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ANALYSIS OF THE USE OF NANOPARTICLES CONTAINING DAPSONE IN THE TREATMENT OF SKIN WOUNDS: A LITERATURE REVIEW

Aline Marques Perez da Rocha

Flávia Cilene Maciel da Cruz Alves

Abstract: This literature review aimed to evaluate the efficiency of dapsone encapsulated by nanoparticles in the treatment of skin wounds. To achieve this objective, as a way to perform a primary selection of articles, strings were applied to the Scielo and PubMed platforms. Data were collected for the years 2012 to 2020. The articles found were subjected to a secondary selection, through the application of previously defined inclusion and exclusion criteria and submitted to a quality assessment scale. As a result, one article was found on the Scielo platform and fourteen on the PubMed platform. After applying the secondary selection, 6 articles were selected for full analysis, 4 for abstract analysis and 6 were excluded. Of the articles selected for analysis, many had similarities in the method of characterization of nanoparticles and in the results when suggesting the use of nanosystems as an alternative to the treatment of skin wounds. Regarding the differences, the most important ones are the method of drug administration (topical, oral or unspecified) and the skin wound targeted by the research (leprosy, acne or unspecified). It was concluded that the use of dapsone in nanosystems is promising for the treatment of skin wounds.
Keywords: SKIN WOUNDS, NANOPARTICLES, DAPSONE.

INTRODUCTION

Skin wounds are described as interruptions in the integrity of the skin [1]. When the healing time is short and granulation tissue is scarce, the wounds are called acute [1]. However, if this period is longer and there is the participation of pressure, shearing or friction forces, the wound is characterized as chronic [1]. It is worth noting that chronic wounds may or may not be associated with underlying diseases [1].

Currently, leprosy, a pathology in which skin wounds occur, stands out in terms of prevalence in Brazil [2]. The disease, whose etiological agent is Mycobacterium Leprae, has a chronic evolution, direct transmission through contact with bacilliferous patients and can lead to the onset of deformities, as well as skin ulcers [2]. The wounds resulting from this condition must be efficiently treated, as they constitute entry points for microorganisms that cause infection, which, once aggravated, may culminate in amputation [3]. For many years, the only treatment for leprosy was based on an oil known as "chalmoongra", whose therapeutic efficacy was uncertain. However, in the mid-1940s, it was discovered that a sulfone produced good results in the treatment of the pathology [3]. Later, others were discovered, but all were derived from what is now called dapsone [4].

Acne, on the other hand, is a chronic dermatosis that affects people, especially in adolescence [5]. Its pathophysiology is complex, but involves sebum hyperproduction associated with follicular hyperkeratinization, resulting from the presence of the bacterium Propionibacterium acnes and the inflammation generated by such colonization [5]. All of these factors culminate in acne, a disease of the pilosebaceous follicle that is related to andogenic action in its genesis [5]. Dapsone is also a promising medication for this dermatosis, and can even be used in conjunction with other medications to treat severe forms [6]. Therefore, a pioneer and currently considered a "first-line" drug in the fight against leprosy, dapsone is a sulfone that stands out among other medications and has been the target of national and international research regarding the improvement of its effects [4; 7-9].

Its highlight, among other pharmacological properties, is its dual role, both antimicrobial and anti-inflammatory, with great potential

in the treatment of skin pathologies [7]. Thus, the drug is commonly [8-9] used in the treatment of diseases caused by pathogens, such as leprosy, and chronic inflammatory dermatological diseases, either as a single therapy or in combination with other drugs. However, systemic exposure to the drug causes numerous side effects, including dyspepsia, g6PD-dependent hemolytic anemia, methemoglobinemia, toxic hepatitis, photosensitivity, psychosis, and sulfone syndrome [4]. In order to minimize this problem, drug delivery systems have been developed using nanotechnology [2].

Nanotechnology can be conceptualized as the collective actions involving research, development, and innovation, based on the special properties of matter at the nanometric scale [10]. It is important to note that when a material is a billionth of a meter in size, i.e., has dimensions on the nanometric scale, it takes on new properties that are different from those that the same material would have on larger scales. Numerous reasons contribute to this reality, among which we can mention the high surface/volume ratio and the confinement of charge carriers in reduced sizes [11]. In this sense, this area of research is promising in the construction of solutions to various problems, such as those involving the diagnosis and treatment of pathologies [10].

Within the nanotechnology field, there are nanocarriers that show great promise in terms of drug release, which becomes more controlled and in a specific location. In this sense, the use of nanoparticles and nanocarriers with dapsone is promising in the therapeutic approach for skin wounds by inhibiting the nonspecific distribution of drugs used in the treatment of these lesions and increasing the bioavailability of the drug[8].

Thus, the present project on the functioning of nanoparticles involved in the drug delivery system is essential in promoting greater efficacy and reducing adverse effects.

METHODS

With the aim of evaluating the efficiency of dapsone encapsulated by nanoparticles in the treatment of skin wounds, this literature review used the Scielo and PubMed platforms as a database for the selection of articles.

The primary selection process was carried out by accessing the Scielo platforms via the link https://scielo.org/pt/ and PubMed via the electronic address https://www.ncbi.nlm.nih.gov/pubmed/. In the first database, the following descriptor was applied "Dapsona and (Nanoparticles or nanosystems)". In the second, the descriptor "dapsone"[MeSH Terms] OR "dapsone"[All Fields]) AND (("nanoparticles"[MeSH Terms] OR "nanoparticles"[All Fields]) OR nanosystems [All Fields])("dapsone"[MeSH Terms] OR "dapsone"[All Fields])" was used. Filters were not used on any platform to refine the selection of articles. For this literature review, articles in both Portuguese and English were accepted. The articles then underwent a secondary selection by applying the following inclusion and exclusion criteria:

Inclusion criteria

a) The articles must present the following keywords: dapsone, nanoparticles, in addition to mentioning some skin pathology (leprosy, acne, etc.). For non-free articles, the abstract was analyzed; for free articles, the entire article was analyzed.

b) The articles must present a statement that shows some contribution of the experiment performed to improving drug administration. For non-free articles, the article must be analyzed. For free articles, the abstract was analyzed; for free articles, the conclusion was analyzed in addition to the abstract.

c) Only articles published in or after 2012 were considered.

d) Free articles were analyzed in full. As for non-free articles, only the abstract was considered in the analysis.

Exclusion criteria

a) Articles that failed to address nanoparticles or nanosystems were disregarded.

b) Articles that failed to address dapsone were disregarded.

c) Articles that did not mention any skin pathology were disregarded.

d) Articles that failed to present some contribution of the experiment to improving drug administration were disregarded.

e) Articles published before 2012 were disregarded.

f) Articles that were not available for free were disregarded for full analysis. For these articles, only the abstract was analyzed.

Subsequently, the articles selected by the secondary selection were subjected to a scale for quality assessment. The parameters used are presented below:

SCALE FOR QUALITY ASSESSMENT		
1. Is the problem well defined?	Yes	+1
	No	- 1
2. Is the methodology described in detail?	Yes	+1
	No	- 1
3. Is the methodology adequate?	Yes	+1
	No	- 1
4. Are the results consistent with the problem presented?	Yes	+1
	No	- 1
5. Were the results well described?	Yes	+1
	No	- 1
TOTAL		

TABLE 1: Quality assessment scale items and possible scores

RESULTS

Regarding the results of this primary selection obtained by using the descriptors, 15 (fifteen) articles were found in total. Figure 1 represents the selection process with the respective results.

Considering as U, the universe of nine articles approved in the secondary selection for both full analysis and abstract analysis, 22.2% were published in 2018 and an identical percentage of articles were published in 2012. Regarding the years 2013, 2015, 2016, 2017 and 2019, the percentage of published articles was 11.1% for each year cited.

It is also noteworthy that of U, 55.6% revealed in their text that they were in vitro studies, 11.1%, a combination of in vitro and ex vivo studies, 11.1%, a combination of in vitro and in vivo studies, 11.1% a combination of in vivo and in silico studies and 11.1% did not explicitly indicate the method.

Regarding the strategy for using nanoparticles or nanosystems, 44.4% of U articles were aimed at developing oral formulations, 44.4% at topical formulations, and 11.1% did not explicitly indicate one of the two routes. In some of the articles, the objectives or conclusions demonstrated that the study was directed at a particular disease. Of U articles, 44.4% were aimed at treating leprosy, 22.2% at acne, 11.1% at leprosy and acne, and 22.2% did not explicitly indicate this direction. All articles approved in the secondary selection were subjected to a quality assessment, in which all obtained the maximum score: 5 points. The following table summarizes the methodologies and results of the studies.

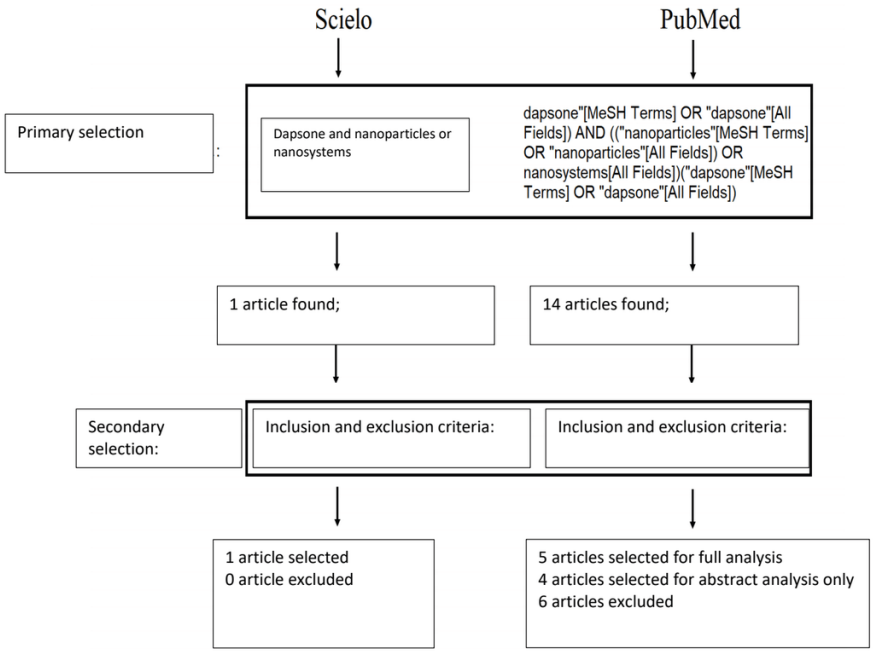

FIGURE 1: Selection process

Author	Title	Methodology	Results
SANTOS et al, 2012	Development and characterization of lipid nanoparticles intended for topical application of dapsone	In vitro study, dapsone encapsulation.	According to comprehensive analysis More controlled drug release with nanoparticles in the treatment of skin pathologies.
CHAVES et al, 2017	Nanosystems as modulators of intestinal dapsone and clofazimine delivery.	In vitro study, evaluating efficacy and cytotoxicity in intestinal cells.	According to abstract analysis Nanoparticles are promising platforms for drug delivery in the treatment of leprosy.
DESHKAR et al, 2018	Formulation and Optimization of Topical Solid Lipid Nanoparticles based Gel of Dapsone Using Design of Experiment.	In vitro dapsone release and ex vivo permeability through rat skin.	According to abstract analysis The gel developed is an alternative to conventional topical acne treatment.
VIEIRA et al, 2016	Design and statistical modeling of mannose-decorated dapsone- containing nanoparticles as a strategy of targeting intestinal M-cells.	In vitro study, optimized solid lipid nanoparticles. Designed to target intestinal microvilli cells (M cells).	According to comprehensive analysis The developed formulation has potential in the treatment of leprosy, due to its targeting.
CHAVES et al, 2017	pH-sensitive nanoparticles for improved oral delivery of dapsone: risk assessment, design, optimization and characterization.	In vitro release of dapsone through nanoparticles.	According to abstract analysis Important dapsone supply capacity, given the sensitivity to pH variations.
ELMOWAFY et al, 2019	Impact of nanostructured lipid carries on dapsone delivery to the skin: in vitro and in vivo studies.	In vitro dapsone release and ex vivo permeability.	According to abstract analysis It showed promising results of controlled release and retention, being promising in the treatment of acne.
BORGES et al, 2013	Nanoemulsion containing dapsone for topical administration: a study of in vitro release and epidermal permeation.	In vitro study of dapsone release and permeability.	According to comprehensive analysis The formulation is an option for the topical treatment of acne and leprosy.
MONTEIRO et al, 2012	Development and characterization of a new oral dapsone nanoemulsion system: permeability and in silico bioavailability studies.	In vitro release study and simulation of permeability in human skin through software.	According to comprehensive analysis Improving the bioavailability of dapsone for oral treatment of leprosy.
BELLO et al, 2015	Sodium montmorillonite/amine-containing drugs complexes: new inights on intercalated drugs arrangement into layered carrier material.	In vitro study of dapsone release using a clay called sodium montmorillonite.	According to comprehensive analysis The efficiency of intercalating amines (such as dapsone) with clay has been proven, improving the effectiveness of distribution systems.

TABLE 1: Methodology and results of the studies found

DISCUSSION

CHAVES et al, 2017, demonstrated that the method in which dapsone and chloralphazimine are combined in their respective nanosystems proved to be suitable for the two drugs to be delivered together and, thus, contribute to the improvement of the treatment of multibacillary leprosy [10].

DESHKAR et al, 2018, in turn, demonstrated that the gel that contained the association of dapsone with the nanoparticle, when compared with the value of the gel that contained only dapsone, presented a higher permeability value through rat skin. Thus, the data point to the potential of solid lipid nanoparticles (SLN) with dapsone in gel as an alternative to traditional topical therapy aimed at acne [11]. VIEIRA et al, 2016, similar to what was done in the article by CHAVES et al, 2017, based on the stability parameters, higher phase transition temperature and entrapment efficiency, the lipid cetyl palmitate proved to be promising. The Box-Behnken design was used, as in the article by DESHKAR et al, 2018. This is an experimental project that contributes to reducing the number of procedures, as well as the material used and time spent. The choice was made based on its benefits, among them, the possibility of avoiding very divergent combinations and for presenting a minimum number of three factors to obtain the different formulations. Thus, the data revealed that mannose coating optimized the internalization of drugs by M cells, with the use of mannosylated solid lipid nanoparticles (SLNs) loaded with dapsone being promising for the treatment of leprosy [12]. CHAVES et al, 2017, used the Box-Behnken design (similarly to the studies by DESHKAR et al, 2018 and VIEIRA et al, 2016) to perform the optimization of the nanoparticles. When comparing the intestinal interactions between free dapsone and EL100-DAP NPs through Caco-2 monolayers, similarly to the study by CHAVES et al, 2017, these interactions were amplified with the nanoparticles. Therefore, EL100-DAP NPs is a promising platform for oral leprosy therapy [13].

The article by ELMOWAFY et al, 2019 demonstrated that the formulation of cationic carriers containing dapsone increased the drug's permeation capacity through the skin, increasing the amount of drug retained in the skin. Thus, the use of this mechanism in the topical application of dapsone in a safe manner is promising [14].

The research demonstrated by the article by BORGES et al, 2013, which used High Performance Liquid Chromatography to measure the incorporation of dapsone, highlighted that formulations containing n-methylpyrrolidone, due to the high drug release associated with low epidermal permeability, were more promising for skin pathologies such as acne and dermatitis herpetiformis. On the other hand, nanoformulations with isopropyl myristate demonstrated high epidermal permeability and, therefore, would be ideal for pathologies such as leprosy that affect the skin more deeply [15].

In the article by MONTEIRO et al, 2012, as well as in the study by BORGES et al, 2013, High Performance Liquid Chromatography was used, but in the present article, unlike the one cited, the study was focused on oral administration. Regarding the bioavailability of the drug associated with the nanoemulsion systems, this parameter was reproducible with a constant concentration profile, which is relevant for drugs with serious adverse effects. Thus, the dapsone nanoemulsion system could be an alternative to antibacterial agents considered class II and adverse effects could be reduced [7].

BELLO et al, 2015, unlike the other authors of this review, intercalated, in addition to dapsone, eight other drugs containing amide with a clay called sodium montmorillonite

(Na-MMT). It was emphasized that the intercalated dapsone in a medium whose pH was ~ 2.0, its predominant forms were protonated. Therefore, these findings improve the construction of drug delivery systems [16].

Thus, it is noted that drug delivery systems consisting of nanosystems are promising for both topical and oral administration of dapsone. However, there is a need for studies to evaluate the impact of using this method on side effects in humans.

CONCLUSION

Based on all the articles analyzed, it is concluded that the use of nanoparticles containing dapsone is promising for improving the treatment of skin wounds caused by various skin pathologies, such as acne and leprosy. Although it has been seen that this use of nanotechnology has much to contribute in this regard, there is a lack of research data in human beings, which requires further studies using this technology in the clinical setting, with the appropriate safety standards.

CONFLICTS OF INTEREST

I declare that I have no conflicts of interest.

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