UNIVERSIDADE D
COIMBRA

Maria Beatriz Silva Gonçalves

Relatório de Estágio e Monografia intitulada "The role of nanosystems on diabetic wound treatment and care" referentes à Unidade Curricular "Estágio", sob a orientação do Dr. Raúl Almeida e da Doutora Filipa Melo e 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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Mestrado Integrado em Ciências Farmacêuticas.

Julho 2021

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Coimbra, 14 de julho de 2021.

Maria Beatriz Silva Gonçalves

(Maria Beatriz Silva Gonçalves)

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"O tempo que passa não passa depressa.
O que passa depressa é o tempo que passou."
- Vergílio Ferreira

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Parte I

Relatório de Estágio em Farmácia Comunitária

Farmácia Santa Ana

Orientador: *Dr. Raúl Almeida*

Abreviaturas

IPSS - Instituições Particulares de Solidariedade Social

MICF - Mestrado Integrado em Ciências Farmacêuticas

MNSRM - Medicamentos não sujeitos a receita médica

MNSRM-EF - Medicamentos não sujeitos a receita médica de dispensa exclusiva em farmácia

MSRM - Medicamentos sujeitos a receita médica

PIM - Preparação individualizada da medicação

RM - Revisão da medicação

SNS - Serviço Nacional de Saúde

SWOT - *Strengths, Weaknesses, Opportunities, Threats*

1. Introdução

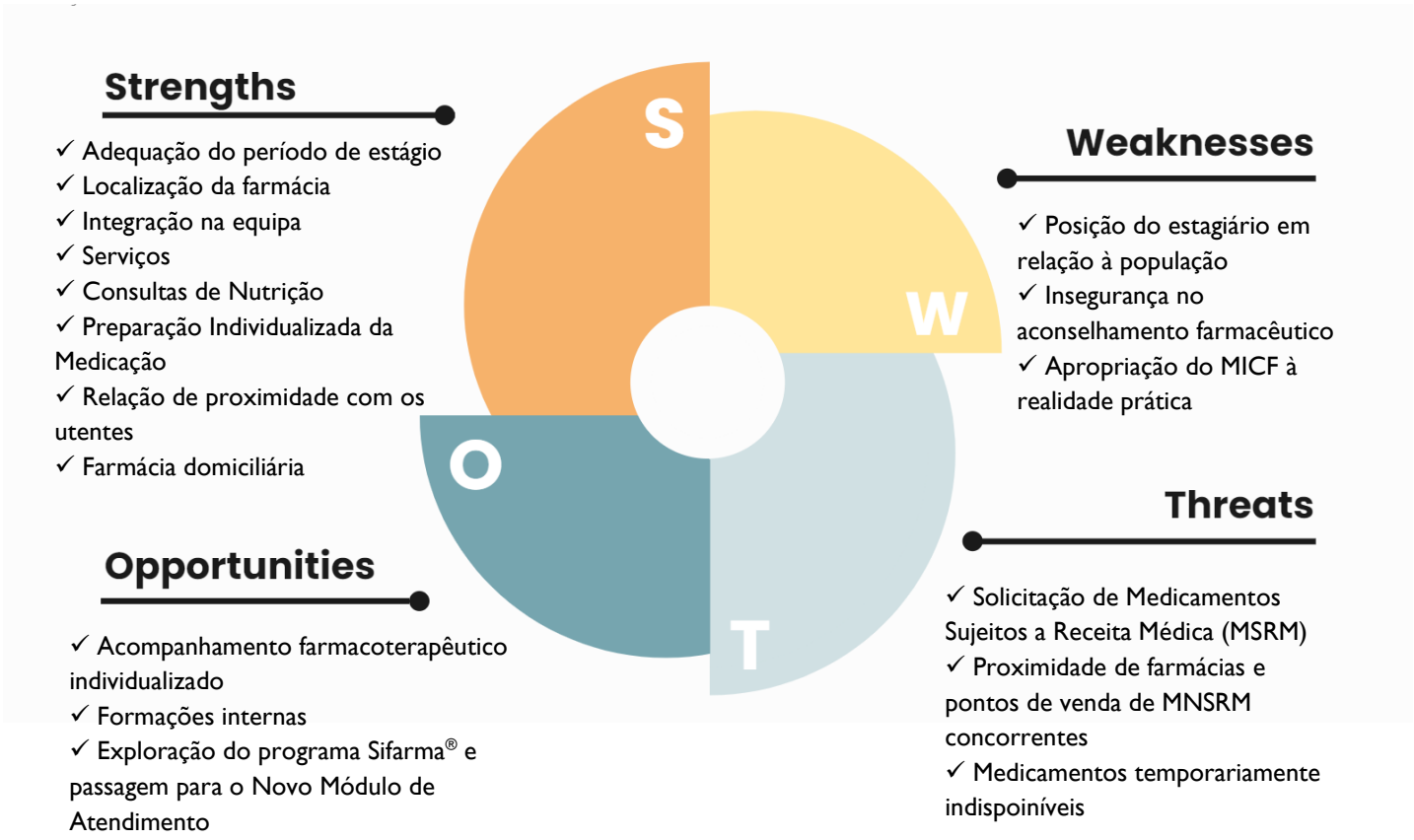
Ao longo do meu percurso académico, a consciência da relevância do estágio em farmácia comunitária foi uma constante. Aliando a aplicação e consolidação de conhecimentos teóricos previamente adquiridos ao contacto com uma realidade indubitavelmente mais prática, é favorecida a aquisição de novas ferramentas e competências que, certamente, serão determinantes para o nosso futuro enquanto profissionais de saúde.

O farmacêutico comunitário assume um papel de extrema importância no que respeita à Saúde Pública. De boticários a farmacêuticos, a evolução desta profissão tem sido notável, focando-se gradualmente no utente, não só a nível dos serviços prestados, mas também adotando uma perspetiva de acompanhamento farmacoterapêutico e de proximidade dos mesmos. Sendo as farmácias, em muitas localidades, as únicas estruturas capacitadas para a prestação de serviços de saúde, estas funcionam como um meio que visa a equidade de acesso a medicamentos e cuidados, tendo em conta a localização geográfica dos utentes. Um bom aconselhamento, garantindo o uso racional de medicamentos não sujeitos a receita médica (MNSRM) ou medicamentos não sujeitos a receita médica de dispensa exclusiva em farmácia (MNSRM-EF) pode, em situações menores, evitar que o utente tenha de recorrer a outras estruturas de saúde. Igualmente relevante é o desempenho e competências oferecidas através destas, a nível técnico, tornando-as uma componente extremamente importante no auxílio ao Serviço Nacional de Saúde (SNS). O farmacêutico é, também, encarregue de promover a adoção de estilos de vida saudáveis e proceder à identificação de doentes de risco. [1]

Ainda que o serviço prestado numa farmácia se estenda a todas as idades, os utentes mais idosos carecem de um nível de cuidado superior, tanto a nível terapêutico como afetivo. Desta forma, num país onde o Índice de Envelhecimento tem vindo a aumentar, é crucial o apoio a estes cidadãos, cuja realidade muitas vezes passa pela solidão e o isolamento. [2]

No âmbito do Estágio Curricular, o presente relatório será sucedido de uma análise SWOT (*Strengths; Weaknesses; Opportunities; Threats*), evidenciando estes pontos cruciais, relativamente ao local da sua realização. O mesmo decorreu na Farmácia Santa Ana, tendo início a 26 de janeiro de 2021 e conclusão a 18 de junho de 2021, sob orientação do Dr. Raúl Almeida. A proximidade da farmácia foi um dos fatores decisivos para a minha decisão, não obstante à excelente equipa técnica e serviço pela qual é caracterizada. Através deste relatório, foi possível exercer uma apreciação global, analisando simultaneamente os fatores internos e externos que influenciam o funcionamento geral da farmácia.

2. Análise SWOT



2.1. *Strengths* (Pontos Fortes)

2.1.1. Adequação do período de estágio

Um ponto que considero de extrema relevância é a planificação inicial do período de estágio. Embora apenas tenha realizado estágio na sua totalidade em Farmácia Comunitária, garantiu-me uma certa segurança a explicação do modo gradual como o mesmo iria decorrer. Inicialmente, o foco foi sobretudo em tarefas de *backoffice,* tais como a reposição e arrumação, receção de encomendas e devoluções. A verificação dos prazos de validade foi algo para a qual fui, desde o início, alertada, uma vez que é extremamente relevante para a correta circulação dos medicamentos, dispositivos médicos e outros produtos na farmácia. A receção de encomendas e a gestão de produtos que apresentam prazo de validade curto, são apenas um exemplo das situações em que este fator deve ser considerado. No último ponto referido, caso o produto não reunisse as condições desejadas, procedíamos à sua devolução.

A etapa seguinte passou pela aprendizagem da realização de uma encomenda, considerando os fornecedores e as suas condições comerciais, e pela gestão de *stocks*, de forma a garantir uma maior rentabilidade dos mesmos. Uma vez que o período inicial foi marcado, essencialmente, por estas tarefas de *backoffice*, a passagem para o *frontoffice* acabou por ser

facilitada, dado o maior à vontade para explorar o programa Sifarma 2000® e Sifarma Módulo de Atendimento.

Esta transição foi, igualmente, progressiva, começando por assistir a atendimentos ao balcão dos vários elementos da equipa técnica. O atendimento é um momento de grande responsabilidade, o qual deve ser adequado às necessidades e contexto clínico do utente. Deste modo foi relevante uma primeira abordagem, mais focalizada na observação, para consolidar conhecimentos a aplicar e, assim, garantir a completa satisfação e segurança do utente. A observação de variados aconselhamentos e colocação em prática, sob supervisão, dos conhecimentos que ia adquirindo acerca do funcionamento do Sifarma, permitiu-me adquirir uma maior segurança para os posteriores atendimentos. A encomenda de produtos esgotados, criação de uma reserva e respetiva dispensa, foram algumas das primeiras etapas que executei no atendimento ao balcão. Seguidamente, contactei com vários tipos de receitas e regimes de comparticipação, essencial para a compreensão da sua aplicação e funcionamento. No decorrer do estágio pude, ainda, observar a realização da conferência do receituário, etapa que se revela de extrema importância para assegurar a conformidade das receitas que chegam à farmácia.

Este método permitiu-me, não só, ter uma atenção redobrada a todas as particularidades exigidas aquando do atendimento, mas também ampliar o meu conhecimento acerca dos regimes especiais existentes e dos diferentes organismos de comparticipação.

2.1.2. Localização da farmácia

A Farmácia Santa Ana encontra-se sediada na freguesia de Ferreira-a-Nova, pertencente ao concelho da Figueira da Foz. Uma vez que se trata de um meio relativamente pequeno, onde esta é a estrutura de saúde mais próxima das freguesias circundantes, a mesma é caracterizada por uma grande afluência e boa fidelização dos utentes. Embora falemos, na sua grande maioria, de uma população mais envelhecida, todas as faixas etárias são abrangidas no atendimento, o que requer, naturalmente, a sua diferenciação. Esse é um fator que considero bastante importante: a adequação do atendimento ao utente que nos é apresentado. Dada a diversidade de idades, foi um ponto crucial a adotar na minha postura enquanto futura farmacêutica. A farmácia dispõe, ainda, de um parque de estacionamento exterior que, além contribuir para a comodidade dos utentes, facilita a entrada e saída dos mesmos nos momentos de maior afluência.

2.1.3. Equipa técnica

A equipa técnica da Farmácia Santa é constituída por profissionais jovens, dedicados e focados em proporcionar aos utentes uma experiência de atendimento que satisfaça as suas necessidades, consoante o contexto clínico que lhes é apresentado. Com o decorrer do estágio, foi notável a coesão e espírito de equipa entre todos os membros. Desde o primeiro dia que, sempre que alguma dúvida surgia, nenhum elemento hesitava em ajudar. Para mim, esta calorosa receção e o fomentar de uma boa relação com os meus colegas, foram essenciais para alcançar um maior nível de confiança e segurança e, sobretudo, aprender.

O farmacêutico é, em muitas situações, um bom ouvinte. Assim, o tato para lidar com determinadas situações e o cultivar de uma boa relação com o utente, são pontos que considero cruciais para o bom funcionamento de uma farmácia. A boa disposição da equipa, profissionalismo e empatia para com os utentes, são apenas mais algumas das características desta equipa que, em muito, contribuem para a fidelização dos mesmos e, consequente, sucesso da Farmácia Santa Ana.

2.1.4. Serviços aprovisionados aos utentes

A diversificação de serviços prestados aos utentes constitui, sem dúvida, um ponto forte desta farmácia. A oferta de cuidados primários de saúde aos utentes inclui a medição de parâmetros fisiológicos e bioquímicos, tais como a avaliação dos níveis de Colesterol, Triglicéridos, Glicémia, Pressão Arterial e Índice de Massa Corporal. Para a monitorização destes parâmetros, a farmácia dispõe de um gabinete totalmente equipado, e com as condições necessárias, para garantir a correta realização dos mesmos. Este espaço é, também, utilizado para a administração de vacinas e injetáveis, proporcionando ao utente uma maior comodidade.

O ambiente privativo permite um contacto mais próximo com o utente e uma melhor perceção do seu perfil, que será preponderante para concretizar um bom aconselhamento. A análise dos resultados obtidos nas medições é, igualmente, essencial para o acompanhamento farmacoterapêutico do utente e, caso necessário, encaminhar o mesmo para uma consulta médica.

A multiplicidade dos serviços prestados, a sua aprendizagem e posterior colocação em prática, permitiram-me adquirir ferramentas que considero fundamentais. Além disso, a interpretação

e explicação dos resultados constitui, indubitavelmente, uma mais-valia para a educação da população e monitorização dos parâmetros fisiológicos e bioquímicos da mesma.

2.1.5. Consultas de Nutrição

A presença da nutricionista Daniela Gomes é, sem dúvida, benéfica. Este serviço é extremamente importante para a promoção de um estilo de vida mais saudável, que muitas vezes pode ser decisivo para a saúde do utente. Aliado à análise inicial do seu perfil, a nutricionista define um plano de alimentação e as medidas não farmacológicas que devem ser adotadas. Entre estas estão, por exemplo, a prática de exercício físico, aumento da ingestão de água e a cessação tabágica, variando entre cada caso. Também por se tratar de uma pessoa muito profissional, dotada de uma grande empatia e amabilidade, a sua contribuição tem sido relevante para elevar o alcance da farmácia a novos clientes.

2.1.6. Preparação individualizada da medicação

A Preparação Individualizada da Medicação (PIM) constitui um serviço fundamental e diferenciador, quando comparado com as farmácias envolventes. A polimedicação é uma realidade para muitos utentes e que, muitas vezes, é difícil de gerir. Desta forma, este serviço permite fazer uma correta gestão da medicação do utente, de acordo com a sua posologia e horário de administração. O objetivo final, será sempre que o utente tome o medicamento certo, no dia certo, à hora certa. [3]

Dado o envelhecimento da população nesta localidade e a proporção de pessoas em Instituições Particulares de Solidariedade Social (IPSS) envolventes, este sistema tem vindo revelar-se um sucesso e é cada vez mais requisitado pelos utentes. A boa relação que a farmácia mantém com estas IPSS é um excelente elo de ligação, não só porque permite uma maior monitorização da terapêutica do utente, como contribui, de forma benéfica, para o rendimento da mesma.

Neste momento, a produção do PIM é realizada por um farmacêutico que assegura a introdução, no sistema informático, dos dados de cada utente, consoante a sua instituição. Estes dados incluem o nome, idade e medicação, juntamente com horário e posologia da mesma.

Cada utente possui um *stock* da sua respetiva medicação, o qual é atualizado antes de cada produção. Após essa etapa, sucede-se a produção da PIM, normalmente com uma duração de

15 dias. Esta produção é enviada, através do software informático, para uma máquina automática que, de acordo com o esquema posológico do utente, faz a correta distribuição dos medicamentos. Esta é constituída por um tabuleiro de 45 poços que, quando completo, desencadeia o início da produção de blisters individualizados com a medicação, que incluem a data, horário (jejum e/ou pequeno-almoço e/ou almoço e/ou lanche e/ou jantar e/ou deitar) e posologia da mesma. [4]

Na minha opinião, este serviço além de ser relativamente recente e inovador, traduz-se numa maior segurança para os doentes polimedicados e permite, ao farmacêutico que está a realizar a PIM, adquirir um conhecimento mais vasto acerca dos vários medicamentos, suas características, posologia e modos de administração.

2.1.7. Relação de proximidade com os utentes

Como referido anteriormente, a equipa da Farmácia Santa Ana é muito reconhecida pelos utentes por tentar manter um contacto próximo dos mesmos. Nomeadamente durante a situação pandémica que vivemos atualmente, durante a qual muitas famílias perderam entes próximos ou estão a passar por uma fase mais delicada a nível pessoal e profissional, é importante ter em atenção a forma como abordamos o atendimento. Apercebi-me, no atendimento ao balcão, que as pessoas encontram no farmacêutico um profissional de saúde em quem confiam os seus problemas e que, muitas vezes, uma palavra amiga pode fazer toda a diferença.

Fora do contexto da pandemia, esta é uma farmácia muito participativa quer em eventos dinamizados pelas Juntas de Freguesia envolventes e pela Câmara Municipal, quer em iniciativas promovidas pela própria, tais como caminhadas e a comemoração do Dia Mundial da Criança. Estas atividades são essenciais para a manutenção de uma relação próxima com os utentes, a qual considero de extrema importância nesta profissão.

2.1.8. Entrega de medicamentos ao domicílio

A Farmácia Santa Ana dispõe, desde 2020, do serviço de entrega de medicamentos ao domicílio. Este serviu para colmatar, numa fase mais complicada da pandemia provocada pelo COVID-19, as falhas no acesso à medicação, por parte dos utentes. Contudo, dada a constante existência de medicamentos esgotados ou temporariamente indisponíveis, a farmácia disponibiliza, desde essa data, a possibilidade de entregar os medicamentos ao domicílio, ao

invés do utente ter de se deslocar à mesma. As entregas abrangem diversas localidades e são realizadas num veículo que assegura as condições adequadas para os medicamentos, durante a sua deslocação.

Este serviço é, sem dúvida, uma mais-valia para a farmácia e para os utentes, permitindo a igualdade de acesso aos medicamentos, dispositivos médicos e outros produtos, aos que não têm essa possibilidade, ou cuja deslocação é, desta forma, facilitada. É importante referir que, através deste serviço, só é feita a dispensa e entrega de MSRM após a apresentação da respetiva receita médica.

2.2. *Weaknesses* (Pontos Fracos)

2.2.1. A posição do estagiário em relação à população

Durante os meses de estágio em farmácia comunitária, deparei-me diversas vezes com a sensação de insegurança por parte de alguns utentes, quando esclarecia algumas dúvidas aos mesmos. Tratando-se de uma farmácia antiga, localizada num meio relativamente pequeno e no qual existe uma excelente fidelização dos utentes, estes preferem, em determinados casos, o atendimento por um elemento da equipa técnica já conhecido, no qual reconhecem uma maior experiência e capacidade de aconselhamento.

No meio rural, deparei-me com diversas situações do foro veterinário, as quais, apesar de contribuírem bastante para o meu conhecimento nessa área, geravam mais incerteza aos utentes, aquando do meu aconselhamento.

Contudo, ao longo do tempo foi possível criar um contacto mais próximo com a população, minimizando as situações em que outros elementos eram preferidos em detrimento do estagiário.

2.2.2. Insegurança no aconselhamento farmacêutico

O aconselhamento durante o atendimento foi, sem dúvida, o fator mais desafiante durante o meu estágio curricular. Apesar do conhecimento adquirido em diversas unidades curriculares do Mestrado Integrado em Ciências Farmacêuticas (MICF), o confronto com situações reais deixou-me, sobretudo no início, um pouco insegura. Ainda que tendo presente a componente teórica, acerca dos diversos medicamentos e dispositivos médicos na maioria das situações, surgiram outras em que, embora identificando o princípio ativo, o conhecimento sobre algumas marcas e produtos ainda era limitado.

Em situações menores, a farmácia é, na maioria das vezes, o primeiro local ao qual o utente recorre. Logo, de forma a ultrapassar estas dificuldades, foi útil fazer uma revisão de alguns conceitos sobre as situações mais recorrentes, tais como casos de obstipação, diarreia, constipações ou dores musculares e, assim, conseguir realizar um aconselhamento mais completo e fidedigno.

2.2.3. Apropriação do MICF à realidade da farmácia comunitária

Este ponto acaba por ir ao encontro da insegurança sentida durante o aconselhamento farmacêutico. O MICF é um curso que considero bastante completo, pela variedade de conhecimento que adquirimos em diversas áreas, desde a química à clínica, da gestão à veterinária. Contudo, quando nos deparamos com a realidade da Farmácia Comunitária e o primeiro contacto com o mundo profissional, a componente teórica que nos é transmitida parece não ser o suficiente. O aconselhamento farmacêutico é uma temática que foi abordada em algumas unidades curriculares. Na minha opinião, essa abordagem poderia ser ainda mais intensiva e realizada de uma perspetiva mais prática.

Dada a frequência de casos de aconselhamento veterinário, nem sempre senti que estava completamente segura da forma como aconselhar o utente. Desta forma, penso que seria benéfico para o MICF se essa área, por exemplo, fosse mais aprofundada em termos de aconselhamento.

2.3. *Opportunities* (Oportunidades)

2.3.1. Disponibilização de acompanhamento farmacoterapêutico individualizado

O farmacêutico, durante o exercício da sua profissão, deve promover o uso racional do medicamento, a reconciliação da medicação e notificar possíveis reações adversas associadas à toma da mesma. A Revisão da Medicação (RM) engloba a análise de vários fatores, tais como todo o perfil pessoal do utente e o contexto associado a esta necessidade. A mesma pode estar relacionada, entre outros, com as características do utente, por exemplo em doentes polimedicados ou com alterações recorrentes da terapêutica, aspetos que dificultam a gestão e utilização da mesma ou a ocorrência de reação adversas à atual medicação.

Desta forma, enquanto profissionais de saúde, os farmacêuticos exercem uma função crucial com vista a evitar possíveis erros e problemas subsequentes ao uso da medicação. Evitar a duplicação da terapêutica, interações entre fármacos, verificar a adequação da posologia e

frequência de administração e a adesão à terapêutica, são algumas das medidas que devem ser adotadas. [5]

Assim, numa farmácia em que a maioria dos utentes fidelizados apresenta uma idade superior a 65 anos, considero relevante a disponibilização de uma revisão individual da terapêutica dos utentes. Este serviço deveria ser realizado por um farmacêutico em ambiente privativo, o que seria possível dada a existência de um gabinete privado com as condições necessárias. Na minha opinião seria uma ótima aposta, não só por forma a facilitar a adesão à terapêutica por parte do utente, como para prevenir o surgimento de problemas relacionados com a mesma. O processo de RM deve ficar registado e, consoante as necessidades de saúde verificadas no utente, este pode ser encaminhado para determinados serviços, como a PIM. Desta forma, a RM pode ser uma mais-valia não só para o utente, mas também para a promoção dos serviços farmacêuticos da Farmácia Santa Ana, transformando um ponto forte numa oportunidade.

2.3.3. Participação em formações internas

Durante o estágio curricular, pude assistir a algumas formações teóricas, que acabaram por se revelar bastante úteis para relembrar determinadas abordagens terapêuticas. Entre elas, destaco uma realizada pela Pfizer®, acerca de dispositivos médicos utilizados no tratamento de infeções fúngicas. Igualmente importante foi a formação da Tilman®, que abordou a aplicação da fitoterapia a MNSRM, nomeadamente em problemas musculares, obstipação, náuseas e infeções urinárias.

O constante contacto com este conhecimento exterior, além do partilhado pelos meus colegas de trabalho, foi essencial para que pudesse proporcionar ao utente uma melhor experiência de atendimento. Além disso, a apresentação de determinadas marcas foi determinante para que, consoante a situação que me era apresentada, conseguisse alcançar uma melhor solução de aconselhamento.

2.3.4. Exploração do programa Sifarma® e do Novo Módulo de Atendimento

O Sifarma® é a ferramenta de gestão e atendimento mais utilizada no panorama nacional de farmácias. Embora algumas ferramentas ainda não estejam completamente atualizadas no Novo Módulo de Atendimento, a exploração do mesmo é crucial para potenciar o atendimento, não só pela maior intuição induzida pelo mesmo, como pela maior rapidez em executar as diferentes ações. [6]

Na Farmácia Santa Ana, o Novo Módulo de Atendimento foi implementado como projeto piloto, o que permitiu aos elementos da equipa técnica contactar, desde cedo, com o mesmo e, cada vez mais, fazer a transição do Sifarma 2000® para o formato mais recente. Desta forma, foi-me possível contactar com ambas as versões informáticas e, desta forma, analisar as diferenças e vantagens entre elas.

Com a evolução tecnológica, a adequação das farmácias a esta realidade é de extrema importância. Assim, a completa implementação do Novo Módulo de Atendimento e exploração das diferentes ferramentas deste sistema, tal como o Sifarma.Gest®, constitui um benefício para o sucesso da farmácia.

2.4 *Threats* (Ameaças)

2.4.1. Solicitação de MSRM

Um dos grandes obstáculos com os quais me deparei no decorrer do estágio foi a solicitação, por parte dos utentes, de MSRM sem a apresentação da mesma. Se, por um lado, alguns utentes argumentavam que a medicação solicitada era habitual e só voltariam a ter consulta após algum tempo, o mesmo não acontecia noutras situações. Como profissionais de saúde, penso que temos um papel decisivo na educação para a saúde da população e, desta forma, devemos seguir a nossa ética e conduta de trabalho, com vista a promover o uso racional do medicamento. Em determinados atendimentos, fui abordada pelo/a utente sobre a possibilidade de dispensar MSRM, pedidos aos quais o farmacêutico não pode atender. Apesar da explicação nem sempre ser bem recebida pelos utentes, chegamos ao final do dia com a sensação de dever cumprido, zelando pela saúde do utente e por uma sociedade mais consciente da gravidade destes comportamentos.

2.4.2. Proximidade de farmácias e pontos de venda de MNSRM concorrentes

Uma das ameaças que a Farmácia Santa Ana enfrenta neste momento, passa pela possibilidade de encerramento das unidades de saúde de Santana, Maiorca e posterior centralização na Unidade de Saúde Familiar de Alhadas. Atendendo ao facto de que muitos utentes que frequentam a farmácia são provenientes destas localidades, este centralismo pode levar à perda de utentes para a Farmácia de Alhadas, nomeadamente dada a forte hipótese da abertura de uma segunda farmácia nessa localidade. Contudo, como referido anteriormente, a conduta

desta farmácia é pautada por um grande profissionalismo e proximidade dos utentes, que pode ser determinante para evitar esta situação.

Apesar de não haver nas proximidades nenhum local de venda de MNSRM que constitua concorrência direta à farmácia, o constante surgimento de novas parafarmácias acaba por ser uma ameaça. Se, por um lado, podem influenciar as pessoas relativamente à comparação entre os preços praticados em ambos os locais, por outro, a sua existência em grandes superfícies comerciais, pode ser uma mais-valia no acesso do utente a estes medicamentos e/ou outros produtos de venda autorizada.

2.4.3. Medicamentos temporariamente indisponíveis

A rutura de *stock* nas farmácias portuguesas tem sido motivo de elevada atenção. Este problema é, muitas vezes, originado pelo elevado volume de medicamentos enviados para países onde serão vendidos a preços mais altos e pela Indústria Farmacêutica que por vezes não consegue, através da sua produção, atender às necessidades das farmácias.

Foram várias as vezes que, ao longo do estágio, o medicamento prescrito pelo médico ao utente estava temporariamente indisponível, não conseguindo solicitar aos fornecedores a embalagem pretendida. Este problema pode mesmo levar a que o utente tenha de realizar uma nova consulta, uma vez que, não tendo alternativa terapêutica, tem de interromper o tratamento prescrito previamente. Além da falta de fármacos, o desconforto causado ao utente aquando do atendimento, pode ser uma ameaça. [7]

3. Casos Clínicos

3.1. Caso 1

Um senhor, de aproximadamente 70 anos, dirige-se à farmácia e afirma que, após ter estado fora durante o fim de semana, apresenta febre, tosse, uma ligeira dor de cabeça e fadiga corporal. Quando questionado se a tosse era seca ou com expetoração, o utente referiu que apresentava alguma expetoração. Através desta informação, percebi que se tratava de um quadro gripal.

As principais medidas não farmacológicas passaram por incentivar o utente a manter uma dieta equilibrada e a repousar. Além disso, um ponto extremamente importante na recuperação destas situações é o aumento da ingestão de líquidos, sobretudo em utentes mais frágeis como os idosos ou as crianças, que têm um maior risco de desidratação. Contudo, após aceder à

terapêutica ativa do utente e proceder a algumas questões, confirmei que sofria de insuficiência cardíaca e que esta medida não era, de todo, aconselhável. Ao longo do MICF fomos diversas vezes alertados para alguns pontos que podem ser cruciais para conseguirmos perceber o historial da pessoa, através da medicação que a mesma toma. E essa perspicácia foi, e é, importante quando nos deparamos com estes casos, pois após identificar o Lasix® como medicamento presente na terapêutica ativa deste utente, consegui prestar um aconselhamento farmacêutico mais prudente e seguro. Trata-se de um diurético de ansa potente, cujo princípio ativo é a furosemida.

Nos doentes com insuficiência cardíaca há uma estimulação do eixo Renina-Angiotensina-Aldosterona. Desta forma, há um aumento da retenção de Na^+ e de H_2O, com consequente aumento de volume. A indevida força de contração do coração conduz à acumulação de líquido nos vasos, o edema. Este pode verificar-se nos tecidos periféricos, provocando um inchaço dos membros inferiores ou a nível pulmonar, traduzindo-se em dificuldades respiratórias. [8]

Traçado o perfil do utente, aconselhei a toma de 1 comprimido de Paracetamol 500 mg de 8/8h, antipirético e analgésico, com o objetivo de minorar o estado febril, aliviar a fadiga e dor de cabeça. Além disso, por forma a liquidificar as secreções, indiquei um mucolítico. A escolha do mesmo teve em conta as seguintes questões: se o Sr. tinha asma, por forma a aconselhar um mucolítico que não a exacerbasse, ou se era diabético, dada a possível presença de sacarose como excipiente. O mesmo afirmou que não tinha diabetes, mas era asmático, pelo que removi das opções de tratamento os mucolíticos constituídos por Bromexina e Ambroxol, pois aumentam o volume das secreções e desencadeiam a broncoconstrição. A opção final acabou por ser o Fluimucil® 4%, 40 mg/ml solução oral, cujo princípio ativo é a acetilcisteína, com uma posologia de 5 ml (3 id). Esta, ao contrário dos anteriores, permite uma liquidificação das secreções sem aumento do volume das mesmas.

3.2. Caso 2

Uma utente do sexo feminino, dirigiu-se à farmácia solicitando um antibiótico, pois afirmava que a filha, de 22 anos, estaria com sintomas de uma infeção urinária. A utente trazia, inclusivamente, uma caixa de antibiótico previamente utilizado pela filha, questionando se não poderia ser o mesmo. De imediato tive de explicar à utente que não lhe poderia dispensar esse medicamento, pois além de ser um MSRM seria irresponsável fazê-lo, dado que só através de um diagnóstico mais exaustivo seria possível perceber se aquele antibiótico era o indicado para tal situação. Desaconselhei totalmente este tipo de comportamento, visando que a

resistência aos antibióticos é um problema que pode ser evitado, se consciencializarmos a população.

Após esta explicação, fiz algumas questões à utente de modo a perceber quais os sintomas que a jovem apresentava, a duração e intensidade dos mesmos. A utente revelou que a jovem há 2 dias havia começado a sentir alguma dor e ardor ao urinar, acompanhada de uma mudança na cor e odor da urina, situação que se havia verificado recorrente.

Desta forma, aconselhei um comprimido de 12/12h de um suplemento alimentar à base de Arando Vermelho, Cavalinha, Uva Ursina e FOS (Cistisil®). O Arando Vermelho (*Vaccinium macrocarpon*) apresenta na sua constituição Proantocianidinas com uniões do tipo A, cujo mecanismo de ação é inibir a aderência de bactérias ao urotélio e, embora não seja eficaz na eliminação de bactérias previamente instaladas, auxilia a prevenção de infeções do trato urinário (ITU). A folha de Uva Ursina (*Arctostaphylos uva-ursi*), é igualmente comum neste tipo de suplementos, uma vez que a sua ação bacteriana, devida à hidroquinona, se tem revelado eficaz no tratamento de infeções ligeiras das vias urinárias baixas. Este é o composto ativo obtido após hidrólise intestinal e metabolização hepática do arbutósido. A ação diurética da cavalinha e o restauro da flora bacteriana promovida pelo FOS (fruto-oligossacáridos) constituem outras vantagens deste suplemento. [9,10]

Além do Cistisil®, indiquei algumas medidas não farmacológicas que deveriam ser adotadas, tais como: o aumento da ingestão de líquidos, evitar o uso de roupa sintética e não adiar a micção aquando da vontade da mesma e manter um cuidado redobrado com a higiene íntima. Atendendo ao último ponto, aconselhei a utilização de uma solução de lavagem adequada ao pH da região íntima, por forma a acalmar a irritação e desconforto causado e mantendo o equilíbrio da flora vaginal, como é o caso do Saforelle Solução de Lavagem®.

No fim do atendimento, recomendei à utente que, caso os sintomas não melhorassem, esta deveria conduzir a filha ao médico. Nesse caso, poderia ser necessário uma análise laboratorial ao sangue, para verificar a gravidade da infeção e à urina, por forma a confirmar a sua existência e identificar o microorganismo responsável pela mesma. Só dessa forma seria possível escolher o antibiótico indicado para esta situação e promover o seu uso racional.

3.3. Caso 3

Utente desloca-se à farmácia, revelando alguma preocupação relativa ao seu filho, após o aparecimento de manchas avermelhadas, edema e prurido na região em contacto direto com a fralda e nas pregas. Quando questionada sobre a idade do bebé, a utente revelou que este tinha 8 meses. A mesma mostrou algumas fotografias, que foram úteis para identificar que se tratava de um caso de dermatite da fralda.

Revelou, ainda, que este chorava bastante devido ao crescimento dos primeiros dentes, o que pode ter sido um fator preponderante no avanço desta dermatite. Aquando do nascimento da dentição, os bebés tendem a apresentar uma salivação mais abundante, dor e, até, febre. Essa constante salivação contribui para a acidificação das fezes que, em contacto com a superfície da pele, provocam o eritema.

Nesta situação, é essencial que se adotem algumas medidas não farmacológicas, tais como as recomendadas à utente, que passam pela mudança frequente da fralda, evitar que o bebé tenha a pele húmida, lavar o rabinho do bebé com água tépida, deixar a pele respirar o mais possível, fazer uma higiene suave e delicada e evitar produtos perfumados e/ou que contenham álcool. Outra recomendação útil foi a massagem gengival com uma gaze humedecida e a ingestão de alimentos frias, por exemplo frutas, para aliviar os sintomas de dor e inflamação.

Neste sentido, aconselhei à utente a aplicação da pomada Nutraisdin® AF, enriquecida em nitrato de miconazol e óxido de zinco, após cada mudança da fralda. O miconazol possui propriedades antimicrobianas essenciais para evitar a proliferação de agentes patogénicos. Por outro lado, a combinação com o poder emoliente, cicatrizante e calmante do óxido de zinco, é crucial na regeneração dos tecidos e no tratamento da pele irritada do bebé. Uma das principais características deste ingrediente ativo é o seu carácter oclusivo, permitindo a criação de uma barreira entre a superfície da pele do bebé e os fluidos corporais. [11]

Ainda por forma a alivar o desconforto e a dor associada à erupção dos primeiros dentes, indiquei a utilização do AloBaby®, um gel oral que origina a formação de uma película e, assim, prolonga o alívio da criança. Aconselhei a sua aplicação numa quantidade suficiente para cobrir a zona afetada, aliada a uma massagem gengival suave, que pode ser realizada através do aplicador com cerdas de silicone. A sua composição de origem natural e não inclusão de anestésicos locais, álcool, açúcar ou substância ativa foram alguns pontos a ter em conta na escolha deste dispositivo médico.[12] Por último, recomendei a utente a, caso não se verificassem melhoras após alguns dias, consultar o pediatra.

4. Considerações Finais

O estágio curricular em Farmácia Comunitária foi, sem dúvida, uma experiência enriquecedora e um grande passo na entrada para o mundo profissional. Desde sempre achei fundamental o conhecimento adquirido ao trabalhar numa farmácia, que contribui para a nossa formação e desempenho em oportunidades futuras. É uma profissão que considero desafiante, na medida em que todos os dias somos confrontados com situações diferentes, que colocam à prova os nossos conhecimentos por forma a oferecer ao utente o melhor aconselhamento.

Se ao longo do MICF me surgiram algumas dúvidas sobre o trabalho em Farmácia Comunitária, as mesmas foram-se dissipando ao longo do meu estágio curricular, que se revelou uma verdadeira surpresa. A equipa da Farmácia de Santana foi incansável nesta jornada, ao transmitir-me a sua sabedoria e integrar-me, da melhor forma. Também o contacto mais próximo com a população, permitiu-me perceber o nosso propósito enquanto farmacêuticos e valorizar, ainda mais, todos os profissionais de saúde que todos os dias saem de casa para dar o melhor de si ao outro.

Além de especialista no que respeita ao medicamento, o farmacêutico possui um papel determinante na promoção da saúde pública e bem-estar dos utentes. Este altruísmo é, para mim, o verdadeiro sentido desta profissão.

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Anexos

Anexo I – Etapas envolvidas no processo de PIM.

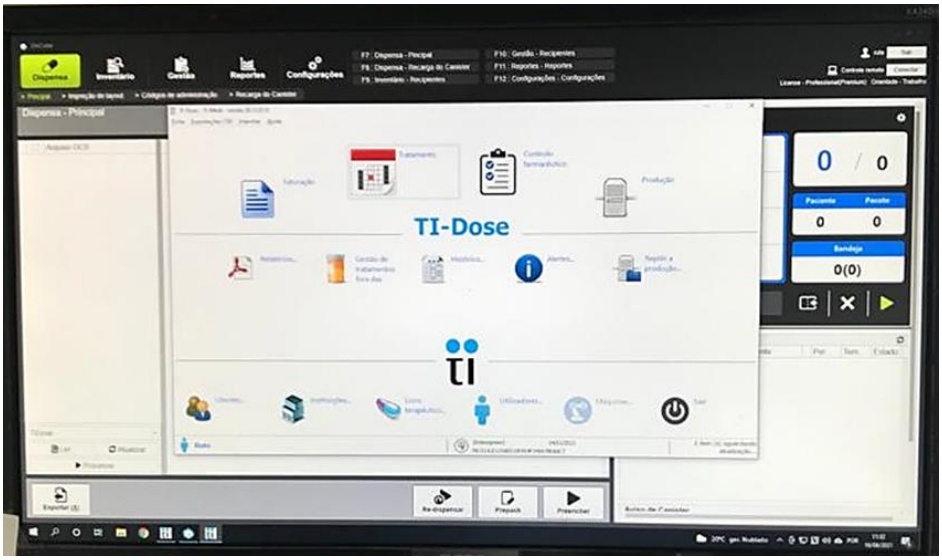


Figura 1. Programa informático utilizado para a introdução dos dados do utente.

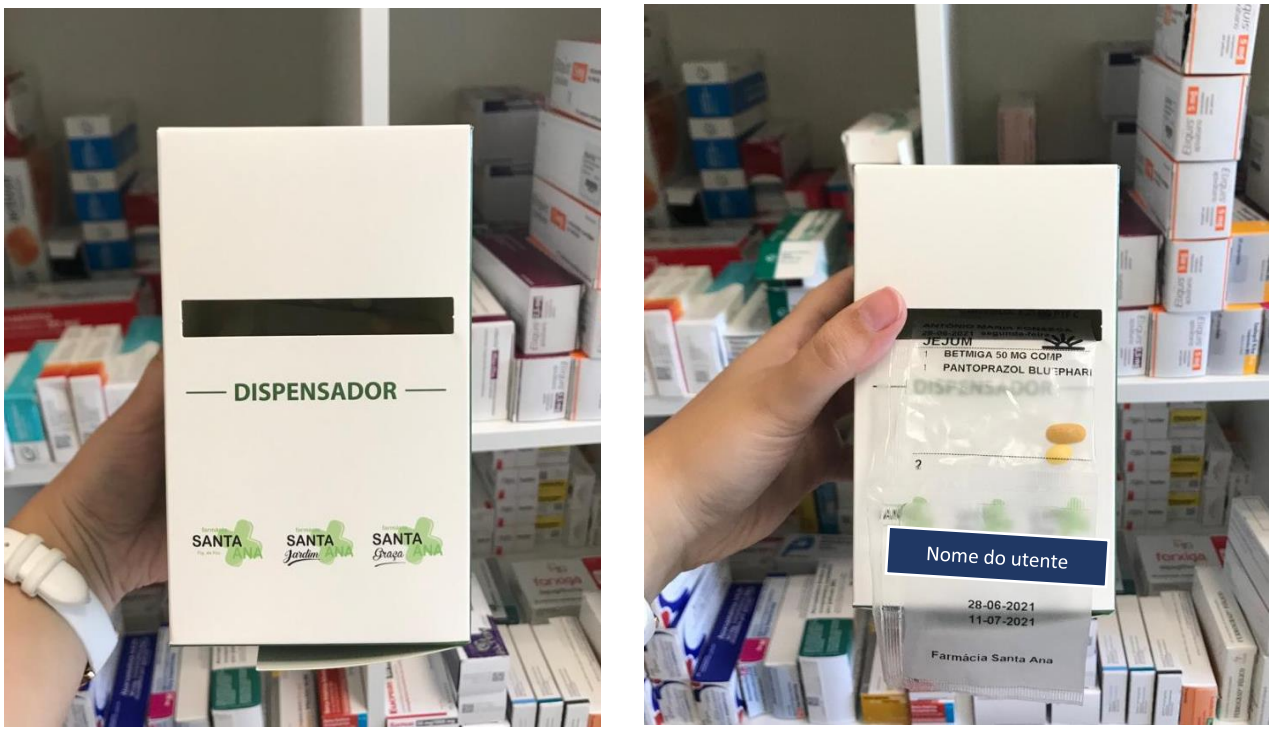


Figura 2. Dispensador fornecido aos utentes utilizadores do serviço da PIM, com identificação de cada saqueta relativamente ao modo da toma.

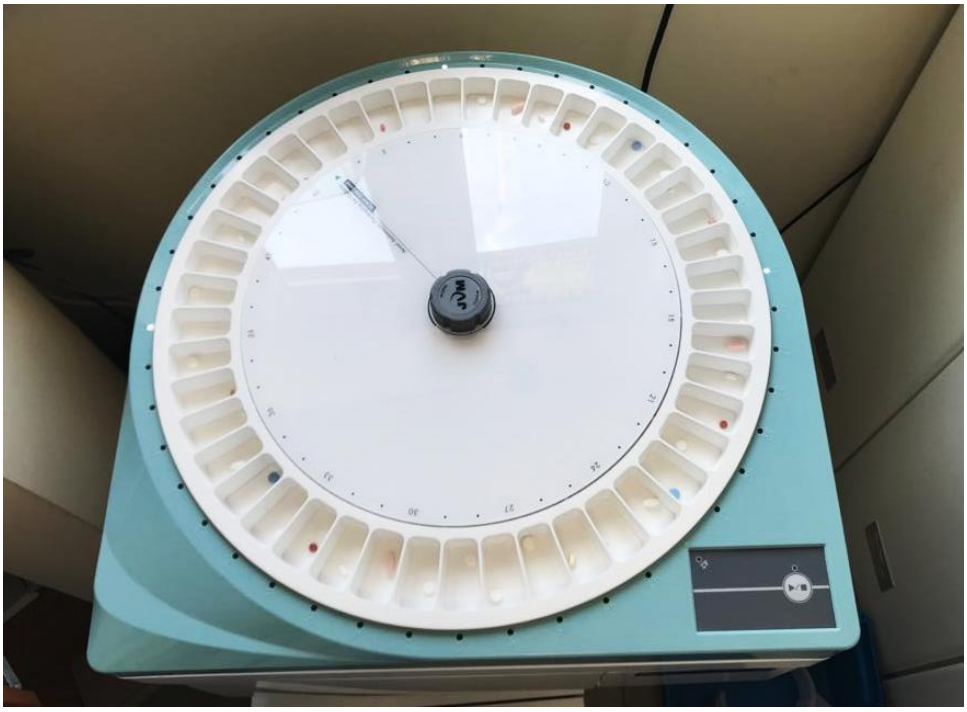


Figura 3. Máquina automática utilizada pela Farmácia Santa Ana para a PIM.

Parte II

"The role of nanosystems on diabetic wound treatment and care"

Orientadora: Doutora Filipa Melo

Abbreviations

ADCSs - Adipocyte-derived stem cells

AgNPs - Silver nanoparticles

AS - Astaxanthin

AT1-receptor - Angiotensin receptor 1

AuNPs - Gold nanoparticles

BC - Bacterial cellulose

BMSCs - Bone marrow mesenchymal stem cells

CNPs - Cerium oxide nanoparticles

CNT - Carbon nanotube

COX-2 - Cyclooxygenase-2

CPO - Calcium peroxide

CXCL2 - C-X-C motif chemokine ligand 2

DCH - Doxycycline

DFO - Deferoxamine

DM - Diabetes mellitus

DMRIE - Dimyristyloxypropyl-3-dimethyl-hydroxyethyl ammonium

DNA - Deoxyribonucleic acid

DOTMA - 1,2-di-O-octadecenyl-3-trimethylammonium propane

ECM - Extracellular matrix

ELs - Elastic liposomes

ERK 1-2 - Extracellular signal-regulated protein kinase 1-2

EV - Extracellular vesicles

FDA - Food and Drug Administration

FGF - Fibroblast growth factor

GF - Growth factors

GM3S - Ganglioside-monosialic acid 3 synthase

GMCY - Palm glyceryl monocaprylate

GMSCs - Gingival mesenchymal stem cells

GS - Gentamicin sulfate

HIF-1- Hypoxia-inducible factor-1

HUCMSCs - Human umbilical cord mesenchymal stem cells

IGF-1- Insulin-like growth factor-1

iNOS - Inducible nitric oxide synthase

IRAK1- Interleukin-1 receptor-associated kinase 1

LMWP - Low molecular weight protein

LUVs - Large unilamellar vesicles

miR146a - MicroRNA-146a

MLVs - Multi-lamellar vesicles

MMP - Matrix metalloproteinase

MRSA - Methicillin-resistant *Staphylococcus aureus*

MSCs - Mesenchymal stem cells

MWCNTs - Multi-walled carbon nanotubes

NAR - Naringenin

NE - Nanoemulsion

NF-kB - Nuclear factor kappa-light-chain-enhancer of activated B cells

NLC - Nanostructured lipid carriers

NO - Nitric oxide

PAMAM - Polyamidoamine

PCL - Polycaprolactone

PDGF - Platelet-derived growth factor

PEG - Polyethylene glycol

PEI - Poly (ethylene imine)

PEO - Poly (ethylene oxide)

PLA - Polylactide

PLGA - Poly (lactic-co-glycolic acid)

PPD - 20(S)-protopanaxadiol

PUAU - Polyurethane

PVA - Polyvinyl alcohol

PVP - Polyvinyl pyrrolidone

RAS - Radially aligned scaffolds

rhEGF - Recombinant human epidermal growth factor

ROS - Reactive oxygen species

SC - *Stratum corneum*

SF - Silk fibroin

SiRNA - Small-interference RNA

SLN - Solid lipid nanoparticles

SUVs - Small unilamellar vesicles

SWCNTs - Single-walled carbon nanotubes

TEWL - Transepidermal water loss

TGF-β - Transforming growth factor-beta

TNF- α - Tumor necrosis factor-alpha

TP - α-tocopherol

TRAF6 - Tumor necrosis factor receptor-associated factor 6

TSS - Toxic shock syndrome

Val - Valsartan

VAS - Vertically aligned scaffolds

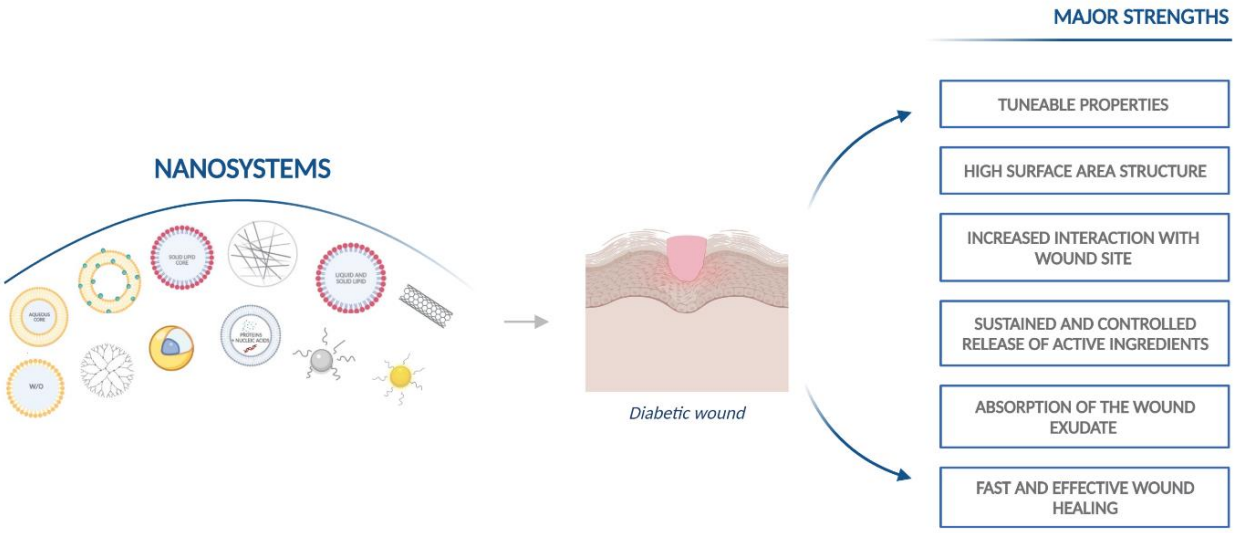
VEGF - Vascular endothelial growth factor

ZM - *Zataria multiflora*

ZnONPs - Zinc oxide nanoparticles

Abstract

Nowadays, diabetic wounds are one of the most common health problems. Improving and accelerating long-term recovery, avoiding mass hospitalization and consequently amputation, providing a better quality of life, and reducing the expense that this condition requires are current priorities in this context. The application of nanotechnology in diabetic wound healing is a developing subject, which is proving to be a powerful and effective tool. It becomes necessary to know the various nanosystems and analyze their healing performance when applied to the injured site. From lipid nanosystems to polymeric, metal-based, and other promising nanosystems, these are the most studied nanosized carriers, taking into account their potential in this respect. This review aims to address both the scope of treatment and care. Several compounds present improved properties when loaded into nanosystems, from bioactive ingredients, growth factors (GFs), mesenchymal stem cells, and nucleic acids, to drugs, mainly antibiotics. All these components can be extremely important to hasten the healing process, by having suitable characteristics, such as good biocompatibility, stimulating angiogenesis, and the synthesis of extracellular matrix (ECM) compounds, decreasing the inflammation around the wound, among others. The role of antibiotics in this subject is extremely important since one of the major hindrances to achieve successful healing is the possible bacterial infection. Nanotechnology seems to be a strong ally in the treatment of diabetic wounds, promoting greater efficiency in the delivery and bioavailability of the active ingredients at the site of action, despite some limitations that will also be discussed in this review.



Keywords: diabetic wound; hydrogel; nanocarrier; nanosystem; therapeutical agents; topical administration; wound healing.

Resumo

Atualmente, as feridas desencadeadas pela diabetes *mellitus* constituem um dos problemas de saúde mais frequentes. Desta forma, os objetivos prioritários no seu tratamento passam por potenciar e acelerar a recuperação, evitando consequências drásticas como uma possível amputação, promover uma melhor qualidade de vida ao utente e reduzir os custos associados a esta condição. A aplicação da nanotecnologia no tratamento de feridas de diabéticos é um tema em desenvolvimento, que se está a revelar uma ferramenta poderosa e eficaz. Para tal, é necessário proceder a uma análise profunda dos diferentes nanosistemas, de modo a reconhecer as características que os tornam bons candidatos para este efeito e o modo como atuam localmente na pele lesada. Desde os nanosistemas lipídicos, até aos poliméricos, metálicos, entre outros, estes são os mais intensivamente estudados atendendo à sua potencial aplicação nesta temática. Neste trabalho, é adotada uma perspetiva quer dos tratamentos, quer dos cuidados, fazendo referência aos diferentes compostos, cujas propriedades podem ser potenciadas quando transportados através destes nanosistemas. Entre eles encontram-se diversos ingredientes ativos, fatores de crescimento, células estaminais, ácidos nucleicos e fármacos, sendo a maioria destes antibióticos. Todos estes compostos podem exercer um papel crucial na celeridade do processo de cicatrização, através da estimulação da angiogénese, síntese de componentes da matriz extracelular, apresentação de uma boa compatibilidade com a pele lesada, diminuição da inflamação, entre outros. A função inerente aos antibióticos é, também, extremamente importante no tratamento de feridas em diabéticos, uma vez que a infeção bacteriana é um dos principais obstáculos ao sucesso do mesmo. A nanotecnologia pode, deste modo, ser uma grande aliada no tratamento de úlceras em diabéticos, através da promoção de uma maior eficácia na distribuição e biodisponibilidade de determinados ingredientes ativos e fármacos no local de ação pretendido. Contudo, há ainda algumas limitações associadas ao seu uso que serão, de igual forma, discutidas ao longo deste trabalho.

Palavras-chave: administração tópica; agentes terapêuticos; cicatrização; ferida diabética; hidrogel; nanopartículas; nanosistemas.

1. Introduction

Chronic wounds are generally caused by a predisposition that affects the skin tissue integrity, due to internal mechanisms. This review is focused on the ones that constitute complications of diabetes mellitus (DM), a metabolic disease associated with significant changes, concerning wound healing.[1] Diabetic wounds often lead to a worse quality of life, with a high prevalence of hospitalizations, and amputation may even be necessary. One of the greatest causes of failure along the healing process is the constant increase of blood sugar levels, represented through a chronic hyperglycemic state. This can be explained by the fact that extremities do not receive an appropriate blood supply, which leads to lower levels of nutrients and oxygen. Consequently, angiogenesis is hindered, delaying the skin regeneration process.[2] An increased skin barrier permeation and a lower immune response favor possible contamination of the wound. Once infected, pathogens like Beta-hemolytic *Streptococcus*, *Staphylococcus aureus, Pseudomonas aeruginosa,* and even *Enterococcus spp.* are the most commonly found in diabetic wounds. Additionally, the patients with thinner and delicate epidermis have frequently abnormal responses in the different phases of the healing process. Also, a bacterial infection will hinder the recovery, since there will be an exacerbation of the inflammatory response and will, consequently, make it more difficult to heal.[1,3] Diabetic wounds are often related to peripheral neuropathy, as it causes a deficient consciousness of the patient's pain, leading to late recognition of the wound state.[4] The primary causes of delayed wound healing in diabetic patients are presented in Figure 1.

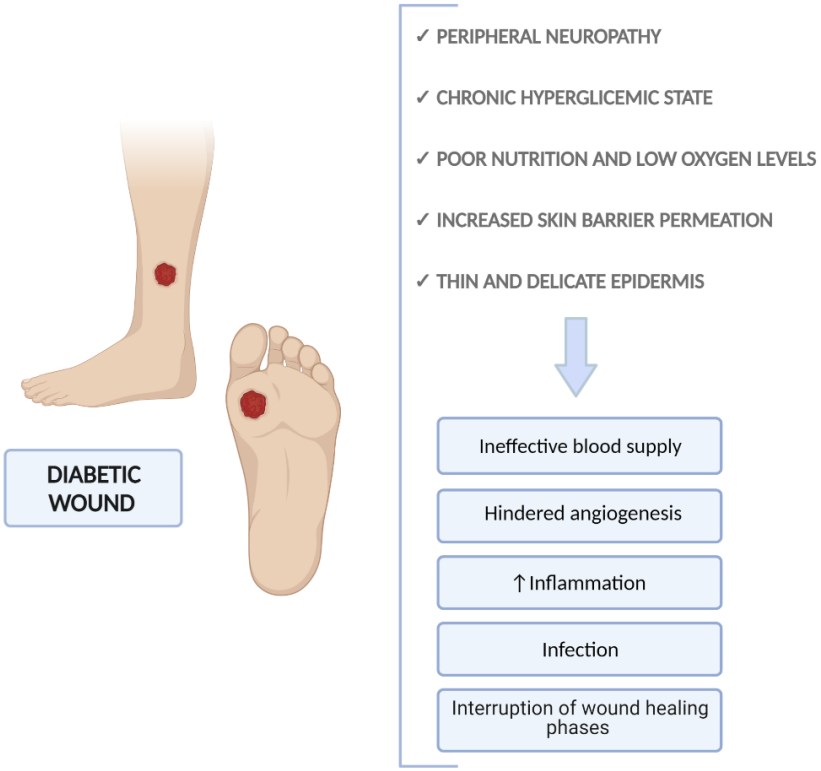


Figure 1. Primary causes of delayed wound healing in diabetic patients.

This situation requires not only a slow and intensive recovery but also a massive investment in treatment and care. Given this, several types of research have proved the effectiveness of nanosystems in this subject, intending to enhance this process and, hence, decrease some of the limitations related to it. The role of nanosystems in the whole healing phase is highly relevant. In a standard case, this process would begin with hemostasis, followed by the recruit of pro-inflammatory agents, several GFs, and cytokines, in the inflammatory phase. Then, during the proliferative phase, angiogenesis would be enhanced, as well as the deposition of collagen, re-epithelization, and ECM synthesis. To finalize the process, granulation tissue would be formed and, hence, the development of a scar to end the wound closure. However, in diabetic patients, there are several flaws in this process and various associated consequences (Figure 2).[5]

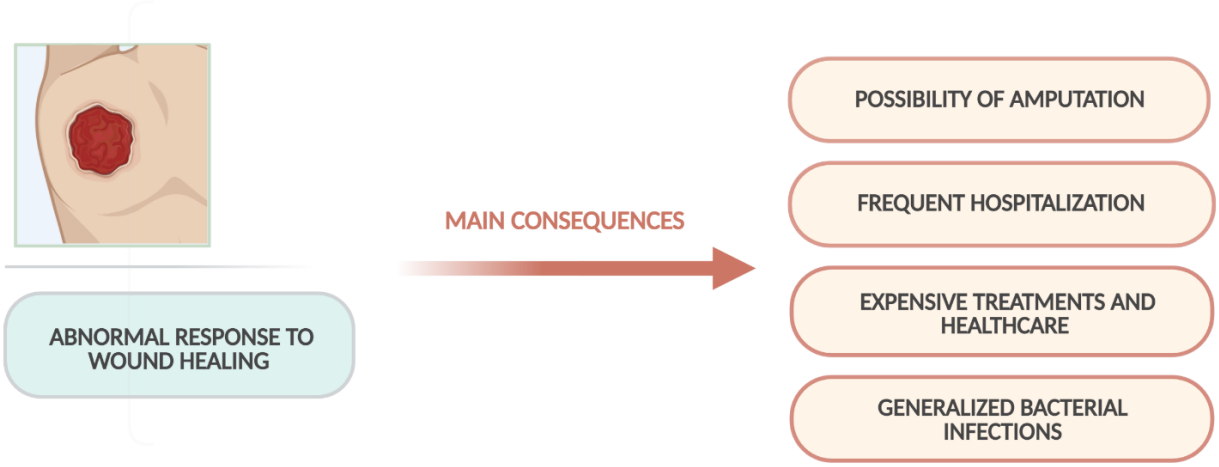


Figure 2. Main consequences of an impaired skin regeneration and wound closure in diabetic patients.

Regarding drug delivery, it can be enhanced through the development of nanosystems. They allow an increased drug bioavailability and a boost of the half-life time while reducing the dose frequency and improving the pharmacokinetics.[6] Although several therapeutical approaches have been a target of significant research, antibacterial drugs are the most used in this regard, to avoid the intrusion of pathogens and biofilm formation, which can be the cause of severe complications. Therefore, in some situations, treatment with antibiotics is imperative. Furthermore, from a dermatological care perspective, recent researches reveal that active ingredients, when loaded to nanosystems such as lipid nanoparticles, nanofibers, metal-based nanoparticles, dendrimers, or even carbon nanotubes, show an impressive boost on their properties. They can provide the removal of destructive tissues and promote successful delivery of each compound, to enhance wound healing. Depending on the wound characteristics, such as its size, type, and exudate quantity, many dressings have been developed for this purpose.[7] This article focuses on how nanosystems can be helpful to overcome the drawbacks related to this pathological condition and, hence, ease the healing process. Considering the auspicious results of recent researches, the most relevant nanosystems to this subject were chosen, to illustrate their ability on improving diabetic wound healing (Figure 3).

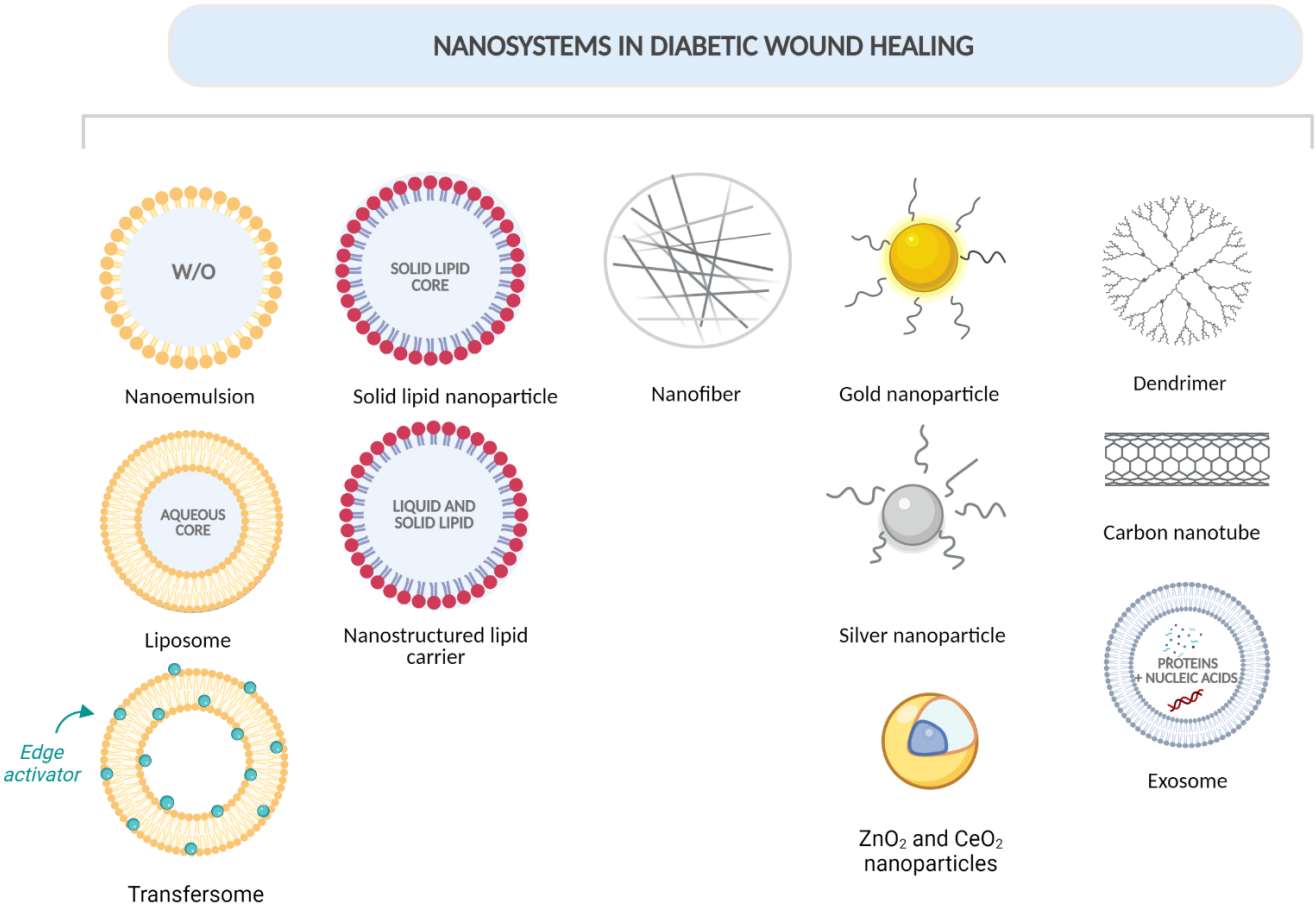


Figure 3. Different nanosystems with application in diabetic wound management.

2. Nanotechnology-based delivery systems for diabetic wound treatment and care

Based on current literature, this review will focus on different nanosystems, whose application has been described as promising to diabetic wound healing. Considering their structure and features, they are divided into lipid-based nanosystems, which include nanoemulsions, vesicular systems, like liposomes and transfersomes, and lipid nanoparticles, represented by nanostructured lipid carriers and solid lipid nanoparticles. Polymeric nanoparticles, more specifically electrospun nanofibers, will also be mentioned. In addition, metal-based nanoparticles, including silver, gold, cerium oxide and zinc oxide, and other nanosystems are showing promising results on this thematic. In the last ones, and because they have been lately discussed due to their encouraging application in this field, dendrimers, carbon nanotubes, and exosomes, are described.

2.1 Lipid-based nanosystems

2.1.1. Nanoemulsions

Described as lipid-based formulations, nanoemulsions (NEs) have a similar composition to the conventional ones, displaying an oily, aqueous, and surfactant content. The presence of a surfactant provides the accomplishment of relevant cellular processes, such as the breakdown of the cell membrane. The major difference between these lipid-based formulations is the droplet size, being much lower in NEs, which allows an exact delivery of active ingredients incorporated, further obtaining a sustained release.[8] Their use has been applied in a variety of biomedical formulations, including diabetic wounds, where there is improved insulin activity and antioxidant action, while also decreasing inflammation, glycemia, and existing exudate.[9]

Diabetic wounds are conducive to develop bacterial infections, including methicillin-resistant *Staphylococcus aureus* (MRSA), delaying the whole recovery process. The possible release of toxins, stemming from this microorganism, is also critical since it's related to the occurrence of toxic shock syndrome (TSS). A group of researchers developed a NE formulation, with palm glyceryl monocaprylate (GMCY). GMCY has been described as a suitable antimicrobial component. However, at the time of the study, palm GMCY activity had never been proved *in vivo*. Through the evaluation of bacterial growth on different bacteria, it was possible to confirm this effect. Nevertheless, there was a high inhibition of *S. aureus* and *E. coli* proliferation, in contrast to the results obtained in *P. aeruginosa*, which were significantly lower, although the growth curve was still influenced. Considering this, the activity of this NE has proven to be more effective in gram-positive bacteria, since it destroyed the cells of *S. aureus*. This formulation also provided improved permeability and destabilization, which were essential to achieve an effective bactericidal effect, and led to a very similar to natural skin reconstruction.[10]

The use of *Zataria multiflora* (ZM), a plant with demonstrated antibacterial activity, and curcumin, a polyphenolic component extracted from *Curcuma longa,* have both shown improved healing when encapsulated in NE. This technology improved their properties, being especially relevant to prevent the volatilization of aromatic components in the first example, and has contributed to stabilizing curcumin incorporation, with a lipophilic character, since this compound holds low absorption.[11,12]

In this context, α-tocopherol (TP), as well as astaxanthin (AS), incorporated into a k-carrageenan NE, were also focal of a study. On the one hand, AS is a carotenoid with potential anti-inflammatory activity, and the capability to decrease reactive oxygen species (ROS), which

is considered its major strength. On the other hand, TP, a form of vitamin E, improves antioxidant activity. The formulation in k-carrageenan NE enables a more stabilized nanosystem, which has been revealed as a suitable option to enhance wound healing, considering the proper regeneration of skin layers.[9] A similar approach achieved success, through the incorporation of a flavonoid, naringenin (NAR) in a chitosan-NE. Chitosan is extremely important to keep the formulation in the injured site for an extended period of time and has a relevant antimicrobial activity. By associating this with the great properties of NAR, such as its biocompatibility and biodegradability, researchers found out an accelerated reduction in the wound size. This fact is supported considering the lower number of cells involved in the inflammatory process, the angiogenesis enhancement, with an increased vascular density, and the thicker epidermis.[13]

To summarize, NE has been described as a suitable choice to improve the activity of insulin and antioxidant agents, decrease inflammation, glycemia, and wound exudate. In addition, improved permeability and destabilization are essential to achieve an effective bactericidal effect and lead to a skin reconstruction very similar to natural. [8,9,10]

2.1.2. Vesicular systems

2.1.2.1 Liposomes

Classified as vesicles, liposomes present a mainly phospholipidic composition, whose primary role is to support a hydrophobic tail and a hydrophilic head. In contact with water, a bilayer structure is shaped, thus the chains with a hydrophobic nature turn inwards and the hydrophilic heads face out. Given this structure, liposomes own the possibility to incorporate and carry different types of drugs. It is achievable considering their attraction or, in contrast, repulsion to the aqueous medium.[14,15] Respecting their size and number of lipid bilayers, these nanosystems are grouped in small unilamellar vesicles (SUVs), large unilamellar vesicles (LUVs), or even multi-lamellar vesicles (MLVs). When it comes to skin application, the superficial layer of the epidermis, *stratum corneum* (SC), becomes the major challenge. The SC structure includes corneocytes, dead cells without core, steeped into a lipidic matrix. Given the fact that liposomes and skin have a similar lipidic composition, it is, therefore, an advantage to prevent undesirable effects and to boost drug diffusion.[15] Besides, they constitute an excellent choice for drug delivery, due to the facility on drug stabilization and to the highest skin penetration. Nevertheless, some limitations can be reported, since liposomes present a fast rate of release, which can lead to the fusion of the particles, and there are still some limitations in incorporating solutions through them. [6,14]

To enhance the drug penetration into the skin, these vesicles may suffer some changes. If classical liposomes are used with the intent of delivering a drug, or an active ingredient to the different layers of skin, it will result in a "reservoir" effect.[15] An explanation for this is the abundance of ceramides in SC, which are classified as sphingolipids. These structures can be distinguished regarding their constitution, which includes different types of sphingoid bases and fatty acids. According to this, SC will function as a lipidic deposit, therefore classical liposomes can't get through this layer.[16] Taking into consideration their properties, liposomes have been widely used for the delivery of lipophilic drugs, nucleic acids, GF, and active ingredients. Lipid-based nanosystems represent an excellent approach to gene therapy, with lower toxicity and drug loss when compared with systemic delivery. To avoid liposome coalescence, and simplify electrostatic interactions with negatively charged nucleic acids, the majority of them are cationic. This is achieved through the association of liposomes with lipids, like 1,2-di-O-octadecenyl-3-trimethylammonium propane (DOTMA) or dimyristyloxypropyl-3-dimethyl-hydroxyethyl ammonium (DMRIE), whose surface has a cationic character.[15] To enhance diabetic wound healing, the use of siRNA can be a powerful procedure, considering the inhibition of ganglioside-monosialic acid 3 synthase (GM3S), which has presented an overexpression in type 2 diabetic patients and leads to difficult healing.

Hence, there is a promotion of keratinocytes migration and also a stimulation of the insulin-like growth factor-1 (IGF-1), allowing the closing of the wound.[15,17] To overcome some drawbacks, scaffolds have been associated with liposomes, so they can ensure more effective properties on skin delivery. The sustaining of drug concentration in a certain local area for a long period of time can be facilitated by using this conjugation. These scaffolds can be classified as organic, inorganic, and metal, according to their components, whose main function is to ensure the conditions to the proper proliferation of the cells, while monitoring the body fluids and blood flowing.[3]

Chronic wounds are typically characterized by the presence of high concentrations of inflammatory cells. Consequently, this leads to the secretion of proteases, including matrix metalloproteinases (MMPs), which results in lower levels of cytokines and GFs. Recently, a study has evaluated its potential on diabetic wound management, by adopting cationic elastic liposomes (ELs) as carriers of hyaluronic acid conjugated with low molecular weight protein (LMWP) and GFs. Conclusions revealed that this combination contributed to optimize dermal regeneration and boost epithelium rehabilitation.[18] Liposomes are also used to carry active ingredients with special characteristics, such as chitosan. One of the potential properties of this active ingredient is the capacity to cover an anionic liposome's surface, due to its

polycationic nature, which leads to an electrostatic interaction among the charges. This will enhance the drug loading and cell uptake, as well as reduce the drug delivery in unwanted sites. Additionally, its adherence to the mucosa enables its absorption, and its ability to prevent the proliferation of gram-negative and gram-positive bacteria makes it an excellent choice in chronic wounds, often associated with microbial infections.[19]

In conclusion, liposomes offer an excellent approach for lipophilic drugs delivery, nucleic acids, GFs and active ingredients and, compared with systemic delivery, have lower toxicological issues and decreased drug loss. However, these nanosystems still have some drawbacks to overcome, such as the reduction of the rapid release rate, and hence the fusion of the particles, and the difficulty of carrying solutions. The lipidic constitution can trigger the "reservoir effect", which will impair the drug or active ingredient delivery.[3,15,17]

2.1.2.2. Transfersomes

Transfersomes are characterized by having flexible, elastic, and deformable properties, which constitute some of the main reasons that contribute to a better permeation of the molecules. When compared to conventional liposomes, the key difference is the presence of an edge activator, usually a single chain surfactant, which enhances the deformability of lipid bilayers, by reducing the interfacial tension. For this reason, these vesicles are able to penetrate intact skin, until specific regions of SC, and will prove equally effective when compared to subcutaneous administration.[20,21]

Phenolic compounds have also been a target of research in this field, since they show excellent properties as antioxidants, contributing not only to reduce the development of ROS but also to decrease the inflammation caused by the wound. Alpha-tocopherol was incorporated in transfersomes to enhance wound closure by boosting the migration of keratinocytes. These vesicles constitute a suitable way to overcome some difficulties of tocopherol administration, such as its poor chemical stability and low solubility. Results confirmed the promising application of transfersomes in this subject since it showed good biocompatibility, great protection against the oxidative process, and accelerated healing. The increased production of fibroblasts was also of extreme importance, considering that their proliferation is crucial to obtain a good cicatrization and restore the injured tissues. Nevertheless, scientific research in this area is still emerging and additional studies are needed.[22]

Drug encapsulation can be an alternative way to reach appropriate wound healing. One of the major issues in the management of diabetic wounds is the lack of oxygenation. Usually, it leads to the production of GFs, such as hypoxia-inducible factor-1 (HIF-1), to help regulate and provide the necessary oxygen levels. However, due to their chronic hyperglycemic state, in diabetic patients, the production of this GF is defective, which results in free iron deposits and higher levels of ROS. Considering this situation, one study used an iron-chelating agent, deferoxamine (DFO), was developed in order to reduce this deposition in skin tissues. In addition, the inflammation would also be decreased and the healing boosted. Transfersomes were used as a suitable choice to load DFO, due to the possible toxicity issues and reduced plasma half-life, when delivered through a systemic pathway. Results confirmed the potential of this transferosomal gel, according to the increased neovascularization, collagen deposition, and the ability to reach deeper through skin layers. The controlled release of DFO has been proven, which constitutes another advantage to their possible application in clinical therapies (Figure 4).[23]

Although these nanosystems can be useful in this field, current studies do not prove enough evidence to sustain their clinical authorization.[22]

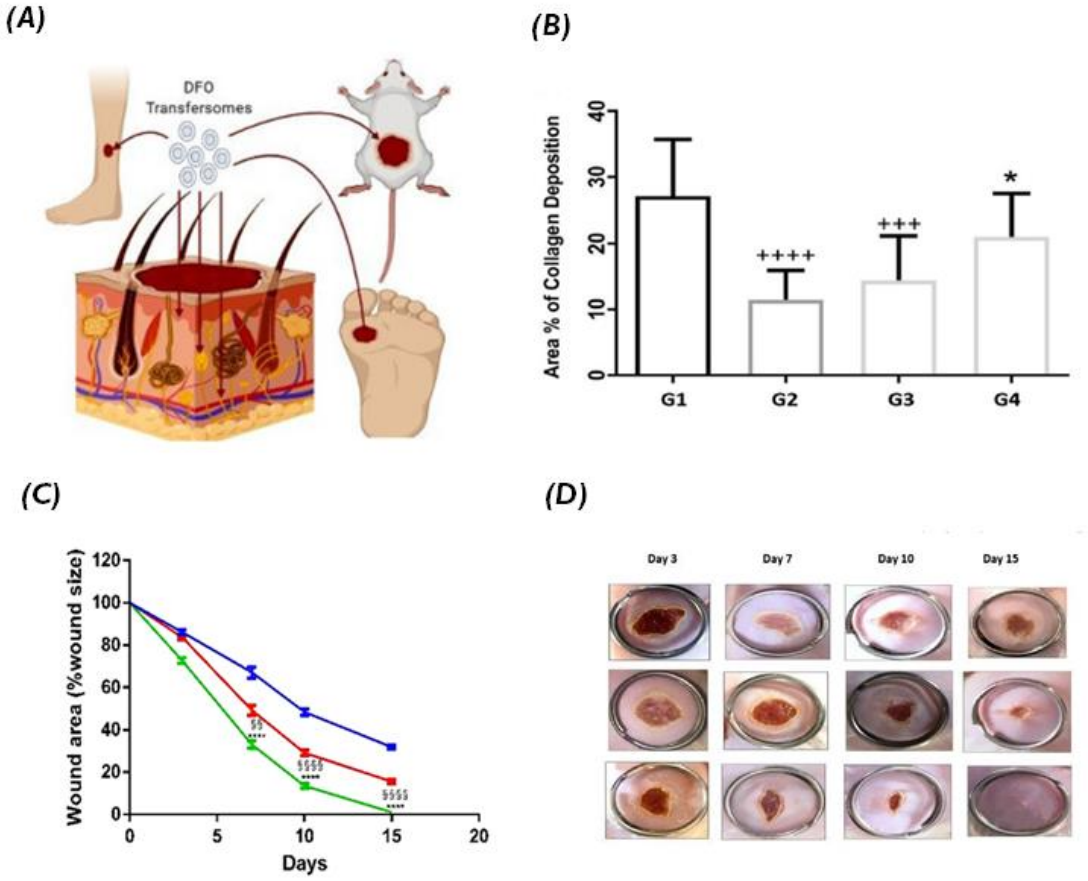


Figure 4. (A) Allusive illustration of DFO transfersomes application in diabetic wound healing. (B) Quantification of collagen deposition which, comparatively with G1 (diabetic animals without an ulcer),

achieved the best results in the group treated with DFO transfersomel gel. (C) Evaluation of wound area, according to the results obtained in the different groups. (D) Photographs of the wound on days 3, 7, 10, and 15. The first row belongs to G2 (plain gel), the second to G3 (DFO solution loaded gel), and the last one to G4 (DFO transfersomel gel). G4 has achieved the best wound closure results on day 15.[23]

2.1.3. Lipid nanoparticles

2.1.3.1. Nanostructured lipid carriers

Nanostructured lipid carriers (NLC) are lipid nanoparticles, widely used in wound management due to their composition and size, which leads to prolonged action of the particles in the wound area, better dissolution and solubilization, and protection against enzyme activity. Their formulation includes not only solid but also liquid lipids (oils). On the other hand, it does not require the presence of an organic solvent, in contrast to solid lipid nanoparticles (SLN), which will be covered in the next topic. To improve the development of new microvessels, promote the migration and proliferation of cells, most importantly, fibroblasts, and collagen deposition, several studies have been carried out.[24] Furthermore, these nanosystems enable the transepidermal water loss (TEWL) reduction, through the formation of an occlusive film, and increased permeation of the substances, due to their substantial surface area.[25] Through encapsulation, and following delivery of drugs, such as antibacterial agents, GFs, or even bioactive agents, NLCs became to be recognized as a great option to manage the treatment and care of chronic wounds.[6]

First of all, the formulation and administration of GFs through nanosystems has been widely used as a strategy to improve their properties, namely their stability. Given this, a research group administrated a formulation of loaded recombinant human epidermal growth factor (rhEGF) into NLC. To provide reliable results, a porcine wound model was chosen. The fact that their dermis composition has identical collagen types and, in both cases, re-epithelization is the initial step in the healing process, makes it a prime choice for this type of study. Topical administration by loaded NLC was found to be an effective way to perfectly regenerate injured tissues and the risk of infection is lower compared to the free rhEGF formulation already on the market.[26]

The formulation of a silicone gel making use of an NLC encapsulated with 20(S)-protopanaxadiol (PPD) was also an approach to this subject. Recent research revealed that PPD, characterized as an aglycone of ginsenosides, showed some significant aspects in this regard, through the stimulation of neovascularization and reducing inflammation in the injury site. Also, the monitoring of collagen deposition is, as well, described as a benefit, to

accomplish regeneration without leaving visible scars. This happens due to their structure and, promotion of hydration and stimulation of electric field mechanisms. NLC contributed to an improved solubility of PPD, and results confirmed the potential of this method, by obtaining scarless healing.[27]

Another promising treatment for diabetic wounds lies in the delivery of drug formulations, as phenytoin and LL37 loaded NLCs. The application of phenytoin is due to its ability to accelerate the healing process and the lack of side effects. In addition, its activity against bacteria and the glucocorticoid antagonism effect, promoting the deposition of collagen and reducing exudate from lesions are its major strengths for successful wound healing. Although the results showed the efficacy of phenytoin-loaded NLC in this thematic, more research is needed to understand the real effectiveness of this method.[25] LL37, an antimicrobial peptide, was also addressed as a possible approach to overcome barriers related to the difficult healing of chronic wounds. The encapsulation in an NLC prevents an accelerated degradation of LL37, a problem found in free peptide formulations, which required higher and most frequent doses. Moreover, its role in modulating the immune response, in the pro-inflammatory process, and the broad spectrum of activity is extremely important to achieve great results in this field. Also, the fact that the formulation has a topical application avoids the effects of systemic administration.[28]

As previously observed, NLCs constitute a helpful tool for wound healing. The increased biocompatibility of their constituents and the promotion of prolonged and continuous release are some of the most relevant properties that make them so suitable for this use.[25,28]

Despite being a useful feature for drug loading, NLCs still have some handicaps, regarding their lack of stability and possible toxicity.[6,24,29]

2.1.3.2. Solid lipid nanoparticles

Even though NLCs are often preferred to SLN, they also constitute an applicable tool to this situation. Firstly, the nano-size and lipid abundance of SLN constitute a few benefits, when the purpose is to promote convenient contact with the injured skin. However, the condensed, crystalline structure and molecular arrangement, which characterize them, are the main responsible for a lengthy process, when they release their components. [6,29]

The primary reason for this is the fact that, due to their lipidic composition, they interact with their components, and, therefore, these are retained into the lipid core. Their preparation

often occurs through emulsification-ultrasonification, as well as NLC. Nevertheless, these nanosystems require an organic solvent for their formulation, which is not necessary for NLC. This is the main reason why their use is limited, compared to other lipid-based nanoparticles.[6]

In this regard, valsartan (Val) was encapsulated into SLN and later incorporated in a hydrogel. The study aimed to enhance the healing process, its quality and to improve the deposition of collagen. SLN were chosen due to their low risk of possible unwanted effects and minimal toxicity, biocompatibility, being biodegradable, and providing an adequate drug release. The integration of these SLN into the hydrogel also contributes to a superior permeation of Val and a closer contact between the drug and the wound site. Additionally, Val is classified as an antagonist of the angiotensin receptor I (ATI-receptor), widely used in the treatment of certain types of hypertension. This active ingredient has proven effective in stimulating skin blood flow. Furthermore, avoids biofilm formation, when used in combination with levofloxacin, or by itself, in topic formulations. This method was reported as effective for its aim, by controlling the inflammatory response and the proliferative phase. This was confirmed due to the lower levels of pro-inflammatory cells, such as NF-KB (nuclear factor kappa-light-chain-enhancer of activated B cells) and MMP-9, in contrast to an increase in transforming growth factor-beta (TGF-β) content. Even though the role of nitric oxide (NO) is extremely relevant during angiogenesis and, in general, wound reparation, its combination with inflammatory cells is potentially involved in the increased activity of cyclooxygenase-2 (COX-2). Considering this, the patients treated with this Val-SLN, presented lower levels of inducible nitric oxide synthase (iNOS), consequent NO production, and COX-2 activity, thus leading to a reduction in inflammation. Furthermore, the conclusions reported that the prostaglandin content in the group treated with these SLN was present at normal levels, which is further proof of its success in this field.[30] Although this may be an option to this topic, as mentioned before, nowadays other options seem to be more advantageous.

2.2. Polymeric-based nanoparticles

Several studies illustrate that the application of polymeric nanoparticles, such as electrospun nanofibers, can be extremely helpful in this subject. It is important to point out their great porosity, size of the pores, which exhibit a small dimension, large surface area, and the ability to reproduce the ECM features and behavior, considering their structure. Besides, nanofibers offer a suitable approach to a wound dressing, due to their antimicrobial activity, good absorption of exudates, oxygen permeability, and maintenance of moisture at the wound site.[31,32]

Nevertheless, some drawbacks can be reported since the presentation of these nanofibers in a single-layer architecture is often associated with an uncontrolled release. To overcome these issues and achieve a sustained release, one approach is to embrace a multi-layered structure. The major advantage of this method is the possibility to adjust the characteristics of each layer, namely concerning their porosity, malleability, biocompatibility, and formulation constituents. Concerning the preparation of nanofibers, several techniques can be chosen. However, electrospinning is the most used, according to the benefits it offers, as it is an effective and easy method.[33] This technique also enables the adjustment of the pore size, which can be a great advantage, not only to hinder the microbial penetration but also to ease the oxygen input.[34]

As mentioned before, diabetic wounds require high expenses. Therefore, many strategies have been designed to shorten the healing process and, at the same time, optimize the treatment and reduce its costs. Considering their attributes of loading and encapsulation, nanofibers are widely used as a way of drug delivery.[33] To this extent, antidiabetic drugs, antibiotics, or even GFs can be encapsulated. While some types of research aim to load the drug alone, into the nanofiber structure, other combinations can be applied. An excellent example of this is a recent study, where gentamicin and vancomycin were loaded into a nanofibrous scaffold, with platelet-derived growth factor (PDGF). In light of the results reported, this conjugation can be very useful as a regenerative treatment for infectious wounds, by promoting angiogenesis and an earlier progression of the healing process. Besides, gentamicin acts against gram-negative bacteria, while vancomycin is a useful approach to *S. aureus* infections. Hence, by applying this method in wounds infected with *S. aureus* and *E. coli*, their properties were confirmed.[35] In addition, another research used an identical combination, through-loading rhEGF and Gentamicin Sulfate (GS) in nanofibrous scaffolds of poly (lactic-co-glycolic acid) (PLGA) and gelatin. Classified as biodegradable synthetic polymers, they promote the proper function of the cells. The results were similar to those previously observed, so these dual delivery systems can be a suitable treatment for diabetic wounds.[3] Chitosan is also used as a component of nanofibers when it comes to local antibiotic delivery. According to recent researches, when formulated in nanosize, its antibacterial activity is improved. However, chitosan may show some instabilities, thus it needs to be neutralized or cross-linked to overcome this matter. The efficacy of this component has been demonstrated when combined with poly (ethylene oxide) (PEO) to deliver teicoplanin. This antibiotic is known due to its potential treatment of infections triggered by gram-positive bacteria. As mentioned before, synthetic polymers are

widely used in these formulations. One of its greatest properties is its biodegradable capability, which avoids an additional procedure to remove the nanosystem afterward.[36]

The delivery of doxycycline (DCH) contained in polylactide (PLA) nanofibers, has also been studied. Besides, to have a broad spectrum of activity, DCH suppresses the activity of some MMP, such as MMP-2 or MMP-9. When upregulated, the inflammation process is extended and there is massive degradation of skin constituents, leading to a delayed wound healing. The encapsulation of this antibiotic in PLA nanofibers, proved to be an effective way to enhance drug stability and avoid photodegradation, especially considering their photosensitivity. The reduction in possible adverse effects, frequent DCH coating, and the continuous release of the drug are, furthermore, important strengths that make this method a useful tool in diabetic wound management.[31] In addition, it is important to refer to the application of antidiabetic drugs on this subject. Through electrospinning, bacterial cellulose and gelatin were selected to formulate nanofibers, to deliver metformin and glybenclamide to the wound site. Superior results were observed in the group treated with glybenclamide. Their recovery was faster, which can be observed through the decreased levels of tumor necrosis factor-alpha (TNF-α) when the experiment was almost concluded. As one of the major pro-inflammatory cytokines, it is extremely crucial for the supply of immune cells and, for that reason, has commonly higher levels in chronic wounds.[37] Pioglitazone represents a different approach to therapeutic nanofibers. Through pressurized gyration and electrospinning, other studies were developed, namely a polyvinyl pyrrolidone (PVP)/polycaprolactone (PCL) nanofibrous complex, and chitosan, gelatin, and polycaprolactone one. These combinations have proven effective as a wound-healing treatment since the scaffolds became wetter and more hydrophilic. Hence, a sustained release of pioglitazone was reported, the proliferation of the cells was boosted and the possibility of systemic side effects was avoided.[38]

From another perspective, the loading of active ingredients into nanofibers is equally important, as a potential care interview on this thematic. Bioactive ingredients have been studied, regarding their ability to prevent bacterial infections and to accelerate the regenerative process. In addition to these properties, berberine, a natural alkaloid extract, further reveals a strong performance as an anti-inflammatory. According to recent research, when loaded to an electrospun nanofiber of gelatin and cellulose acetate, berberine had the strength to promote angiogenesis, synthesize collagen, while providing an appropriate response to reduce inflammation. Besides, this alkaloid proved to be effective against gram-negative and gram-positive bacteria, which is an asset.[34]

Some of the characteristics mentioned before can also be found in nanofibers with sesamol, aloe vera, resveratrol, or curcumin composition. The first one, a phenolic compound, has been of interest to this subject since researchers found that antioxidant supplements can enhance wound healing. Considering that this ingredient has great antioxidant activity and due to its advantageous combination with nanofiber membranes, it can be a promising approach. While nanofiber membranes decreased the IL-10 expression, sesamol promoted an overexpression of IL-6. To understand this mechanism, it should be noted that IL-10 can promote the inhibition of cytokines, such as TNF-α or IL-6. These inflammatory responses were crucial in achieving accelerated wound healing, by inducing the development and proliferation of the main epidermis cells, keratinocytes.[39] Classified as phytochemicals, studies involving resveratrol and curcumin have also demonstrated incisive results. Researches revealed that resveratrol can be helpful, especially regarding the promotion of effective angiogenesis, through activation and support of the vascular endothelial growth factor (VEGF) pathway.[40] In addition, curcumin has shown, in several studies, its capability to improve tissue regeneration, the synthesis of collagen, and promote the formation of new vasculature on, and around, the injured site. However, considering its instability and lower bioavailability when performing *in vitro*, the encapsulation of curcumin in suitable carriers, appealing to synthetic polymers composite nanofibers, such as gelatin, chitosan, PLA, PLGA, or PCL, has been a way to avoid these drawbacks.[41,42]

The use of PCL was focused on in another study. Loaded nanofibers based on hyaluronic acid and keratin, whose production appealed to electrospinning, coaxial, and emulsion, were also described as a great strategy. To improve the interaction with the injured skin, their composition contained PCL and PEO. This can be explained by the fact that PCL is extremely hydrophobic. Therefore, the researchers added PEO, which has a hydrophilic nature, to extend its activity. Conclusions revealed that this can be an up-and-coming approach since it was effective in promoting the viability and proliferation of the cells, showing no cytotoxicity.[43] Another study also mentions the interest in using PCL, due to its wide range of antimicrobial activity, ensuring protection against contamination by gram-negative and gram-positive bacteria.[44]

To reproduce the disposition and structure of skin layers, MSCs are, as well, a suitable way to boost the re-epithelization, improve the expression of keratin proteins and collagen, and reduce the whole wound closure process. Researchers demonstrate that, when loaded to nanosystems, MSCs, adipocyte-derived stem cells (ADCSs), and bone marrow mesenchymal stem cells (BMSCs) are helpful to hasten the healing. In both studies, a 3D nanofiber scaffold

was constructed, to apply it to the wound site. In the case of BMSCs, these scaffolds were aligned in two perspectives, vertically and radially, promoting, mainly, the granulation tissue development and re-epithelization, respectively. Furthermore, by adjusting and enlarging the pore size, not only does cell penetration increase but also inflammation is further regulated through higher levels of M2 macrophages and thus reduced M1 macrophage expression. Results have shown the great potential of vertically aligned scaffolds (VAS) and radially aligned scaffolds (RAS) in this field. On the one hand, the trichome staining of different groups has revealed that VAS enhances the formation of new vessels and collagen deposition. On the other hand, histological studies evaluated the rate of re-epithelization of wounds treated by VAS, RAS, VAS+BMSCs e RAS+BMSCs. They verified that the group treated with RAS had a faster re-epithelization when compared to the other ones. (Figure 5) In light of the results obtained, this can be a potential method for this purpose.[45,46]

Although the mentioned studies can be encouraging for this thematic, the need of obtaining more information about the relation between dose and exposure, the toxicity of these nanosystems, and their mechanism of action is evident.[47]

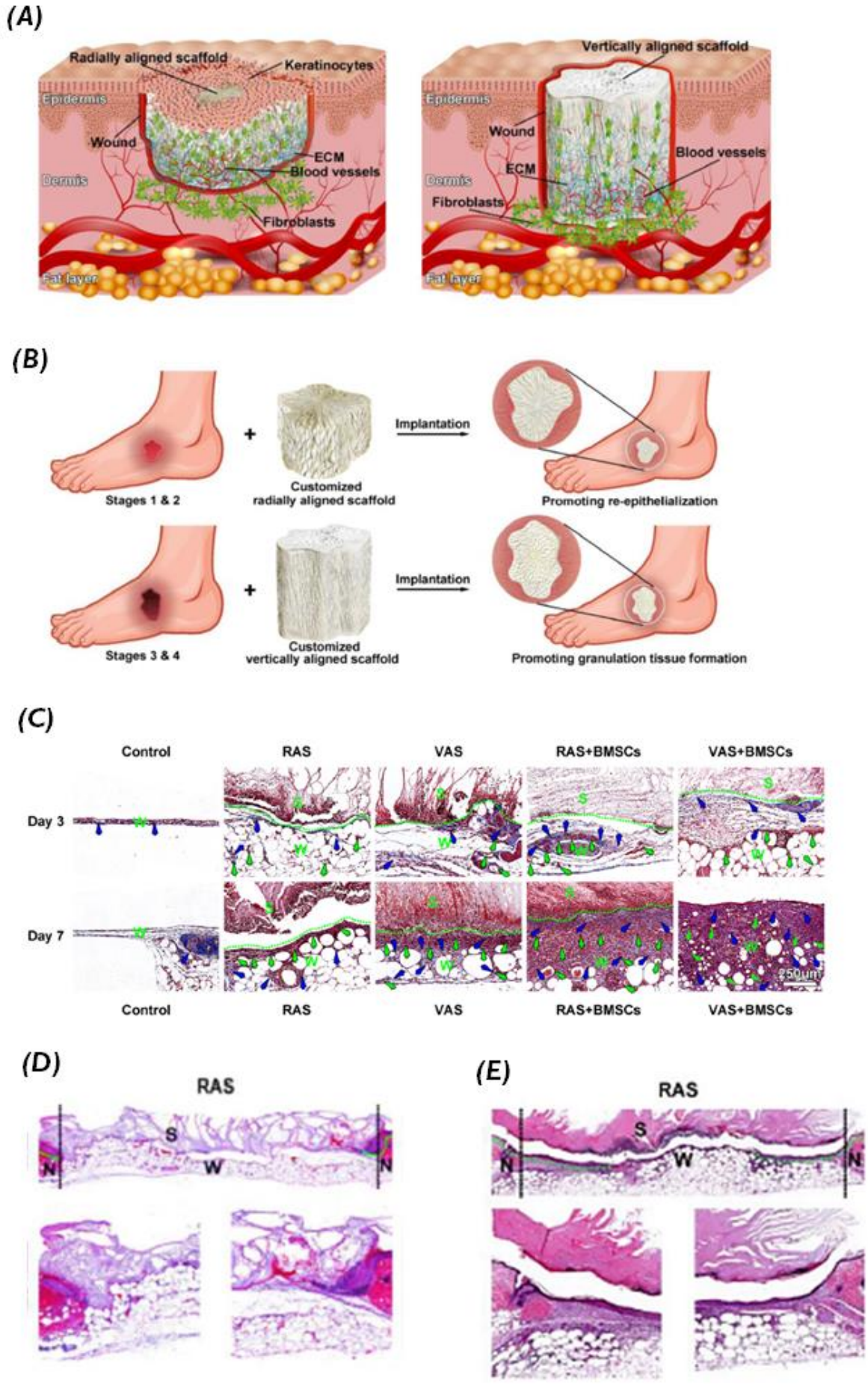


Figure 5. (A) Application of two-perspective aligned scaffolds in diabetic wound healing. (B) Potential mechanism of RAS and VAS in different stages of wound healing. (C) Trichome staining of different

groups has revealed the potential mechanism of VAS and BMSCs loaded VAS (VAS + BMSCs) on promoting granulation tissue formation. This can be explained through the emergence of new blood vessels (represented through green arrows) and collagen fibers formation (represented through blue arrows) between days 3 and 7. (D) Analysis of re-epithelization on day 3 of treatment with RAS. (E) Results show an accelerated re-epithelization on day 7 since a boost on keratinocytes migration has been verified. This fact is shown by the green dots in both figures.[46]

S: scaffold area, W: wound area, N: normal tissue.

2.3. Metal-based nanoparticles

2.3.1. Gold nanoparticles

Taking into consideration their simple preparation and changeable properties, such as size, surface, and shape, gold nanoparticles (AuNPs) have been assuming a fundamental role, as non-viral vectors for gene delivery. Their great biocompatibility and anti-inflammatory properties are a fundamental key to their success.[7,48] Nevertheless, there are still a few hurdles to overcome. These nanosystems present an effective activity *in vitro* and, hence, the great potential for introducing a gene into cells. However, they show a lower one *in vivo*, which can be explained by the fact that there is higher adsorption of the proteins. The synergistic activity resulting from the combination of positively charged AuNPs and LL37, described before as an antimicrobial peptide, has been considered a powerful method, considering recent research. Poly (ethylene imine) (PEI) was the selected reagent for the preparation of these carriers, being responsible for their cationic character. In addition to its antimicrobial activity, LL37 also guarantees protection against viral and fungal infections and has an essential role in promoting wound healing, by intervening in the immune response, promoting proper progression and differentiation of the cells, and boosting angiogenesis. As a nanosystem for gene delivery, results showed its potential activity in eliminating bacteria in diabetic infectious wounds. The formulation into AuNPs also involves better stability of LL37 and lower toxicity of this peptide. Besides, researchers added pro-angiogenic plasmids to this structure, which led to a higher expression of VEGF, hence improving the angiogenesis process.[48]

Another promising approach consists in the delivery of PDGF, by loading it into AuNPs. The research focused on an ultra-sound system, composed of alginate microparticles and PDGF loaded into gold nanoparticles, coated with a combined collagen and glycosaminoglycan scaffold. The greater novelty among this system is the fact that the content is only delivered when activated. Through this technique, a sustained release can be provided, but also the whole process of wound closure can be fuelled and similar to the natural one. However, further *in vivo* studies are needed to ensure high delivery at a precise time and dose, and to use this method as a therapeutic wound treatment.[49]

2.3.2. Silver nanoparticles

Silver nanoparticles (AgNPs) constitute another suitable approach to avoid bacterial infections related to diabetic wounds. Their high surface area represents one of the properties that make this nanosystem so interesting, to achieve easier wound healing. As mentioned in AuNPs, in this case, size and shape adjustments are also possible through their different preparation methods. Characterized by a large spectrum of activity against several bacterial strains, and great anti-inflammatory potential, AgNPs have been widely used as an effective approach to this subject. Their antimicrobial activity includes the ones producing biofilm, which is common in this kind of wound, hence, constituting one of their major qualities.[7] However, these nanosystems still have some limitations, as the difficulty to differentiate bacterial strains and, hence, destroy relevant microbiota. Regarding the resistance of bacteria to AgNPs, more studies need to be done to ensure that there is no development of bacterial resistance. Their accumulation is also described as a drawback since the release of silver ions can unleash on tissues a toxic effect and may boost ROS production. Since stability can be a hurdle the solution lies in using capping agents to improve it.[50]

The development of AgNP based on hydrogel, with chitosan and polyethylene glycol (PEG) composition, has been the subject of a recent study. Results revealed that, in comparison to the group treated with only chitosan and PEG hydrogel, this nanosystem promotes an advanced re-epithelization, a more effective wound closure, showing no scar formation, and enhances the migration of the main epidermis cells. Besides, AgNP has also shown better antioxidant and antimicrobial activities. Although this system induced a faster wound healing and is, for that reason, considered a great option for these treatments, this research was not sufficient to offer a precise explanation of the mechanisms behind the results.[51]

The combination of this chitosan with glycosaminoglycan has also been used in AgNPs scaffolds formulation, due to their synergistic activity, which avoids gram-positive and negative bacteria and enhances the viability and proliferation of fibroblasts. In addition to these strengths, these NP-loaded scaffolds also reduce the possible toxicity induced by silver ions.[52] As mentioned before, the capability of AgNPs to prevent a biofilm formation constitutes a particular advantage, when compared with other nanosystems. Therefore, a research focused on the role of AgNP gel formulation based on Pluronic F-127, a polymer with great biocompatibility on this topic. Besides the antimicrobial properties, this polymer demonstrated other advantages such as the fact that it is liquid at lower temperatures, which is an asset to promote better penetration of the particles and contact with the wound site. Although antimicrobial and anti-biofilm activity was confirmed, the last one was only verified for 30 minutes of its

development, and non-toxicity was demonstrated for 4 hours, so more information needs to be found to validate this method.[53]

In addition, to achieve a scarless cicatrization of burn wounds contaminated with *P. aeruginosa*, the development of a nanocomposite of silver and catechin, with a collagen-based scaffold, was studied. Catechin is characterized as a great ingredient to promote angiogenesis and improve the activity of enzymes such as cyclooxygenase or nitric oxide synthase, hence leading to no scar formation. Their combination with AgNPs has conducted to increased levels of TGF-B3, in contrast to TGF-B1, which is extremely important to obtain healing with no scars. Also, AgNPs help the vascularity formation, through stimulation and reinforcement of some GFs expression, such as VEGF. Due to its enzymatic and thermal instability, a cross-linked agent was added to the formulation to stabilize it. Even though further studies are essential to clarify this technique, conclusions state that this scaffold could enhance the healing of diabetic patients with severe burn wounds.[54]

2.3.3. Cerium oxide nanoparticles

Even though AgNPs have shown their relevant contribution to this topic, other options can be considered in order to prevent possible toxicity problems. Recent studies have described these alternatives, such as cerium oxide nanoparticles (CNPs) and zinc oxide nanoparticles (ZnONPs), as a great way to overcome some drawbacks related to the previously referred NPs. Besides that, CNPs have beneficial properties, such as radical-scavenging mechanism, promotion of cell proliferation, and decrease of oxidative stress. These characteristics are mainly due to their nanocrystalline structure and to the ability of cerium atoms to combine with other ones. This atom presents two reversible oxidative states, varying between 3^+ and 4^+ when there is ROS. In diabetic wounds, the decrease of oxidative stress is achieved by eliminating its excess, as well as maintaining a good ratio between antioxidative enzymes and oxidant species. However, the possible application of this method in treatment and care is still ongoing, since they have to be applied at different stages of the wound healing process, as well as show good compatibility to the skin tissues.[55,56]

Recent researches focus on MicroRNA-146a (miR146a) since it has exhibited promising results in improving the healing of diabetic wounds. MicroRNA (miRNA) is usually known for showing great properties in regulating the production of proinflammatory cytokines and proteins. This specific one has a crucial role in improving the inflammatory response since it promotes the repression of tumor necrosis factor receptor-associated factor 6 (TRAF6) and

the interleukin-1 receptor-associated kinase 1 (IRAK1). Considering this fact, the activity of NF-kB is boosted, hence leading to a higher expression of interleukin IL-6 and IL-8. Through the evaluation of this miRNA expression during diabetic healing, researchers concluded that, in diabetic patients, its expression is decreased. This means that by adding this to other hurdles, the healing process will be impaired.[56,57]

Given this, studies in this field have been done, in order to deliver this miRNA through CNPs. One of them demonstrated that the conjugation between a CNP and miR146a led to the production of a superior number of vessels when compared to the control group. There was increased angiogenesis, and inflammation, observed and quantified using an immunohistochemical technique for the common leukocyte antigen, CD45, decreased. Although previous studies have proven the inefficient treatment with only CNP or miR146A, their conjugation revealed to have a great potential on lowering the length of the process, by promoting the success of each phase of wound healing and heightening the elasticity of skin tissues in a murine model.[57]

Cryogels have also been appointed as a suitable option to promote the delivery of this conjugation. Whereas the main targets are the inflammation process and ROS, hydrogels can be very useful, since they are characterized by presenting a significant content of water, as well as promoting an oxygen-rich environment around the injured skin. However, the fragile and brittle properties of zwitterionic cryogels are a serious handicap to their application. Therefore, to overcome this barrier, a study prepared these gels without getting used to any crosslinker, whose function is to link the polymer chains. This resulted in more pliable cryogels, with strong self-healing properties. Through the determination and quantification, respectively, of microRNA-146a expression and healing duration in diabetic mice, researchers were able to recognize that in the ones treated with the control, with only cryogel composition, the healing closure occurred only on day 20. However, the group treated with CNP-miR146a loaded cryogel had a complete wound closure on day 14, hence showing better results. The quantification of gene expression also confirmed that one week after the start of wound development, miR146a was present in higher levels. As a result, they verified that pro-inflammatory cytokines expression, such as C-X-C motif chemokine ligand 2 (CXCL2) and IL-6, have decreased, in contrast to type 1 collagen.[56]

Another promising method, to deliver CNP-miR146, is the use of nanosilk. This material is characterized for being a polymer with great biocompatibility and degradability. Since the skin of diabetic patients demonstrates lower biomechanical properties, thus leading to impaired healing, researchers used a solution of nanosilk to promote an effective delivery of this

conjugate. When compared to the control group, the process of wound closure lasted less than 3 days in the one treated with nanosilk. They found that TGFβ-1 signaling was related to a decrease in IL-6 and IL-8 expression. This pathway is crucial to achieve a suitable re-epithelization and promote collagen production, by enhancing the function of fibroblasts. Regarding this, the production of myofibroblasts, as a result of the fibroblasts differentiation process, also contributes to accelerating the wound closure. In conclusion, this method may soon be a useful technique, shortly, to protect the wound site and achieve better healing results.[58]

2.3.4. Zinc oxide nanoparticles

Considering their promising activity against bacterial infection, ZnONPs have been lately described as a great nanotechnology development, used to improve wound healing management. Its considerable performance in drug delivery, especially to specific sites, and the ability to induce the process of apoptosis are some of the key achievements. All of these factors result in a decreased likelihood of side effects, such as the ones caused by undesirable levels of toxicity, and more functional results on avoiding bacterial infections, as *S. aureus*. In addition to this, biocompatibility, the non-existent interaction with most active particles, and lower toxicity are considered the major properties that differentiate them from other metal oxide-based NPs. Classified as a wide bandgap semiconductor, the mechanism of action of ZnO is mostly owed to its capability to induce the production of ROS, hence leading to irreversible oxidative impairment and subsequent cell death. The increasing number of ROS damages deoxyribonucleic acid (DNA), thus resulting in the generation of apoptogenic factors and subsequent formation of apoptosomes and cell death. While these nanosystems have demonstrated encouraging results in this field, due to their antidiabetic activity, the most relevant findings lie in their antimicrobial properties and ability to stimulate the re-epithelization of injured skin, as well as the collagen deposition.[59,60]

Considering the metallic character and high surface of this nanosystem, there are still some concerns about their use, due to possible toxicity issues. Because of this, studies have been carried out over time to explore the most beneficial ways to use them and improve their attributes. Nanosized hydrogels and electrospun nanofibers, based on these metal NPs, represent some of the most promising approaches on this thematic in recent years. As mentioned before, one of the major causes of delayed wound healing in chronic wounds is the development of bacterial infections. In contrast to antibiotics' mechanism of action, NPs do not require cell penetration to perform their antibacterial activity. Therefore, this ability

constitutes an advantage, since it means that the possibility of creating resistance to bacteria is lower. A biogenic nanocomposite hydrogel, incorporated with Ag and ZnO, was focused on in a recent study. Leaf extract of *Hibiscus sabdariffa*, characterized by showing great antidiabetic activity, was used to synthesize AgNPs, later coated with a ZnO layer, in order to reduce toxicity concerns. To evaluate their antimicrobial activity, in vitro testing included not only gram-positive bacteria, as *S. aureus* or MRSA, but also *P. aeruginosa*, as gram-negative. Researchers concluded that this nanocomposite was revealed to be efficient since microbial growth has significantly decreased. Nevertheless, in gram-negative bacteria, it was still possible to verify a partial growth. Despite this fact, the additional ability to prevent biofilm formation, biocompatibility, and up-regulation of different GFs are the main properties that contribute to easier wound healing.[60] In this regard, other researches are evidence of this useful method. PVA (polyvinyl alcohol) and chitosan have also been used in these hydrogels, respectively, to achieve suitable biocompatibility and elasticity, and to promote an adequate environment, cell adhesion, antibacterial activity, and hydrophilicity. ZnONPs are also characterized for showing excellent chemical stability, and the potential to reduce the inflammation process. Furthermore, the release of Zn^{2+} ions enhances the migration of epidermis primary cells, hence promoting faster healing. Researchers concluded that this might be a promising application, mainly to avoid bacterial infections. Although the study was not specifically directed to diabetic patients, it may be a great advance in the management of these chronic wounds.[61]

As previously mentioned, electrospun nanofibers are also a relevant tool in this topic, as they can be used for the local application of ZnONPs. A recent study confirmed this was a useful application, by developing a PLGA and silk fibroin (SF) based nanofiber to deliver ZnONPs. The excellent properties of nanofibers, such as promoting collagen deposition, increasing the number of new vessels, the migration of keratinocytes, and re-epithelization of the injured skin were considered. In addition, the delivery of this nanosystem to the wound site would be crucial to boost the biocompatibility, as well as hasten the healing process and wound closure. Evaluation of antioxidant, anti-bacterial activity, and cytotoxicity was done in four types of PLGA/SF nanofibers. The assays were developed in nanofibers with 1, 2, and 3 % of ZnO and a control sample, without this component. Cytotoxicity assessment revealed that, although a higher concentration of these NPs is related to an increased ROS production, thus preventing the proper cell proliferation, their presence in lower concentrations may be useful and safe for these clinical applications. Regarding antioxidant activity, the SF was shown to be the main responsible for this effect since it is characterized by having a protein composition with phenolic properties. Given this, SF helps the promotion of wound healing, mainly by avoiding

oxidative stress, which makes it an excellent choice for the preparation of these materials. Researchers also verified that the anti-bacterial activity increased with a higher concentration of ZnO, against both *S. aureus* and *E. coli* strains. In addition, they concluded that the group with 3 % of ZnO showed the best results on enhancing the re-epithelization, reducing inflammation, promoting the wound closure, cell proliferation, and creation of new vessels, through the stimulation of GFs, such as fibroblast growth factor (FGF) and VEGF (Figure 6).[62]

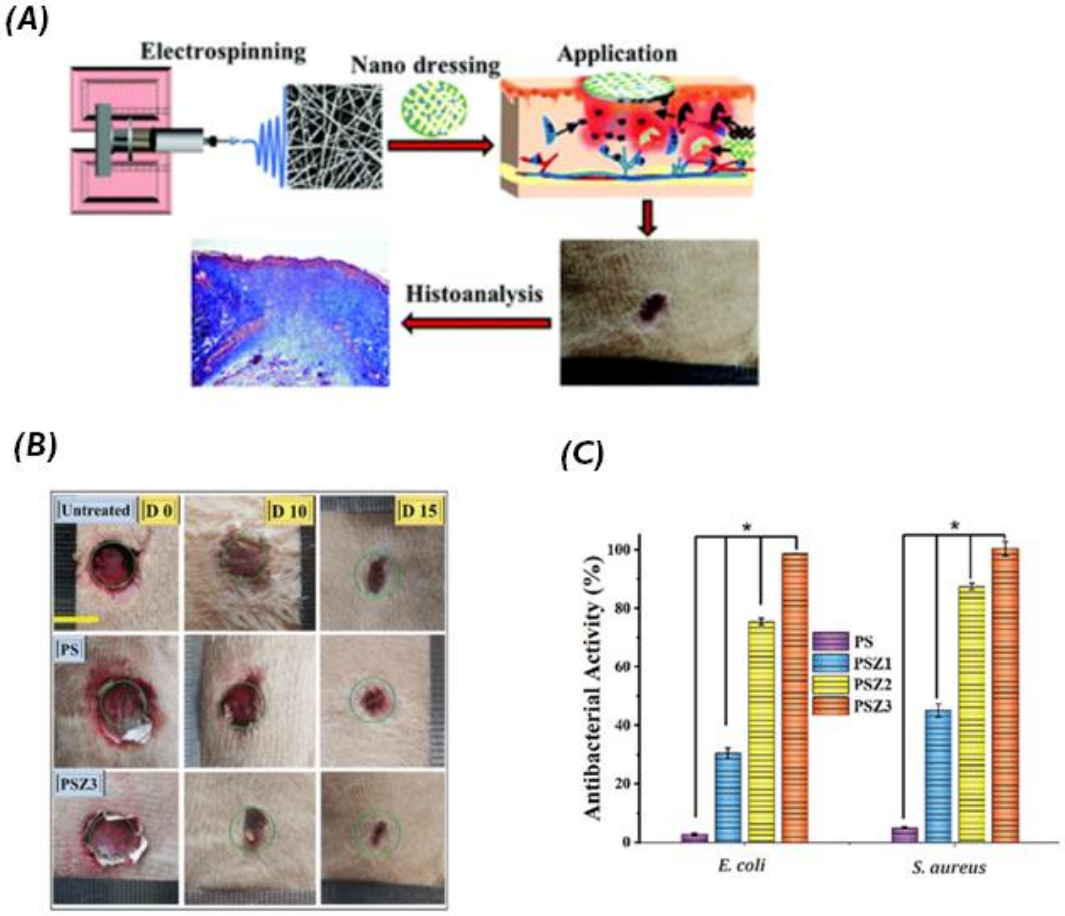


Figure 6. (A) Mechanism behind the application of these ZnONPs in diabetic wound management. (B) Wound closure results on days 0, 10, and 15 in untreated animals, PLGA-SF nanofibers, and PLGA-SF nanofibers with 3% of ZnO. (C) Results of groups treated with 0, 1, 2, and 3% of ZnO, on antibacterial activity, respectively named PS, PSZI, PSZ2, and PSZ3.[62]

Similar results were found in a study in which researchers developed a Chitosan/PVA/ZnO nanofiber to improve diabetic wound healing, through its ability to act against oxidative stress and bacterial infections. When compared to the control group, without ZnONPs, on days 4, 8, and 12, the one treated with these nanofibrous membranes has revealed to be more effective in promoting an increased collagen content, hence leading to an adequate granulation phase. In addition, in the non-control and control groups, antioxidant properties and

antibacterial activity were confirmed, the last one as very effective against both gram-positive and negative bacteria.[60]

To summarize, the development of nanosystems with a metallic composition has been growing in the scientific community as a suitable way to improve the management of chronic wounds. Even though they might show great anti-inflammatory properties and biocompatibility, concerns about their activity *in vivo* are still being discussed.[49]

2.4. Other nanosystems

2.4.1. Dendrimers

Over time, new nanotechnology approaches and strategies to wound healing have been developed. Dendrimers are classified as polymers with a characteristic design and properties that make them a suitable choice to overcome the challenges inherent to chronic wound healing. In consideration of their central core, symmetrical high branched structure, and tuneable functionalized terminations, these nanosystems can be a powerful tool for this topic. The terminal functionalization is extremely important, not only for being an advantageous way to add small size molecules but also to control the drug release and improve their delivery and targeting to the wound site. These terminations are duplicated each time the generation is renewed. Dendrimer generation is determined according to their structure, more specifically through the number of diverging branches. The root of this process is the central core, acting as a fixing point to promote the dendrimer growth by adding successive branches to their structure. The primary strengths of dendrimers are determined through the right choice of their generation, which allows the change and boost of their attributes, hence resulting in a higher connection to the surface site molecules and better biocompatibility features. Another highlight of these nanosystems is their simple preparation.[63,64,65]

Most of the research developed to this time, among all the different types of dendrimers, focuses on polyamidoamine (PAMAM) ones. Nevertheless, toxicity may be a concern on their use, since it can reach worrying levels, as generation and concentration of PAMAM increase. In addition, their charge can affect this, with positively charged ones showing higher levels of toxicity.[64]

As mentioned before, the focus on local inhibition of MMP-9 can be a possible strategy to enhance the healing in diabetic patients. This impediment can be achieved by a gene silencing approach, in particular small interference RNA (siRNA) technology. Therefore, wound healing

is facilitated, considering the lower expression of this MMP. Given this, a study developed a mechanism of siRNA delivery through a cationic dendrimer. To ensure an adequate encapsulation and a correct delivery of the nucleic acid to the wound site, researchers used bacterial cellulose (BC), which has suitable properties for this purpose, such as biocompatibility, non-existent toxicity, high porosity, and great water absorption. This last one is extremely important to absorb the wound exudate. Results have shown the effectiveness of this method, according to lower levels of MMP-9 expression, which are excellent contributions to the wound closure, by promoting the ECM synthesis and the enhancement of the collagen content, hence increasing the wound closure.[66] Regarding this potential, another study adopted a similar method, carried out through the synthesize of a cationic polymer, named B-CD-(D3)7, whose dendron arms are based on β-Cyclodextrin and third-generation PAMAM. Conclusions have revealed the considerable decrease of MMP-9 expression, which was a fundamental key to improve the process. Also, fewer neutrophilic granulocytes were found closer to the injured area, which means that the inflammation was reduced, and there was a boost in the collagen levels. According to these results, the study fulfilled its objective.[67]

While the inhibition of MMP-9 may reveal potential results on this subject, other approaches have been done. To prevent *S. aureus* infection, vancomycin-resistant, a dendrimer suspension was designed with a composition of AgNPs and vancomycin. The incorporation of these components in PAMAM dendrimers showed to be effective to kill and, hence, reduce the existent forms of resistant bacteria, while not inducing resistance. Also, the binding with the bacteria surface was improved. However, more research is needed to confirm the mechanisms behind the higher life-time of this combination, since it can be related to different bacteria strains.[68]

2.4.2. Carbon nanotubes

As previously observed, the characteristic high surface area of nanosystems is one of their major strengths. Carbon nanotubes (CNTs) have been described as a suitable approach to effectively manage the healing process.[69] Classified as one dimension nano-sized carbons, they can be divided into single-walled CNTs (SWCNTs) or multi-walled CNTs (MWCNTs). Their preparation occurs through a process of oxidation in a highly acidic medium, resulting in functionalized endings for molecular copulation. Considering their electrical and mechanical properties, good biocompatibility, and stability, they also constitute a great advantage on this topic. Their tubular structure, surrounded with graphite, is generally closed on one side, and its composition is based on lengthy and thin fullerenes.[29,70,71]

To improve the properties of polymers, CNTs can be used to incorporate them. However, this method can be difficult when it comes to hydrophilic polymers. Since these CNTs present a hydrophobic character, the incorporation of hydrophilic polymers is difficult. To overcome this barrier, a solution lies in the addition of polar groups.[70] The atomical encapsulation is facilitated through these nanosystems since they are characterized by having an inert character. Taking this into consideration, low and high electronegative atoms can be incorporated without difficulty, consequently enhancing the properties of CNTs. Recent research used this method to avoid biofilm formation, through the simple incorporation of heteroatoms into MWCNT. Nitrogen and fluorine atoms (with a high electronegative character) were conjugated with phosphorous and boron (low electronegative character). Results have confirmed their antibiofilm activity against both gram-negative and positive bacteria, mainly due to the conjugation of atoms with different potentials of electronegativity, which was essential to provide a charged surface that allows the inhibition of the biofilm formation and, consequently, the healing.[72]

Nevertheless, some difficulties remain, especially due to their inability to biodegrade and possible toxicity.[29] Therefore, a different approach to the use of hydrogels in a CNT formulation was the focal of another research. In contrast to the previous one, the preparation of hydrogel was based on cellulose, which is a great choice, since it can be helpful to avoid a possible microbial proliferation and has good biocompatibility. Given this, the hydrogel was added to MWCNTs to promote a controlled delivery of bioactive antimicrobial substances, with the primary aim of improving wound healing. Excellent results on cell viability, the ability of the hydrogel to prevent the degradation of the effective antimicrobial therapeutic, and their sustained release were crucial to ensure the success of this method.[71] Glycol-chitosan composed of hydrogel has also revealed its potential in this context, through an efficient improvement of cell migration, hence leading to an easier regenerative process.[73]

2.4.3. Exosomes

Exosomes are small extracellular vesicles (EV), recognized as biomimetic nanosystems, whose structure is organized in a lipidic bilayer. The distinction between different types of EVs is based on their size and cargo content. Their size is well-established, with a range from 30 to 150 nm.[24] As derived products of mesenchymal stem cells (MSCs), their role in cell communication is of the utmost importance to facilitate the wound healing process, by promoting angiogenesis. At the same time, cargo elements contained on the inside, as microRNAs and GF, also contribute to this effect.[74,75,76] Due to their promising regeneration

action, promotion of re-epithelization, and stimulation of the immune response, MSCs-EVs are the most used association for this purpose. Their biological functions are identical to the ones that characterize MSCs.[24,77] Considering the possible interference on biodistribution, the route of administration is a relevant detail, requiring special attention. When focused on therapeutics taking advantage of exosomes, most of the formulations are local injections. This may be a concern, since this type of administration is accompanied by an accelerated clearance rate and, considering their *in vivo* short-life time, may negatively influence their performance. The difficulties in maintaining their viability during the regenerative procedure are also a drawback.[24,74]

The large amount and simple isolation of gingival mesenchymal stem cells (GMSCs) are some of their major strengths. In consideration of this, they have been recently selected over other MSC, due to their improved properties on cell proliferation and migration, regenerative abilities, and steady morphology. A hydrogel sponge, combining silk with chitosan, was developed as a scaffold to improve the activity of exosomes, derived from GMSCs. As previously observed, chitosan is extensively used in dressings design to enhance wound healing, appealing to its attributes on bleeding management and clot formation, biocompatibility, and activity against microorganisms. To evaluate the effectiveness of this method, researchers used an animal model, inducing diabetes in rats by injecting, via intraperitoneal, streptozotocin (STZ). The study has proven to be successful in rats, regarding wound repair, and has the advantage of not being invasive. However, the application in humans can have different results, so more research needs to be done in this aspect. Considering this obstacle, a pig model may be considered, as it is more similar to human skin.[78] Other researchers exhibited the efficacy of exosomes derived from the MSCs of the human umbilical cord (HUCMSCs) through two different studies.[76,77] In the first study exosomes were complemented with a scaffold of PVA/alginate hydrogel, on damaged tissues. One of the benefits of this combination is to promote angiogenesis, by stimulating the production of VEGF. Several proteins, such as CDR31, SR-B1, or SMA, play a crucial role in angiogenesis, by maintaining the homeostatic character of lipidic constituents in skin epithelium and intervening on ECM deposition. The activation of extracellular signal-regulated protein kinase (ERK) 1-2 is also boosted by using this method. Hence, the expression of the proteins above-mentioned will be increased. All these factors are defining for the enhancement of cell proliferation and migration, angiogenesis, and fast tissue regeneration.[76] The second study is based on an injectable formulation, with long-term release and antibacterial properties, making use of a hydrogel with a polypeptide

base. The results were favorable to the wound repair and similar to the previous one. Therefore, this makes these studies a promising application in diabetic wound management.[77]

Chronic wounds, as diabetic ones, are usually characterized by poor vascularization, lower levels of oxygen, and possibly infection. Responding to the increased levels of glycemia, the cells involved in the immune response, such as neutrophils or macrophages, will increase the production and, hence, the appearance of more ROS. As a result, the wound cannot heal properly, and there is an abnormal migration of the cells. To fix this problem, an oxygen-laden exosome was developed (OxOBand), to assure a correct wound closure, enhance the re-epithelization, synthesis of collagen, and promote vascularization. Furthermore, OxOBand provides lower levels of ROS, allowing the decrease of oxidative stress. In order to obtain cryogels, antioxidant polyurethane (PUAU) and calcium peroxide (CPO) were frozen. The exosomes used in this promising therapeutic were derived from adipose stem cells and, according to the results, have shown an excellent percentage of wound closure (Figure 7).[75]

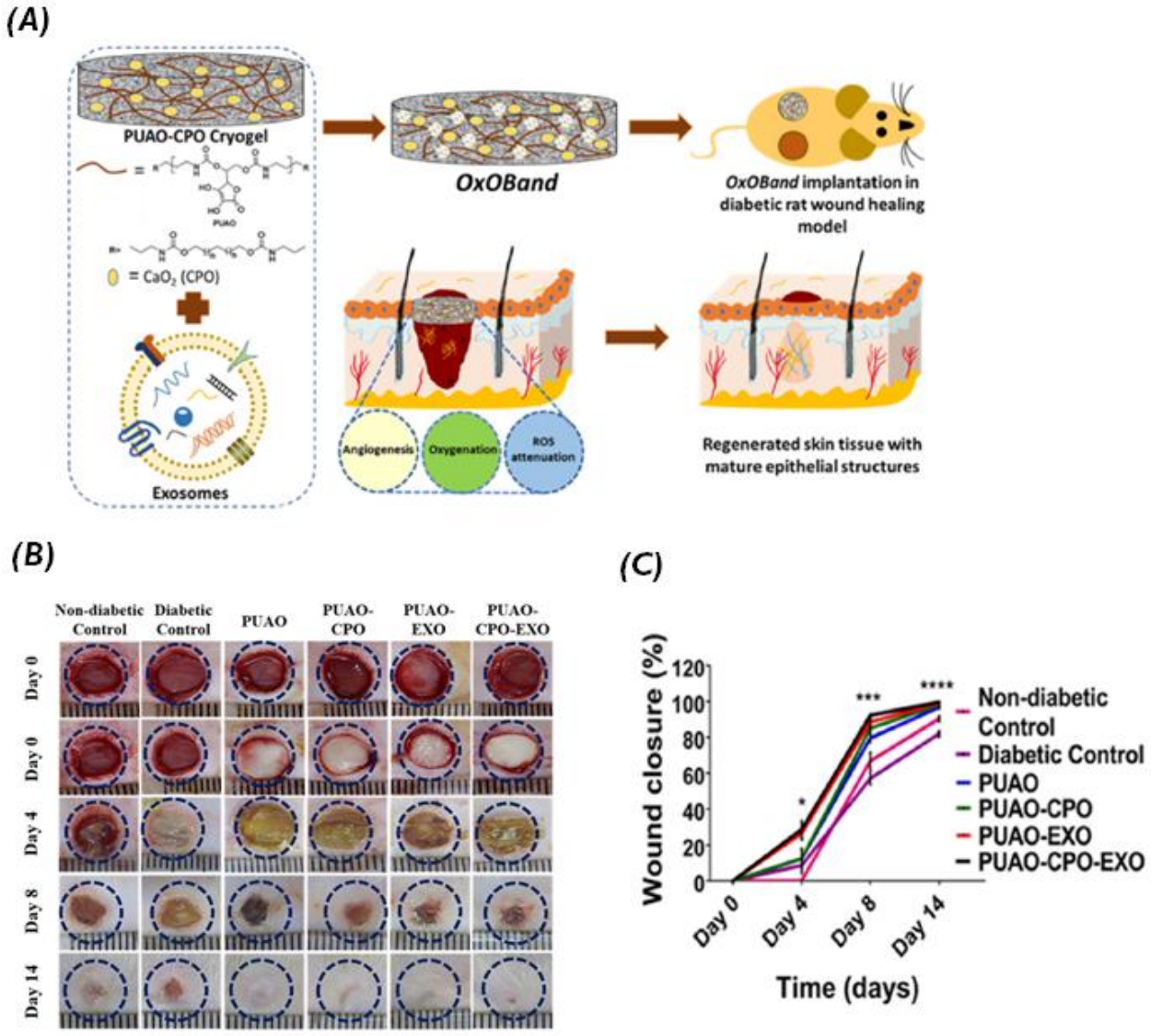


Figure 7. (A) Mechanism behind the development of OxOBand and its implantation in diabetic rats, in order to enhance angiogenesis, oxygenation, and ROS attenuation. (B) Representation of wound healing evolution in different treatment groups from day 0 to 14, showing improved results in the one treated with PUAO-CPO-EXO. (C) Rate of wound closure over 14 days of treatment. Results are consistent with the previous point since the fastest rate was verified in OxOBand treated group.[75]

New research should be done in more reliable models to validate the methods. Considering this, further evaluation of these nanosystems in large-scale models is necessary in order to improve the knowledge about its risk-benefit ratio.[24,77]

3. Safety and regulatory issues

Nowadays, nanotechnology is considered one of the major causes of the industrial revolution and the potential growth of economics.[79] The constant emergence and evolution of new potential therapeutics, in order to improve the treatment and care of chronic wounds, plays a major role in this issue. However, these innovative methods have to face a long pathway,

until they reach approval from regulatory authorities, along with very expensive costs during the manufacturing process (Figure 8). When the composition of medical devices includes nanomaterials, there is the need of obtaining a more exhaustive characterization, of different pharmacokinetics parameters, since this conjugation is classified as high-risk.[20,80] Because of this, nanofibers constitute a great example, considering the crucial monitoring of their properties, such as porosity, arrangement, and structure, to avoid changes in normal biological activity. The development of mechanisms to deliver different components from the same nanosystem and overcome their burst release is of extreme importance, as well. Electrospun nanofibers are one of the most promising nanosystems in this field. Therefore, clinical trials are essential to evaluate their application and compatibility with human skin, when it comes to regenerative processes.[81]

One of the major drawbacks, when preparing and evaluating these nanosystems, is the emergence of toxicological effects. The most critical repercussions include their accumulation in organs, such as the liver, and the ability to reach the brain through the blood-brain barrier. Instability and changes in the morphology of membranes, thus leading to damage of organelles and negative effects on DNA, are also consequences that might be crucial. In consideration of this, Food and Drug Administration (FDA) owns guidance to regulate the nanotechnological products, and assure their safety and efficacy. The process preceding commercialization can take several years, considering all the stages the product has to go through in order to certify its compatibility and evaluate all the risks.[29] Although there are many research and laboratory studies, when it comes to achieving a suitable clinical approach, it is difficult to find a product that fully holds the requirements.[24]

To ensure the non-existence of possible toxicity concerns, studies and research are made to understand the effect of nanosystems in the human body. From the administration route to the length of exposure and posology, these constitute some of the most relevant aspects that must be taken into account. Besides, the evaluation of carcinogenicity is also necessary, when it comes to chronic wound treatment.[80] In this regard, the protection of the environment is of extreme relevance, as well. When nanosystems are released to the environment, related toxicity effects can be harmful, since they can lead to impairment in the food chain and possible damages in the correct development of several species. Considering this, strict regulations to guarantee the protection of the planet should be adopted.[79] According to updated researches, even though there are a few FDA-approved therapies to enhance diabetic wound healing, nanotechnology-based ones are not included.[82]

To briefly summarise, there is a constant need to find more evidence, evaluating the benefits and risks, overcome the whole regulatory pathway, achieve clinical approval and commercialization of the products. Besides, considering the costs required for the process and its large-scale production, the design of these nanosystems should as well be appropriate and simplified.[20]

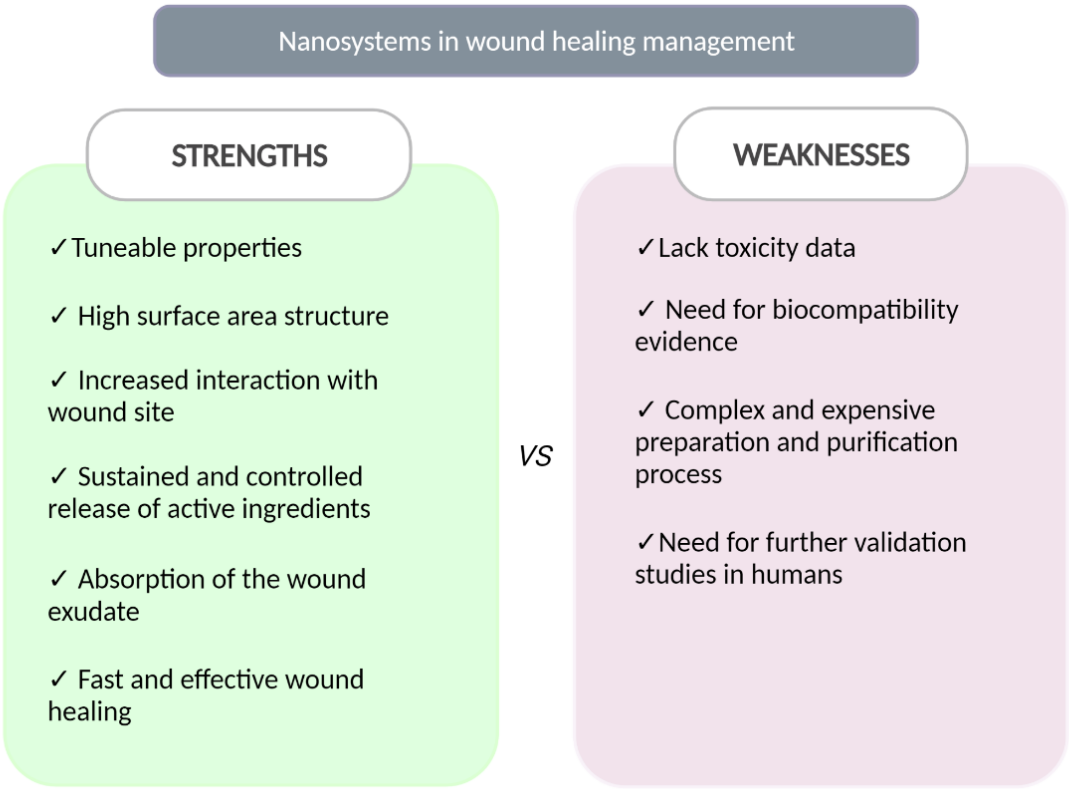


Figure 8. Main strengths and weaknesses of nanosystems in wound healing management.

4. Conclusion and Future Prospects

Considering the constant improvement of nanotechnology features, increasing advances in diabetic wound healing can be noticed. To enhance wound healing and fight the drawbacks that impair this process, many options have been approached. In this regard, nanosystems are considered an up-and-coming way to avoid complications, such as hospitalization and amputation, reduce the costs involved and, more importantly, ensure that patients have a better quality of life. Several studies have revealed great results on improving wound closure, through the prevention of bacterial infections and promotion of the success of each phase of skin regeneration, hence resulting in faster and efficient healing.

In addition to the promising results of loading antibacterial drugs, bioactive compounds, GFs, among others, into nanoparticulate delivery systems, new studies have shown potential in this

subject. From the use of nucleic acids or systems that power a precise triggered delivery, to the use of dendrimers and carbon nanotubes for this purpose, these are only a few examples of the most recent developments in this field.[32,49] Obtaining a scarless wound closure through nanotechnology systems is, definitely, another promising approach.[27] In this regard, the suitable application of encapsulated anti-diabetic oral drugs on promoting wound healing is also a very interesting way to reach the main aim.[37,48]

Nevertheless, there are still some challenges and concerns in this context. Regarding infectious wounds, although these nanosystems represent powerful methods for this purpose, to data, none of them own all the requirements to treat them effectively. Future researches should focus on non-irritable systems that assure a good adherence to the injured site, show suitable properties such as flexibility, be adjustable to each wound type, and provide sustained delivery of drugs, GFs, and other biomolecules to avoid bacterial infection and enhance the healing of injured tissues. Biodegradability is also an extremely relevant strength that should be considered.[35] Besides, hydrogels, which are very common in wound repair, also face some challenges to their use on an industrial scale. If, on the one hand, more studies are needed to improve their properties to their best of activity, monitoring their toxicity and biodegradation, on the other hand, their production in a large dimension is also a drawback.[70] This need for more functionalized properties also applies to other studies, such as nanofibers. It must also be taken into account most of the studies mentioned above are conducted on a small population of diabetic patients or use animals. Therefore, more studies have to be done and clinical trials are of utmost importance to achieve new pieces of evidence closer to reality.[81]

In conclusion, even though these nanosystems still have a few barriers to overcome, researchers are increasingly closer to an appliable method. Therefore, new advances are essential to achieve this goal, which is based on finding in nanosystems a promising tool that enables improved wound healing and speeds up the entire recovery, reducing the complications and expenses involved in this process, and providing diabetic patients with a better quality of life.

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