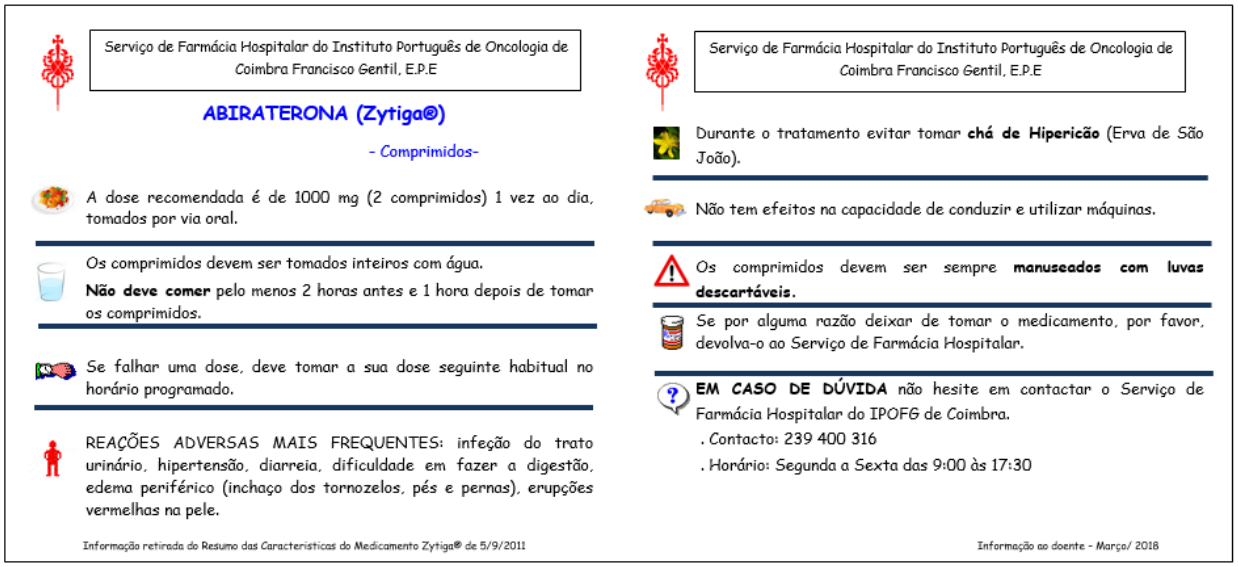
Não deve consumir Toranja ou sumos de toranja.
Não deve consumir Hipericão (erva de S. João).

Se por alguma razão deixar de tomar o medicamento, por favor devolva-o ao Serviço de Farmácia Hospitalar.

EM CASO DE DÚVIDA não hesite em contactar o Serviço de Farmácia Hospitalar de IPOFG de Coimbra.
. Contacto: 239 400 316
. Horário: Segunda a Sexta das 9:00 às 17:30

Informação ao doente - Fevereiro/2018

Imagem 1: Folheto informativo do fármaco Palbociclib cedido no IPOCFG,E.P.E cedido em ambulatório.



Serviço de Farmácia Hospitalar do Instituto Português de Oncologia de Coimbra Francisco Gentil, E.P.E

ABIRATERONA (Zytiga®)

- Comprimidos-

A dose recomendada é de 1000 mg (2 comprimidos) 1 vez ao dia, tomados por via oral.

Os comprimidos devem ser tomados inteiros com água.
Não deve comer pelo menos 2 horas antes e 1 hora depois de tomar os comprimidos.

Se falhar uma dose, deve tomar a sua dose seguinte habitual no horário programado.

REAÇÕES ADVERSAS MAIS FREQUENTES: infeção do trato urinário, hipertensão, diarreia, dificuldade em fazer a digestão, edema periférico (inchaço dos tornozelos, pés e pernas), erupções vermelhas na pele.

Informação retirada do Resumo das Caracteristicas do Medicamento Zytiga® de 5/9/2011

Serviço de Farmácia Hospitalar do Instituto Português de Oncologia de Coimbra Francisco Gentil, E.P.E

Durante o tratamento evitar tomar **chá de Hipericão** (Erva de São João).

Não tem efeitos na capacidade de conduzir e utilizar máquinas.

Os comprimidos devem ser sempre **manuseados com luvas descartáveis.**

Se por alguma razão deixar de tomar o medicamento, por favor, devolva-o ao Serviço de Farmácia Hospitalar.

EM CASO DE DÚVIDA não hesite em contactar o Serviço de Farmácia Hospitalar do IPOFG de Coimbra.
. Contacto: 239 400 316
. Horário: Segunda a Sexta das 9:00 às 17:30

Informação ao doente - Março/ 2018

Imagem 2: Folheto informativo do fármaco Abiraterona cedido no IPOCFG,E.P.E cedido em ambulatório.

Parte II

Relatório de Estágio em Farmácia Comunitária

(Farmácia Alves Coimbra)

Abreviaturas

AINE – Anti-Inflamatórios Não Esteroides

DCI – Denominação Comum Internacional

MICF – Mestrado Integrado em Ciências Farmacêuticas

MNSRM – Medicamento Não Sujeito a Receita Médica

MSRM – Medicamento Sujeito a Receita Médica

1. Introdução

Das muitas atividades onde o serviço farmacêutico se pode integrar, a farmácia comunitária assume o maior local de ação direta entre o profissional de saúde e os indivíduos da sociedade, é o local onde o farmacêutico pode exercer maior influência sobre a saúde dos militantes da sociedade. Mais ainda pelo facto de, atualmente, a farmácia se assumir como a primeira escolha à qual a sociedade recorre na procura de esclarecimentos relacionados com a sua saúde ou com a sua terapêutica, estando o farmacêutico no centro dessa interação. Embora se assumam também como o último local de contacto entre um profissional de saúde e o utente, uma vez que é o local onde recorrem após contacto com outros profissionais de saúde e a partir do qual iniciam ou modificam terapêuticas, assumindo o farmacêutico uma posição fulcral para garantir que as terapêuticas prescritas tenham o maior sucesso.

Este estágio em farmácia comunitária surge, assim, no seguimento da Diretiva 2013/55/EU, do Parlamento Europeu e do Conselho, de 20 de novembro de 2013 que, no artigo 44º, ratifica seis meses de estágio curricular em farmácia comunitária e/ou hospitalar para a formação de acesso ao título de farmacêutico [1]. Assim, no âmbito da conclusão do Mestrado Integrado em Ciências farmacêuticas (MICF), realizei o estágio de farmácia comunitária na Farmácia Alves Coimbra, em Penacova, entre o dia 12 de março e o dia 28 de junho de 2018, com orientação do Dr. João Monteiro.

Este estágio acaba por ser um momento de elevada aprendizagem para qualquer futuro farmacêutico, levando a que este fomente o contacto com os utentes, que seja sujeito à pressão das escolhas do utente e às suas dúvidas momentâneas, levando ao teste dos conhecimentos aprendidos durante a realização do curso. Permite ainda observar a multiplicidade de serviços que uma farmácia contempla e para o qual o farmacêutico tem de estar informado afim de garantir o bom funcionamento da mesma e o bem-estar e saúde dos utentes, que é o principal foco.

O presente relatório serve para relatar a experiência de estágio na Farmácia Alves Coimbra, uma farmácia bem-conceituada no centro da Vila de Penacova. Face a isto, enumero através de uma análise SWOT (*Strenghts, Weaknesses, Opportunities* e *Threats*) uma retrospectiva do que foi este estágio, focando os pontos fortes a manter, os pontos fracos a melhorar, as oportunidades que podem ser implementadas e as ameaças que se devem tentar ultrapassar.

2. Sistema Operativo

O *software* utilizado é o Spharm, criado e desenvolvido pela SoftReis e que se caracteriza por ser um programa de utilização fácil e intuitiva, preparado para o operador conseguir resolver questões de forma rápida, facilitando o atendimento. Permite gestão de compras, vendas, *stocks* e validades. Também permite a criação de fichas de utentes, assim estes concordem, onde ficam armazenadas diversas informações relativas ao doente e a toda a medicação que já lhe foi cedida, permitindo um melhor aconselhamento e conhecimento do utente e evita erros de cedência. É muito importante já que, no ato da dispensa, permite aceder à composição quantitativa e qualitativa do medicamento, potenciais interações, posologias e, ainda, a um grande número de RCM.

Faz a gestão de *stocks* de forma automática, enviando as encomendas ao fornecedor de forma a manter sempre o *stock* estabelecido para aquele fármaco e laboratório. Também possui formulário específico para a cedência de Psicotrópicos, processamento de devoluções, entre outras funcionalidades como a visualização de gráfico de vendas de um certo produto.

3. Análise SWOT

Pontos Fortes	Pontos Fracos	Oportunidades	Ameaças
Localização e Horário	Conteúdos programáticos do MICF	Dermocosmética	Outros locais de Venda de MNSRM
Equipa técnica	Associação entre nomes comerciais dos medicamentos e princípios ativos	Formações	
Fidelização dos utentes	Preparação de manipulados	Serviços disponibilizados na farmácia	
Gestão e dinamização da farmácia			
Conferencia de receituário e receção de encomendas			
Aconselhamento Farmacêutico			

Tabela 1: Análise SWOT do meu estágio curricular em Farmácia Comunitária.

3.1. Pontos Fortes

3.1.1. Localização e horário de funcionamento da farmácia

A farmácia Alves Coimbra situa-se, atualmente, na Avenida António Gomes nº1, em Penacova. É uma das duas farmácias que existem na vila. Alterou recentemente as suas instalações para as proximidades do Centro de saúde obtendo, assim, uma posição privilegiada, estando, como exige a Portaria nº.1430/2007 [2], a 100 metros em linha reta dos limites exteriores do Centro de saúde. Além do centro de saúde, existem ainda, a poucos metros, três clínicas, sendo uma especializada em serviços de cardiologia, bem como uma extensão de serviços dentários e outra que oferece serviços especializados de ginecologia, dermatologia, entre outros serviços. A terceira destina-se apenas a serviços veterinários. Face a isto, o grupo de utentes que se deslocam à farmácia é muito heterogéneo no que se refere a faixas etárias e recursos cognitivos e monetários. Além destes utentes ocasionais, existem muitos outros que se encontram fidelizados aos serviços e recorrem a eles para obter a medicação e as informações necessárias às suas terapêuticas contínuas, facilitando o contacto Farmacêutico-utente e permitindo, assim, uma melhor intervenção por parte do profissional de saúde. Outra das vantagens da localização, é o facto de ser fácil a comunicação entre o médico prescritor e o farmacêutico, facilitando pequenas alterações e esclarecimento de dúvidas no sentido de

fornecer ao doente as melhores informações. O funcionamento da farmácia é de Segunda a Sexta das 8 horas e 30 minutos às 21 horas, sendo que aos sábados se encontra aberta das 9 às 13 horas, encerrando para almoço até às 14h e 30 minutos, reabrindo no período da tarde até às 18 horas e 30 minutos. Este horário está bem visível na porta principal, sendo também bem percetível quando a farmácia se encontra em serviço permanente. Este ocorre em períodos intervalados de uma semana (na semana de interregno está em serviço permanente a outra farmácia da vila) estando a farmácia aberta de forma continua durante 24h, inclusive Domingos e Feriados. Durante estas semanas de serviço permanente, após as 21h, o atendimento é feito via Postigo até à hora de abertura do dia seguinte.

3.1.2. Equipa técnica

Quanto aos recursos humanos, apoia-se numa equipa de Farmacêuticos e Técnicos jovem e motivada, que junta as capacidades técnico-científicas à total disponibilidade para satisfação das necessidades e exigência dos utentes, usando a fácil empatia e a simpatia para garantir a fidelização e bem-estar dos utentes. Segundo o decreto-lei 171/2012, de 1 de agosto [3], o pessoal que integra os serviços da farmácia está no quadro Farmacêutico e Não-farmacêutico, tendo a Farmácia Alves Coimbra a seguintes constituição:

Dra. Maria Manuela Gonçalves	Diretora Técnica
Dr. João Monteiro	Farmacêutico
Bruno Clemente	Técnico de Farmácia
Paulo Dinis	Técnico de Farmácia
Vítor Silva	Técnico de Farmácia
Graça Paiva	Técnica de Farmácia
Dra. Cláudia Torres	Nutricionista
Dra. Cátia	Podologista

Tabela 2: Equipa técnica da farmácia Alves Coimbra.

Todos os profissionais que prestam serviços na farmácia se encontram devidamente identificados, com cartão com nome e título profissional.

Cada membro da equipa tem funções especificas, nomeadamente, gestão de encomendas e de produtos, dinamização e marketing, receção de encomendas, conferência do receituário, entre outras. Embora todos se encontrem apetrechados para fazer aconselhamento ao Balcão. Esta especificação de tarefas acaba por ser uma vantagem, e acabou

por ser importante no meu processo de aprendizagem, uma vez que para cada questão, sabia sempre a quem recorrer.

3.1.3. Fidelização dos utentes

É o lema utente satisfeito é utente fidelizado que define a máxima de trabalho na Farmácia Alves Coimbra e este surge no sentido de prestar os melhores cuidados e aconselhamentos a todos os utentes da farmácia, sendo esta uma das preocupações constantes de toda a equipa. Durante o estágio, tive oportunidade de perceber o que é uma farmácia cuja fidelização assume mais de 80% dos utentes diários e que muitas vezes chegam mesmo a procurar membros específicos da equipa técnica, um ponto forte no meu ponto de vista. Uma boa base de utentes fidelizados é muito importante para a saúde financeira de uma farmácia e espelha a qualidade de serviço. De referir também a elevada confiança e compreensão de todos os utentes que tive a honra de aconselhar ao balcão, pondo de parte um medo que tinha de ser menosprezado pelo facto de ser cara nova e ser estagiário. No entanto, isso não se sucedeu nunca e houve uma recetividade por parte dos utentes para que fosse eu a atendê-los.

3.1.4. Gestão e dinamização da farmácia

Dos maiores pontos fortes deste estágio foi, sem dúvida, toda a aprendizagem relacionada com o funcionamento do *backoffice* da farmácia. Desde o início que pude auxiliar no desempenho de inúmeras tarefas como conferência e receção de encomendas, armazenamento dos medicamentos, gestão de devoluções, organização de lineares, gestão de campanhas, conferência de faturas, revisão do receituário, contagem física de *stocks*, entre outros. O facto de poder ter desempenhado estas tarefas, logo desde o início do estágio, permitiu que entendesse melhor a forma como se processa o funcionamento da farmácia, bem como toda a dinâmica do circuito do medicamento e a conhecer melhor a apresentação física de cada um dos medicamentos, o que me foi muito vantajoso aquando da transição para o balcão, já que era muito mais fácil saber onde estava e utilizar o tempo do atendimento para aconselhar o utente. Além de que, estas tarefas são fundamentais para o bom funcionamento de uma farmácia. Em termos de dinamização da farmácia e dos seus produtos, também acompanhei o destaque que se ia dando aos produtos sazonais e/ou abrangidos por campanhas especiais, que eram expostos em zonas quentes, isto é, com maior visibilidade, de acordo com as regras do *marketing*.

3.1.5. Conferência de receituário e receção de encomendas

Hoje em dia, a conferência do receituário é uma tarefa de muito pouco volume face ao que se verificava antes pelo facto de a maioria das receitas ser desmaterializada. Embora, mesmo com pouco volume é uma tarefa de extrema importância para uma farmácia, uma vez que um simples erro pode comprometer o pagamento de um dado valor de comparticipação, quer por parte do Estado, quer por parte de outras entidades comparticipadoras (que ali existia muito, já que muitos dos utentes eram beneficiários).

Durante o estágio pude contactar com alguns tipos de receitas e diversos tipos de organismos de comparticipação e fiz a conferência supervisionada de alguns lotes de receitas e considero que foi uma boa aprendizagem, que embora se vá usar cada vez menos, é importante saber como se faz pois existem casos onde num dia podemos estar sujeitos apenas a receitas manuais e é importante saber como verifica-las para evitar perdas de dinheiro. Desde o início do estágio que também contactei de perto com todo o processo de receção de encomendas, quer encomendas diárias, quer encomendas diretas que a farmácia faz aos diversos laboratórios. Considero este um processo muito importante para o bom funcionamento da farmácia, pelo que foi bastante proveitoso perceber e compreender a gestão que tem de ser feita todos os dias para que estejam disponíveis, em tempo útil, os produtos e os medicamentos que os utentes necessitam. Assim, tive oportunidade de realizar tarefas como conferencia de encomendas, receção de encomendas no sistema informático e gestão de produtos e medicamentos reservados para utentes específicos. Pude também fazer, algumas vezes, a criação de encomendas diárias para armazenistas e encomendas para determinados laboratórios.

3.1.6. Aconselhamento farmacêutico

O papel do farmacêutico, ao nível da farmácia comunitária, é muito mais do que o ato de dispensa de medicamentos. Trata-se de ir ao encontro dos problemas e dúvidas do utente e esclarecê-lo da melhor forma relativamente à sua terapêutica. As funções do farmacêutico passam, assim, por educar o utente para questões de saúde pública, ceder os medicamentos e acompanhar o seu processo terapêutico. Todas estas funções são um desafio diário, que implicam um conhecimento muito abrangente de várias matérias. Deste modo, o maior desafio é sem dúvida o atendimento ao balcão e o aconselhamento farmacêutico. Felizmente, pouco depois do início do estágio tive oportunidade de ir acompanhando o atendimento ao público de vários elementos da equipa técnica, tendo esta aprendizagem sido essencial para os meus próprios atendimentos. Este processo foi essencial para esclarecer todas as dúvidas que

tinha em relação ao sistema informático *Spharm* e para observar os aconselhamentos farmacêuticos prestados aos utentes. Esta foi, sem dúvida, a tarefa que mais contribuiu para o meu crescimento enquanto futuro farmacêutico, dando-me a perceção de que o farmacêutico pode ter um papel preponderante na escolha da terapêutica mais adequada para cada utente. Por exemplo, foram inúmeras as situações em que surgiam utentes com dores de garganta, fruto da época em que iniciei os atendimentos ser propicia a resfriados. Nestas situações, optava por a cedência das pastilhas antissépticas e anestésicas Strepsils®, se em virtude das questões colocadas observa-se que se tratava apenas de uma situação aguda. Tive outro caso onde a senhora, quando a questionei se tinha alguma contraindicação a medicamentos, me disse que tinha tido um enfarte há cerca de 1 ano, ai optei por as pastilhas Euphon® já que estas são desprovidas de AINE´s e assim evitava a possibilidade de ocorrência de hemorragias. Em ambas dizia que deviam ser colocadas na boca até dissolução total, e deviam ser espaçadas de 2-3horas e não utilizadas por períodos superiores a 3 dias. A sintomatologia de nariz entupido também era algo frequente e em caso de febre ausente, optava por um Rhinomer® (solução hipertónica salina), com aplicação, normalmente, de 4 vezes por dia em cada narina. Outro caso que me chamou à atenção foi uma senhora que foi à farmácia levantar a medicação da mãe acamada e me solicitou 4 caixas de supositórios Dulcolax® e ainda mais 4 de comprimidos. Achei estranho e questionei se já tinha experimentado outro tipo de soluções que não estes laxantes de contacto, disse-me que só estes é que resultavam eficazmente. Solicitei que levasse um laxante expansor de volume para experimentar, alertando que os efeitos não seriam notórios com tanta rapidez, mas que estes iriam obrigar o intestino a estimular o peristaltismo de forma mais natural e que não eram tao nocivos numa situação crónica. Disse ainda que devia experimentar uma alimentação mais rica em fibras vegetais para de forma natural também conseguir aumentar o peristaltismo.

3.2. Pontos Fracos

3.2.1. Conteúdos programáticos do MICF

Depois de passar pela experiência do estágio, que nos aproxima mais do que é a realidade da farmácia comunitária, sou da opinião que é necessário fazer um ajuste dos conteúdos programáticos do MICF, de forma a adequa-los mais à realidade da prática profissional do farmacêutico. Apesar de considerar que a formação adquirida durante o MICF é da máxima importância, por vezes senti algumas dificuldades em determinadas áreas e matérias como preparações de uso veterinário, dermocosméticos e medicamentos oftálmicos. Apesar de alguns destes conteúdos já serem abordados ao nível do MICF, penso que deveriam

ser mais aprofundados, dada a sua relevância e a expressão que têm ao nível da farmácia, permitindo assim que os conhecimentos nestas áreas estejam mais consolidados.

3.2.2. Associação entre nomes comerciais e princípios ativos

Uma das principais dificuldades para qualquer estagiário é a associação entre os nomes comerciais dos medicamentes e os princípios ativos, sendo que eu não fui exceção. Neste aspeto, é muito importante o trabalho de backoffice, uma vez que permite ir fazendo essa associação com tempo e sem a pressão de estarmos perante um utente bem como a recepção de encomendas e o seu armazenamento, que facilitam o conhecimento de alguns nomes e apresentações físicas bem como o local onde se encontram. Esta questão assume ainda mais importância quando os próprios utentes não sabem o medicamento que tomam normalmente, tendo assistido a algumas situações em que, também devido à minha falta de experiência, foi complicado identificar o medicamento que o utente pretendia, valendo-me o facto de muitos deles serem fidelizados e poder aceder à última prescrição. Neste sentido, e apesar das prescrições médicas serem na sua maioria feitas por Denominação Comum Internacional (DCI), seria importante, ao longo do MICF, ir introduzindo alguns nomes comerciais, uma vez que são uma realidade durante a vida profissional dos farmacêuticos.

3.2.3. Preparação de Medicamentos Manipulados

Os medicamentos manipulados assumem um papel importante em patologias específicas, como a sarna, em situações de ajuste de dose, muito comuns em pediatria, ou no sentido de obter preparações que ainda não existam no mercado, quer devido à sua baixa rentabilidade económica, quer à fraca estabilidade dos seus constituintes. Este foi dos pontos mais fracos que identifiquei, uma vez que, na Farmácia Alves Coimbra não é uma prática devido à baixa solicitação que não justificava uma unidade de preparação de Manipulados, a sua preparação foi retirada das instalações, sendo que os Manipulados requisitados na Farmácia Alves Coimbra eram pedidos a outras farmácias do grupo. Assim, nunca tive a oportunidade de executar um, nem de preencher a sua ficha de cálculo de preço.

3.3. Oportunidades

3.3.1. Dermocosmética

Só há pouco tempo a Farmácia Alves Coimbra investiu numa maior gama destes produtos, muito fruto da abertura da clínica de Dermatologia nas imediações e da maior procura destes produtos. Nos últimos tempos, representantes das várias gamas que a farmácia

começou a adquirir levaram até à farmácia formações afim de elevar os conhecimentos da equipa técnica acerca dos produtos e potenciar as suas vendas e rotação. Embora muito já esteja implementado, considero que ainda pode ser feito muito mais por este ramo que é cada vez mais solicitado a nível das farmácias comunitárias.

3.3.2. Formações

Durante o estágio tive a oportunidade de participar em algumas formações, quer em relação a produtos de cosmética, quer em relação a dispositivos médicos ou suplementos alimentares. Além de toda a aprendizagem do dia a dia, mensalmente havia sempre formações. Na minha opinião, estas formações são importantes para se esclarecerem algumas dúvidas em relação a produtos que não conhecemos tão bem, de forma a responder às necessidades e às dúvidas dos utentes da melhor forma, pois só assim podemos acrescentar valor ao utente e a farmácia.

3.3.3. Serviços disponibilizados pela farmácia

A Farmácia Alves Coimbra tem ao dispor dos seus utentes um leque de serviços, que além de contribuírem para uma dinamização maior do espaço da farmácia, oferecem mais valias para os utentes. Por diversas vezes, ao longo do estágio, pude observar e participar na medição de parâmetros bioquímicos, nomeadamente medição da tensão arterial, da glicémia e do colesterol total, um serviço realizado pelos farmacêuticos e restante equipa técnica. Estes serviços são cada vez mais requisitados pelos utentes e permitem conhecer melhor a forma como a medicação, caso estejam a fazer, está a sofrer o efeito desejado. Além destes serviços, a farmácia tem disponível um serviço de consultas de nutrição (todas as quintas-feiras das 15h às 20h) e de podologia (todas as Sextas das 15h às 20h), dois serviços que além de acrescentarem valor ao utente, contribuem muito para o valor da farmácia. Ainda assim, considero que seja importante explorar outro tipo de serviços farmacêuticos, ou seja, revisão da medicação, organização semanal da medicação e acompanhamento farmacoterapêutico, serviços bastante importantes e que podem ser extremamente úteis principalmente para a população mais idosa.

3.4. Ameaças

3.4.1. Locais de venda de MNSRM

No nosso país, o mercado dos Medicamentos Não Sujeitos a Receita Médica (MNSRM) foi liberalizado em 2005, com a autorização de venda destes medicamentos fora das farmácias e o sob um regime de preços livre. Esta liberalização levou a uma grande procura de MNSRM noutros locais autorizados, que não a farmácia, por serem, à partida, mais baratos pelo facto de as grandes superfícies comerciais conseguirem negociar um grande volume de compras conseguindo melhores condições comerciais e, dessa forma, praticar preços mais apelativos para os utentes. No entanto, existe um serviço que diferencia as farmácias, em relação as estes locais: o aconselhamento por parte do farmacêutico, que bem utilizado, se assume como um fator chave na escolha das farmácias em detrimento desses postos de venda de MNSRM, prevenindo possíveis erros relacionados com a automedicação. Esta liberalização da venda de MNSRM constitui uma ameaça em termos económicos para as farmácias, aliada à descida do preço dos Medicamentos Sujeitos a Receita Médica (MSRM), tendo levado a uma diminuição da rentabilidade das farmácias, nos últimos anos. No sentido de contradizer esta tendência, a farmácia pode ter uma ação diferenciadora através do aconselhamento e conhecimento técnico do farmacêutico.

4. Conclusão

Com a conclusão do meu estágio curricular posso afirmar que se tratou de uma experiência muito proveitosa para o meu desenvolvimento quer a nível pessoal quer a nível técnico-científico. Todas as etapas que passei ao longo deste estágio se revelaram uma mais valia para a consolidação dos conhecimentos adquiridos e para adquirir novos.

Com a sua realização consegui entender melhor qual o papel do farmacêutico na vida da sociedade bem como, a imensa responsabilidade que, sempre, deve estar presente no nosso quotidiano de forma a servir de forma exata e da melhor maneira possível os interesses e a saúde dos utentes que nos procuram.

Do vasto número de tarefas realizadas, a que me despertou mais interesse foi o atendimento ao balcão embora todas as outras atividades também tenham tido uma quota-parte importante no meu desenvolvimento pois aumentaram o meu número de conhecimentos e tornaram-me apto a reagir a qualquer adversidade com que seja confrontado no mercado de trabalho. Mas o atendimento ao balcão foi sem dúvida a mais desafiante e interessante pois cada pessoa tinha maneiras diferentes de ver as coisas, questionavam coisas

diferentes, solicitavam coisas diferentes e assim, tinha de me moldar a cada uma das pessoas que tinha na frente e isso explora muito os nossos conhecimentos. Neste aspeto também há que referir o enorme acompanhamento e ajuda que a equipa técnica da farmácia Alves Coimbra me proporcionou tanto em esclarecer melhor os utentes como no discurso a utilizar face a cada um deles.

Outra das coisas que se revelaram muito importantes para o sucesso do estágio foi a integração que tive a felicidade de conseguir dentro da equipa técnica da farmácia, que me colocou à vontade para questionar e esclarecer todo o tipo de dúvidas, colocar em prática todos os meus conhecimentos, aprender procedimentos e competências que desconhecia bem como aprender a vertente mais humana e social da profissão. Apesar da farmácia ser um local de prestação de serviços de saúde e de venda de medicamentos, na sua base é um negócio. Neste sentido, o estágio foi muito importante para perceber o balanço que deve existir em relação à ética profissional, de forma a que os valores negociais nunca se sobreponham aos valores da profissão farmacêutica. Neste aspeto, o objetivo primordial é cuidar da saúde do utente e satisfazer as suas necessidades, tentando também acrescentar valor à farmácia.

É de salientar que este estágio não encerra o processo de aprendizagem, visto se tratar de uma profissão de constante formação e aquisição de novos conhecimentos face às alterações que o mundo científico sofre em curtos espaços de tempo.

Por fim, deixar uma palavra de sincero agradecimento a toda a estrutura da farmácia Alves Coimbra pelo bom ambiente que me proporcionaram para conseguir aprender e pôr em prática 5 anos de aprendizagem, foi deveras importante que a primeira experiência no mundo real fosse feita desta forma e neste ambiente de amizade e partilha mútua, de ajuda e disponibilidade total para qualquer esclarecimento.

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Parte III

Nanotechnology approaches for the topical delivery of Minoxidil

Abbreviations

5-α-R: 5-α-Reductase

AGA: Androgenic Alopecia

AA: Areata Aalopecia

BMP- Bone Morphogenic Protein

CD: Cyclodextrin

COL: Chitosan Oligosaccharide Lactato

DHT: Dihydrotestosterone

DP: Dermal Papilla

DSC: Differencial Scanning Calorymetry

EGF: Epidermal Growth Factor

EMA: European Medicin Agency

FGF: Folicullar Growth Factor

FT-IR: Fourier-Transform Infrared Spectroscopy

HP-β- CD: Hydroxypropil-Cyclodextrin

HPLC: High Performance Liquid Chromatography

IGF: Insulin-Like Growth Factor

KATP: ATP Channel

LUV: Large Unilamellar Vesicle

Me-β-CD: Methyl-β-Cyclodextrin

MLV: Multilamellar Large Vesicle

MXD: MXD

NE: Nanoemulsion

NLC: Nanostructured Lipid Carrier

NMR: Nuclear Magnetic Resonance

O/W: Oil in Water

O/W/O: Oil in Water in Oil

PCL: Polycapolactone

PEV: Penetration Enhancer-Containing Vesicle

PLA: Polylactic Acid

PLGA: Poly(Lactic-co-Glycolic) Acid

PLO: Pluronic- Lecithin Organogel

PGA: Polyglycolic Acid

PVA: Polyvinyl Alcohol

ROX: Oxygen Radical

SLN: Solid Lipid Nanocarrier

SUV: Small Unilamellar Vesicle

SC: Stractum Corneum

TEWL: Transepidermal Water Loss

TSP: Thrombospondin

UV: UltraViolet

VEGF: Vascular Endothelial Growth Factor

1.Introduction

Minoxidil (MXD) belongs to the group of peripheral vasodilators, acting to reduce peripheral vascular resistance and reduce blood pressure. Thus, it is used as an antihypertensive in cases where a conventional therapy can not be used. It is also used in large scale in the therapy of androgenic alopecia for its vasodilatory characteristics, activating the ATP-dependent potassium channels (Chandrashekar, Nandhini *et al.,* 2015, Tricarico, Maqoud *et al.,* 2018). As topical application, its systemic absorption is reduced as well as its binding to plasma proteins upon oral administration. It is a growth of the scalp since it prolongs as anagenic and antiapoptotic phases in the dermal palettes of the follicles. It contains the cutaneous insertion pen, which limits the use in cutaneous treatments. The low solubility rate in water is therefore incorporated into the vehicle of alcoholic nature which contains ethanol, propylene glycol and water, but nevertheless has drawbacks, since when applied to the skin the alcohol evaporates and MXD crystals are formed which do not show the characteristics that are translated as cutaneous barriers and therefore the same in the area of the epidermis under the effect of and secondary and undesirable as eritrema, dermatitis and pruritus (Mali, Darandale *et al.,* 2013, Matos, Reis *et al.,* 2015). If absorbed at the level of the bloodstream, this molecule will be able to generate cardiovascular effects that can turn out to be harmful.

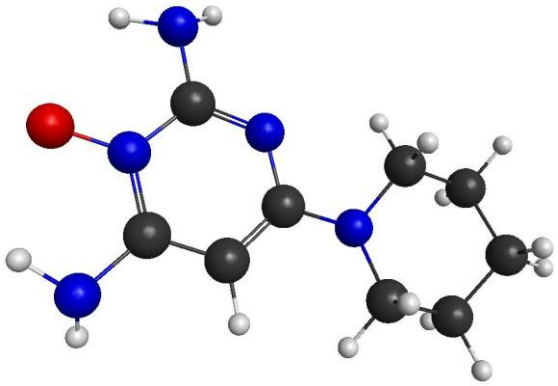


Image 1: MXD molecular structure.

Table 1: Chemical and physical properties of MXD.

Properties	Minoxidil	References
CAS registry number	38304-91-5	(O'Neil, Smith *et al.,* 2001)
Chemical formula	$C_9H_{15}N_5O$	(O'Neil, Smith *et al.,* 2001)
Appearance	White to off-white, crystalline poder	(O'Neil, Smith *et al.,* 2001)
Odor	Odorless	(O'Neil, Smith *et al.,* 2001)
Zeta potencial	−42.40 mV	(O'Neil, Smith *et al.,* 2001)
Molecular weight	209.253 g/mol	(O'Neil, Smith *et al.,* 2001)
Water solubility	$2{,}2*10^{-3}$ g /mL	(O'Neil, Smith *et al.,* 2001)
Melting point	248 °C	(O'Neil, Smith *et al.,* 2001)
Partition Coefficient [log P (o/w)]	1.24	(Abd, Benson *et al.,* 2018)
pKa	4,6	(O'Neil, Smith *et al.,* 2001)
UV spectra	Maximum absorption (ethanol): 230, 261, 285 nm (0.01 N sulfuric acid: 232, 280 nm; (0.01 N potassium hydroxide): 231, 261.5, 285 nm	(O'Neil, Smith *et al.,* 2001)

Alopecia is a dermatological disease, commonly known as hair loss, which affects about 50% of Caucasians. It can be classified into 3 types: androgenic, areata and chemotherapy-induced (Santos, Avci *et al.,* 2015). It does not present as a deadly disease but is capable of causing high psychological effects that can lead to unpredictable behavior. This depressive state is related to the fact that it is a complication that leads to changes in appearance (Fang, Aljuffali *et al.,* 2014) and that causes discomfort in the patient(Mathes, Melero *et al.,* 2016). It can be caused by diet, stress and environmental changes and is characterized by an anagenic phase becoming smaller, with weaker and less thick follicles. It increases the speed with which it passes from the anagenic to the telogenic phase, leading to a final state of very few hair and very weak (Tsujimoto, Hara *et al.,* 2007) and with a gradual decrease in capillary density (Lopedota, Denora *et al.,* 2018).

The most common refers to androgenic, where there is a genetic variation of the follicles caused by Dihydrotestosterone (DHT) (Santos, Avci *et al.,* 2015) or due to poor circulation, which causes it to decrease the supply of follicular nutrients, reducing its regenerative capacity (Tsujimoto, Hara *et al.,* 2007) . This androgen acts on the hair follicles, decreasing them and, thus, causing loss of hair density. This compound is synthesized by the

enzyme 5-α-reductase (5-α-R) from adrenal steroids. This enzyme has three subtypes (5-α-R1, 5-α-R2, 5-α-R3) being responsible for the increase of DHT in the follicles the 5-α-R1. DHT inhibits capillary growth, reducing the anagen phase of the follicles, which reduces maturation and causes hair fibers to weaken and the transformation into thin and fragile follicles, leading to the absence of growth and its fall (Santos, Avci *et al.,* 2015).

MXD was the first drug approved for the treatment of alopecia (Canada in 1986) (Matos, Reis *et al.,* 2015), discovered because one of the side effects of its use was a strange heap of hair (Tricarico, Maqoud *et al.,* 2018).This was due to the discovery of its high potential in the increase of the expression of the endothelial growth factor to the level of the cells of the dermal papilla (DP) that leads to the capillary increase surrounding the hair follicles and that it reveals a great advantage in the capillary growth since, this capillary increase favors follicular development and its proliferation and growth(Tricarico, Maqoud *et al.,* 2018), increasing the anagen phase (Liao, Lu *et al.,* 2016) by potentiating β-Catenin activity (Matos, Reis *et al.,* 2015). By increasing the blood supply to the basal cells of the follicles, the flow of nutrients increases. In cells it is transformed into MXD sulphate and thus acts on the sulfonylurea receptor leading to the release of ATP that is decomposed by ATPase. This metabolite will act at the adenosine receptors of the cells of the DP, stimulating the production of VEGF that stimulates cell growth. It also acts at the genetic level leading to increased expression of genes such as those that give rise to caspases 3, 8 and 9 that are apoptotic inducers. Genes such as Wnt4, TGFβ2, SMAD7, UCP2, Knce, among others that are inducers of the anagen phase of the capillary cycle, whose expression increases this phase, and therefore, capillary growth. It also increases the transcription of inflammatory genes such as TNFα, Nfkb1 and Cgrp and also what causes stimulation of mitochondrial biogenesis, increasing cellular energy (Pgc1a). It also has action on the potassium-dependent ATP channel (KATP), increasing the expression of its subunits (Kir6.1 and SUR2B). Its performance in this channel and the induction of the gene AKT2 (gene that induces carcinogenesis), which is very active in the cells of the DP, greatly enhances its effects. Another effect attributed to it is the reduction of 5α-R, thus inhibiting the formation of DHT, which is responsible for hair loss(Tricarico, Maqoud *et al.,* 2018).

Sulfate transferase modulates the levels of tissue MXD and this metabolite controls the expression of prostaglandins such as D2 and E2 and also the phase in which the capillary cycle is found, favoring the entry into active growth, which is called an anagen phase. Thus, it favors the follicular cycle and increases hair growth(Tricarico, Maqoud *et al.,* 2018).

2.Hair

2.1.Physiology and structure

The skin is the largest organ of the human body and, therefore, is an efficient way for both dermatological and systemic therapy (Fang, Aljuffali *et al.,* 2014). It is assumed to be 16% of total body weight and with a high surface area, in the order of 1.8 m^2 (Hillery, Lloyd *et al.,* 2002). It consists of three layers: epidermis, dermis and subcutaneous tissue. It also presents complementary structures such as the nails, hair and the sebaceous, apocrine and eccrine glands (Barel, Paye *et al.,* 2014).

The epidermis is the most superficial barrier of this tissue and the human body. It is composed of a stratified epithelium that assumes a physical and chemical barrier to external agentsIt does not show blood vessels and the cells that make it are called keratinocytes that undergo differentiation from the basal layers to the most superficial layer. These cells have a barrier and secretory function, secreting proteins that lodge in their proximities creating in these spaces a kind of tissue of connection between the functional units of the epithelium. This tissue is subdivided into five layers that differ from each other in the differentiation state of keratinocytes (Hillery, Lloyd *et al.,* 2002). The inner most is called the basal stractum and is where the keratinocytes that have not yet been divided are found, and therefore the layer responsible for the onset of cell differentiation. Above this layer is the site where the highest percentage of reproduction and maturation of keratinocytes occurs and which already contains desmosomes (connectivity between keratinocytes) and languerhans cells (responsible for the immune response of the skin) and which is called the stratum spinosum. Immediately afterwards, we have the granular stratum where the cells have already been shown to be anucleated and with granular cytoplasm (keratohialin granules - allows the keratin ligaments to be connected due to the presence of histidine and cystine). The stratum lucidium is what makes the transition between the anterior and the *Stratum Corneum* (SC) (Barel, Paye *et al.,* 2014). The SC is the most sternal tissue and shows corneocytes in the final stage of maturation, that is, absent from cellular organelles involved by lipid bilayers (Hillery, Lloyd *et al.,* 2002). It consists of cholesterol, ceramides and fatty acids, acting as a barrier for external agents and also for drugs (Shim, Seok Kang *et al.,* 2004). One of the potentialities of this dermal layer is its functioning as a reservoir of water because it becomes adsorbed on the proteins that constitute the envelope surrounding the keratinocytes. One of these proteins is keratin, which in the hydrated state confers mechanical stability, preventing diffusion. It consists of a lipid and protein brick wall, where the lipids are not dispersed but organized in the extracellular spaces in the multilamellar form around the corneocytes (Elias and MENON 1991). These organized

lipid layers influence the permeability of this structure and cause different parts of the body to have different acceptations to the passage of molecules by diffusion. The lipids that comprise them also differ from place to place (Lampe, Burlingame *et al.,* 1983).This barrier is predominantly lipophilic due to its high lipid constitution and, therefore, drugs having these characteristics are more easily absorbed and accumulated, followed by a controlled release process in the tissues. It presents about 15-20 multilamellar layers, the cells having inside it keratin that is integrated in a matrix of filaggrin and may present different thicknesses, different number of corneodesmosomes, amount of keratin or filaggrin, depending on the differentiation and the composition of that place of the body (Prausnitz, Mitragotri *et al.,* 2004) undergoes a desquamation process every 2-3 weeks, which leads to the renewal of the surface corneocytes and, thus, reestablishes the properties of the cutaneous barrier. Its greatest function is to avoid losses, especially water, to avoid dehydration (Escobar-Chávez 2012).

The underlying layer is called Dermis and consists primarily of connective tissue. It represents 90% of its surface (Hillery, Lloyd *et al.,* 2002) of the skin and is divided in two layers: the papillary region that is superior and establishes contact with the dermis and the dermis-reticular region, that is situated in a position more in and near the subcutaneous barrier. The cells that comprise it are called fibroblasts that have expressive secretory capacity releasing collagen fibers (responsible for firmness and shape of the skin), proteoglycans (related to viscosity) and elastin (giving elasticity and cutaneous flexibility to the medium). Its primary function is to support the epidermal layer and to incorporate blood vessels, lymphatics and nerves. It has a dense network of vascularization that allows the absorption of topical compounds that penetrate this layer into the bloodstream. Below the dermis we have the subcutaneous tissue (Barel, Paye *et al.,* 2014).

Other structures to take into account in this tissue are the auxiliaries as is the case of hair follicles, nails, sweat glands and sebaceous. The hair follicles or capillaries occupy about 0.1% of the surface of the skin. But in the areas of the head and face these assume a percentage of 10%, which is a fairly high intensity when compared to other areas of the human body. The diameter of these also differs according to the part of the body considered, being the largest one reached in the zone of the hair(Fang, Aljuffali *et al.,* 2014). They are characterized by being a structure that interrupts the skin layer and allows the administration of compounds through the skin, allowing the entry of larger particles (Patzelt, Richter *et al.,* 2011).They are responsible for hair growth and come from the dermal layer. To the capillary follicle are attached various structures such as sebaceous glands, sodoriparas and mecanoreceptores that respond to touch. The stem is composed of three layers: cortex, medulla and cuticular structure and is

exposed to the exterior at the SC level. The cortex shows the granules of melanin, which depending on the granules it contains, impart color to the stem(Santos, Avci *et al.,* 2015). They have abundant keratin fibers and their growth can be classified as dermal or epithelial depending on their embryology. Underlying the follicle we have an onion-like structure where the stem cells that undergo differentiation are contained and whose process originates the stem. This structure is called the hair bulb and houses the cells of the DP and the cells of the dermal sheath. The first are active cells responsible for the growth of the follicle called "control towers", since they act at the level of growth and differentiation thus interfering with the degree of cornification of the follicle. The number of papillary cells is closely related to the size of the follicle. The cells of the sheath, which appear below the papilla cells in the bulb, are mesenchymal fibroblasts with a high number of periocytes, that is, with a high network of blood vessels. These are responsible for the induction of the follicle and are the reservoir of the cells that will constitute the DP.

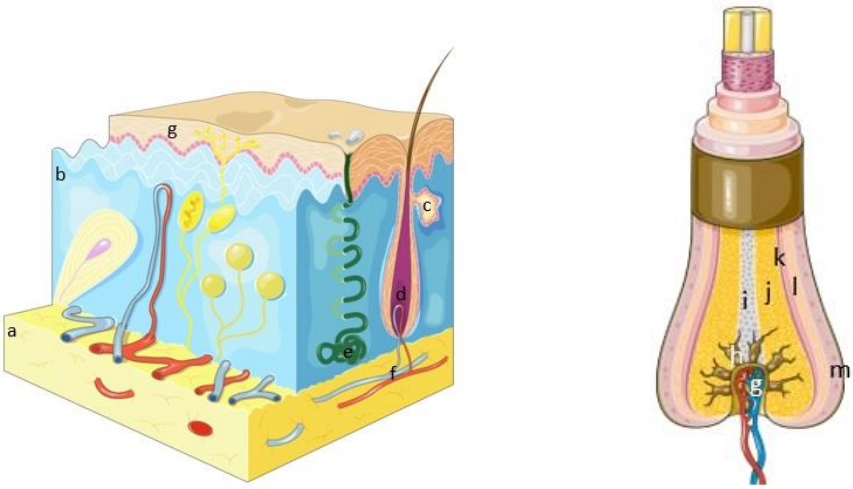
The capillary cycle comprises three stages: growth (anagen phase), transition (catagenic phase) and dormancy phase - before capillary closure (telogen phase). It is estimated that 90% of the follicles are in the anagen phase and the capillary cycle takes on average 4 months(Santos, Avci *et al.,* 2015). This cycle is regulated by stem cells, which are multipotent, of the follicles and by the interaction between mesenchymal and epithelial cells (Fang, Aljuffali *et al.,* 2014). This cellular differentiation can be potentiated by external factors that stimulate the resumption of the anagen phase, leading to a new proliferation and follicular growth and, consequently, capillary growth and begins at the embryonic stage of the human being (Tricarico, Maqoud *et al.,* 2018). These growth promoters act at the level of the mother cells. Thus, it is important to ensure a high presence of VEGF and a low concentration of the factor that inhibits VEGF (Thrombospondin 1 (TSP-1)). There are other factors whose presence or absence interferes with the normal development of the cycle, such as the fibroblast growth factor (FGF) that is produced by the papilla cells in the anagen phase and stimulates follicular growth when interacting with the FGF receptor, this happens with subtype 7 of this. Epidermal Growth Factor (EGF) modifies cells responsible for proliferation, inducing the passage of the telogenic phase to the anagen phase and increasing the duration of the latter, thus ensuring the beginning of a new cycle and a high time of proliferation of the mesenchymal cells. We also have insulin-like growth factor (IGF), which is a polypeptide produced at the level of the hepatic or genital cells and is assumed to be vital during fetal folliculogenesis and anagen maintenance. Its subtype 1 (IGF-1) is synthesized by (DP) cells in the anagen phase and induces growth (matrix augmentation and catagenic inhibition). Another factor is the WNT that

consists of glycoproteins with about 400 amino acids and acts as a signaling molecule because, despite being mainly in the cytoplasm, it can penetrate the nucleus and influence the genetic transcription. This affects follicular development, differentiation and regeneration and its subtypes 3a, 7 and 10b have direct effects at the follicle level. Shh only acts on growth, not being given other relevant functions. Bone morphogenic protein (BMP) acts in the control of folliculogenesis and in the formation of blood vessels. More recently, a protein receptor has been discovered that acts on the epidermis and has a causal relationship with heredity since it acts in the early stages of hair development and is therefore difficult to modulate it to have a practical effect on hair loss in people middle-aged. This receiver is called Edar. It further involves gene control as the case of stat3 which is a gene transcription promoter with a dependent (spontaneous cycle) and an independent (after cycle start) phase (Santos, Avci *et al.,* 2015).

The skin is also made up of sebaceous glands that open in a zone near the infundibulum of the follicle and associate with it, where they release their lipid content called sebum (Fang, Aljuffali *et al.,* 2014) and which is composed essentially of cholesterol and fatty acids. Sebum results from a degradation of the vesicular cytoplasm and is activated at puberty, being inactive up to now. This product has a lubricating function both at the cutaneous and capillary levels. These glands are sensitive to hormonal stimuli and allow the release of sebum on the surface through a hole of 10-210 μm in diameter.

Other structures are the sweat glands that are present in the dermis in a number in the order of 2.5 billion. There are two types of these glands that differ from one another depending on the type of production and can be apocrine or eccrine. The eccrines are present throughout the body and the content is produced at the level of the deep dermis with release of its duct to the level of the surface of the epidermis. These function to regulate temperature and eliminate waste and begin their action soon after birth. Its excretion is not very viscous since it is only based on water and salts and the excretion is controlled by sympathetic stimuli. On the other hand, we have the apocrine that only appear in the area of the armpits, genitals and nipples. Its excretion is viscous since it includes lipids and proteins. They originate from the subcutaneous tissue with release of the duct at the level of the hair follicle. They only appear at puberty and only excrete when stimulated by stress or sexual activity. These latter are capable of producing odors by the fact that the secreted liquid interacts with bacteria on the surface of the skin and is metabolized.

Thus the skin presents high functions such as barrier, temperature regulation, excretion of toxic, support, immune, vitamin D production as a consequence of sun exposure (Barel, Paye *et al.,* 2014).



A *B*

Image 2: A: Skin structure (a: dermis; b: epidermis; c: sebaceous gland; d: hair follicle; e: Sweat Gland; f: blood vessels); B: Hair Follicle structure (g: blood vessels; h: dermal papilla; i: medulla; j: cortex; k: perionyx; l: internal radicular sheath; m: external radicular sheath).

2.2.Alopecia

Alopecia is a disease characterized by progressive hair loss and can affect the entire population in any age group. It is divided into three major groups: Androgenic alopecia (AGA), Areata alopecia (AA) and induced alopecia (by chemotherapy). The androgenic has unknown etiology and is characterized by losses at the level of the tempora, vertex and top of the scalp, with gradual loss of capillary thickness (Roque, Dias *et al.,* 2017). It is known that the establishment of the disease is due to a hormonal steroid alteration (Androgens) and mutations in the receptors of these molecules. Therefore, a man with these changes shows a low level of testosterone and a high blood content of this unrelated hormone and other androgens including DHT, which is obtained from testosterone by 5α-R. The hair follicles are reduced by the increase of DHT due to the high presence of: 5α-R1 in the scalp of the people affected by the disease (Santos, Avci *et al.,* 2015, Roque, Dias *et al.,* 2017) although within the follicle (DP) it is type 2 that causes (Roque, Dias *et al.,* 2017). It is thus assumed as a disturbance of the follicular cycle caused by the decrease of the anagenesis state, which lead to the non-follicle growth and to the early beginning of a new cycle. This leads to short, thin hair due to incomplete cycles. The front part of the scalp begins to be visible. Follicular growth or dormancy depends on IGF activity in DP cells, since IGF-1 causes capillary growth when insulin

is absent. IGF-1 provides cell signaling for cycle regulation and potentiates differentiation, having an antiapoptotic effect during the anagen phase. IGF-1 is regulated by the binding partner of IGF that is in the DP. The presence of DHT inhibits IGF-1 (Santos, Avci *et al.,* 2015).

2.3.Drug delivery strategies

There are four areas where the drugs can undergo internalization: sebaceous duct, bulbar region, hair matrix and capillary infundibulum. The corneocytes at these sites are small and slightly undifferentiated, which reduces the physical barrier and increases the ease of efficient delivery of topical medications. It is also worth mentioning its high reservoir potential compared to SC, which allows a sustained release of the drugs (10 times longer than SC) (Santos, Avci *et al.,* 2015).

Because the main function of the skin is that of barrier against external agents, the administration of components topically leads to the absorption of these must be made by selected pathways that can cross the cutaneous barriers. The topical entry can be made by four routes: two transepidermal (intercellular or transcellular) and two transapendegal (sweat glands or hair follicles). Normally, the molecules subject to entry into the skin do not select only one of the pathways but a combination of several that allow their entry to be more efficient and whose selection depends on the physicochemical characteristics of the molecule and the excipients that help in its constitution (Barel, Paye *et al.,* 2014).

In transepidermal pathways, the transcellular pathway is characterized by the matrix (cell cytoplasm) of the keratinocytes and phospholipid membranes. The molecules that undergo the greatest passage through this pathway are the hydrophilic ones in aqueous medium that pass through diffusion through the SC. This path requires an adequate partition coefficient since it has to overcome the phospholipid bilayers constituting the cell membranes of the keratinocytes and the surrounding spaces. It is not assumed to be a major pathway followed by topical molecules. Urea facilitates this pathway as this compost alters the keratinous structure of the epidermis, facilitating passage. On the other hand, the intercellular route is made through the surrounding lipid matrix and small spaces that form between the cells. Small molecules penetrate through diffusion because of their lipophilicity, reduced molecular weight, solubility and hydrogen bonds. Larger molecules only pass through the lipids. In this way, the molecules are absent of charge and have a lipophilic character. To cross the SC it is convenient to use reduced size because the smaller the size the less the contact with

the layer, the better the hydration because it reduces the packaging of the corneocytes, increasing the space between the cells of the layer and thus, the permeation increases (Barel, Paye *et al.,* 2014).

The introduction of molecules through the skin barrier can still be done through the glands, whether they are sebaceous or sudoriparous, since both create exteriors through their ducts, which are continuous channels that cross the entire SC, become an important pathway for molecules to pass through this superficial barrier of the epidermis. Access to the bloodstream is facilitated (Wosicka and Cal 2010).There are also hair follicles which, because they have a high network of capillaries in their immediate vicinity, are a route to be taken into account for this administration since the molecule will easily reach the bloodstream. Small molecules are likely to undergo this follicular pathway and reach the bloodstream or be lodged in the lower parts of the follicle, establishing therein a kind of extended release reservoir of the molecule of interest. MXD, being a small drug, will be an excellent candidate to undergo this pathway. The massage effect in the topical application assumes to high importance, since it induces the capillary movement that creates a suction wave of the particles administered into the follicle. This path also has handicaps, such as capillary growth and the release of sebum, which, by being in the opposite direction, limit the penetration of the particles, which is why to avoid high flow of sebum. The structure of hair determines the entry of molecules, since they act as attractors on the molecules applied, "pulling" them into the hair follicles as the hair moves (Barel, Paye *et al.,* 2014).

The transfolicular pathway, vis-a-vis the transcellular, has the advantage of being more favorable to molecules of high molecular weight and hydrophilic, and the penetration through the follicles depends on the size, and their size varies between 300 and 600 μm and therefore, the greater penetration occurs with molecules that are comprised between these sizes of diameter (Bibi, Ahmed *et al.,* 2017). Molecules with 10-20 μm do not pass the SC but evidently accumulate in the openings of the follicles after massage, which makes it appear the hypothesis of development of drugs that reach current through this path without being subject to the cutaneous barrier (Wosicka and Cal 2010).

Drugs and other molecules of cutaneous application can also undergo translocation phenomena that consist in the recognition by the dermis of the compounds that pass in the epidermis and, thanks to its high vascularization and dendritic cells (macrophages). This recognition leads to easier and faster capture (Barel, Paye *et al.,* 2014).

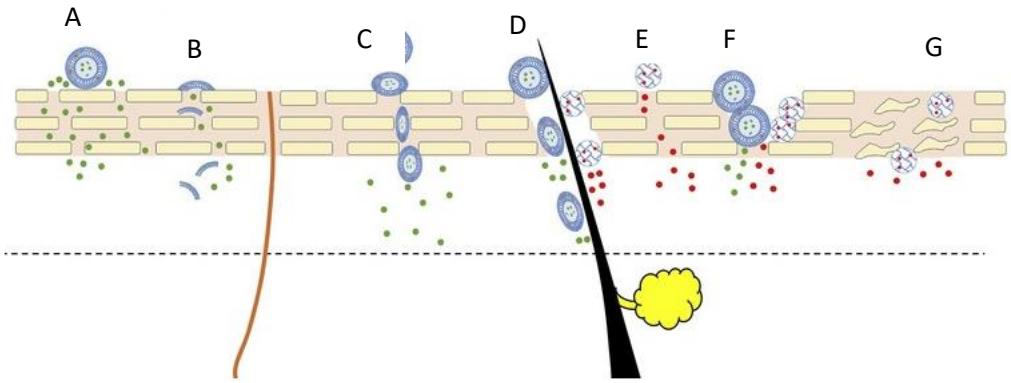


Image 3: schematic of potential pathways of skin permeation: A: Drug release by vesicles; B: fusion with SC lipids; C: intact penetration (flexible vesicles); D: follicular targeting; E: solid nanoparticles drug release; F: Furrow deposition and release; G: intact nanoparticles penetration in damaged skin. Source: (Nastiti, Ponto *et al.,* 2017)

3.Minoxidil topical delivery systems

3.1.Formulation requirements for topical administration of Minoxidil

Transdermal administration presents a more effective and high potential alternative, when compared with the oral or parenteral route. These advantages are due to the fact that it uses a non-invasive system for the human being and that manages to guarantee high concentrations in the natural circulation (Thomas and Finnin 2004). There are drugs that take on a small therapeutic window and whose care requires more control in order to avoid the associated toxicity. This handicap can be solved through this route, since this guarantees a more prolonged and phased administration of the active principle, keeping the concentration in the biophase within the therapeutic values (Bibi, Ahmed *et al.,* 2017). Another advantage of this type of pharmacological administration is that the blood peaks are less and the valves are too, i.e., a linear concentration is maintained over time which contributes to a better therapeutic efficacy and with less side effects (Thomas and Finnin 2004).

Compared with oral drug administration, there is no possibility of degradation in the gastrointestinal tract in the transdermal route, the possibility of drug-lowering in the bloodstream is reduced by the first-pass effect, and the acceptability at the target audience, as it is not subject to unpleasant tastes. Finally, it is easy to remove and with its removal are eliminated any possible side effects that are occurring (Bibi, Ahmed *et al.,* 2017).

The effect of these molecules is only achieved if they are able to interact with the target cells, in which case they must be able to penetrate the superficial layers of the skin. This fact is closely related to the physicochemical properties of the molecules and their coatings, and

therefore their formulation must take into account parameters such as size, shape, charge, lipophilicity, stability and penetration efficiency (Desai, Patlolla *et al.,* 2010).

The size and shape must be very optimized in this type of structures because they play a central role in the physical stability, release and cellular penetration, so it is known that for these molecules to penetrate at the SC level they must have a size in the order of 5-7 nm in order to pass through simple diffusion through the lipid bilayer. Particles in the order of 36 nm may utilize aqueous pores to be transported through SC. With sizes of 3-10 μm, the transfollicular route must be followed. The reaching of deeper layers is achieved with a size in the order of 643 nm and this penetration decreases as the size of the nanoparticle increases. Nanoparticles with adequate lipophilicity, molecular weight below 600 Da (above this weight do not penetrate the cutaneous barrier), high partition coefficient are candidates with high probability for use in transdermal administration (Bibi, Ahmed *et al.,* 2017).

There are different shapes that can be adopted by particles such as spherical, elliptical, cubic, triangular, etc. This is because the lipid molecules do not always have a rigid structure. Rigid and deformable forms combined with the orientation of the nanostructure affect aggregation and skin penetration (Baroli 2010).

The surface charge and the polarity are also important factors. The surface charge allows the adherence of the structure to the target cell membrane, interferes with the diffusion coefficient through the skin membrane, and further selects the skin penetration pathway to follow. The cutaneous membrane has a negative charge density due to the high presence of sulfated proteoglycans. This presence of negative charge is also a barrier mode, since the skin repels all negatively charged molecules that approach its surface (Uchechi, Ogbonna *et al.,* 2014).Thus, it is expected that changes in the surface charge of the nanoparticles will facilitate transport. An example of this is the increased polymer density with charge facilitating transport across the membranes. Lipids with charge span 3-4-fold more easily the endothelial cells than lipids without surface charge. Therefore, it is to be expected that positively charged surface loaded structures will cross skin barriers more quickly and efficiently than neutral structures. The diffusion coefficient is also one of the parameters to be taken into account in the formulation of these structures and depends on the size, shape and temperature. This influences the penetration, selection and entry (Bibi, Ahmed *et al.,* 2017).

Stability is an important parameter since its lack implies physical and chemical actions that alter the properties of the structure and the drug that lead to possible phenomena of altering important parameters of the nanaparticle and thus decrease the entry efficiency at the

level of the skin such as aggregation with each other and with the vehicle, precipitation, all factors that change the diffusion coefficient and the permeation (Baroli 2010).

The pH of the carrier and the pKa of the agent are of interest, since only the non-ionized fractions cross the cutaneous barrier (Bibi, Ahmed *et al.,* 2017). The Partition coeficiente (log P O/W) is required for penetration by the lipid matrix of the skin and through the aqueous pores (Baroli 2010) If it is very lipophilic it passes easily through the SC but has problems passing the hydrophilic pores while the hydrophilic molecules do not penetrate through the SC. Thus, molecules with high solubility in the vehicle have high thermodynamics and therefore are more likely to penetrate the skin (Bibi, Ahmed *et al.,* 2017).

In the transdermal route are also associated problems that are fundamentally related to the fact that the skin has associated barrier mechanisms to prevent contact with the inner organs of environmental agents. An example of this is the SC, which is assumed to be an effective barrier to the penetration of hydrophilic molecules. In order to circumvent this aspect, numerous differentiated molecules have been developed in the last years and are considered as viable strategies for the administration of drugs through the skin. They are presented as nanostructures and, compared to conventional molecules, they are more stable, less toxic because they avoid the use of organic solvents that cause irritation, with higher cellular uptake. These molecules of the future are capable of only releasing the drug at the target site and in the required concentration. Because they have a high volume surface, they can store high amounts of material in a short volume, which allows the creation of skin-level reservoirs and a controlled release of the drug at the site of action for long periods of time, thus guaranteeing a localized effect with a low probability of occurrence of side effects (folicular targetting) and The fact that they present themselves as small molecules and with an encapsulated structure, also the drug is more protected from degradative reactions like chemical or enzymatic degradation (Zhao, Brown *et al.,* 2010, Bibi, Ahmed *et al.,* 2017). They are very small molecules, they easily cross capillaries and, therefore, the arrival to the target organ is effectively guaranteed.These intrinsic characteristics of the nanoparticles are very important to ensure good interaction between the drug and the therapeutic target and to avoid degradation of the drug and the coating prior to its application(Bibi, Ahmed *et al.,* 2017).

3.2.Conventional formulations

Most of these formulations consist of ethanol, water and propylene glycol. There are several skin solutions commercialized that have in common the fact of having a percentage of

2% or 5% in MXD accompanied by propylene glycol, ethanol and water. Its pH is in the order of 8 and its application should be done twice a day. The fact that they have propylene glycol causes irritation, heat redness and sometimes contact dermatitis. These are adverse effects to the use of MXD and its excipientes (Balakrishnan, Shanmugam *et al.,* 2009, Mura, Manconi *et al.,* 2009, Silva, Santos *et al.,* 2009, Padois, Cantieni *et al.,* 2011, Mali, Darandale *et al.,* 2013, Uprit, Kumar Sahu *et al.,* 2013, Lopedota, Cutrignelli *et al.,* 2015, Matos, Reis *et al.,* 2015, Liao, Lu *et al.,* 2016, Wang, Chen *et al.,* 2017, Lopedota, Denora *et al.,* 2018, Tricarico, Maqoud *et al.,* 2018).

3.3.Nanotechnology-based formulations

Such formulations offer numerous advantages. One of them is the fact that, at the cutaneous level, they create controlled release reservoirs in which the systemic effects are minimal. It has a high success rate for the release of hydrophilic, lipophilic and macromolecular drugs that would otherwise not be able to be administered topically. Thus, they increase the residence time, the skin penetration index and facilitate transport through the skin layers, promoting the drug-target contact. This type of particles also entails some disadvantages such as the high battery of tests that are required to make a characterization of the molecule and its pharmacological, pharmacokinetic and toxicity profiles. The toxicity of these molecules is also possible if the molecules are not biodegradable, this is because the characteristics of the normal scale material may not be the same as those at the nanoscale (Bibi, Ahmed *et al.,* 2017).

The metabolites produced by these structures are also difficult to quantify due to a lack of techniques, as well as the passage from the laboratory to the industrial scale is an obstacle to the costs of the materials and specialization required for production. The purity variability of the phospholipids is also shown to take account of the formulation of these compounds (Escobar-Chávez 2012).

Thus, the nanostructures can be divided into vesicular systems (liposomes, transferosomes, niosomes and ethosomes), lipid nanoparticles, polymeric nanoparticles, dendrimers and squarticles arise. Vesicular systems have received great attention because they exhibit excellent properties such as the fact that they can harbor hydrophilic and lipophilic molecules, increase the half-life of the molecules, are biodegradable, non-toxic and also have a high rate of release at the site target (Modi and Bharadia 2012). Features such as size, shape and nature lamellar have the ability to adapt to composition changes and thus, permeators can be added to increase their passage through the skin and the formation of deposits (Muzzalupo,

Tavano *et al.,* 2011). They are still optimal in permeation through the sebaceous follicles, capillaries and glands exponentially increasing the amount of drug that reaches the target cells (Choi and Maibach 2005).

3.3.1.Liposome

Liposomes appear as a spherical hole composed of cholesterol and phospholipids that form a bilayer. Its polar part is organized in such a way that an interface is generated between it and the aqueous medium. Thus, the polar agents are incorporated in the aqueous phase and the lipophilic ones in the lipid phase that is between the bilayer (Bibi, Ahmed *et al.,* 2017).

These molecules exhibit a high permeation potential because they have a lipid content very similar to that of the lipid layer of the epidermis. They can undergo two types of preparation: film hydration or solvent injection (Bibi, Ahmed *et al.,* 2017). Depending on the chosen method we can obtain 3 categories of liposomes (small unilamellar vesicles (SUVs), large unilamellar vesicle (LUVs) and multilamellar large vesicle (MLVs) (Neubert 2011).

The first two present only one lipid bilayer while the multilamellar ones present a high number of concentric bilayers. As for sizes, SUVs range between 10-100 nm, LUVs between 100-500 nm and MLVs have sizes greater than 500 nm, which, as we have seen, is an important parameter to define the penetration efficiency either by the intercellular pathway either by the transcellular route, since the pores of the skin have holes in the order of 0.3 nm in normal cases, and can ascend to 20-40 nm in cases of cutaneous disease. Thus, cutaneous penetration decreases as the size of the liposome increases although, if the entry is made using the auxiliary units of the skin, size ceases to be an important factor (Choi and Maibach 2005).

Another important factor in skin penetration is thermodynamics, which in this case depends on the percentage of cholesterol and also on the nature of phospholipids. Its way of entering the skin is not well defined but some theories are proposed that explain this phenomenon. The adsorption of the liposomes in the SC with subsequent fusion with the lipids thereof with release of the content is one of the proposals. The disintegration of the liposomes in the skin surface acting as a permeator (rupture of the cellular packaging of the skin and fluidises the lipids constituting the SC) is also hypothesized. The entrance through the pilosebaceous units and the reservoir effect that they can play or, still, can penetrate to the skin of intact form (Bibi, Ahmed *et al.,* 2017).

These molecules present various problems which relate to both formulation and release. Examples of this are stability, difficult sterilization, poor drug packaging capacity and poor reproducibility of the process (Bibi, Ahmed *et al.,* 2017). The size change of the particles leads to phenomena of aggregation, fusion, oxidation, hydrolysis due to the synthesis liquid of the liposomes due to it using unsaturated phospholipids that are more susceptible to oxidation processes. The use of hydrogenated phospholipids and the gel matrix wrapping at the end of the formulation appear to be viable solutions. Another problem is the fact that when local reservoirs are formed, local effects are observed in SC, which has no advantages. Thus, it has been ascertained the possibility of incorporation of propylene glycol in the formulation, since this increases the elasticity and thus the skin penetration of these particles (Bibi, Ahmed *et al.,* 2017).

3.3.2. Transferosome

Transferosomes are presented as a new class of liposomes characterized by having improved attributes compared to previous ones such as ultraflexibility, elasticity and the fact that they are deformable. They are composed of an aqueous interior delimited by a complex lipid bilayer. The high elasticity is conferred by an excipient activator present in the lipid bilayer. They present a self-regulated form and composition that gives them an efficient passage of various types of barriers. Composed of two ingredients: amphipathic phospholipids (Phosphatidylcholine) in the bilayer oriented to the aqueous environment and a surfactant such as Tween 80, Span 80, among others that has as function to increase the deformation of the vesicle and destabilize the lipid bilayer. In its formulation is still indispensable the alcohol (ethanol or methanol). Because they are deformable, they adapt their shape to the shape of the pores to be overcome and, thus, they can easily cross the SC, recovering the initial shape after the passage. They are non-invasive structures of sustained release in the target. When applied under non-occlusive conditions, they penetrate the skin as a result of a stress action and following the aqueous gradient that setstles in the epidermis. They are then presented as excellent nanostructures for topical administration of either low molecular weight molecules or high molecular weight molecules(Bibi, Ahmed *et al.,* 2017).

3.3.3. Niosome

Niosome is a Vesicle similar to liposome in structural and physical terms capable of incorporating aqueous and non-aqueous molecules (Mali, Darandale *et al.,* 2013). They are also

presented as improved alternatives to liposomes characterized as improved nonionic surfactant particles in matters of composition and stability. They are biocompatible, non-immunogenic and biodegradable and are used for controlled release at the target site (Bibi, Ahmed *et al.,* 2017).

They can be produced by three different methods: reverse phase evaporation, ether injection and stirring techniques.They increase the rate of penetration through the skin barrier by altering the organization and composition of the lipids (fused with this) of SC by the presence of surfactant and also by the flexibility and deformation capacity they have (Mali, Darandale *et al.,* 2013, Bibi, Ahmed *et al.,* 2017). Another advantage is that the amount of drug that reaches the bloodstream decreases, thereby decreasing the side effects that would be expected and increasing the amount of drug reaching the target site (Mali, Darandale *et al.,* 2013).

These vesicles show decreases in side effects and their transdermal penetration efficiency depends on the composition of cholesterol and nonionic surfactant, with Tween 20 being the most effective. The decrease in the amount of cholesterol increases the penetration. Nanosomes composed of Tween 60 or Span 60 are the best in terms of cutaneous release (Bibi, Ahmed *et al.,* 2017).

According to the author *Balakrishnan,* MXD niosomes are prepared by the film-hydration method with non-ionic surfactants and cholesterol. The amount of MXD entering the niosomes is quantified by High Performance Liquid Chromatography (HPLC) with a ultravioleta (UV) detector. The amount of MXD to be encapsulated depends on the surfactant used but should not exceed 25 mg, since above this value lower values of cutaneous penetration were obtained, due to the saturation that this increase causes effect. They are more stable if a charged particle such as diacetylphosphate is added to the bilayer, which prevents aggregation of these particles. The largest aggregates are derived from the use of Span 80 as a surfactant. The zeta potential of these MXD particles increases with the hydrophobic character of the surfactants ie increases with increasing HLB value being higher in Brij 52 and Span 20. A dialysis process increases particle size but decreases the heterogeneity between them, decreasing penetration. Span 60 and Brij 52 are surfactants that show less stability. Heterogeneity and high sizes also contribute to this low stability and the fact that they have lower zeta potential, which indicates less electrostatic repulsion and increases the possibility of aggregation. Span 40 is the surfactant that shows better stability. These vesicles fuse with the skin, which forms a high concentration gradient of the encapsulated drug through the skin and thus enhances penetration. In the case of particles

containing MXD as an active ingredient and prepared by the alcohol injection method, parameters such as cutaneous entry efficacy, size and stability were evaluated. From these studies it was verified that the size depends on the content of cholesterol and nonionic surfactant that is used and that they are molecules that can be constituted by aqueous or non-aqueous phase, being, therefore, an alternative to the liposomes since they show great stability and a low cost associated with surfactant. These MXD molecules show an increase in cutaneous permeation, a reduction in systemic absorption (which is seen as a very beneficial effect on this molecule and this treatment in that the desired effect is locally and thus avoiding the cardiovascular effect that MXD can cause as a vasodilator of origin) and a highly sustained release into the target cells. Its entry into the skin occurs by adsorption to the surface of the epidermis with subsequent fusion with its interface which generates a high gradient of concentration of the drug and promotes the permeation of this one by being lipophilic. These types of structures may or may not have cholesterol in their composition. In the absence of cholesterol, it was found that the highest permeation percentage occurs using Span 60 surfactant. The use of Span 80 is contraindicated by the fact that precipitation of MXD occurs which will float in the aqueous vehicle. The increased penetration efficiency of these MXD-containing molecules occurs with increasing particle size since the amount of water inside the particles increases and thus increases the percentage of entry. In the case of surfactants, it is important to note the size of the alkyl hydrophobic layer which is larger the larger the carbon chain, ie, it will be larger in span 60 (C18) than in Span 20 (C12), because a smaller chain implies a lower capacity to store a hydrophobic drug. Span 60 and Brij 52 increase the size and heterogeneity of the particles, and also their size and zeta potential are low, thus having low stability. Thus, there is a greater stability and an increase in the hydrophobicity of the bilayer constituting the structure with the use of Span 40 and with a higher amount of cholesterol. The case of Tween 20 is that this increases the solubility soon increases the entrance of MXD face to the Span 20. All this is verified with a fixed amount of active principle because increasing this one occurs a decrease of the penetration and a increase of size as it increases the saturation precipitation of the aqueous medium and the hydrophobic bilayer. Although they can be formulated without cholesterol, it plays a pivotal role in the structure since it facilitates deposition and skin permeation, as well as facilitating the entry of the active principle into the target cell. Slightly larger sizes are favored at 200 nm as they show greater deposition at the level of the interior of the follicle and below this threshold the stability of the particles is reduced and with immediate disintegration upon contact with the skin surface, which significantly reduces the percentage of entry into the target cells. In view of this, this author observed that the dialysis decreases the amount of MXD absorbed and, comparing the

samples that did not undergo this process, the control showed an absorption of 0.48%, and the samples with Brij 52, Span 20 and Span 40 exhibited 5.42%, 19.41% and 16.37%, respectively. Span 40 still increases its zeta potential from -33.22 mV to -34.81 mV, indicating that it maintains high stability after three months. Its size remains at 250 nm during the stability study time. Thus, for the use of these molecules in topical administration of MXD, sizes of the order of 200 nm should be preferred and fixed drug composition using Span 40 as a surfactant (more stable and with greater storage capacity) and with some percentage of cholesterol to facilitate deposition and cell entry. In view of the control, it is found that the amount of drug absorbed at the follicle level increases (0.48% to 16.37%)(Balakrishnan, Shanmugam *et al.,* 2009).

Mali et al., developed another study using Niossomes prepared by an ethanol injection method where he evaluated parameters such as particle size and morphology, encapsulation efficiency, stability as well as skin deposition In Vitro. The studies were carried out for Niossomes with and without Cholesterol and using Dicetylphosphate (0.15 mM) as a stabilizer of load and using Span 20 and 60 and Tween 20 as surfactants and fixing the amount of MXD in 25 mg. He noted that only Span 60 surfactant is capable of forming missing cholesterol particles and only Span and tween 20 do not precipitate cholesterol. Span 80 and Tween 80 were not included in the study since they formed cholesterol precipitates that floated in the water. The maximum encapsulation was observed using Span 60 as surfactant because it has the largest alkyl layer and an increase in size and encapsulation efficiency with increased cholesterol was observed. The increase in size increases the amount of water in the vesicle and thus the inflow of MXD and further, the increase in cholesterol concentration increases the hydrophobicity of the lipid bilayer as well as its stability. Thus, the author selected Span 60 for subsequent studies, where he observed that increasing the amount of MXD above 25 mg leads to a decrease in the encapsulation capacity and a precipitation of the drug. Observation of its morphology revealed collapsed vesicles. Stability studies revealed that greater stability was achieved with a Span 60: cholesterol ratio of 1:2, as the particles are larger in size at 90 days and stability is related to size since the decrease in size is due to osmotic activity. The best are the above 200 nm since very small these suffer disintegration (219 nm). These enter by surface fusion and through the concentration gradient where cholesterol facilitates passage and cell deposition at the level of the follicles. In vitro deposition and permeation revealed that the best values (44% permeation and 17% deposition) are also obtained with the ratio of 1:2 and if the permeation value is very similar to that of the commercial solution, the difference is enormous, and the niosome deposits about 9 times more, allowing to affirm that these

particles potentiate the target effect and favor the treatment of alopecia. (Mali, Darandale *et al.,* 2013).

3.3.4.Ethosome

Ethosome emerge as new nanostructure composed of phospholipids, ethanol and water. Malleable and soft vesicles of varying sizes between tenths of nm and μm. They are a modified form of liposome by increasing the content of ethanol or isopropyl alcohol. The phospholipids constituting these structures may be phosphatidylserine, phosphatidic acid or phosphatidylcholine. They can penetrate deep layers of the skin and permeate SC through the intercellular route through the alteration that they promote in the lipidic organization of this. Due to the increased amount of alcohol, the lipid membrane is less firm, so the structure becomes more malleable, which increases its passage through the SC of the skin. These liposome derivatives have the ability to penetrate either in occlusive or non-occlusive conditions and penetration occurs through synergism between vesicles, ethanol and lipids of the skin(Bibi, Ahmed *et al.,* 2017).

The release of the encapsulated drugs takes place in two steps: in the first, the alcohol interacts with the polar heads of the lipids and increases the fluidity and decreases the density of the multilamellar layer, by reducing the transition temperature of the lipids of the SC. Thus, these structures fuse with the membrane lipids of the skin and release their contentes (Elsayed, Abdallah *et al.,* 2007).

3.3.5.Penetration enhancer-containing vesicle

Penetration enhancer-containing vesicles (PEVs) are particles produced by sonication and constituted by Lecithin, Transcutol®, Labrasol® and Cineol. The second is a diethyleneglycol etherster whose function is to increase the intercellular lipids. Labrasol acts as a non-ionic surfactant with HDL of 14, and results from the mixture of fatty acids in the form of mono-, di-, and triacylglycerides and also of propylene glycol esters. Cineol is a terpene and acts to increase penetration by breaking down the hydrogen bonds that occur between the ceramides of SC. Thus, they alter the lipid bilayer surrounding SC corneocytes, which potentiates their deposition at the level of the epidermis and the low concentration in the dermis. Transcutol® is non-toxic and biocompatible and mixes with the lipids of SC without altering its structure. The presence of Transcutol® makes them smaller, although with Cienol and Labresol they show a higher penetration rate. Its deformation capacity expones to the

percentage of drug reaching the target. They are particles that show high percentage of entrance and an excellent stability (zeta potential of -52 mV). Its size varies between 140 nm and 195 nm. The deformability of these particles depends on the ability of the "edge activator" (surfactant) to interfere with lipid packaging and facilitate penetration. By incorporating MXD as active principle, potentiate the effect of this in the proliferation and apoptosis of cells of the DP, with positive effects for four to six months.

The cineole-containing molecules demonstrate an encoding capacity of MXD of 71%, labrasol of 61% and transcutol of 59%. This seems strange because cineol is the molecule where MXD is less soluble but this molecule has a high encapsulation capacity, which is very good since this terpene has a high capacity to break the hydrogen bonds of the ceramides and thus increase the deposition of MXD. The nanoparticles containing labrasol are the ones that can put more particle in the epidermis (8.95%) followed by those of cineol (4%), with three having in common the fact that the drug that reaches the dermis is almost nil. The labrasol achieves this because it is a mixture of amphipathic components that act as "edge activator" and for having a greater elasticity, enhancing the entry of the drug. This produces a kind of deposit in the lipid layers where the MXD undergoes sustained release. The commercial solution used as a control also has a controlled release which occurs because it has a large amount of ethanol which decreases the barrier function of the skin. As for the percentage of drug released, cineol releases 17% and labrasol 20% and if it is pre-treated (commercial solution of MXD) decreases to 12% and 9%, respectively. The particles containing cineol and labrasol must be able to penetrate intact inside the skin in order to create a reservoir from which the MXD (Mura, Manconi *et al.,* 2009).

3.3.6.Nanoemulsion

Nanoemulsions (NEs) are particles characterized by increasing the solubility of the components they incorporate and by providing good sensory characteristics. They have low interfacial tension and a small size and are also thermodynamically stable. *Abd, Eman et al.,* carried out a recent study using these particles and using Eucalyptol and oleic acid as promoters of skin penetration. The MXD content was 2%, in an O/W dispersion. And several parameters such as solubility and penetration / diffusion in SC, the amount that reached the deepest layers of the skin and the maximum flow in 24 h were evaluated. Eucalyptol was chosen because of its low skin irritation. The results were done in parallel with controls drawn from hydroalcoholic solutions of MXD and revealed that eucalyptol NEs had a higher flow and solubility in SC than controls and that of oleic acid since it changes the properties of the lipid

barrier of SC, thus increasing the possibility of diffusion and, consequently, the penetration of the particles and the drug. Regarding the retention, we observed that constituted by Eucalyptol has a higher retention but if we speak only of target effect, which in our case is the follicles, those of oleic acid are enhanced by increasing the solubility of MXD and have a greater compatibility with lipids constituents of human sebum. Thus, although Eucalyptol is superior in terms of the parameters evaluated, those of oleic acid have proved to be more advantageous in terms of the drug we are evaluating and the effect we want it to exert and the place where it is made (Abd, Benson *et al.,* 2018).

3.3.7.Solid lipid nanoparticle and nanostructured lipid carrier

Innovative pharmacological release system with dermatological and cosmetic application. They exhibit high physical stability, tolerability, and release can be controlled. This type of particles is divided into two types: solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). The former are composed of lipids which are solids at body temperature and are prepared by replacing the liquid lipids in the emulsion with solids or with a mixture of solids and liquids (Bibi, Ahmed *et al.,* 2017). They are composed of three ingredients: solid lipid, water and emulsifier with the lipid to be dispersed in the water with the aid of the surfactant which also acts as emulsion stabilizer (Wang, Chen *et al.,* 2017). The preparation methods are various and include ultrasonication techniques, multiple emulsions, high pressure homogenization, membrane contraction, microemulsion and emulsions with either solvent evaporation or solvente injection (Bibi, Ahmed *et al.,* 2017). SLNs are prepared by hot or cold homogenization (Pardeike, Hommoss *et al.,* 2009). These (SLNs) are well tolerated, with good target effect, capable of being produced on an industrial scale (Uprit, Kumar Sahu *et al.,* 2013). They enter the skin by the easy interaction between these and the sebum of the skin due to its similar structures. The phospholipids of these structures interact with cutaneous sebum and promote the entry of vesicles into the hair follicles (Bibi, Ahmed *et al.,* 2017), ensuring an advantage in terms of toxicity (Padois, Cantieni *et al.,* 2011). Thus, SLNs are a colloidal system which combines the advantages of emulsions, liposomes and polymer particles in a single System avoiding the use of organic solvents (Wang, Chen *et al.,* 2017).

In addition to modulating the pharmacological release characteristics of the active ingredient they incorporate also has as a characteristic the hydration of the skin through an occlusion system that increases the amount of water and favors the penetration of drugs. They also prevent the chemical degradation of the compound to be administered. They avoid organic solvents and have high stability. They are stable both for lipophilic and hydrophilic

molecules and do not present problems if their production passes on a large scale(Gomes, Martins *et al.,* 2014). The low size of these particles (NLCs and SLNs) increases the contact with the SC, allowing the increase of the entry of molecules through the skin (Uprit, Kumar Sahu *et al.,* 2013).The limitations of such systems are the low incorporation capacity and the possibility of uncontrolled release of the compound (Silva, Santos *et al.,* 2009, Wang, Chen *et al.,* 2017). When SLNs lose the water they contain, modifications occur in the matrix, which crystallizes, inducing the expulsion of the drug that penetrates the skin pathways (Uprit, Kumar Sahu *et al.,* 2013).

In the case of MXD correspond to particles formed by semi-synthetic triglycerides with polysorbate and with a percentage of 5% in MXD. Appearing SLN's with a size in the order of 190nm that favors its entrance via sweat glands. They are produced by emulsification followed by ultrasonic homogenization. They have a pH in the order of 7, which is advantageous since the pH of the skin is between 4.8 and 6.1, because the commercial solutions use a pH close to 8 that alters the skin characteristics, leading to adverse reactions. Compared with the commercially available pharmaceutical forms of MXD, they have a higher skin penetration at the epidermis level and a lower Derme level, demonstrating the lower absorption into the bloodstream and greater bioavailability of the active principle at the target site. Its Zeta potential is -30 mV, which shows good physical stability and uses non-ionic surfactants. It is observed that in the encapsulation process 94% of the MXD is encapsulated and divided by the two phases (lipidic and aqueous) which helps these particles to undergo a programmed release. They are not corrosive or cause skin irritation unlike commercial solutions tested (Padois, Cantieni *et al.,* 2011).

The second type of lipid nanoparticles, the NLCs, appeared in the attempt to override these handicaps since the latter have high incorporation capacity and minimum leaching capacities. They are composed of both solid and liquid lipids with a solid lipid matrix embedded in a liquid or with the liquid lipids adsorbed to the surface of the solid matrix with the aid of a surfactant (Patlolla, Chougule *et al.,* 2010). The lipids, the surfactants and the drug are mixed and stored below the lipid melting temperature (70 °C). The mixture contains solid and liquid lipids and is dispersed in aqueous solution at high temperatures with the aid of a stabilizer such as polysorbate 60 (Gomes, Martins *et al.,* 2014). The addition of the oil avoids crystallization and allows the incorporation of high concentrations of active principle. Its reduced size enhances contact with SC cells, promoting adhesiveness and hydration. The drug is only released by erosion or Swelling phenomena, which causes its release to undergo a slow and controlled process (Wang, Chen *et al.,* 2017).

Gomes, Martins show that MXD influences size and that the size of these NLCs is in the order of 200 nm (able to penetrate to the follicles) and with low dispersion (0.25), which reveals size homogeneity. The zeta potential of these particles is in the order of -30 mV, which shows a good physical stability that is verified during 28 days since it prevents the aggregation due to the high electrostatic force, revealing characteristics that can be used in the treatment, and this value is affected by the incorporation of MXD. These particles are spherical in shape and have a smooth surface and show a lower crystallinity of the lipids when incorporating the drugs. In vitro release was assessed where short, controlled and continuous release was observed. In these particles the penetration of MXD after 24 h is reduced, which is traceable, and can be increased with the use of alcoholic solutions. This evaluation was made in pig ear skin and detected by UV / VIS (Gomes, Martins *et al.,* 2014).

Wang et al., did a study where he started from the coinage of MXD where the excipients that show the best attributes are stearic acid as solid lipid and oleic acid as liquid lipid. They have a zeta potential of -32.9 mV, a cutaneous penetration in the order of 92% and a size of around 281 nm. They are produced by high pressure homogenization using stearic and oleic acid and a surfactant such as Span 80 or Tween 80. They are based on a mixture of oleic acid, triestartin, cholesterol and soy lecithin (lipid phase) and water with surfactant (Tween 80). This surfactant proves to be very advantageous since it hydrates the surface of the layer and thus increases the stability of the particle. Triestartin and oleic acid should be in a proportion of 2:1, because this alone confers a size within the limits considered to enter follicularly (280 nm). They are adsorbed to the surface of the epidermis and cause an increase in skin hydration. The excess of oleic acid decreases the viscosity and, consequently, the surface tension leading to smaller and smoother particles, which increases the process of skin penetration. The increased surfactant content, such as the Span 80, decreases the size and increases the rate of entry and the ability of the particle to make a controlled release. Thus, it has been found that the greatest entry and stability is achieved with 2% MXD, 8% oleic acid, 4% stearic, 1.5% Tween 80 and 0.5% span 80, the stability of these being particles at either 4 °C or 25 °C. They show a high retention at the follicular level (in the order of 165 μg), which reduces the systemic effects, and therefore the adverse effects e The NLCs during their three months of stability do not alter their size or cutaneous entry capacity, as opposed to SLNs that it is verified that they have less capacity of entrance and increase of size. Another advantage of NLCs is that MXD is dissolved in the two oils, achieving a more controlled release than in SLNs. Permeation studies revealed that MXD-liniment (commercial solution) and NLC's had a very close permeation value, 996.9 and 1027.8 $\mu g/cm^2$ and about twice the SLN's

(571.7 μg/cm^2). They (NLC´s) also have a higher permeation rate than solid ones because they have a higher encapsulation rate and because they intercalate in the lipid structure of SC, altering the normal lipidic packaging of this zone (Wang, Chen *et al.,* 2017).

The only possible disadvantages are the risk of uncontrolled explosion or exaggerated growth. These MXD particles can also be incorporated in a 2% carbopol 934 gel, which gives them an excellent viscosity and pH in the order of 7.4 and increases the time of contact of the skin with the substance as well as the semi-solid consistency (Silva, Santos *et al.,* 2009). It guarantees a rapid release until cutaneous saturation with controlled release and subsequent to the needs of the compound. In this gel, the MXD is dispersed homogeneously and does not show an endothermic peak in the differential scanning callorimetry (DSC), therefore, it presents in amorphous mode, which facilitates its diffusion. Incorporated into a gel, they are semi-solid particles, which minimizes their side effects. They show good physical stability (6 months) where no crystals of the drug can be observed and it can be affirmed that this remains dissolved in the oleic acid inside the nanoparticle. The hydrogels present only one phase, differing from the biphasic ones because they do not have lipid phase but high amount of water being formed by the latter, a gelling polymer and propylene glycol. The NLCs are incorporated prior to the gelation process. The nanoparticles incorporated in carbopol have a size of 450 nm and those of Perfluorocarbon of 320 nm, which depends on phenomena of aggregation inside the hydrogel. As for neutralization it can be made by sodium hydroxide, tromethamine and Neutrol®, although the first one greatly increases the risk of aggregation by decreasing the repulsion interparticulas, thus the triethanolamine was selected. The NLCs revealed a spherical shape with a smooth surface, producing semi-solid systems when mixed with hydrogels, thus increasing the permeability potential of the drug at the target site (Silva, Santos *et al.,* 2009).

Zhao et al., observed that Lipid Nanoparticles, produced by phase inversion method, with sizes from 49 to 55 nm are neutral and with a low zeta potential due to the surfactant used and containing a triglyceride core (HLB = 2) and with a high encapsulation capacity which suggests high affinity of MXD for lipids. The encapsulation efficiency was low (less than 50%). Although they have low zeta potential, they show good stability. It was observed that these particles release less quantity than the commercial solution used as a control and that the nanoparticles released more MXD if they were in the form of Foams (use of HFA227) forming an O/W/O solution that collapses when releasing the drug, observing sustained biphasic release. The surfactant used in Foams increases the solubility of MXD (Zhao, Brown *et al.,* 2010).

Uprit et al., carried out a study where the intention was to evaluate how a Carbopol Gel of NLCs containing MXD could increase capillary growth. It has been found that increasing the concentration of the solid lipid causes an increase in particle size, and the ideal size is obtained with a ratio of 2:1 between Tristearin and oleic acid (280 nm), the increase in acid reduces the viscosity inside the NLC, leading to smaller and smoother particles. The zeta potential of these particles is -42.40 mV, which shows an excellent physical stability which can be increased with the use of Tween 80 as a surfactant, as this allows a greater hydration of the surface layer. An electron microscopy study was performed where it was observed that most of the particles are spherical and some deviate from this pattern due to the fact that the lipids change, leading to a change in shape. If the particles contained only Tristearin, they would be cuboids. The encapsulation capacity was 86%. When analyzing the release profile we can say that we are facing a biphasic release, with rapid onset followed by sustained release and this is explained by the small size and the high percentage of oleic acid. The mixture is made at elevated temperatures and the solidification at low, leads to a protection of solid lipid with a liquid lipid interior. The size interferes because the reduction of this increases the surface area, increasing the speed of the release. Analyzing the DSC spectrum it was observed that the MXD is in the amorphous phase and fully dispersed in the NLCs. The gel was formed with 2% carbopol 934, and its application proves to be advantageous in damaged skin, guaranteeing a good spreading. It is shown pseudoplastic and, therefore, easy to scatter. Also the gel exhibits a biphasic release rapidly in a first step and in a controlled manner in a second, with 92% being released. Thus, it can be said that these particles are a good option since they increase the properties of controlled and sustained release in the time, they avoid irritating organic solvents, they can be applied in injured skin due to the easy spreading of the gel and yet to increase the capacity of encapsulation (Uprit, Kumar Sahu *et al.,* 2013).

These two types of nanoparticles (SLNs and NLCs) are widely used in cosmetics since encapsulation prevents enzymatic degradation and controls the release so that it is adequate to the needs and prolongs in time thus increasing the duration of the therapeutic action. Its size is reduced (below 200 nm). They have proven advantages such as on-the-spot administration of the action with minimal side effects, not being irritant or toxic in that they are composed of biodegradable lipids. They can be applied on irritated skins and with changes in their natural functions since they have a very low irritation índex. The increase in the permeation that characterizes them can be explained by three mechanisms: adhesiveness, occlusion and hydration. They prevent the loss of water and open the junctions between corneocytes, which increases penetration (Bibi, Ahmed *et al.,* 2017).

3.3.8.Polymeric nanoparticle

Polymeric nanoparticle is a type of nanoparticles, as the name implies, are composed of polymers which, in dermatological applications, are natural or synthetic. The natural ones are, fundamentally, polysaccharides or proteins although they are not very used because of their high purity (Roque, Dias *et al.,* 2017) variation and the fact that they need a denaturing agente. Chitosan is the most commonly used natural polymer composed of a cationic polysaccharide and extracted from crustacean cells (Bibi, Ahmed *et al.,* 2017).

The synthetic polymers used are Polyglycolic Acid (PGA), polylactic acid (PLA) and polycapolactone (PCL) and copolymers such as Poly(Lactic-co-Glycolic) Acid (PLGA). All of them present themselves as biocompatible, and biodegradable and capable of eliciting sustained release from the target (Roque, Dias *et al.,* 2017). PLA is the most used because it has the ability to form protective film on the surface of the skin. These particles can be prepared by: nanoprecipitation, dispersive polymerization, inverse salting out, polymer emulsification, solvent displacement, solvent evaporation (Bibi, Ahmed *et al.,* 2017) and with sizes between 228-365 nm achieves a good penetration in the target sites (Morgen, Lu *et al.,* 2011). And the drugs can be distributed in different ways. They may be adsorbed to the surface, incorporated in the interior or dispersed in the matrix. Release of the drug will depend on how it is distributed and the nanoparticle can undergo processes of diffusion by the polymer wall, matrix erosion, erosion and diffusion. These phenomena lead to the release of the encapsulated drug in a controlled and extensive manner over time (Bibi, Ahmed *et al.,* 2017). Those of PLGA have a size in the order of 200-400 nm and enter by follicular route (Roque, Dias *et al.,* 2017), being that with massage they penetrate more deeply (Morgen, Lu *et al.,* 2011). PLGA has carboxylic terminations in its chains that give it a negative charge which is an advantage because these molecules are quite attracted to the skin, which despite having negative charge of the carbohydrates present on its surface and which confer this charge, has lipids of SC that confer positive charge and maximize the attraction to these molecules (Roque, Dias *et al.,* 2017). On the other hand, those of PLA have a diameter of 228-365 nm and reach low tissues, thus making a controlled and sustained release. They enter the skin via the glands and in the hair follicles they form a kind of reservoir with high local concentration with the smaller ones being made easier by these routes (Morgen, Lu *et al.,* 2011). They suffer from this cutaneous permeation pathway because they are not able to penetrate SC and because entering these secondary pathways minimizes systemic effects (Bibi, Ahmed *et al.,* 2017).

Morgen, Lu et al., 2011 performed a test using rabbit ear tissue where it was possible to observe that there was no alteration of the particles, that have a size of 100 nm with a

concentration in stabilizer (sodium glycholate, NaGC), in three months, nor to aggregate them, allowing to infer that these had good stability beyond a good encapsulation efficiency (90%) that varies with the concentration of the nanoparticle. The in vitro study performed on rabbit tissues showed that there was a basal accumulation of MXD in SC although nothing is observed in the epidermis or dermis, ensuring that the complex has a target effect, ensuring fewer side effects, and moving to the follicles unlike the commercial solution where there is a trace from the epidermis to the dermis, revealing that it has no localized effect. Commercial and nanoparticulate solutions have drug release values in very similar sebaceous glands although commercial solutions alter SC and thus increase permeability, and as it penetrates through multiple pathways, much drug reaches the dermis leading to highly potent systemic effects. The nanoparticles, as they preferentially enter the transfolicular pathway, show a permanence of the drug at the follicular level, which potentiates the effect and reduces the side effects. Because they have a lower dose of MXD and lack of organic solvents, they are a very acceptable alternative to the commercially available solutions to avoid both cutaneous and systemic adverse effects and also reduce the number of applications (sustained release) and increase the number of drugs that reach the place of action (Morgen, Lu *et al.,* 2011).

A study by *Patzelt et al.,* has revealed that in the use of these particles the size interferes with the depth with which the drug reaches the follicle. This study, which was done on pig skin cells, showed that silica and PLGA particles penetrate deeper if they are between 400 and 700 nm in size, which is due to the similarity between the thickness of the hair (Patzelt, Richter *et al.,* 2011). Also studied are PLGA nanospheres which are prepared by the solvent emulsion method and having lactic acid and glycolytic acid in it (75:25). Its size varies between 182 and 210 nm and enter follicular way given its low size and surface tension. In a study using this type of nanoparticles embedded in a roxithromycin organogel in which the tendency of accumulation of these particles around the holes of the follicles was observed, creating a reservoir which allows to reduce the doses to apply and the frequency of application. The penetration depends on the opening or not of the follicles, in which the closure is explained by the presence of the corneocytes of the skin in telogen phase. O seu tamanho tem de ser na ordem dos 300 nm para penetrar pela via folicular. Particles are more stable if they undergo steric stabilization with Polyvinyl Alcohol (PVA), which will reduce zeta potential, adhere to the surface and thus increase stability, which is longer if the particles are stored at 4 °C. A particular size suitable and the use of Pluronic- Lecithin Organogel (PLO) (rather than a lipophilic carrier) as carrier increases the concentration of these particles in sebaceous units and promotes follicular deposition due to their viscositySeveral ratios of drug: polymer were

evaluated, and the highest encapsulation efficiency was verified in the higher dosage of active principle, although it was with a ratio 10:490 that the most advantageous size was verified and a greater percentage of drug released at the end of 24 h. (Glowka, Wosicka-Frackowiak *et al.,* 2014)

In 2004, *Shim, Seok Kang et al.,* carried out a study using Poly (ε-caprolactone) -block-poly (ethylene glycol) with 0.5 g of MXD observing parameters such as permeation through the abdominal skin of rodents. The polymer was prepared by ring-opening polymerization and the complex by a solvent evaporation method and two sizes of nanoparticles were used: 40 nm and 130 nm. It was observed that the smaller ones achieved cutaneous deposition of 3% while the larger ones achieved a percentage of 2%. Thus, it is obtained that the smaller particles have an easier diffusion, and the amount of MXD retained in the skin does not depend on the size. Comparing with commercial solutions at 30% ethanol it is observed that these complexes can more easily incorporate the drug into the skin. This suggests the existence of a specific penetration pathway, such as the sweat, sebaceous or follicular route, and because they are too large to pass SC. The use of flowering revealed a higher concentration of this complex along the follicles fortifying the hypothesis of these molecules to undergo one of the secondary routes of skin absorption (Shim, Seok Kang *et al.,* 2004).

Zhao, Brown et al., using polymeric nanoparticles with sizes in the order of 260 nm, with negative charge (zeta potential of -20 mV) and constituted by propyleneglycol monocaprylate (HLB = 6). They were produced by solvent displacement. The encapsulation efficiency was 20% (very low). Its zeta potential gives it good physical stability. It was also seen that they released less and more slowly the drug than lipid nanoparticles tested in the same study. It was observed that these particles release less quantity than the commercial solution used as a control and that the nanoparticles released more MXD if they were in the form of Foams (use of HFA227) forming an O/W/O solution that collapses when releasing the drug, observing sustained biphasic release. The surfactant used in Foams increases the solubility of MXD (Zhao, Brown *et al.,* 2010).

Chitosan is a naturally occurring, cationic and biodegradable polymer (Matos, Reis *et al.,* 2015). In a study by *Matos et al.,*, properties such as the ability of these particles to have a sustained release character of MXD as well as the potential to reach the target, which in this case, are the capillary bulbs were quantified. The best particle characteristics were obtained with the highest ratio MXD: chitosan (1:1), showing a better inlet capacity and a smaller size (235 nm). As for the Zeta potential, which gives stability to the suspension since it prevents agglomeration, no differences were observed with the variation of the ratio between MXD

and chitosan although this value was lower than the value obtained for pure Chitosan. Thus, the best group is the one with the best encapsulation capacity. The particles are spherical. When released, compared to the control, we observed a reduction of 189 μg/cm^2/h to 35.4 μg/cm^2/h and that is all the more sustained the smaller the size of the particular. With regard to retention, at follicular level it is observed that the maximum accumulation is 5.9 μg/cm^2 (observed at 6 h) and that this value is able to remain constant until 12 h after application with the use of polymeric nanoparticles, always above 4.5 μg/cm^2, thus being always greater than the control solution. This fact makes it predicted to be more effective in the treatment of alopecia, since it reduces the number of applications because it last longer its effect. This study reveals that a concentration ten times lower than commercial solutions is able to accumulate more slowly in the follicles and in higher concentration, depositing within the follicles, thus exerting a very strong target effect and potentiating the action of the drug. It was also analyzed the deposition of these particles at the SC level, with values similar to the control solution, which supports the hypothesis that the passage of these nanoparticles of MXD is preferentially done by follicular route. Thus, it can be assumed that these particles show potential in the treatment of alopecia, since they increase the amount of drug that reaches the target site (follicle) and its residence time, potentiating the drug effect (Matos, Reis *et al.,* 2015).

Another study using microparticles boosted by iontophuresis that, given the particles have a positive character, iontophuresis will function as anode. This study evaluated the particle size at 3 μm and had a zeta potential of + 5.9 mV. At the pH of the formulation (5.5) about 90% of the MXD is in the non-ionized form, entering by electroosmosis and electrorepulsion. The amount of MXD that reaches the follicles and the SC was evaluated in a control, and the one that reaches the cutaneous barrier is homogeneous over time, but the one that reaches the follicular receptors increases with the passage of time, which proves the aptness for the target of these molecules. The control shows less capacity than the microparticles either with iontophuresis or without, although with this process also increases the amount of MXD that reaches the structures. The amount of MXD in the follicles versus the control is about double with microencapsulation and iontofuresis. Thus, it can be concluded that this process increases the arrival of MXD to the lower layers of the follicles where it will exert its effect (Gelfuso, Barros *et al.,* 2015).

3.3.9.Squarticles

Nanoparticles formed from tallow-derived lipids and fatty acid esters. They have two types: NLC and NEs, in which the first has a size in the order of 177 nm and the second in 194 nm, homogeneously. NEs appear to be more mobile and more deformable and exhibit a MXD encapsulation of 64%. The zeta potential of these particles is negative because of the phospholipid load, and is in the order of -60 mV, which shows high stability. MXD, at the level of the DP, will cause vasodilation of the perifollicular vessels and increase the proliferation of the papillae. To avoid side effects of the drug and to control its release and stability, the best route is to resort to encapsulation. These particles (NLC and NE) exhibit much lower toxicity than polymeric and metal nanoparticles.

In these two types of molecules, drug release depends on their interaction with sebum, where squalene present in nanostructures is expected to facilitate fusion. Formulation: are prepared in two distinct phases (an aqueous containing water and PF68 -previne aggregation- and a lipid with squalene, which in NE is 7% and in NLC is 3.5%) which are then mixed by ultracentrifugation. NE and NLC are distinguishable by the different materials they present in the nucleus. The NEs present a greater size and the same encapsulation capacity of MXD (63.5%) when compared to the NLC, but the NLC are the only ones that evidence increased deposition (588 μg/g) of MXD compared to the control (227 μg/g), and this deposition is done only in the follicles, which decreases associated systemic effects due to the fact that the drug is retained and does not reach the blood vessels, since it evidences a lower flow in relation to the control and a greater uptake of MXD in the follicle than in the NEs (increases by 5.2 times) with the NLC (increases by 7 times), thus allowing to say that these forms are more selective. It was also observed that the entry of MXD into the follicles increases with the removal of sebum because the sebum slows down its absorption, and the highest release of minox is observed in NLC. As for the release, and as is apparent, it is lower in the control because of the lower solubility and the NE has a profile similar to the control against the cellulose membrane. NLCs release about twice as much, although all release about 80% in the first 8 hours. The DP are located at the base of the follicles and play an important role in the hair growth, thus constituting the major target of action of MXD that regulates VEGF and the vascularization of that site. VEGF is responsible for hair follicle enlargement, growth and thickness. The presence of blood vessel growth factor (VEGF) is required for the induction of sufficient angiogenesis in the hair follicles. MXD is responsible for the elevation of this factor, and it is verified that this increase is greater when using NLC for the administration of the molecule (increase of 2.3 against the control), than in the NE, where the growth is confusable

with that of the molecule control. By the method of microscopic flurrying the author observed that in the control most of the flurry is verified at the superficial level which evidences a low capacity of entrance, being that in the level of Squarticles more penetration is observed to the deep one. Observing the two types of squarticles it is observed that the NLC do not demonstrate a homogeneous distribution in contrast to NE where the distribution occurs in all cutaneous layers of the animal organism (Female Nude Mice). NEs have the lowest toxicity and the highest viability (concentration increase does not change viability, unlike NLC). Despite this, none of the formulations (NE or NLC) cause erythrema in the skin (Aljuffali, Sung *et al.,* 2014).

3.3.10.Cyclodextrin

Cyclodextrins (CDs) are composed of a conical channel structure, allowing the incorporation of molecules that have low solubility, in order to increase it (Lopedota, Cutrignelli *et al.,* 2015).

One of these complexes may be methyl-β-cyclodextrin (Me-β-CD), which differs from a normal one because it is chemically modified and may contain various degrees of methylation that confer greater lipophilicity and may act as a potentiator of the cellular entry of drugs incorporated therein by increasing its concentration on physiological surfaces. Hydrogels have the function of increasing the time of contact with the target as well as of giving better properties for cutaneous use. In this case, the gel may be Carbopol 940, alginate or hydroxyethylcellulose and must be present without odor and without aggregates. Its pH is indicated for skin administration leading to a good acceptance. A study by Lopedota *et al.,* in 2015 used this complex (Me-β-CD), prepared by a Freeze-drying method with a final concentration of MXD of 5% w/v. An Nuclear magnetic resonance (NMR) study with this complex revealed that the MXD possesses the H3 and H5 protons within the CD cavity and in the DSC scanning the peak corresponding to the MXD fusion is not observed when it is incorporated into the Me-β-CD, in its amorphous state, a state of greater energy. One of the studied parameters is the effective drug, where it was noticed that the gels only provoke an accumulation in the tissues after 24 h, and this accumulation is 3-fold superior to the commercial ones (106 $\mu g/cm^2$ versus 33 $\mu g/cm^2$). From the results it can be seen that the best gel is that of Alginate, it is the only one that demonstrates an acceptable retention of MXD besides increasing the adhesiveness and permeability in the skin barrier. This study revealed that the absence of crystals is important since they cancel out the effect, and for this purpose agents may be used to prevent this crystallization, as is the case with calcium alginate. Thus,

the hypothesis that calcium alginate gel as a vehicle of the MXD:Me-β-CD complex is a very viable alternative for the treatment of androgenic alopecia.(Lopedota, Cutrignelli *et al.,* 2015)

An experiment performed by Lopedota *et al.,* using CDs as a template to sodium alginate (α-D-mannuronic and R-L-guluronic acid residues and characterized as anionic and biocompatible and biodegradable and with a pseudoplastic rheological profile) and as a drug MXD. This polymer can be incorporated into CDs, complexes which are assumed as inclusion compounds for molecules whose solubility is compromised, increasing this parameter as well as the dissolution of the molecules that it incorporates into water, further enhancing both chemical and physical stability and absorption. There are several types of CDs, the HP-β-CD being less cytotoxic in that it has less ability to obtain cholesterol from the cells. In this study, parameters such as compound solubility, thermodynamics, NMR, stability and release were evaluated. The solubility of MXD in water increases linearly with the increase in the ratio of HP-β-CD although it does not increase the dissolved amount or change the dissolution profile. More MXD is dissolved using HP-β-CD at 0.65 because the reduction of the esterified obstacles increase inclusion in the lipophilic cavity and as 0.65 there are fewer substituents there are fewer obstacles to the inclusion of MXD in the CD cavity. The thermodynamic study reveals that formation of the MXD/HP-β-CD complex is a spontaneous process, revealing values of ΔH and ΔS. Observing the MXD NMR study that was done only on the MXD molecule, only on the HP-β-CD and the MXD/HP-β-CD complex. The results revealed that the more sensitive protons H-3 'and H-4' and these will be included in the CD well and confirmed that the MXD molecule is incorporated into the cavity of CD. The alginate gel was added as a pH value controller in the range of 6.5-6.8, thus avoiding skin irritations. Release studies revealed slower release in the hydrogel when compared to the commercial solution that was used as a control. This is because the drug to be released is forced to pass an alginate matrix, which delays the release and further reduces the amount of unbound strands of CD, altering the affinity of the polymer. A flow of 0.87 mg/cm^2/h was observed, much lower compared to the commercial solution used which showed a value in the order of 1.3 mg/cm^2/h. An ex vivo study using porcine skin showed better accumulation when the CD hydrogel (65.5 μg/cm^2) was used when compared to the commercial solution (30.17 μg/cm^2) which may be due to the fact that the CD establish relations with the lipids of the skin, acting as a penetration enhancer. As for stability, the tests revealed a permanence of the parameters during three months, and even when subjected to stress (increase in temperature, humidity and light) no physical or chemical changes were observed, which shows that CD protect the molecule of MXD, since as it is known this is degraded by the luminosity and in the case of the complex

no changes are observed unlike what happens in the solution when subjected to these conditions and where the spectrum of UV-Vis reveals a peak in the zone of the yellow, that indicates alteration of the molecule . In a histological study carried out in pig cells, in the cells where the hydrogel was applied some scaling and spaces between the corneocytes were observed whereas when the commercial solution is used there is a rupture between SC cells and the remaining epidermis, forming a kind of air bubble between the layers, which indicates that the commercial solutions alter the skin layers (Lopedota, Denora *et al.,* 2018).

Complementing the previous results, Tricarico *et al.,* based on the fact that HP-β-CD increases the solubility of MXD in water, allowing to dissolve MXD at a concentration of 6% (w/w), this inclusion being faster and easier than in solutions. An alginate gel of these complexes was also prepared in order to increase adherence to the scalp. The primordial parameters evaluated in this study were the toxicity and the efficacy of this new pharmaceutical form, using a live animal model (rats), in which they monitored capillary growth in the dorsal area in the period of four weeks after depilation (induction of the anagen phase), also using histological analysis and biopsies. The complex was prepared by three different methods in order to assess whether this had an influence. Freeze-Drying, Kneading, SprayDrying and Physical Mixing. The method that further increases the solubility of MXD in water is FreezeDrying (after 10min it has almost 100% dissolved). The encapsulation capacity is also higher in FreezeDrying (90.5%), although all methods have a value greater than 50%. Analysis of the DSC spectrum reveals that in the Freeze-Drying and Spray-drying method the MXD melting peak (190 °C) disappears, appearing in the others, indicating that there were no crystals of MXD in the complex, being in the amorphous state, conferring greater energy which facilitates its diffusion and also because it ensures better encapsulation of the drug and a better and more controlled release at the target level than the follicles. This type of particles decrease the interfacial tension between the solid particles and the aqueous medium, facilitating the dissolution of these in the medium. The Fourier-Transform Infrared Spectroscopy (FT-IR) analysis of the MXD isolated and incorporated in the CD, showed alteration (frequency and intensity) of the bands characteristic of the pharmacological molecule, by the absence of Van der Walls bonds in the new connections. The observation of the animal model revealed that there were no significant differences in capillary growth between the experimental groups (Control, Commercial Solution and MXD gel 3.5% w/w) in the first two weeks, and in the third group there was a capillary increase in the treated groups either with the commercial solution or with the gel, whose growth in these two groups was total at the end of the four weeks. Although the growth was similar for the two groups, a

microscopic analysis revealed that the group treated with the gel exhibited a greater number of follicles, more cutaneous thickness, greater diameter of the hair bulb and a greater follicular output and of genes like Wnt4, TGFβ2, among others that are responsible for these increases at the follicle level and indicators that it is in the anagen phase. It also increases the genes that lead to the expression of the ATP channels (kir6.1 and SUR2B), leading to increases in cutaneous thickness. It also potentiates the KATP2 pathway, which negatively regulates the androgenic pathway, decreasing the synthesis of DHT. Thus, this study shows that this gel, stable, easy to handle and apply and absent from adverse skin reactions, is a potentiator of hair growth at levels higher than commercial solutions, and can be a viable alternative to commercial solutions given its superior beneficial effects, (Tricarico, Maqoud *et al.,* 2018) and decreases the side effects of the molecule such as headache and hypotension (Lopedota, Denora *et al.,* 2018).

Table 2: Phisical characteristics of nanoparticles (size, zeta potencial and stability).

Nanosystem	Preparation method	Particle size (nm)	Zeta potential (mV)	Stability	Ref
Niossomes	Etanol injection	252	-33.22	Greater with Span 40	(Balakrishnan, Shanmugam *et al.,* 2009)
	Ethanol Injection	219	-----	Greater with Span60: Cholesterol Molar Ratio (2:1)- 3 months	(Mali, Darandale *et al.,* 2013)
PEVs	Sonification	140-195	-52	4-6 months	(Mura, Manconi *et al.,* 2009)
NLCs	Ultrasonication	281	-32,9	3 months (4°C and 25°C)	(Wang, Chen *et al.,* 2017; Uprit, Kumar Sahu *et al.,* 2013)
SLNs	Melt emulsification	190	-30	6 months	(Padois, Cantieni *et al.,* 2011)
Polymeric nanoparticles **(PLA and PCL)**	Emulsion by solvent evaporation	280-340 (as greater as the amount of polymer)	3-4 (reduces to 0.3 with higher adsorption of PVA)	3 months (Enhancement a 4°C)	(Glowka, Wosicka-Frackowiak *et al.*, 2014)
(Chitosan)	Atomization	235	+38.6	3 months	(Matos, Reis *et al.*, 2015)
(PLA)	Solvent displacement	260	-20	good	(Zhao, Brown *et al.*, 2010)
CD	Mixed in Mortar	----	----	3 months	(Lopedota, Denora *et al.*, 2018)

Table 3: The in vitro results of MXD nanoparticles.

Nanosystem	Studied parameters	Cellular model	Main Results	Ref
Niossomes	Permeation and cell imput	Franz cells with ear skin	Increased cholesterol increases deposition and permeation More follicular accumulation and more sustained release	(Mali, Darandale *et al.,* 2013)
PEVs	Permeation	Pig Skin	Labrasol with higher release capacity followed by cineole Capacity decreases with pretreatment Creation of deposits from where the MXD is released	(Mura, Manconi *et al.,* 2009)
SLNs	Permeation Drug encapsulation Skin irritation	Franz cells	Permeation around 915µg/g in epidermis and 181µg/g in Dermis Encapsulation arround 94% Totally non-corrosive	(Padois, Cantieni *et al.,* 2011)
NLCs	Permeation and cell imput e skin irritation	Mice Skin in Franz cells	Permeation of 92%, high follicular retention, cutaneous irritability index of 0.17	(Wang, Chen *et al.,* 2017)
NLCs Gel Carbopol 934	release	Franz diffusion cells	Biphasic release with release of 92%	(Uprit, Kumar Sahu *et al.,* 2013)
Polymeric nanoparticles	Drug amount in hair follicles and SC	Pig ear skin	Double over control; Significant increases in relation to solutions; Increased deposition versus control	(Matos, Reis *et al.,* 2015)
CDs	Drug Release and accumulation in skin	Pig skin	Less release compared to commercial solutions (85.2% versus 70.8% in hydrogel) but more than double MXD accumulation in the skin (65.5 µg/cm^2 versus 30.17 µg/cm^2 of the control)	(Lopedota, Denora *et al.,* 2018)

4.In vivo studies

Few in vivo studies have been performed for this type of particles. One was performed for CD using rats after depilation. It was performed using the product against a control and against commercial solutions. It is known that epilation induces the anagen phase. It was observed that MXD undergoes complete dissolution in 10 minutes with the CD and that with the commercial solutions only after 60 min it dissolves 65%. It was found that in the first two weeks there are no practical effects and that in the 3rd week with the commercial solutions and the CD increase the hair size of the depilated area. After the 4th week, all mice treated with the two solutions containing MXD present the hair full area (Tricarico, Maqoud *et al.,* 2018).

A study was performed using PLGA Nanospheres with three types of hair growth enhancers (Hinokitinol, 6-Benzylaminopurine and Glycyrrhetinic acid) against a total white control (no application of anything) and a commercial solution in 30% ethanol and a solution with the nanospheres in 30% ethanol, too. The results showed that solutions of 30% ethanol without nanoencapsulation obtained some capillary growth although it is not very observable after 15 days. When capillary enhancers are used in nanospheres, capillary growth is almost double that of these drugs in only 30% ethanolic solution, since the nanospheres are able to penetrate the pores, increasing the passage to the anagen phase and, consequently, capillary growth (Tsujimoto, Hara *et al.,* 2007).

Shim, Seok Kang et al., also performed an in vivo study using 2 experimental groups (1st: anagen phase, 2nd in telogen phase) and testing Poly (ε-caprolactone) -block-poly (ethylene glycol) and MXD complexes that revealed that retention of MXD was about 1.8 to 2.5 times higher in the anagen phase, 1.5 times larger in the small particles (40 nm) than in the large ones (130 nm), and there were no differences between the nanoparticles and the controls (Shim, Seok Kang *et al.,* 2004).

Table 4: The In vivo studies of effects of MXD nanoparticles.

Nanosystem	Studied parameters	Animal model	Main Results	Ref
PLGA Nanospheres	Hair Growth	C3H mice	Capillary incrase in the depilated areas of the dorsal on rats	(Tsujimoto, Hara *et al.,* 2007)
Poly(ε-caprolactone)-block-poly(ethylene glycol)	Skin retention	C57BL/6 Mice	1.8-2.5-fold higher in anangen phase 1.5-fold higher in small particles	(Shim, Seok Kang *et al.,* 2004)
Cyclodextrins	Hair Growth	Laboratory Mice	Capillary incrase in the depilated areas of the dorsal on rats	(Tricarico, Maqoud *et al.,* 2018)

5. Toxicity issues

The toxicity of these particles is closely related to the fact that they create in the capillary follicles a reservoir, where the active principle is lodged and liberated. Thus, it may occur that in this process an uncontrolled release of the active principle occurs, leading to an excess that can be absorbed at the level of the capillaries of the dermis leading to adverse effects at the local level and at the cardiovascular level due to the vasodilatory effect of MXD. Another possible case is the fact that the penetration of these particles causes changes in the skin cells that lead to the production of oxigen radical (ROX) that induce oxidative stress and, consequently, cell apoptosis. It is also possible that they induce autophagy of the keratinocytes constituting the cutaneous layers.

Regarding skin irritation, all of them were subjected to tests that measure the index of skin irritation against marketed solutions and all showed an index of irritation very close to 0 but that is increasing as the time of exposure increases.

The author *Aljuffali* observed that the NE formulated at any of the concentrations tested were nontoxic to the cells of the DP, guaranteeing a viability of 100% of these cells. In the case of NLC, the viability is only 76% but it was observed that in the lower concentrations these do not alter these cells. A test of the potentiality of skin irritation by these particles was also performed, evaluating TEWL, Erythrema and cutaneous pH, and in the first parameter (TEWL-measures the degree of SC integrity) only showed increase with continuous use for 7 days and is justified by the increase in hydration of the SC that causes rupture and has equal values in either the Squarticles or the control. In the case of erythrema and pH no signs were

observed at the level of the Nanoparticles which suggests a high tolerability of the skin to these particles (Aljuffali, Sung *et al.,* 2014).

When elucidating the profile of encapsulation and release of NLC's and MXD SLN's, Wang *et al.,* obtaining that the Liniment used to simulate commercial solutions and that contained alcohol and propylene glycol caused erythema in values much higher than the nanoparticles of MXD used (score of 2.50 in 72 hours). comparing the two nanoparticles (SLNs and NLCs), obtained equal values (0.33 in 72 h). Thus, it was concluded that these formulations can be used in cutaneous administration without the manifestation of adverse effects at the cutaneous level, which is not the case with commercial solutions (Wang, Chen *et al.,* 2017).

6.Regulatory affairs

Although there are no conclusive studies yet, it is observed that in these particles there is interest in the study and evidence of its effectiveness in capillary growth and safety in the face of side effects that existed with commercial lotions and that with these methods were extinguished. Thus, it is possible that in the coming years some of these particles containing MXD will be released on the market. For this purpose it is necessary that the laboratories interested in the commercialization of these cosmetics must submit to the European Medical Agency (EMA) the patent application or to the regulatory body of the country of commercialization. In order to submit this application to EMA it must be located in the European Union and must present documents about the product to be marketed.

After the first application, the date that is important for the exploitation of the patent, and after one year an international application may be required that encourages an investigation by the responsible international bodies that subject the new formulation to preliminary examination tests in order to evaluate their characteristics and potential application of this new wording in the markets which require it. This preliminary evaluation is required by the applicant and enters after being approved in a national phase, where the manuscript will be translated, over all the formulation, in the languages of the countries that will implement them. The duration of this whole process, from the international application and the national phase, is 30 months. The duration of the patent is 20 years (Barel, Paye *et al.,* 2014).

7.Conclusion and future perspectives

In recent years, androgenic alopecia have assumed very high proportions in the Caucasian population, reaching values in the order of 2% of the world population (Aljuffali, Sung *et al.,* 2014) and leading to psychological problems due to altered image (Tsujimoto, Hara *et al.,* 2007). Opportunities for treatment of this pathology are closely related to hydroalcoholic solutions of MXD which lead to a number of serious skin problems, many uses, and poor treatment capacity. These problems inherent to the treatment of an increasingly visible disease in the young population have led to the research of alternatives by the cosmetic industries of alternatives that minimize the side effects and potentiate the therapeutic effect of this molecule that is known to have positive effects in the treatment of this pathology (Lopedota, Denora *et al.,* 2018). In view of this, there have been high studies with nanoscale particles containing MXD and in which the possibility of solving the problems inherent in the commercial solutions of this drug and of potentiating its therapeutic effect has been evaluated (Mali, Darandale *et al.,* 2013).

The results have been very revealing and satisfactory. With these molecules it is observed that the adverse effects observed at the cutaneous level are practically absent (Aljuffali, Sung *et al.,* 2014, Wang, Chen *et al.,* 2017). It has also been found that these molecules increase the protection of the drug, both chemical and physical, against external agents, increasing its stability and also its water solubility which, as is known in the literature, is reduced. With these particles, potentiation of the drug effect is achieved. Since these achieve a very high target effect, creating a deposit in the vicinity of the hair follicle, where the MXD will exert its effect. This target effect with reservoir solves one of the problems of the commercialized solutions, the multiple applications, since a quick initial and later prolongation is achieved in the order of 18-24 h, which guarantees a more effective treatment (drug always at the place of effect) and less (Uprit, Kumar Sahu *et al.,* 2013).To further increase the potentialities of these particles, some of them were tested incorporated into a Carbopol gel which increases their rheological properties, enhancing better scattering and better absorption at the cutaneous level (Tricarico, Maqoud *et al.,* 2018).

These novel dosage forms use welltolerated, biodegradable, non-toxic and non-immunogenic excipients capable of penetrating the skin by modifying SC lipids or secondary pathways, which are the direct connection to the lower layers of the follicle. These also prevent their arrival into the systemic circulation, which is a great advantage given the systemic effects of the drug. But it is not only about advantages, there are still many handicaps to be solved in the future. The future prospects are aimed at estimating the entry of toxic particles

into the nanoparticles. Extensive studies are needed in voluntary groups to clarify the release and the way nanoparticles act *in vivo*. Animal models are also required to allow a strict classification of the profile of these molecules as well as their toxicity and release profile. Clarification of the mechanisms of action of encapsulated drugs and the way in which encapsulation in its various types alters the release and effects it causes in humans is also a factor to be improved in the future in order to better understand these new drugs. The cellular aspects arising from the use of these nanoscale drugs are poorly understood and established, so it is hoped that in the future they will be better clarified. The prophylactic use of these technologies in skin diseases such as alopecia is an advantage to be guaranteed and exploited (Bibi, Ahmed *et al.,* 2017). In view of this, it may be said that these complexes may in the future resolve very effectively this pathology if the best formulations are continued to be deepened and found.

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