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Original Articles

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Anhydrous fluid serum as vehicle for drug delivery formulations: sterility test results for bacterial and fungal growth

Sérum anidro fluido como veículo para formulações de drug delivery: resultados do teste de esterilidade para crescimento bacteriano e fúngico

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ABSTRACT

Introduction: Topical delivery of drugs is essential in Dermatology. Due to the difficulty of permeation of the stratum corneum, drug delivery techniques have been highlighted. The use of non-specific formulations for this purpose makes raises the concern of possible adverse events and the microbiological safety of these formulations.

Objective: To assess bacterial and fungal growth in anhydrous fluid serum through simple sterility test.

Materials and methods: The simple sterility test was performed on an anhydrous serum containing lipophilic and hydrophilic active substances. This test was performed three months after the manufacture of the product.

Results: The formulation studied was approved in the simple sterility test conducted three months after the manufacture of the product, even without the use of preservatives in the formulation.

Discussion: The assessed formulation was approved in the sterility test possibly due to the fact that the serum vehicle has mineral and anhydrous origin, characteristics that do not favor the proliferation of microorganisms.

Conclusions: Although only the vehicle counting specific assets has been tested, the results of this study are promising and demonstrate the need for future studies broadly encompassing this subject.

Keywords: Drug Administration Routes; Brazilian Pharmacopeia; Skin Cream

RESUMO

Introdução: *A entrega tópica de medicamentos é essencial na Dermatologia. Devido à dificuldade de permeação do estrato córneo, as técnicas de drug delivery vêm recebendo destaque. O uso de formulações não específicas para este fim nos faz atentar para possíveis efeitos adversos e para a segurança microbiológica destas formulações.*

Objetivo: *Avaliar crescimento bacteriano e fúngico no sérum anidro fluido por meio do teste de esterilidade simples.*

Materiais e métodos: *O teste de esterilidade simples foi realizado em um sérum anidro contendo ativos lipofílicos e hidrofílicos. Este teste foi realizado três meses após a manufatura do produto.*

Resultados: *A formulação estudada foi aprovada no teste de esterilidade simples realizado três meses após a manufatura do produto, mesmo sem uso de conservantes na formulação.*

A formulação em estudo foi aprovada no teste de esterilidade possivelmente devido ao fato de o veículo sérum ser de origem mineral e anidra, características que não favorecem a proliferação de micro-organismos.

Conclusões: *Embora somente o veículo contando ativos específicos tenha sido testado, os resultados deste estudo são promissores e demonstram a necessidade de estudos futuros que englobem de forma mais ampla o assunto.*

Palavras-chave: *Vias de administração de medicamentos; Farmacopeia brasileira; Creme para a pele*

INTRODUCTION

Topical delivery of drugs in Dermatology is key to successful effectiveness. Medicines and active principles applied to the skin need to penetrate and reach a target structure. The epidermis' barrier function is maintained by the stratum corneum's double lipid layer, which is the main limiting factor for topical delivery of medications. [1] Drug penetration through untouched stratum corneum occurs by diffusion and via cutaneous appendages to a lesser extent. In addition, only lipophilic molecules smaller than 500da are able penetrate it, and only 1% to 5% of the substances applied to the skin are effectively absorbed and become bioavailable. [2] The drug delivery technique corresponds to using chemical, mechanical or physical methods aimed at optimizing the penetration of drugs. [2] The use of non-specific formulations for drug delivery can lead to undesirable effects, such as irritative and allergic dermatitis, foreign body granulomas, and cutaneous infection. [3]

Many cosmetic formulations available on the market contain chemical preservatives and additives in their formulation, making them unsuitable for use in drug delivery. Moreover, contamination of the formulations by microorganisms may occur, making them unsuitable for this purpose. [4]

MATERIALS AND METHODS

The growing demand for adequate formulations for drug delivery that can be applied immediately after medical dermatological procedures gave motivation the authors of the present paper to perform a sterility test on the anhydrous serum vehicle that is claimed to have properties that promote the safe delivery of the medication containing the following lipophilic and hydrophilic active principles: 6% hydroxyprolisilane® (increases synthesis of collagen and elastin, improves healing), 4% MDI Complex® (anti-inflammatory, reduces erythema and edema), 1% PBR® (re-epithelizing properties), 0.1% madecassoside (inhibits a series of inflammatory cytokines, has regenerative action and stimulates collagen I), and 4% panthenol (promotes healing and regeneration) Table 1-Farmatec® Pharmacy, Porto Alegre (RS), Brazil).

The formulation was tested for its ability to remain sterile – including after the vial had been opened – simulating what occurs when the product is applied by a physician at a practice and / or is used by the patient at home.

The simple sterility test was performed as described in the Brazilian Pharmacopoeia - 5th Edition (Farmacopeia Brasileira - 5ª edição, item 5.5.3.2 for sterile products) (Pharmacontrol - quality control laboratory, Porto Alegre RS, Brazil). The same test is applied for sterile injectable and topical formulations, having been performed three months after the sample was manufactured. In addition, the vial was opened and used during a three-month period with a view to emulate conditions of use at the physician's practice. The test employs two culture mediums, which are previously tested to ensure their capacity to promote bacterial growth by directly inoculating two units of the manufactured 4.5 ml batch (corresponding to 5% of the total batch): (i) liquid medium of 1-thioglycollate for aerobic and anaerobic bacteria and (ii) fluid soybean-casein medium for aerobic bacteria, yeasts and fungi. The anhydrous serum – the substance studied in the present paper – remained incubated for a period of 14 days. After the first tested vial passes the sterility test, the batch's sterility is confirmed by incubating all manufactured vials in the culture mediums for 14 days, under the conditions described above. No microbial growth should occur. No active microbial growth should take place, and its occurrence corresponds to failure in passing the sterility test.

RESULTS

The sterility test confirmed the absence of microbiological contamination for bacteria, fungi and yeasts (Figure 1). Therefore, the studied formulation was approved in the sterility test, even without the presence of preservatives and three months after having been manufactured.

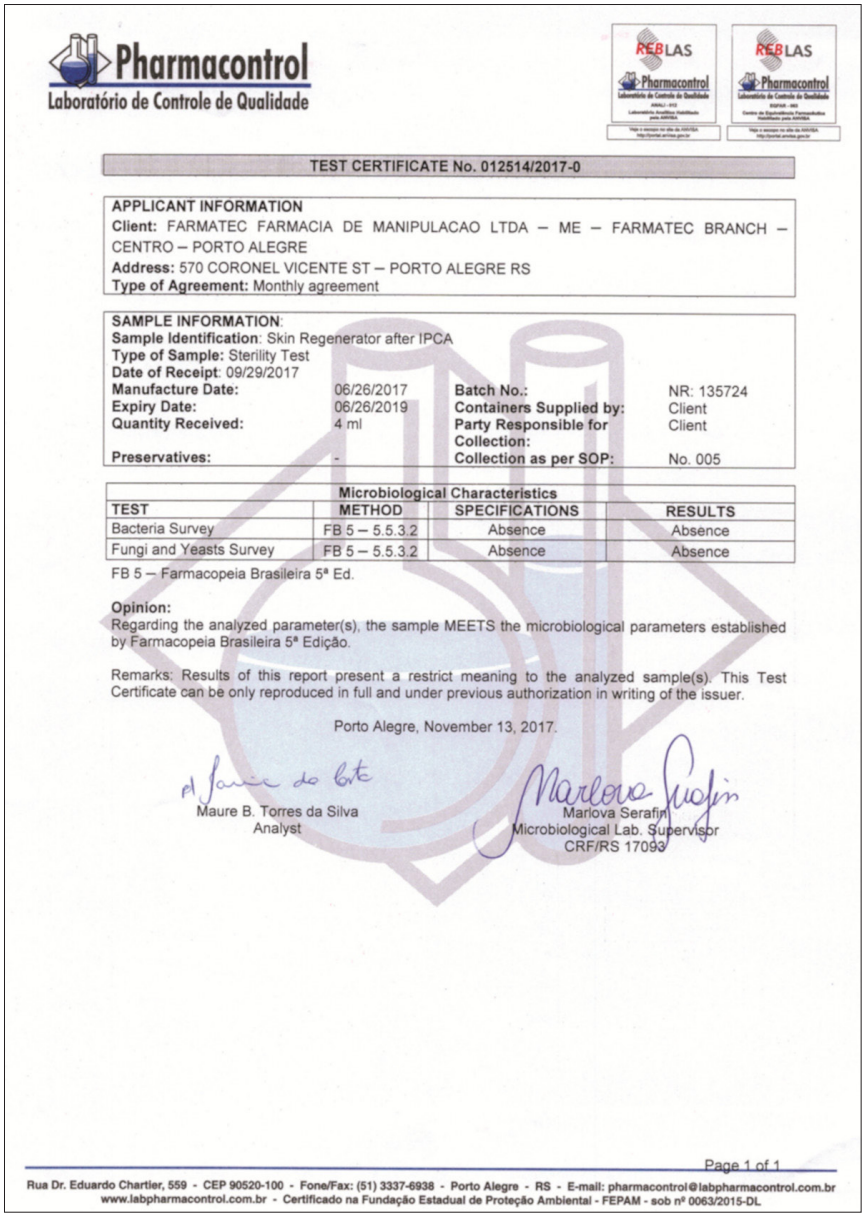
DISCUSSION

Choosing the right vehicle for drug delivery is crucial: creams, lotions, gels, and some serums are not adequate due to their high viscosity, which decreases transepidermal / transdermal delivery of active ingredients. [4] The ideal formulation for drug delivery should be devoid of and repel water, as well as being mineral in order to provide a barrier against transepidermal water loss (TEWL). In addition, it should favor healing and dermal permeation of hydrophilic and lipophilic substances. Furthermore, the formulation's pH should resemble that of the skin, give that a higher pH may lead to skin irritation and rupture of the cutaneous "acid mantle". [5] The anhydrous vehicle does not cause burning sensation and does not require the addition of preservatives and chemicals, theoretically offering microbiological safety related to bacterial and fungal proliferation. Moreover, the anhydrous serum promotes occlusion. [6] It is worth to note that, regardless of the drug delivery technique chosen to optimize drug permeation, occlusion is beneficial to increase the efficacy of the method, since it delays the recovery of the cutaneous barrier, leaving the stratum corneum permeable for longer. [7]

The authors believe that the studied formulation's successful outcome in the sterility test is linked to the fact that the vehicle is of mineral and anhydrous origin, which are features that do not allow the proliferation of microorganisms, which in turn favor the hypothesis that the formulation is safe for drug delivery, even if used immediately after ablative procedures.

Table 1: Baseline characteristics of the sample

Active ingredient	Active ingredient
Hydroxyprolisilane®	Hydrophilic
MDI Complex®	Hydrophilic
PBR®	Lipophilic
Madecassoside	Lipophilic
Panthenol	Hydrophilic



Pharmacontrol
Laboratório de Controle de Qualidade

REBLAS Pharmacontrol

TEST CERTIFICATE No. 012514/2017-0

APPLICANT INFORMATION
Client: FARMATEC FARMACIA DE MANIPULACAO LTDA – ME – FARMATEC BRANCH – CENTRO – PORTO ALEGRE
Address: 570 CORONEL VICENTE ST – PORTO ALEGRE RS
Type of Agreement: Monthly agreement

SAMPLE INFORMATION:
Sample Identification: Skin Regenerator after IPCA
Type of Sample: Sterility Test
Date of Receipt: 09/29/2017

Manufacture Date:	06/26/2017	**Batch No.:**	NR: 135724
Expiry Date:	06/26/2019	**Containers Supplied by:**	Client
Quantity Received:	4 ml	**Party Responsible for Collection:**	Client
Preservatives:	-	**Collection as per SOP:**	No. 005

Microbiological Characteristics			
TEST	**METHOD**	**SPECIFICATIONS**	**RESULTS**
Bacteria Survey	FB 5 – 5.5.3.2	Absence	Absence
Fungi and Yeasts Survey	FB 5 – 5.5.3.2	Absence	Absence

FB 5 – Farmacopeia Brasileira 5ª Ed.

Opinion:
Regarding the analyzed parameter(s), the sample MEETS the microbiological parameters established by Farmacopeia Brasileira 5ª Edição.

Remarks: Results of this report present a restrict meaning to the analyzed sample(s). This Test Certificate can be only reproduced in full and under previous authorization in writing of the issuer.

Porto Alegre, November 13, 2017.

Maure B. Torres da Silva
Analyst

Marlova Serafin
Microbiological Lab. Supervisor
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www.labpharmacontrol.com.br - Certificado na Fundação Estadual de Proteção Ambiental - FEPAM - sob nº 0063/2015-DL

Figure 1:
Simple sterility test results: the formulation was approved in the simple sterility test performed three months after the product had been manufactured

CONCLUSION

Choosing the right vehicle is crucial regardless of the method being used to promote drug delivery. For this reason and aiming at ensuring procedural safety, studies on specific vehicles for drug delivery are of great interest. Although only the anhydrous serum vehicle containing hydroxyprolisilane®, MDI Complex®, PBR®, madecassoside and panthenol has been tested, the outcomes observed in the present report are promising and can serve as a foundation for more comprehensive studies on the subject in the future.

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Approval of the final version of the manuscript; study design and planning; manuscript preparation and Drafting; data collection, analysis and interpretation; research guidance; intellectual participation in propaedeutic and / or therapeutic management of the cases studied; critical review of the literature.

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