IJPSR (2020), Volume 11, Issue 7 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 29 July 2019; received in revised form, 01 September 2019; accepted, 02 March 2020; published 01 July 2020

EFFECTIVENESS OF PHENYLPROPANOID DERIVATIVES AS PRESERVATIVE IN ALUMINIUM HYDROXIDE GEL-USP

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Keywords:

Phenylpropanoid, Ester, Amide, Preservative, Pharmaceutical formulation, Log CFU/ml

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ABSTRACT: A growing concern of microbial resistance and potential risks associated with existing synthetic preservatives have put industries and researchers under immense pressure to develop newer and safer alternatives based on moieties obtained from natural sources. The purpose of this study was to evaluate the preservative effect of the selected derivatives of naturally occurring phenylpropanoids. Aluminum Hydroxide Gel-USP was employed as a pharmaceutical formulation which has been challenged with *Staphylococcus aureus* MTCC 737, *Escherichia coli* MTCC 443, *Pseudomonas aeruginosa* MTCC 1688, *Aspergillus niger* MTCC 282 and *Candida albicans* MTCC 227 as per USP 2004. The selected ester and anilide derivatives demonstrated good antimicrobial potential against all the challenged microorganisms. The preservative efficacy results were comparable to that of standard preservatives, methyl, and propyl-parabens. The benzoin caffeate (CE48) derivative was found to be superior preservative amongst the other derivatives and as well as from both the standards mainly against *S. aureus*, *A. niger* and *C. albicans*. Thus, natural moiety based antimicrobial derivatives has the potential to be chosen as a preservative in pharmaceutical formulations over the existing synthetic preservatives.

INTRODUCTION: Pharmaceutical formulations, especially products with a high degree of water content face a greater risk of microbial contamination which leads to loss of therapeutic properties of the product and affects consumer safety. To reduce the spoilage of pharmaceutical preparations from microbial bio-burden mainly pioneered during manufacturing, storage or repetitive use of multi-dose containers, the preservatives with antimicrobial properties are incorporated in the formulations [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(7).3197-03

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(7).3197-03

Preservatives are chiefly effective in preventing bacterial proliferation, inhibiting yeast and controlling mold growth [1, 2]. But, in many cases emergence of microorganisms resistance to existing chemical preservatives, for instance, sorbic acid, benzoic acid, triclosan, paraben, methyl-paraben, propyl-paraben, glutaraldehyde, formaldehyde, imidazolidinyl urea, chlorhexidine, dimethyl dimethylol hydantoin, and quaternary ammoniums compounds has been well reported [3, 4].

Even though the synthetic preservatives may have several advantages, but some of them are associated with adverse allergic reactions and other life-threatening health hazards. Sulphur dioxide and sulphite may cause loss of vitamin B1. These cause various allergic reactions such as asthma, nausea, headaches, eczema, diarrhea, and skin or stomach infection, especially in sulphite hypersensitive

individuals [5]. Parabens interferes with estrogen metabolism (inhibits 17β-HSD1 and 17β-HSD2), and cause skin reactions including, rash, contact dermatitis, urticaria, *etc*. [2, 6] The use of benzoic acid and benzoates preservatives has been reviewed which may cause adverse side effects such as non-immunological contact urticaria, convulsions, asthma, and metabolic acidosis, *etc*. [7]

Official methods employed for assessment of the effectiveness of the preservative systems have been well described in different pharmacopeias such as British Pharmacopeia and the United States Pharmacopeia (USP). Preservative efficacy test, also known as preservative challenge test or antimicrobial effectiveness test, is a method consisting of artificial inoculation of the product with the representative microorganisms (Gram-positive and negative bacteria, mold, and yeast) to determine the loss of their viability [8]. Phenolic compounds are plant secondary metabolites consisting of two classes (i) hydroxybenzoic acid and (ii) hydroxycinnamic acids also known as phenylpropanoids as it contains C_6-C_3 carbon skeleton [9]. Phenolic compounds have been well cited in the literature for their preservative efficiency such as gallic acid, anacardic acid, ferulic acid, chlorogenic acid [8, 10-12]. Phenylpropanids such as ferulic, caffeic, sinapic and p-coumaric acids and their derivatives have a wide array of biological activities such as antimicrobial, antioxidant, anti-inflammatory, anti-diabetic, anticancer, and neuroprotection, *etc*. [13-19]

A growing concern of microbial resistance and potential risks associated with currently used chemical/synthetic preservatives have put industries and researchers under immense pressure to search for new and safe alternatives based on natural moieties such as phenylpropanoids. Therefore, the present work was designed to investigate the preservative effectiveness of the ester, amide and anilide derivatives of phenylpropanoids using aluminum hydroxide gel, which have been challenged with five representative microorganisms (one gram-positive bacteria, two gram-negative bacteria, yeast, and mold) and their efficacy was compared with methyl and propyl-paraben, used as standard preservatives [20, 21].

MATERIALS AND METHODS:

Composition and Preparation of Test Formulation: For estimation of preservative effectiveness, aluminum hydroxide gel-USP 2004 (AHG) was employed as the pharmaceutical preparation [11, 20-21]. All ingredients used in the preparation of test formulation were purchased from commercial sources and were of pharmaceutical grade.

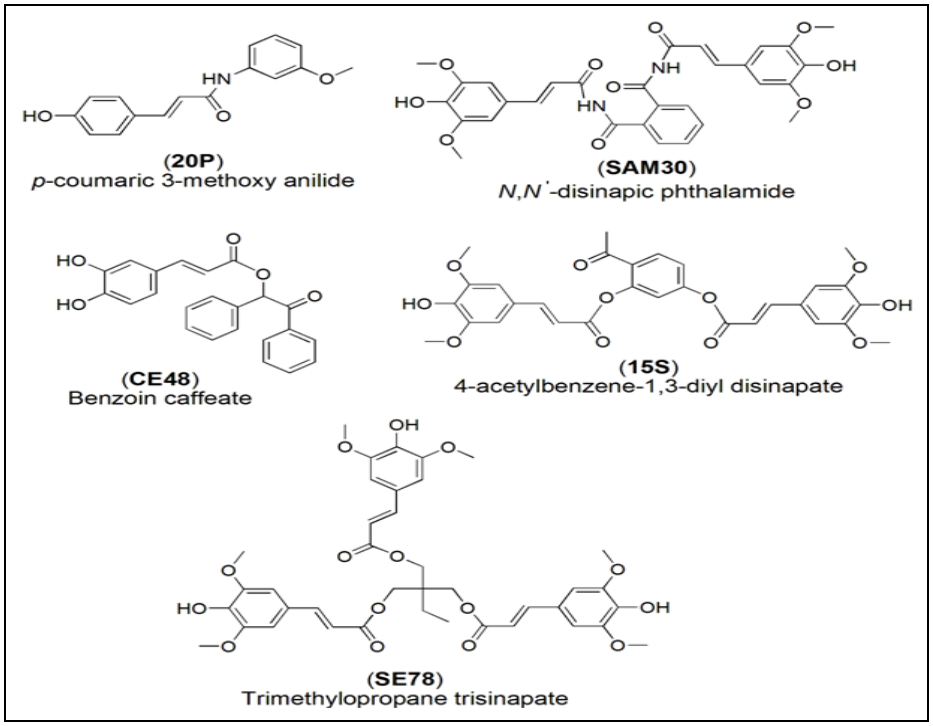

FIG. 1: STRUCTURES OF SELECTED PHENYLPROPANOID DERIVATIVES

For the preparation of AHG, aluminum hydroxide gel (36 g) and mannitol (7 g) were pulverized with water (50 ml) in a mortar. Methyl-paraben (0.2 g), propyl-paraben (0.02 g), saccharin (0.05 g) and peppermint oil (0.005 ml) were dissolved in 1ml alcohol. Both the above-mentioned mixtures were mixed well and by using purified water q.s. the final volume of the formulation was made up to 100 ml. The formulation was autoclaved for 15 min at 120 °C.

For evaluation of preservative efficacy, methyl and propyl-paraben from the above formulation were replaced by the preservatives given in **Fig. 1**. The equimolar quantity of preservatives (phenyl-propanoid derivatives) was calculated using methyl-paraben (0.0013 mol) as a reference and then inoculated into AHG [21].

Challenge Microorganisms: The microorganisms used in this study include *Staphylococcus aureus* MTCC 737, *Escherichia coli* MTCC 443, *Pseudomonas aeruginosa* MTCC 1688, *Aspergillus niger* MTCC 282 and *Candida albicans* MTCC 227. All these strains were procured from Microbial Type Culture Collection (MTCC), Institute of Microbial Technology, India.

Inocula Preparation: The bacteria were grown on nutrient agar (Himedia, Mumbai) at 37 °C for 24 h, while yeast and mold were cultured on sabouraud dextrose agar (Himedia, Mumbai) for 48 h at 37 °C and 7 days at 25 °C, respectively.

After the incubation suspensions of each test microorganisms were harvested and diluted in sterile 0.9% NaCl solution to yield a microbial count of 10^4 CFU/ml [21].

Preservative Effectiveness Test Protocol: The preservative effectiveness of AHG in the presence and absence of preservative was challenged by inoculating the preparation with microbial cell suspension (10^4 CFU/ml). To ensure the homogeneous distribution of microorganism, the inoculated formulation was well agitated prior to its incubation. After inoculation, AHG was incubated at room temperature for four consecutive weeks (28 days) and samples were collected at each one-week interval that is 0, 7, 14, 21 and 28 days. The viable count of microorganisms was performed on nutrient agar (bacteria) and sabouraud dextrose agar (fungi) plates [11, 21]. Each experiment was done in triplicate, and further log values of CFU/ml of AHG were determined and compared with the criteria of acceptance for preservatives prescribed by USP.

RESULTS AND DISCUSSION: The pharmaceutical formulation used in present work for preservative efficacy testing was AHG (an official antacid preparation), which was preferred owing to the fact that pharmaceutical formulations especially antacid preparations are very difficult to preserve as compared to other simple aqueous formulations [22]. Results of preservative effectiveness in AHG artificially contaminated with representative microorganisms are summarized in **Table 2-6**. The log values of CFU/ml of the pharmaceutical formulation were represented as mean ± standard deviation (SD) and further compared as per the rule of USP 2004 for acceptance of preservative effectiveness/ ineffectiveness. In accordance with the USP 2004 protocol for antacid prepared with an aqueous base, preservative effectiveness is considered achieved if no increment from an initial calculated viable count of representative microorganisms (*S. aureus*, *E. coli*, *P. aeruginosa*, *A. niger*, and *C. albicans*) at 14^{th} day and 28^{th} day was observed. No increment is described as $\log_{10}$ value not more than 0.5 higher than the previously observed value.

Preservative Effectiveness in Aluminium Hydroxide Gel Challenged with *S. aureus:* The results obtained for the preservative effectiveness tested in AHG with *S. aureus* are represented in **Table 2**. All the selected preservatives and as well as standard preservatives fulfilled the USP criteria when tested on the 14^{th} day from the initial inoculation *i.e.*, ≥ 0.5 log reduction observed relative to the initial count of *S. aureus* in AHG. Except for derivative SAM30 (*N, N'* disinapic phthalamide) all other preservatives were found to be effective on the 28^{th} day as no increment in log reduction falls within the limit recommended by USP and thus passed the preservative efficacy test. SAM30 was effective on the 14^{th} day but did not meet the USP requirements on the 28^{th} day (change of 0.73 log CFU/ml from 14^{th} to 28^{th} day) and hence fails the preservative efficacy test. Overall results of preservative effectiveness against *S. aureus* was comparable to standards (methyl and propyl-

paraben), in fact, CE48 (benzoin caffeate), 20P (*p*-coumaric 3-methoxy anilide) and SE78 (trimethyl-olpropane trisinapate) were found to be more effective than both the standards tested.

TABLE 2: PRESERVATIVE EFFECTIVENESS OF SELECTED PRESERVATIVES IN ALUMINIUM HYDROXIDE GEL CHECKED WITH A CHALLENGE OF *S. AUREUS*

Preservative added	Log_{10} CFU/ml				
	0h	7th day	14th day	21st day	28th day
20P	4.623 ± 0.010	4.014 ± 0.024	4.102 ± 0.016	4.054 ± 0.022	4.014 ± 0.024
SAM30	4.735 ± 0.005	4.102 ± 0.020	3.864 ± 0.027	4.452 ± 0.009	4.591 ± 0.011
CE48	4.509 ± 0.016	3.999 ± 0.044	3.920 ± 0.024	3.954 ± 0.000	3.884 ± 0.033
15S	4.509 ± 0.016	4.286 ± 0.013	4.301 ± 0.000	4.271 ± 0.014	4.609 ± 0.012
SE78	4.681 ± 0.009	4.000 ± 0.000	4.263 ± 0.011	3.954 ± 0.000	3.816 ± 0.105
Methyl-paraben	4.684 ± 0.005	4.308 ± 0.012	4.580 ± 0.009	4.308 ± 0.012	4.452 ± 0.023
Propyl-paraben	4.719 ± 0.010	4.540 ± 0.007	4.301 ± 0.018	4.195 ± 0.016	4.286 ± 0.013

Results are represented as mean ± SD, n=3

Preservative Effectiveness in Aluminium Hydroxide Gel Challenged with *E. coli:* Results of the preservative effectiveness evaluated in AHG challenged with *E. coli* are summarized in **Table 3**. As shown by the results the ester, amide, and anilide derivatives of phenylpropanoid falls under the acceptable range of preservative effectiveness testing as per USP 2004. Preservatives' effectiveness was comparable to both methyl and propyl-paraben, used as a preservative standard against *E. coli*.

TABLE 3: PRESERVATIVE EFFECTIVENESS OF SELECTED PRESERVATIVES IN ALUMINIUM HYDROXIDE GEL CHECKED WITH A CHALLENGE OF *E. COLI*

Preservative added	Log_{10} CFU/ml				
	0h	7th day	14th day	21st day	28th day
20P	4.616 ± 0.006	4.246 ± 0.115	4.294 ± 0.011	4.194 ± 0.031	4.000 ± 0.000
SAM30	4.650 ± 0.006	4.467 ± 0.144	4.462 ± 0.012	4.415 ± 0.017	4.572 ± 0.018
CE48	4.431 ± 0.016	4.113 ± 0.033	4.386 ± 0.008	4.335 ± 0.031	4.535 ± 0.027
15S	4.457 ± 0.009	4.272 ± 0.247	4.301 ± 0.000	4.194 ± 0.031	4.452± 0.018
SE78	4.556 ± 0.012	4.091 ± 0.020	4.286 ± 0.011	4.202 ± 0.046	4.166 ± 0.017
Methyl-paraben	4.452 ± 0.009	4.335 ± 0.023	4.176 ± 0.000	4.301 ± 0.022	4.263 ± 0.014
Propyl-paraben	4.293 ± 0.025	4.236 ± 0.056	4.156 ± 0.014	4.040 ± 0.040	4.028 ± 0.024

Results are represented as mean ± SD, n=3

Preservative Effectiveness in Aluminium Hydroxide Gel Challenged with *P. aeruginosa:* Results of the preservative effectiveness determined in AHG inoculated with *P. aeruginosa* are given in **Table 4**. According to the log CFU/ml of pharmaceutical formulation tested against *P. aeruginosa* all the selected preservatives satisfied the criteria of preservative effectiveness in AHG tested on 14th and 28th day given by USP 2004. Overall results suggested that preservative SE78 was superior to both the reference preservatives in terms of preservative antimicrobial effectiveness in AHG challenged with *P. aeruginosa*, while 20P was found to be more effective than propyl-paraben.

TABLE 4: PRESERVATIVE EFFECTIVENESS OF SELECTED PRESERVATIVES IN ALUMINIUM HYDROXIDE GEL CHECKED WITH A CHALLENGE OF *P. AERUGINOSA*

Preservative added	Log_{10} CFU/ml				
	0h	7th day	14th day	21st day	28th day
20P	4.647 ± 0.006	4.066 ± 0.042	4.176 ± 0.000	4.146 ± 0.000	4.067 ± 0.022
SAM30	4.572 ± 0.014	4.102 ± 0.020	4.175 ± 0.024	4.436 ± 0.019	4.531 ± 0.013
CE48	4.472 ± 0.009	4.195 ± 0.016	4.294 ± 0.011	4.175 ± 0.029	4.000 ± 0.000
15S	4.415 ± 0.017	4.011 ± 0.063	4.361 ± 0.015	4.113 ± 0.033	4.462 ± 0.015
SE78	4.315 ± 0.024	3.952 ± 0.0485	3.969 ± 0.022	4.040 ± 0.040	3.985 ± 0.026
Methyl-paraben	4.587 ± 0.007	4.144 ± 0.052	4.185 ± 0.013	4.286 ± 0.013	4.176 ± 0.000
Propyl-paraben	4.687 ± 0.005	4.089 ± 0.053	4.255 ± 0.020	4.271 ± 0.014	4.175 ± 0.029

Results are represented as mean ± SD, n=3

Preservative Effectiveness in Aluminium Hydroxide Gel Challenged with *A. niger*: Results attained for the preservative effectiveness investigated in AHG contaminated with A. *niger* are mentioned in **Table 5**. Derivatives SAM30 and 15S did not comply with the USP limits on the 28th day of the experiment as the change in log CFU/ml is more than 0.5 log units from the previously measured value. Hence, both SAM30 and 15S fail the preservative efficacy test. All other derivatives (20P, CE48 and SE78) and as well as standards (methyl and propyl-paraben) were found to be active on both 14th and 28th day of the experiment, as the change/increment in log values were found to be in harmony with limit required for passing the preservative effectiveness test. Thus, except for SAM30 and 15S, all other tested preservatives qualify the preservative efficacy test. Preservative 20P was found to be more efficient than methyl-paraben and CE48 more effective than propyl-paraben in AHG challenged with *A. niger*.

TABLE 5: PRESERVATIVE EFFECTIVENESS OF SELECTED PRESERVATIVES IN ALUMINIUM HYDROXIDE GEL CHECKED WITH A CHALLENGE OF A. *NIGER*

Preservative added	Log_{10} CFU/ml				
	0h	7th day	14th day	21st day	28th day
20P	4.472 ± 0.023	4.336 ± 0.011	4.247 ± 0.012	4.166 ± 0.017	4.255 ± 0.024
SAM30	4.540 ± 0.007	3.593 ± 0.111	4.195 ± 0.013	4.014 ± 0.024	4.696 ± 0.005
CE48	4.672 ± 0.009	4.078 ± 0.036	4.078 ± 0.030	4.091 ± 0.020	3.694 ± 0.601
15S	4.595 ± 0.006	4.135 ± 0.019	4.014 ± 0.020	4.054 ± 0.022	4.576 ± 0.007
SE78	4.684 ± 0.014	4.124 ± 0.039	3.952 ± 0.040	4.079 ± 0.000	4.041 ± 0.000
Methyl-paraben	4.640 ± 0.015	4.501 ± 0.008	4.386 ± 0.008	4.271 ± 0.026	4.477 ± 0.014
Propyl-paraben	4.681 ± 0.009	4.467 ± 0.009	4.431 ± 0.013	4.278 ± 0.023	4.230 ± 0.026

Results are represented as mean ± SD, n=3

Preservative Effectiveness in Aluminium Hydroxide Gel Challenged with *C. albicans*: Results of the preservative effectiveness examined in AHG inoculated with *C. albicans* are provided in **Table 6**. The derivative SAM30 did not fall within the required USP limits on the 28th day of the experiment as the change in log CFU/ml observed was more than 0.5 log units from the previously measured value hence, fail the preservative efficacy test. All other derivatives (20P, CE48, 15S, and SE78) and as well as standards (methyl and propyl-paraben) were found to be effective on both the 14th and 28th days of the experiment, as the increment in the log values observed was less than 0.5 log units. Thus, met the USP requirements and passes the preservative efficacy test. Based on overall results of preservative efficacy in AHG contaminated with *C. albicans* two derivatives that are CE48 and 20P exhibited better results than both the standard preservatives tested, while SE78 was found to be more active than propyl-paraben.

TABLE 6: PRESERVATIVE EFFECTIVENESS OF SELECTED PRESERVATIVES IN ALUMINIUM HYDROXIDE GEL CHECKED WITH A CHALLENGE OF *C. ALBICANS*

Preservative added	Log_{10} CFU/ml				
	0h	7th day	14th day	21st day	28th day
20P	4.505 ± 0.014	4.437 ± 0.009	4.286 ± 0.011	4.194 ± 0.031	4.125 ± 0.019
SAM30	4.681 ± 0.009	4.113 ± 0.033	4.175 ± 0.0237	4.101 ± 0.039	4.613 ± 0.011
CE48	4.185 ± 0.016	3.665 ± 0.578	3.693 ± 0.491	4.040 ± 0.040	3.985 ± 0.026
15S	4.640 ± 0.011	4.040 ± 0.040	4.145 ± 0.025	4.135 ± 0.019	4.591 ± 0.011
SE78	4.656 ± 0.015	3.985 ± 0.026	3.985 ± 0.025	4.067 ± 0.022	3.983 ± 0.050
Methyl-paraben	4.637 ± 0.015	4.452 ± 0.023	4.457 ± 0.014	4.255 ± 0.024	4.486 ± 0.016
Propyl-paraben	4.690 ± 0.009	4.481 ± 0.030	4.425 ± 0.021	4.212 ± 0.040	4.238 ± 0.030

Results are represented as mean ± SD, n=3

The ester derivative of phenylpropanoid CE48 was found to be more effective against *S. aureus*, *A. niger*, and *C. albicans*. While another ester derivative SE78 was found to be more active against *P. aeruginosa*. Although, SAM30 an amide derivative of phenylpropanoid was effective against bacterial strains studied but were found to be inactive against both *A. niger* and *C. albicans*. Similar results were reported in which some of the amide derivatives of ferulic and p-coumaric acid

was less effective against *A. niger* and *C. albicans* [11, 21]. Moreover, anilide and ester derivatives of phenylpropanoid were more effective than both the standards especially against *A. niger* and *C. albicans.*

The preservative effectiveness of the derivatives 20P, CE48, and SE78 against all the representative microorganisms were found to be in accordance with the prescribed USP guidelines. Thus, Based on overall findings it is suggested that the above-mentioned derivatives have the potential to be used as a preservative in pharmaceutical products especially in formulations related to category 4 of USP, 2004.

CONCLUSION: In the present study, phenyl-propanoids derivatives selected for preservative effectiveness testing mainly anilide and ester derivatives (p-coumaric 3-methoxy anilide, benzoin caffeate, and trimethylolpropane trisinapate) have displayed excellent activity against all five challenged microorganisms. The benzoin caffeate (CE48) derivative was found to be superior preservative among the other derivatives and as well as from both the standard mainly against *S. aureus*, *A. niger* and *C. albicans*. Thus, over finding suggests that natural moiety based antimicrobial derivatives have the potential to be chosen as a promising preservative in pharma-ceutical products, especially in formulations related to category 4 of USP 2004.

ACKNOWLEDGEMENT: Nil.

CONFLICTS OF INTEREST: The author declares no conflict of interest.

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How to cite this article:
Neelam, Sharma KK, Lather A and Khatkar A: Effectiveness of phenylpropanoid derivatives as preservative in aluminium hydroxide gel-USP. Int J Pharm Sci & Res 2020; 11(7): 3197-03. doi: 10.13040/IJPSR.0975-8232.11(7).3197-03.