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A REVIEW ON: PRESERVATIVES AND THEIR USAGE TO BE TRANSPERENTLY RESTRAINED IN PHARMACEUTICAL PREPARATIONS

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ABSTRACT

Pharmacists have been looking for a breakthrough in preservatives preparation for several decades but they have attained a effective results in late 1990's only. Preservatives are substances that commonly added to various foods and pharmaceutical products in order to prolong their shelf life. The addition of preservatives to such products, especially to those that have higher water content, is essential for avoiding alteration and degradation by microorganisms during storage. Preservatives prolong the shelf-life of pharmaceutical products by preventing their spoilage. Anti-oxidants such as butylated hydroxy toluene (BHT), butylated hydroxy anisole (BHA), and propyl gallate slow or stop the breakdown of fats and oils. However their excessive usage can also lead to carcinogenic properties in whoever administered them as additives. Most of pharmaceutical industries are using preservatives more than safe concentration to increase shelf life of the drug. So, there is a need for transparency in concentration of additives used in pharmaceutical preparations. Following transparency will not allow companies to go beyond safe concentration and also patients administering them can restrain themselves to safer concentration intake.

KEYWORDS: Butylated hydroxy toluene (BHT), butylated hydroxy anisole (BHA).

INTRODUCTION

A preservative is a natural or synthetic chemical that is added to products such as foods, pharmaceuticals, paints, biological samples, wood, etc. to prevent decomposition by microbial growth or by undesirable chemical changes.

The preservatives used during earlier times were vinegar, salt and sugar. Preservation methods during modern periods involve sterilization including irradiation, filtration and addition of preservatives. Most of these preservatives are man-made chemicals. Many of the synthetic food and cosmetic additives are considered to be safe, but some of them were found to be carcinogenic and toxic and it is better to limit their use in pharmaceutical preparations to safer concentrations.

PRESERVATIVE CAPACITY: The cumulative level of contamination that a preserved formulation can tolerate before becoming so depleted as to become ineffective.

IDEAL PROPERTIES

- It should not be toxic.
- It should not be irritant.
- It should be cost effective.
- It should be physically and chemically stable.
- It should be compatible with other ingredients used in formulation.
- It should act as preservative in small concentration i.e. it must be potent.
- It should maintain activity throughout product manufacturing, shelf life and usage.
- It should be act as good antimicrobial agent and should exert wide spectrum of activity.[1]

CLASSIFICATION OF PRESERVATIVES

BASED ON MECHANISM OF ACTION

- **Antioxidants**
- **Antimicrobial agents**
- **Chelating agents**

Antioxidants

Antioxidants are used in the pharmaceutical products to prevent deterioration from oxidation. Antioxidants are classified into 3 groups.

TRUE ANTIOXIDANTS or ANTIOXYGEN

Known to inhibit oxidation by reacting with free radicals blocking the chain reaction.

Eg: alkygallates butylated hydroxyanisol, butylated hydroxytoluene, nordihydroguaiaretic acid and the tocopherols.

REDUCING AGENTS

These agents have lower redox potentials than the drug or adjuvant which they are intended to protect, and are therefore, more readily oxidized. Reducing agents may act also by reacting with free radicals.

Examples are ascorbic acid, the potassium and sodium salts of sulphurous acid.

ANTIOXIDANT SYNERGISTS

Which usually have little antioxidant effect themselves but probably enhance the action of antioxidants in the first group by reacting with heavy metal ions which catalyze oxidation.
Eg: citric acid, editic acid and its salts, lecithin and tartaric acid.[2]

Antimicrobial preservatives

These are preparations used to kill or to inhibit the growth of micro-organisms inadvertently introduced during manufacture or use. They are used in sterile preparations such as eye drops and multi dose injections to maintain sterility during use.

❖ Antimicrobial preservatives are classified into two main subgroups:

- Anti-fungal preservatives

➢ Anti-fungal preservatives include compounds such as benzoic and ascorbic acids and their salts, and phenolic compounds such as methyl, ethyl, propyl and butyl p-hydroxybenzoate (parabens).

- Anti-bacterial preservatives.

➢ Antibacterial preservatives include compounds such as quaternary ammonium salts, alcohols, phenols and mercurial's.

Chelating agents

The agents which form the complex with pharmaceutical ingredient and prevent the degradation of pharmaceutical formulation.
Eg. Disodium ethylenediaminetetraacetic acid (EDTA), Polyphosphates and Citric acid.

CLASSIFICATION BASED ON SOURCE

1. Natural Preservatives

These preservatives are obtained from natural sources like plants, animals, mineral sources etc.
Eg. Neem oil, Salt, Lemon, Honey.

2. Artificial Preservatives

These preservative are man made by chemical synthesis active against by various micro-organisms in small concentration.

Eg. Benzoates, Sodium benzoate, Sorbates, propionets, nitrites.[3]

PRESERVATIVES USED IN VARIOUS FORMULATIONS

Preservatives commonly found in most Oral pharmaceutical products (such as tablets, capsules, suspensions and syrups), Dental products (such as toothpaste, mouthwash and gargles), Dermal products (mostly cosmetic personal care products, such as cream, lotion, ointment, soap, bath gel, hair spray, shampoo and conditioner), Nasal products (such as nasal drops, sprays and aerosols) Parenteral products including vaccines, Rectal products (such as suppositories and enema) and Ophthalmic products (such as eye drops, ointments and contact lens solutions).

Oral pharmaceutical products

Preservatives used: Methyl, ethyl, propyl Parabens and their combinations; Sodium benzoate; Benzoic acid; Calcium lactate; Sorbates of calcium,sodium and potassium; Sorbic acid.[4]

Dental pharmaceutical products

Preservatives used: Sodium benzoate, Benzoic acid, Potassium sorbate, Sodium phosphate, Triclosan, Cetylpyridinium, Methyl and ethyl parabens.[5]

Dermal pharmaceutical products

Preservatives used: Benzalkonium chloride, EDTA, Benzoic acid, Thiomersal, Imidurea, Chlorhexidine, Chlorocresol, Phenyl salicylate.[6]

Ophthalmic pharmaceutical products

Preservatives used: Benzalkonium chloride, EDTA, Benzoic acid, Thiomersal, Imidurea, Chlorhexidine, Polyaminopropylbiguanide, Sodium perborate, Boric acid.[7]

Nasal pharmaceutical products

Preservatives used; Benzalkonium chloride, EDTA, Phenylcarbinol, Potassium sorbate, Chlorobutanol.[8]

Rectal pharmaceutical products

Preservatives used: Benzyl alcohol, benzoic acid, sodium benzoate, methyl hydroxybenzoate, chlorhexidine gluconate

Parental pharmaceutical products

Preservatives used: Methyl, ethyl, propyl Parabens and their combinations; Benzyl alcohol; Cholorobutanol, Thiomersal, Formaldehyde.[9]

CODES ASSIGNED BY INS FOR PRESERVATIVES

The International Numbering System for Food Additives (INS) has been prepared by the Codex Committee on Food Additives and Contaminants (CCFAC) for the purpose of providing an agreed international numerical system for identifying food additives in ingredient lists as an alternative to the declaration of the specific name which is often lengthy and a complex chemical structure.

The INS in numerical order (Section 3) is set out in three columns giving the identification number, the name of the additive and the technological functions. The identification number for labelling purposes usually consists of three or four digits such as 100 for Curcumins and 1001 for Chlorine salts and esters.

No.	Name of Additive	Technical Function(s)
200	Sorbic Acid	Preservative
201	Sodium Sorbate	Preservative
202	Potassium Sorbate	Preservative
203	Calcium Sorbate	Preservative
209	Heptyl p-Hydroxybenzoate	Preservative
210	Benzoic Acid	Preservative
211	Sodium Benzoate	Preservative
212	Potassium Benzoate	Preservative
213	Calcium Benzoate	Preservative
214	Ethyl p-Hydroxybenzoate	Preservative
215	Sodium Ethyl p-Hydroxybenzoate	Preservative
216	Propyl p-Hydroxybenzoate	Preservative
217	Sodium Propyl p-Hydroxybenzoate	Preservative
218	Methyl p-Hydroxybenzoate	Preservative
219	Sodium Methyl p-Hydroxybenzoate	Preservative
220	Sulphur Dioxide	Preservative, Antioxidant
221	Sodium Sulphite	Preservative, Antioxidant

222	Sodium Hydrogen Sulphite	Preservative, Antioxidant
223	Sodium Metabisulphite	Preservative, Bleaching Agent, Antioxidant
224	Potassium Metabisulphite	Preservative, Antioxidant
225	Potassium Sulphite	Preservative, Antioxidant
226	Calcium Sulphite	Preservative, Antioxidant
227	Calcium Hydrogen Sulphite	Preservative, Antioxidant
228	Potassium Bisulphite	Preservative, Antioxidant
230	Diphenyl	Preservative
231	Ortho-Phenylphenol	Preservative
232	Sodium o-Phenylphenol	Preservative
233	Thiabendazole	Preservative
234	Nisin	Preservative
235	Pimaricin (Natamycin)	Preservative
236	Formic Acid	Preservative
237	Sodium Formate	Preservative
238	Calcium Formate	Preservative
239	Hexamethylene Tetramine	Preservative
240	Formaldehyde	Preservative
241	Gum Guaicum	Preservative
242	Dimethyl Dicarbonate	Preservative
249	Potassium Nitrite	Preservative, Colour Fixative
250	Sodium Nitrite	Preservative, Colour Fixative
251	Sodium Nitrate	Preservative, Colour Fixative
252	Potassium Nitrate	Preservative, Colour Fixative
260	Acetic Acid, Glacial	Preservative, Acidity Regulator
261	Potassium Acetates	Preservative, Acidity Regulator
261 (i)	Potassium Acetate	Preservative, Acidity Regulator
261 (ii)	Potassium Diacetate	Preservative, Acidity Regulator
262	Sodium Acetates	Preservative, Acidity Regulator, Sequestrant
262 (i)	Sodium Acetate	Preservative, Acidity Regulator, Sequestrant
262 (ii)	Sodium Diacetate	Preservative, Acidity Regulator, Sequestrant
263	Calcium Acetate	Preservative, Stabilizer, Acidity Regulator.[10]

SOME COMMON PRESERVATIVES USED IN PHARMACEUTICAL PREPARATIONS WITH THEIR CONCENTRATIONS.[11]

Preservative	Class	Concentration in preparations (in %)			
		Oral Liquid	Parenterals	Opthalmic/ Nasal	Ointments and creams
Methyl Paraben	Amino aryl acid esters	0.25	0.01-0.5	0.1	0.001-0.2
Ethyl Paraben		0.1-0.25	0.01-0.5	0.1	0.001-0.2
Propyl Paraben		0.5-0.25	0.005-0.02	0.1	0.001-0.2
Butyl Paraben		0.1-0.4	0.015	0.1	0.001-0.2
Benzyl Alcohol	Alkyl/ aryl alcohols	3.0	0.5-10		
Chlorobutanol		0.5	0.25-0.5	0.5	0.5
Phenol	Phenols	0.1-0.5	0.065-0.02		0.25-0.5
Meta cresol		0.15-0.3	0.1-0.25		0.1-0.3
Chloro cresol		0.2	0.1-0.18		0.1-0.3
Benzoic acid	Alkyl/aryl acids	0.1-0.2			
Sorbic acid		0.1-0.2			
Thiomersal	Organic mercurial	0.1	0.01	0.01	0.01
Phenylmercuric nitrate		0.002-0.1	0.002	0.004	0.002
Bronopol	Diols	0.01-0.1			
Propylene Glycol		15-30			
Benzylkonium Chloride	Quatenary Ammonium Compounds	0.002-0.02	0.01	0.004-0.02	0.01
Benzethonium Chloride		0.01-0.02	0.01	0.004-0.01	0.01

Description of pharmaceutical preservatives

Methylparaben

Synonyms

4-hydroxybenzoic acid methyl ester; methyl p-hydroxybenzoate.

Chemical Name

Methyl-4-hydroxybenzoate.

Functional Category

Antimicrobial preservative.

Applications in Pharmaceutical Formulation or Technology

Methylparaben is widely used as an antimicrobial preservative in cosmetics, food products, and pharmaceutical formulations. Methylparaben is widely used as an antimicrobial preservative in cosmetics, food products, and pharmaceutical formulations.[12]

DOSE FORM	CONCENTRATION
IM, IV, SC injections	0.065–0.25
Inhalation solutions	0.025–0.07
Intradermal injections	0.10
Nasal solutions	0.033
Ophthalmic preparations	0.015–0.2
Oral solutions and suspensions	0.015–0.2
Rectal preparations	0.1–0.18
Topical preparations	0.02–0.3
Vaginal preparations	0.1–0.18.[13]

Safety

Parabens are nonmutagenic, nonteratogenic, and noncarcinogenic. Immediate hypersensitivity reactions following injection of preparations containing parabens have also been reported. Delayed-contact dermatitis occurs more frequently when parabens are used topically, but has also been reported to occur after oral administration.[14] Concern has been expressed over the use of methylparaben in infant parenteral products because bilirubin binding may be affected, which is potentially hazardous in hyperbilirubinemic neonates.[15]

Benzyl Alcohol

Synonyms

Benzenemethanol; alpha-hydroxytoluene; phenylcarbinol; phenylmethanol; alpha-toluenol.

Chemical Name

Benzenemethanol.

Functional Category

Antimicrobial preservative; disinfectant; solvent.

Applications in Pharmaceutical Formulation or Technology

Typical concentration used is 2% v/v in oral and parental preparations, and it has been reported to be used in protein, peptide and small molecule products, although its frequency of use has fallen from 48 products in 1996, 30 products in 2001, to 15 products in 2006.[16] Benzyl alcohol 10% v/v solutions also have some local anesthetic properties, which are exploited in some parenterals, cough products, ophthalmic solutions, ointments, and dermatological aerosol sprays.[17]

Safety

Ingestion or inhalation of benzyl alcohol may cause headache, vertigo, nausea, vomiting, and diarrhea. Overexposure may result in CNS depression and respiratory failure. Reports of adverse reactions to benzyl alcohol used as an excipient include toxicity following intravenous administration[18]; Neurotoxicity in patients administered benzyl alcohol in intrathecal preparations; Hypersensitivity, although relatively rare; and a fatal toxic syndrome in premature infants.[19]

Cresol

Synonyms

Cresylic acid; cresylol; hydroxytoluene; tricresol.

Chemical Name

Methylphenol.

Functional Category

Antimicrobial preservative; disinfectant.

Applications in Pharmaceutical Formulation or Technology

Cresol is used at 0.15–0.3% concentration as an antimicrobial preservative in intramuscular, intradermal, and subcutaneous injectable pharmaceutical formulations. It is also used as a C Cresol 203 preservative in some topical formulations and as a disinfectant. Cresol is not suitable as a preservative for preparations that are to be freeze-dried.[20]

Safety

Adverse reactions to cresol are generally associated with the use of either the bulk material or cresol-based disinfectants, which may contain up to 50% cresol, rather than for its use as a preservative. However, a recent case of cutaneous hypersensitivity reaction to the m-cresol

component of an insulin formulation detected via intradermal and patch testing has been reported.[21] Cresol is similar to phenol although it is less caustic and toxic. However, cresol is sufficiently caustic to be unsuitable for skin and wound disinfection. In studies in rabbits, cresol was found to be metabolized and excreted primarily as the glucuronide.[22]

Sorbic Acid

Synonyms

Acidum sorbicum, crotylidene acetic acid; hexadienic acid; hexadienoic acid; 2,4-hexadienoic acid; 1,3-pentadiene-1-carboxylic acid.

Chemical Name

Hexa-2,4-dienoic acid.

Functional Category

Antimicrobial preservative.

Applications in Pharmaceutical Formulation or Technology

Sorbic acid is an antimicrobial preservative[23] with antibacterial and antifungal properties used in pharmaceuticals, foods, enteral preparations, and cosmetics. Generally, it is used at concentrations of 0.05–0.2% in oral and topical pharmaceutical formulations, especially those containing nonionic surfactants. Sorbic acid is also used with proteins, enzymes, gelatin, and vegetable gums.[24] It has been shown to be an effective preservative for promethazine hydrochloride solutions in a concentration of 1 g/L.[25]

Safety

Sorbic acid is used as an antimicrobial preservative in oral and topical pharmaceutical formulations and is generally regarded as a nontoxic material. However, adverse reactions to sorbic acid and potassium sorbate, including irritant skin reactions[26] and allergic hypersensitivity skin reactions. Other adverse reactions that have been reported include exfoliative dermatitis due to ointments that contain sorbic acid,[27] and allergic conjunctivitis caused by contact lens solutions preserved with sorbic acid.[28]

CONCLUSION

As we have observed that most of artificial preservatives have toxic properties. Preservatives such as Sodium benzoate, sodium and potassium nitrates; TBHQ, BHA have chances of showing carcinogenic properties in pateints who administered them as additives. Primarily,

most of pharmaceutical industries are using preservatives more than safe concentration to increase shelf life of the drug. So, we should try to replace artificial preservatives with natural preservatives which are safe; but a suitable replacement is always hard to find until then me must use preservatives with less adverse effects and avoid carcinogenic agents. To illustrate all the preservatives mentioned above are noncarcinogenic moreover, their benefits outweigh adverse effects.

REFERENCES

1. PB Nielsena, A Müllertzb, T Norlinga, HG Kristensen, The effect of a-tocopherol on the in vitro solubilisationof lipophilic drugs; Int J Pharm, 2001; 222(2): 217–224.
2. ICH. 2004. Guidance for Industry – Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV.
3. Constantinides PP et al. Tocol emulsions for drug solubilization and parenteral delivery. Adv Drug Delivery, 2004; 56(9): 1243–1255.
4. Strickley RG, Iwata Q, Wu S and Dahl TC: Pediatric Drugs – A review of Commercially Available Oral Formulations. J Pharm Sci., 2008; 97: 1731-1774.
5. Steinberg D, Hirschfeld Z, Tayeb I, Ben-Yosef S, David A and Friedman M: The effect of parabens in a mouthwash and incorporated into a sustained release varnish on salivary bacteria. J Dentistry, 1999; 27: 101-106.
6. Esposito E, Bortolotti F, Nastruzzi C, Menegatti E and Cortesi R: Diffusion of preservatives from topical dosage forms: A comparative study. J Cosmet Sci., 2003; 54: 239-250.
7. Baudouin C, Labbè A, Liang H and Brignole-Baudouin F: 'Preservatives in eye drops: the good, the bad, and the ugly'. Prog Retinol Eye Res., 2010; 29: 312-334.
8. Marple B, Roland P and Benninger M: Safety review of benzalkonium chloride used as a preservative in intranasal solutions: an overview of conflicting data and opinions. Otolaryngol Head Neck Surgery, 2004; 130: 131-141.
9. Myer BK, Ni A, Hu B and Shi L: Antimicrobial preservative use in parenteral products: past and present. J Pharm Sci., 2007; 96: 3155-3167.
10. http://www.fao.org/tempref/codex/Meetings/CCFAC/ccfac31/INS.
11. https://pharmapathway.com/preservatives-used-in-pharmaceutical-industry.
12. Decker RL, Wenninger JA. Frequency of preservative use in cosmetic formulas as disclosed to FDA—1987. Cosmet Toilet, 1987; 102(12): 21–24.
13. handbook-of-pharmaceutical-excipients-6th-ed.pg.no-442.

14. Micha¨ elsson G, Juhlin L. Urticaria induced by preservatives and dye additives in food and drugs. Br J Dermatol, 1973; 88: 525–532.
15. Loria CJ et al. Effect of antibiotic formulations in serum protein: bilirubin interaction of newborn infants. J Pediatr, 1976; 89(3): 479– 482.
16. Meyer BK et al. Antimicrobial preservative use in parenteral products: past and present. J Pharm Sci., 2007; 96(12): 3155–3167.
17. handbook-of-pharmaceutical-excipients-6th-ed.pg.no-64.
18. Evens RP. Toxicity of intravenous benzyl alcohol [letter]. Drug Intell Clin Pharm, 1975; 9: 154–155.
19. Grant JA et al. Unsuspected benzyl alcohol hypersensitivity [letter]. N Engl J Med, 1982; 306: 108.
20. FAO/WHO. WHO expert committee on biological standardization. Thirty-seventh report. World Health Organ Tech Rep Ser 1987; No. 760.
21. Kim D, Baraniuk J. Delayed-type hypersensitivity reaction to the metacresol component of insulin. Ann Allergy Asthma Immunol, 2007; 99: 194–195.
22. Cresol. The Pharmaceutical Codex, 11th edn. London: Pharmaceutical Press, 1979; 232.
23. Charvalos E et al. Controlled release of water-soluble polymeric complexes of sorbic acid with antifungal activities. Appl Microbiol Biotechnol, 2001; 57(5–6): 770–775.
24. Weiner M, Bernstein IL. Adverse Reactions to Drug Formulation Agents: A Handbook of Excipients. New York: Marcel Dekker, 1989; 179.
25. Van-Doorne H, Leijen JB. Preservation of some oral liquid preparations: replacement of chloroform by other preservatives. Pharm World Sci., 1994; 16(Feb 18): 18–21.
26. Clemmensen OJ, Schiodt M. Patch test reaction of the buccal mucosa to sorbic acid. Contact Dermatitis, 1982; 8(5): 341–342.
27. Fisher AA. Cutaneous reactions to sorbic acid and potassium sorbate. Cutis, 1980; 25: 350, 352, 423.
28. Coyle HE et al. Sorbic acid sensitivity from Unguentum Merck. Contact Dermatitis, 1981; 7: 56–57.