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(71) Applicant: **3M INNOVATIVE PROPERTIES COMPANY** [US/US]; 3M Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US).

(72) Inventors: **DAHIWADKAR, Avanti D.**; Concorde Block, UB City, 24 Vittal Mallya Road, Bangalore 560001 (IN). **SCHOLZ, Matthew T.**; 3M Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US).

(74) Agent: **ADAMSON, Trisha D.**, et al.; 3M Center, Office of Intellectual Property Counsel, Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US).

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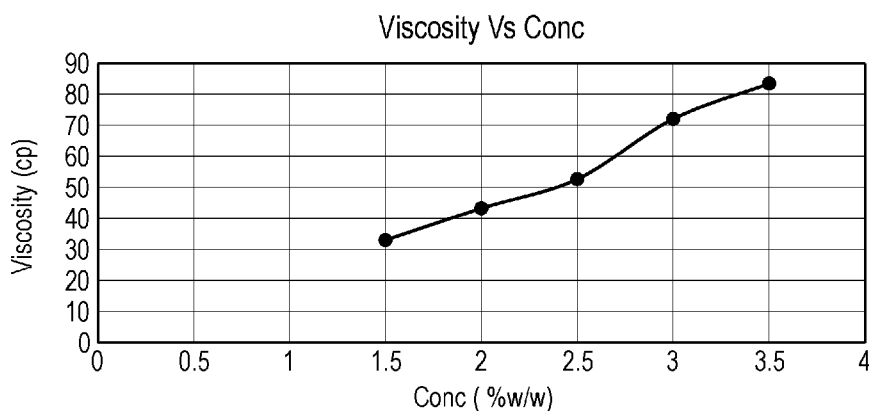


Fig. 1

(57) Abstract: The disclosed antiseptic composition has improved stability, flow control and tinting ability is provided. The antiseptic composition comprises a cationic antiseptic, an anionic tinting agent, a polymer that serves as a stabilizer and preferably a viscosity builder, an alcohol-based solvent and optionally a plasticizer and viscosity builder.

ANTISEPTIC SKIN PREP COMPOSITION

FIELD

5 An antiseptic composition with improved stability, flow control and tinting ability is disclosed.

BACKGROUND

Antiseptic solutions are applied to a patient's body prior to surgery or other medical procedures where there is a risk of infection. These solutions act instantly as well as provide persistent antimicrobial activity. Commonly employed antiseptic solutions are sometimes colored such that the solution
10 becomes visible when applied on the skin. This is preferred to allow identification of prepped areas. However, coloring agents can make the solution unstable resulting in precipitate formation that is visible within a few days at room temperature.

The foregoing drawback has been commonly addressed by mixing the colorant into the antiseptic solution only before applying it to the skin. For example, in US7422388 a two-part system consisting
15 of a foam impregnated with a dye and a separate container for the antiseptic solution without dye has been designed such that the dye and cationic antiseptic solution come in contact only at the time of prepping when the solution flows through the foam.

Other single systems have been stabilized using polymeric colorants formed by a polymerization reaction between a polymer component and a dye as described in WO 2013/074860. This procedure
20 calls for polymerization reactions during manufacturing, which is complicated as opposed to simple mixing. It is desirable for the antiseptic composition to remain stable for as long as possible and possess a long shelf life.

US9821066 consist of acrylic based film forming polymers but have limited stability of up to 3 months at room temperature when aged in a sealed container impermeable to water and lower alkyl
25 alcohols (C1-C4), as well as lack viscosity. Some have used cationic excipients in an aqueous medium (surfactants, quaternary ammonium compounds that form a micelle complex with the anionic dye in aqueous solutions) as described in WO 2009/068144 A1. In other work, cationic antiseptics are stabilized with anionic dyes using various concentrations of non-ionic surfactants in an aqueous system. Some work has been done to study the process of addition of water, dye, alcohol and
30 chlorhexidine gluconate to arrive at a stable formulation. However, a stable formulation for the duration of the shelf life of a typical product could not be obtained with the process or compositions recommended.

In developing nations, prepping of skin is generally done using a gauze dipped in the antiseptic solution to paint the body. Due to the low viscosity and surface tension of alcohol solutions, there is wastage of solution in the form of dripping and pooling at the sides. Optimizing the viscosity of the prep for better flow control and to form a uniform layer can help reduce wastage.

5 PVP-I based skin preps are very commonly used but have a longer drying time and require multiple layers of prepping. A combination of 2% w/v chlorhexidine gluconate and 70% v/v isopropyl alcohol has both these advantages over PVP-I but lack the ability to tint. However, when an anionic dye is used as a tinting agent in a system consisting of a cationic antiseptic, the solution becomes unstable resulting in precipitate formation that is visible within a few days at room temperature. Hence these
10 solutions are not tinting in nature or lack sufficient stability.

Accordingly, there is a need to develop a stable, viscous antiseptic solution with at least one anionic dye in sufficient quantity to be visible on the skin of the patient, having good flow control, improved stability while maintaining sufficient adhesion.

SUMMARY

15 In general, the disclosure features a composition for antiseptic solution having properties of improved stability, visibility, good flow control and adhesion. In an aspect, the present disclosure provides a composition comprising at least one cationic antiseptic agent, at least one anionic colorant, at least one polymer or copolymer, at least one C₁-C₄ lower alcohol-based solvent and optionally a plasticizer.

In an embodiment, the disclosure provides for an antiseptic composition, said composition utilizes a
20 synergizing effect manifested by a combination consisting of chlorhexidine gluconate, an anionic dye and a polymer which is stable and enhances visibility on the skin while yielding good flow control in a hydro alcoholic system with more than 60%v/v of a lower alcohol. The composition demonstrates excellent stability, viscosity of about 1-100cp for better flow control to reduce dripping during application using a gauze, sponge or applicator and dye in an appropriate quantity to tint the skin for
25 better visibility.

In still another embodiment, the non-ionic, polar polymer prevents the precipitation of a complex between the cationic antiseptic and the anionic colorant, over a duration of up to 24 months at real time conditions.

In an embodiment, the present disclosure provides for a composition for an antiseptic solution
30 comprising:

- (a) about 0.1 to 2.5 wt. % of at least one cationic antiseptic;
- (b) about 0.01 to 0.1 wt. % of at least one anionic colorant;

(c) about 0.1 to 10 wt. % of a non-ionic, polymer or copolymer with polar binding sites wherein the polar site has a nitrogen carrying a positive charge and an oxygen carrying a negative charge;

(d) at least 60% by weight of a lower alcohol-based solvent;

(e) optionally a plasticizer.

5

Further scope of applicability of the present invention will become apparent from the detailed description given hereinafter. However, it should be understood that the detailed description and specific examples, while indicating embodiments of the invention, are given by way of illustration only, because various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

10

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing summary, as well as the following detailed description of preferred embodiments of the invention, will be better understood when read in conjunction with the appended drawings. For the purpose of illustrating the invention, there are shown in the drawings embodiments which are presently preferred. It should be understood, however, that the invention is not limited to the precise arrangements and instrumentalities shown. In the drawings:

15

FIG 1: Graph 1: Viscosity Vs Concentration (PVPK 120)

20

FIG 2: Graph 2: Prepping of erythrosine at different dye concentrations

FIG 3: Precipitate visible in an unstable solution with Ponceau 4 R dye (left) when compared to a stable solution with Quinoline Yellow dye (right)

DETAILED DESCRIPTION

In describing and claiming the invention, the following terminology will be used in accordance with the definitions set forth below. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described herein. As used herein, each of the following terms has the meaning associated with it in this section. Specific and preferred values listed below for individual components, substituents, and ranges are for illustration only; they do not exclude other defined values or other values within defined ranges for the components and substituents.

25

30

As used herein, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise.

The use of numerical values in the various ranges specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word "about". Thus, slight variations above and below the stated ranges can be used to achieve substantially the same results as values within the ranges. Moreover, in the disclosure of these ranges, a continuous range is intended, covering every value between the minimum and maximum values, including the minimum and maximum end points of the range.

As used herein, the term "disinfect", "disinfecting", "disinfection" shall mean the elimination of many or all microorganisms.

As used herein "antiseptic" refers to the ability of the composition to destroy microorganisms (e.g., skin flora, a bacterium, a fungus or virus), thereby rapidly disinfect the area applied on and prevent an infection or disease that may be caused.

As used herein, the term "stable" refers to the antiseptic composition which after 24 hours is clear and leaves no residue solid visible to the human eye. Moreover, the stable antiseptic solutions of the invention do not leave residue solids visible to the human eye after any standard stability test.

"Precipitation" here means the formation of any solids in the antiseptic composition of the present disclosure. Precipitation here means the particulate contamination that consists of extraneous, mobile, undissolved particles unintentionally present in the solution. Precipitation, particulate contamination can be measured by standard tests that are intended to provide a simple procedure for the visual assessment of the quality of the antiseptic solution.

According to one embodiment, an antiseptic skin prep solution comprises (a) a cationic antiseptic agent (b) at least one anionic colorant (c) a non-ionic, polymer or copolymer with polar binding sites wherein the polar site has a nitrogen carrying a positive charge and an oxygen carrying a negative charge (d) an C₁-C₄ lower alcohol based solvent (e) at least one plasticizer, wherein the non-ionic, polar polymer prevents or postpones the precipitation of the cationic antiseptic and the anionic colorant, over a duration of up to 24 months at 23C. It is believed that this is achieved by forming a complex with the anionic colorant.

In one aspect of the invention, the antiseptic composition may comprise a cationic antiseptic agent. As used herein, a "cationic antiseptic" is any molecular entity having at least one positive charge and conferring an antimicrobial effect. The cationic moiety may be a quaternary amine or a protonated primary, secondary, or tertiary amine. As will be understood by one of skill, a given molecular entity

may have properties of both a cationic excipient and an antiseptic. For example, the cationic antiseptic is selected from a group of chlorhexidine salts, PHMB salts, octenidine salts, alexidine salts, benzethonium salts, and combinations thereof.

According to one embodiment of the present disclosure, the cationic antiseptic provides a residual action and chlorohexidine digluconate (CHG) is employed in a representative composition.

CHG is an especially effective antiseptic as it exhibits a strong affinity for binding to skin, high antibacterial activity, and prolonged residual effects. It has been found that CHG is a broad range, rapid acting, and an excellent preoperative skin preparation. Further, CHG exhibits rapid activity against both gram-positive and gram-negative bacteria. Representative example of a CHG solution (Basic Pharma Life Science P Ltd.) is a 20% CHG.

The concentration of the cationic antiseptic is present in the range of 0.1-2.5% by weight of the composition.

The "dye" as described in the disclosure is alternatively referred to herein as a "colorant" or "tint". According to the present disclosure, the colorant is an anionic colorant. The anionic dye is any colorant that imparts a color to the antiseptic composition. According to one embodiment, the amount of anionic dye included in the composition is sufficient to be visible to the naked eye on a patient's skin when the composition is wet as well as once it is dried. One skilled in the art will appreciate that two or more anionic dyes may be combined and employed together.

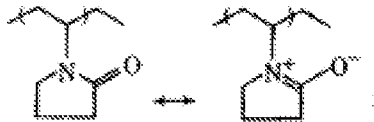
An exemplary anionic dye is an FDA approved anionic dye added in sufficient concentration to tint the skin. Non-limiting examples of such exemplary anionic dyes include FD & C Red No.3, FD&C Yellow No. 6, FD&C Blue No.1, D&C Yellow 10, Brilliant Blue, D&C green, Carmoisine. Exemplary illustrated anionic dyes are Carmoisine, Erythrosine, Sunset yellow, Brilliant Blue, D&C Green.

In one embodiment, the total concentration of anionic dye will be from about 0.01-0.25% and preferably 0.015-0.1% by weight of the composition.

In one embodiment, the antiseptic skin prep composition comprises a polymer or copolymer. The polymer added is a high weight average molecular weight, non-ionic polymer with polar binding sites and a solubility parameter in the range of 18 to 28 (preferable around 24), such as polyvinyl pyrrolidone that builds viscosity in a hydro-alcoholic solution and prevents the formation of an insoluble precipitate of CHG-dye over a period of a minimum of 1 month to 24 months at 23C in a sealed impermeable container. A solution of this nature has improved stability, viscosity of about (1-100 cp) for better flow control to reduce dripping during application using a gauze, sponge or applicator and dye in sufficient quantity to tint the skin for better visibility.

According to one embodiment, the concentration of dye to polymer in the antiseptic skin prep composition is in the ratio of 1:1 to 1:1000.

The following structure shows the charges on polyvinyl pyrrolidone and its affinity towards anionic species due to the positive charge on nitrogen. Without being bound to any theory, poly (vinyl pyrrolidone) is an electrolyte with an affinity for anionic species, enhancing the stability of the solution.



In an embodiment, the concentration of polymer will be from about 0.1 to 10 wt % by weight of the composition.

The non-ionic, polar polymer or copolymer is selected from a group consisting of poly (vinyl pyrrolidone), copolymers of PVP/VA, PVP/butene, polyamine oxides, polyethyloxazoline and/or combinations thereof where VA is vinyl acetate.

It is preferable that the polymer is a high weight-average molecular weight polymer greater than 100,000 g/mol, preferably greater than 300,000 g/mol, and more preferably 900,000 – 3000,000 g/mol.

According to an embodiment of the disclosure the polymer employed is PVPK 120.

The solvent includes an alcohol, preferably isopropyl alcohol, ethanol or n-propanol present in a concentration greater than 60% v/v. A plasticizer may be added to prevent cracking of the prepped film.

In an embodiment, the composition has a pH in the range of 5 to 7.5.

According to yet another embodiment, process of preparing an antiseptic skin prep composition comprises at least the following steps: of mixing until dissolution at least one anionic dye, cationic antiseptic and non-ionic, polymer or copolymer with polar binding sites wherein the polar site has a nitrogen carrying a positive charge and an oxygen carrying a negative charge with a molecular weight of at least 100,000 g/mol with a lower alcohol solvent and water wherein said components are present in the antiseptic solution in an amount sufficient to tint a patient's skin when applied thereto and wherein the non-ionic, polar polymer prevents or postpones the precipitation of a complex between the cationic antiseptic and the anionic colorant, over a duration of up to 24 months at real time conditions of 23 C.

All constituents employed in the final recommended composition are cosmetically and pharmaceutically acceptable with no significant toxicity. A high weight average molecular weight polyelectrolyte (polyvinyl pyrrolidone) provides the preferred viscosity and stability to a system with min 60% v/v of a lower alcohol (isopropyl alcohol/n-propanol/ethanol). 2% w/v chlorhexidine gluconate provides the residual activity and a FD&C dye as an anionic dye is present in sufficient quantity to tint skin of various shades.

According to the present disclosure, the viscosity of an exemplary composition is in the range of 1 to 100 cp.

Advantageously, the composition remains stable without any visible precipitate for up to 24 months at a temperature of 23-25 deg C when sealed in an impermeable container such as glass or PET (Polyethylene terephthalate) that act as a barrier to alcohol and water evaporation.

The composition remains stable without any visible precipitate for up to 6 months at a temperature of 40 deg C when sealed in an impermeable container.

An embodiment of the present invention is directed to a kit comprising, a cationic antiseptic agent and non-ionic polymer in solution separated from an anionic colorant, the components mixed just prior to use remain stable without precipitation for at least 5 mins, more preferably 30 mins, most preferably for an hour at 23deg C

The method of the present invention includes a method of disinfecting a surface comprising applying the antiseptic composition disclosed above to a surface. The surface can be human skin. The method may further include the steps of scrubbing the antiseptic on the skin, allowing the antiseptic composition to dry, and optionally apply an adhesive coated sheet commonly referred to as an incise drape over the dry antiseptic composition.

Illustrative example compositions which may be produced include those set forth below. The illustrative example compositions demonstrate certain particularly desired embodiments of the invention as well as preferred weight percentages as well as preferred relative weight percentages/weight ratios with regard to the respective individual constituents present within a composition.

EXAMPLE 1

Stability of cationic antiseptic and an anionic dye in a hydro-alcoholic system

An anionic dye, carmoisine, was added in sufficient quantity to tint the skin to a 2% CHG and 70% IPA(isopropyl alcohol) solution. The solutions were sealed in impermeable containers and allowed to

sit at 23C. At a pH where CHG is active a dark precipitate was observed in 5 days. Precipitation was accessed by shaking the sealed barrier container and visually looking for precipitate.

Table 1: Cationic antiseptic and anionic dye without stabilizer

Carmoisine	IPA	20% CHG solution	Water	pH	Precipitation Day
0.07	65.65	12.65	21.63	5.6	5
0.05	65.65	12.65	21.65	>7	12

5 EXAMPLE 2

Comparative test of polymers for solubility in a hydro alcoholic system, thickening and ability to postpone precipitation

Polymers were tested for solubility, thickening and stabilizing effects. Various polymers were dissolved in an ethanol/isopropyl alcohol and water mixture. CHG and Carmoisine were added to the composition. The solutions were sealed in standard 100 ml TARSON PET containers of internal diameter 4.5cm and allowed to sit at 23C. The viscosity was measured, and homogeneity or stability was observed immediately and for 30 days.

Table 2: Test of viscosity builder (All values are in w/w %)

	1	2	3	4	5	6	7	8	9	10
Water	21.6	21.4	21	21.63	20.83	20.69	21.01	19.96	23.1	19.62
IPA	65.6	65.1	65.6	65.65	65.65		65.65	65.65	62.52	65.65
Ethanol						65.98				
PolyOX (WSR N-12K)			0.6			0.6	0.06	0.06	0.6	
PolyOX (WSR 205)					0.8					
CMC				0.6						
HEC		0.8								
PVPK 120										2
20% CHG	12.6	12.5	12.6		12.65		12.65	12.65	12.65	12.65
Carmoisine	0.05	0.05	0.05		0.05		0.05	0.05	0.05	
OFX 190									1	
Tween 80							1			

Triton x100								1		
HEDTA							0.06	0.06	0.06	
Viscosity (cp)	NA	NA	38.7	NA	35.5	38			38	37.5
Stability on Day 0	Yes	No. Precipitation in 10 mins	Yes	No. Settle down in 30 mins	Yes	Yes	Yes	Yes	Yes	Yes
Homogeneous on Day 30@ RT	No. Dark precipitate observed on day 5	NA	No. White precipitate observed in the first week and then dark precipitate	No	No. White precipitate observed in the first week and then dark precipitate	No	No. Dark precipitate formed after 2 weeks	No. Dark precipitate formed after 2 weeks	No. Dark precipitate formed	Yes
Solubility in IPA/water	Yes	No	Yes	No	Yes	NA	Yes	Yes	Yes	Yes

IPA = Isopropyl alcohol from Deepak Fertilizers & Petrochemicals Corp. Ltd

Ethanol 95% = Sterling Chemicals & Alcohols Pvt. Ltd

20% CHG solution = Basic Pharma Life Science P Ltd.

5 POLYOX NF 12 = high molecular weight Poly ethylene oxide from Dow Chemical International Pvt. Ltd.

POLYOX WSR 205 = high molecular weight Poly ethylene oxide from Dow Chemical International Pvt. Ltd.

PVPK30 = Polyvinylpyrrolidone from Ashland

10 PVPK120 = high molecular weight Polyvinylpyrrolidone from Ashland

HEC = Hydroxyethyl cellulose, DOW Chemicals

CMC = Carboxymethyl cellulose from Sigma-Aldrich

Carmoisine = Acid Red 14 from Neelikon

OFX 190 = Dow Corning(I)Pvt Ltd

Tween 80 = Non-ionic surfactant and emulsifier from Sigma-Aldrich

Triton x100 = nonionic surfactant from Sigma-Aldrich

Exp 1 as tabulated above shows that a solution without a viscosity builder or polymer has no significant viscosity and is not stable with visible precipitate in 5 days. Exp 3, 5, had a non-ionic polymer of ethylene oxide, POLYOX, of different molecular weights and concentrations. As the concentration increased there was a significant build up in viscosity of the solution. However, within a few days, a white precipitate began to settle at the bottom of the formulation followed by a dark precipitate later. Upon examination it was found that the interaction of CHG with calcium ions in POLYOX was causing the white precipitate. In Exp 7,8,9, HEDTA was used to scavenge the free Calcium resulting in no white precipitate, however the dark precipitate was still observed even when a non-ionic surfactant (Tween 80, Triton X-100) and OFX 190 (dimethicone copolymer) was added to stabilize the CHG-Dye interaction. POLYOX did postpone the interaction of dye and CHG but not sufficiently.

Other viscosity builders and film forming polymers were tried in Exp 2,4 . HEC and CMC were insoluble in IPA/Water mixtures at the given ratio. HEC was soluble in Ethanol/Water mixture but separated out over time. PVPK 30 was soluble with good film forming but did not build any viscosity.

In Exp. 10, PVPK 120 was used and the best results were observed in terms of stability, viscosity build up and film forming. PVPK 120 is high molecular weight non-ionic, polymer with polar binding sites wherein the polar site has a nitrogen carrying a positive charge and an oxygen carrying a negative charge such that they interact with the anionic dye and cationic antiseptic to postpone precipitation.

Other polymers having similar structures were also studied for their stabilizing effect.

EXAMPLE 3:

Non-ionic polymers or co-polymers having similar structures with polar groups having a positively charged nitrogen and negatively charged oxygen in a hydro-alcoholic solution in the presence of CHG and an anionic dye were also studied for their stabilizing effect. The solutions were sealed in standard 4oz. glass jars of internal diameter 4.5cm by Fisher Scientific, Pittsburgh PA and allowed to sit at 23C for 17 days.

Table: 3 Precipitation measurement of solutions with non-ionic polymers with nitrogen and oxygen when compared to a control having no polymer.

	Control	Z711	Z712	2000	1-Step	G904	Gaf755	E335	Aqz500
	1	2	3	4	5	6	7	8	9

Sunset yellow (Yellow #6) dye	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
CHG 20%	10	10	10	10	10	10	10	10	10
Isopropanol	70	70	70	70	70	70	70	70	70
water	17.98	17.48	17.48	16.65	15.98	17.98	11.98	17.98	18.98
Diaformer Z711 40% in EtOH polyamine oxide		2.5							
Diaformer Z712 40% in ETOH polyamine oxide			2.5						
in EtOHRAM Resin 2000 poly(betaine) methacrylate 30%				3.33					
3M amine oxide polymer 25% in water					4				
Ganex 904 VP/butene copolymer 100%						1			
gafquat 755 VP/DMAEM copolymer							1		
PVP/VA E335 30/70 50%								2	
Aquazol 500 polyethyloxazoline 100%									1
Precipitation on a level of 0 to 5 on day 17 at room temperature (23C)	2	0	0	0	0	1	7	0	0

Diaformer Z711 is an acrylates/lauryl acrylate/stearyl acrylate/ethylamine oxide methacrylate available from Clariant Corp. Personal Care Branch Mt. Holly NC

5 Diaformer Z712 is an acrylates/lauryl acrylate/stearyl acrylate/ethylamine oxide methacrylate available from Clariant Corp. Personal Care Branch Mt. Holly NC

3M amine oxide polymer is a copolymer of stearyl methacrylate (10%)/isobutyl methacrylate (20%)/amine oxide of dimethylaminoethyl methacrylate (50%) and methyl methacrylate (20%) and was prepared similar to Example 90 of US patent 7323163

Ganex 904 P is a butene/vinyl pyrrolidone copolymer available from Ashland

10 Gafquat 755 is a Vinyl pyrrolidone/dimethylaminoethyl methacrylate copolymer available from Ashland

PVP/VA is a vinyl pyrrolidone/vinyl acetate 30/70 copolymer available from Ashland
 Aquazol 500 is available from Polymer Chemistry Innovations, Inc., Tucson, AZ

Exp 1 is the control with precipitation level of 2 observed on a scale of 0 to 5. Exp 2,3,4,5,6,8,9 are non-ionic polymers with nitrogen and oxygen that postpone the precipitation beyond 15 days. Exp 7, Gafquat used is a cationic polymer resulting in quick and heavy precipitation with dye.

Exp 5, is made with the 3M one step prep polymer is an amine oxide copolymer of stearyl methacrylate, isobutyl methacrylate, Dimethylaminoethylmethacrylate, methyl methacrylate

EXAMPLE 4

Viscosity profile with concentration and measuring drying time

Table 4: Viscosity, drying time measurements and dripping observation with increase in PVPK120 concentration

	DiffPVP-1	DiffPVP-2	DiffPVP-3	DiffPVP-4	DiffPVP-5
Water	21.421	20.921	20.384	19.884	19.384
IPA	65.65	65.65	65.65	65.65	65.65
Carmoisine	0.05	0.05	0.05	0.05	0.05
PVPK120	1.5	2	2.5	3	3.5
20% CHG solution	11.12	11.12	11.12	11.12	11.12
10% Lactic Acid	0.259	0.259	0.296	0.296	0.296
Initial pH	7.14	7.06	6.98	7.13	7.05
Final pH	6.18	6.14	6.15	6.22	6.27
Viscosity (spindle LV-02 62, 200RPM, 25 C)	33	43.2	52.6	72	83.4
Drying Time (min:sec)	3:50	4:16	4:36	3:45	3:46
Dripping	Slight	No	No	No	No

Viscosity was measured at 25C using a Brookfield DV2T viscometer available from Brookfield Engineering using spindle LV-02 (62). Graph 1 of Fig. 1 shows that the viscosity increases as the concentration increases. An area on the hands of a human subject below the elbow was prepped and observed for drying time and dripping for each concentration. There was minimal dripping observed for viscosities above approximately 40 cp corresponding to about 2% PVPK 120 concentration. The

prepping was done using a soaked open cell polyurethane sponge. The drying times as PVPK 120 concentrations changed did not vary much and all dried in under 5 mins. Adding a plasticizer like glycerol ensured a uniform film without cracking was observed when prepping was done with a gauze as well as a polyurethane foam.

5 EXAMPLE 4

Comparative test: Stability and tinting of various dyes

Many dyes were tried in the formulation and their stability was observed over 30 days at room temperature (23 °C). These were prepped on skin of light and dark tone and the tinting was observed.

Table 4: Prepping with different dyes

Exp No:	DiffDye-1	DiffDye-2	DiffDye-3	DiffDye-4
Water	19.28	19.28	19.28	19.28
IPA	65.65	65.65	65.65	65.65
Brilliant Blue	0.05			
Carmoisine		0.05		
Ponceau 4 R			0.05	
D&C Green				0.05
PVPK120	2	2	2	2
CHG	12.65	12.65	12.65	12.65
Lactic Acid	0.37	0.37	0.37	0.37
Stability day 0	S	S	S	S
Stability day 15	S	S	NS	S
Stability day 30	S	S	NS	S
Tinting	Y	Y	Y	N

S = Stable, NS = Not Stable, Y = Yes, N= No

It was observed that, Ponceau 4R Dye precipitated on the second day. The others (Brilliant Blue, D&C Green, Carmoisine) were stable over 30 days at room temperature with no precipitation

observed. PVPK 120 postpones the precipitation of anionic dyes with CHG to various degrees. It was observed that the azo dye structure with 3 sulphonate groups precipitated out of solution quicker. Erythrosine dye demonstrates good solubility in alcohol systems potentially due to more hydrophobic nature as compared to azo dye sulphonates.

EXAMPLE 5

Erythrosine at different concentrations to tint the skin.

In this example, tests were conducted to optimize the concentration of erythrosine at which the tinting is clear on skin of different tones (light, dark). Graph 2 (Fig. 2) depicts the prepping of erythrosine at different dye concentrations.

EXAMPLE 6

Stability Studies

Stability studies to observe for precipitation and other parameter was conducted under the following conditions sealed in an inert container impermeable to alcohol and water

- 1) 40 C for 6 months
- 2) 30 C for 24 months

Sample made using erythrosine dye in sufficient quantity to tint the skin, 2% CHG, 70% IPA and 2.5% PVPK 120 and water qs.

Table 5: Real Time stability data of samples ED-29 and accelerated aging data of sample ED-30

Stability condition	Experiment No:	Months	Appearance	CHG% w/v	pH	Viscosity
23 C	ED-9	Initial	Pink with no precipitate	2.0	5.8	52
	ED-9	24M	Pink with no precipitate	1.9	6.0	53
30 C	ED-30	Initial	Pink with no precipitate	2	5.8	60
	ED-30	24M	Pink with no precipitate	2	6.1	55
40 C	ED-29	Initial	Pink with no precipitate	2	5.8	60
	ED-29	6	Pink with no precipitate	2	6.4	60

The data shows that a solution with a cationic antiseptic (CHG) and anionic dye (erythrosine) remains stable upto 24 months at real time conditions and for a minimum of 6 months under accelerated aging conditions when a vinyl pyrrolidone polymer viscosity builder of high molecular weight is added. The enhanced viscosity also helps in flow control such that dripping of liquid is minimized.

The dye structure also impacts stability. Carmoisine which is an azo dye precipitated quicker (as seen in the table below) than erythrosine which is an organoiodide compound.

Table 6: pH and appearance, real time stability data and accelerated aging data of sample PT-3 using Carmoisine dye

6 th month ICH protocol	6.73	3-5 particles
Real time – 3 months	6.66	No precipitate
Real time – 6 months	6.69	1-2 particles

5

While the invention has been described above with respect to certain embodiments thereof, numerous other forms and modifications will be apparent to those skilled in the art. The appended claims and the invention generally should be construed as covering all such obvious forms and modifications that are within the true spirit and scope of the invention.

10 It will thus be seen that the objects set forth above, among those made apparent from the preceding description are efficiently attained and since certain changes may be made in the above construction without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

15

We claim,

1. An antiseptic skin prep composition comprising

(a) cationic antiseptic agent

(b) anionic colorant

5 (c) a non-ionic, polymer or copolymer with polar binding sites wherein the polar site has a nitrogen carrying a positive charge and an oxygen carrying a negative charge

(d) C₁-C₄ lower alcohol-based solvent

wherein the composition exhibits no visible precipitation when stored in a sealed inert barrier container having an internal diameter of 4.5 cm at 23 deg C for at least 17 days.

10 2. The antiseptic skin prep composition as claimed in claim 1, wherein the cationic antiseptic is present in the range of 0.1-2.5% by weight of the composition.

3. The antiseptic skin prep composition of any one of the preceding claims, wherein the anionic colorant is present in the range of 0.01-0.1% by weight of the composition.

15 4. The antiseptic skin prep composition of any one of the preceding claims, wherein the non-ionic, polar polymer or copolymer is present in the range of 0.1 to 10% by weight of the composition.

20 5. The antiseptic skin prep composition of any one of the preceding claims, wherein the concentration of dye to polymer is in the ratio 1:1 to 1:1000.

6. The antiseptic skin prep composition of any one of the preceding claims, wherein the antiseptic composition comprises at least 60% by weight of a lower alcohol.

25 7. The antiseptic skin prep composition of any one of the preceding claims, wherein the cationic antiseptic is selected from a group of chlorhexidine salts, PHMB salts, octenidine salts, alexidine salts, benzethonium salts, and combinations thereof.

30 8. The antiseptic skin prep composition of any one of the preceding claims, wherein the anionic colorant is selected from a group of anionic dyes including FD & C Red No.3, FD&C Yellow No. 6, FD&C Blue No.1, D&C Yellow 10 Brilliant Blue, D&C green and Carmoisine.

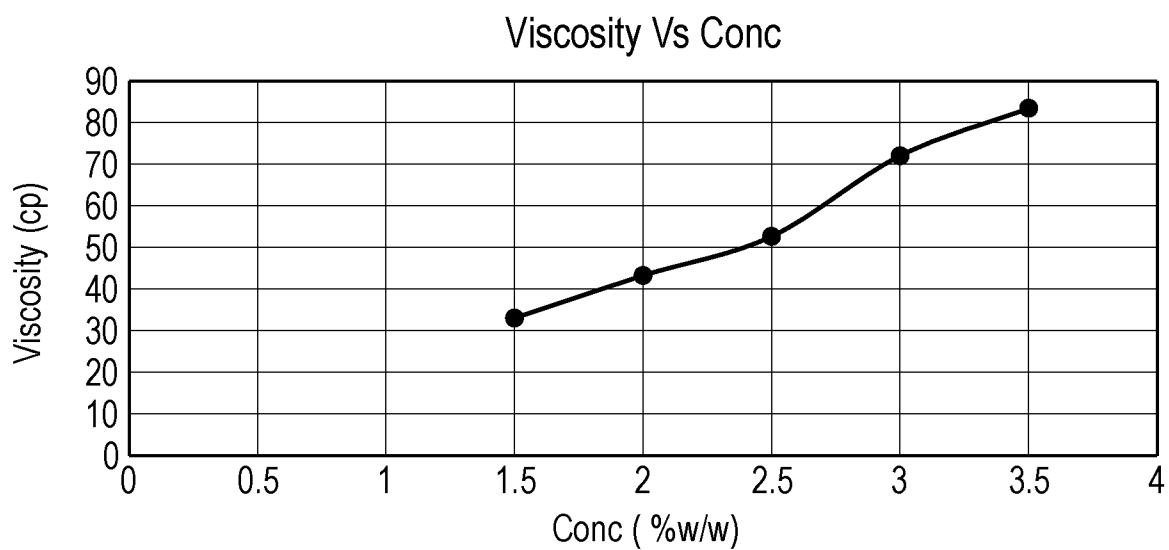
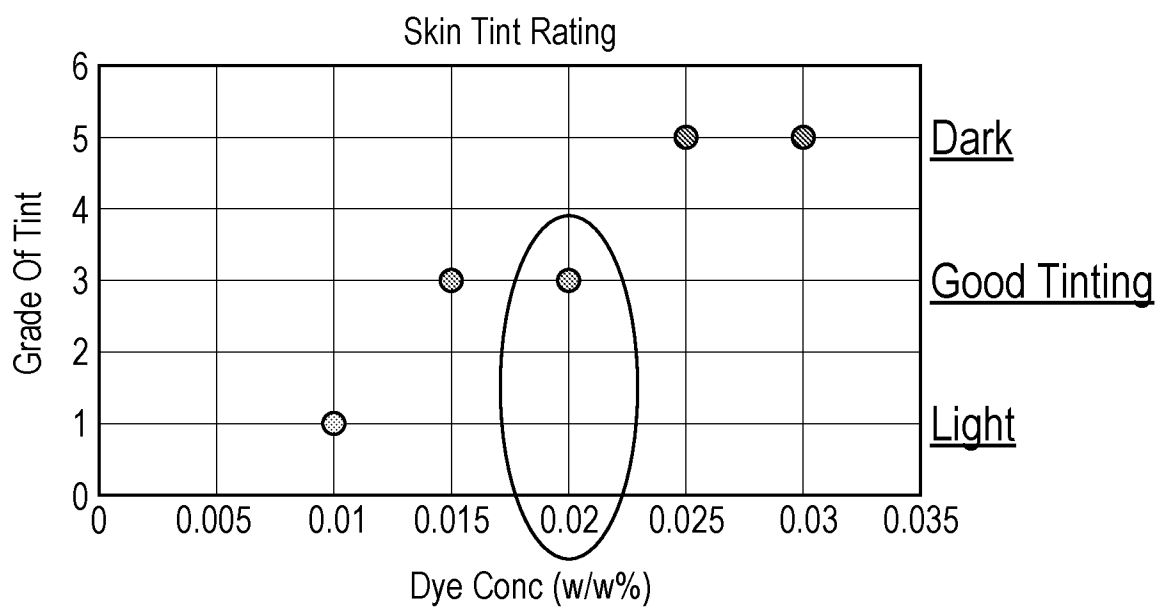
9. The antiseptic skin prep composition of any one of the preceding claims, wherein the non-ionic, polar polymer or copolymer is selected from a group of polyvinyl pyrrolidone, copolymers of PVP/VA, PVP/butene, polyamine oxides, polyethyloxazoline, or combinations thereof.
10. The antiseptic skin prep composition as claimed in claim 9, wherein the polymer comprises PVP K120.
11. The antiseptic skin prep composition of any one of the preceding claims, wherein the weight average molecular weight of the polymer is 100,000 – 3000,000g/mol.
12. The antiseptic skin prep composition of any one of the preceding claims, wherein the alcohol-based solvent is selected from a group of C1-C4 lower alcohols such as isopropyl alcohol, ethanol, n-propanol or combinations thereof.
13. An antiseptic skin prep solution of any one of the preceding claims, wherein the viscosity of solution is in the range of 1 to 100 cp when measured using a Brookfield DV2T viscometer, spindle LV-02 at 23C.
14. The antiseptic skin prep composition of any one of the preceding claims, comprising a plasticizer.
15. The antiseptic skin prep composition as claimed in claim 14, wherein the plasticizer is glycerol.
16. The antiseptic skin prep composition of any one of the preceding claims, wherein said composition remains stable without any visible precipitate for at least 6 months at a temperature of 40 deg C.
17. The antiseptic skin prep composition of any one of the preceding claims, wherein said composition is used with gauze, foam or prepping solution dispenser
18. A kit comprising, a cationic antiseptic agent and non-ionic polymer in solution separated from an anionic colorant, the components mixed just prior to use remain stable without precipitation for at least 5 mins at 23 deg C.
19. A process of preparing an antiseptic skin prep composition comprising:

mixing until dissolved at least one anionic dye, at least one cationic excipient and at least one non-ionic, polymer or copolymer with polar binding sites wherein the polar site has a nitrogen carrying a positive charge and an oxygen carrying a negative charge with a lower alcohol and water containing solvent.

5

20. The process of claim 19, wherein said components are present in the antiseptic solution in an amount sufficient to visibly color a patient's skin when applied thereto and wherein the non-ionic, polar polymer prevents or postpones the precipitation of a complex between the cationic antiseptic and the anionic colorant, for at least 17 days at 23 deg C.

1/2

**Fig. 1****Fig. 2**

2/2

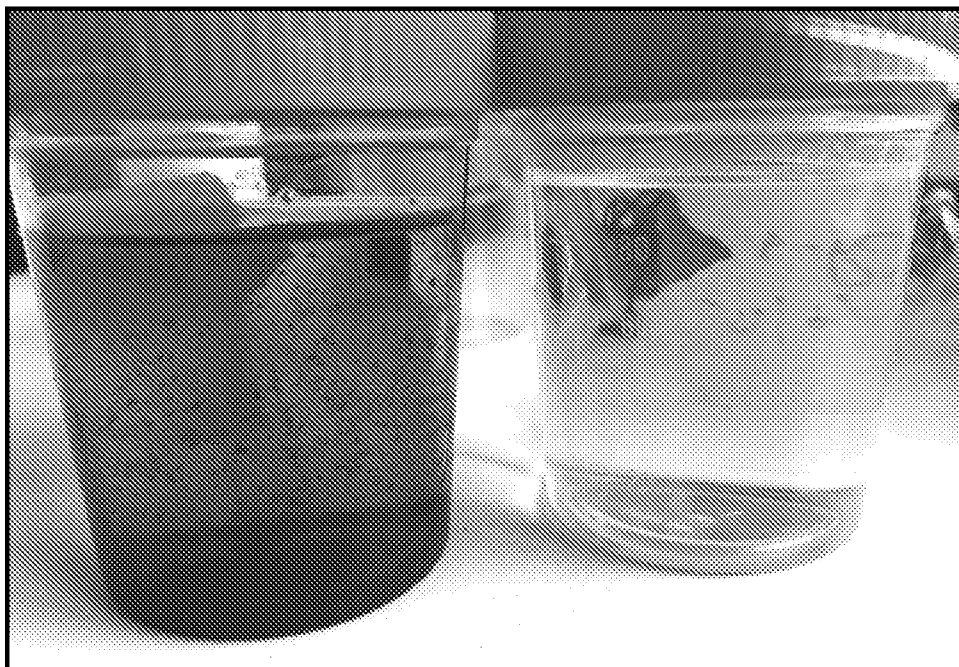


Fig. 3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 20/53173

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 33/10; A61K 35/644; A61K 8/19 (2020.01)

CPC - A61K 31/375; A61K 33/10; A61K 35/644; A61K 36/185

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2014/0261454 A1 (Carefusion 2200, Inc.) 18 September 2014 (18.09.2014) Abstract, para [0024], [0025], [0029], [0032], [0040], Table 1	1-3
X	US 2016/0213001 A1 (3M Innovative Properties Company) 28 July 2016 (28.07.2016) para [0014], [0057], [0066], [0220]	18
A	'N-Tert-Octylacrylamide', PubChem, create date 26 March 2005 (26.03.2005) retrieved from the internet on 30 June 2020 (30.06.2020) at <https://pubchem.ncbi.nlm.nih.gov/compound/N-Tert-Octylacrylamide>] figure 1.1	1
A	US 2007/0254854 A1 (Magallon et al.) 01 November 2007 (01.11.2007) entire document	1-3, 18
A	US 2017/0014358 A1 (Tuffley) 19 January 2017 (19.01.2017) entire document	1-3, 18



Further documents are listed in the continuation of Box C



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

06 July 2020

Date of mailing of the international search report

27 AUG 2020

Name and mailing address of the ISA/US

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Facsimile No. 571-273-8300

Authorized officer

Lee Young

Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/IB 20/53173

Continuation of Box III

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I: Claims 1-3 and 18 is directed towards an antiseptic skin prep composition and kit comprising (a) cationic antiseptic agent (b) anionic colorant (c) a non-ionic, polymer or copolymer with polar binding sites wherein the polar site has a nitrogen carrying a positive charge and an oxygen carrying a negative charge (d) CL-C4 lower alcohol-based solvent wherein the composition exhibits no visible precipitation when stored in a sealed inert barrier container having an internal diameter of 4.5 cm at 23 deg C for at least 17 days.

Group II: Claims 19-20 is directed towards a process of preparing an antiseptic skin prep composition comprising: mixing until dissolved at least one anionic dye, at least one cationic excipient and at least one non-ionic, polymer or copolymer with polar binding sites wherein the polar site has a nitrogen carrying a positive charge and an oxygen carrying a negative charge with a lower alcohol and water containing solvent.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I requires towards an antiseptic skin prep composition and kit comprising (a) cationic antiseptic agent, wherein the composition exhibits no visible precipitation when stored in a sealed inert barrier container having an internal diameter of 4.5 cm at 23 deg C for at least 17 days, not required by Group II.

Group II requires a process of preparing an antiseptic skin prep composition comprising: mixing until dissolved at least one anionic dye, at least one cationic excipient and at least one non-ionic, polymer or copolymer with polar binding sites wherein the polar site has a nitrogen carrying a positive charge and an oxygen carrying a negative charge with a lower alcohol and water containing solvent, not required by Group I.

Shared Technical Features:

Groups I and II share the common feature of an antiseptic skin prep composition comprising anionic colorant and a non-ionic, polymer or copolymer with polar binding sites wherein the polar site has a nitrogen carrying a positive charge and an oxygen carrying a negative charge, and a lower alcohol-based solvent.

However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is anticipated by US 2014/0261454 A1 to Carefusion 2200, Inc. (hereinafter 'Carefusion'). Carefusion discloses an antiseptic skin prep composition (Abstract: "An antiseptic solution"; para [0029] "Aspects of the present invention include a method of disinfecting a surface comprising applying the above-dis closed antiseptic solution to the surface. The surface may be human skin") comprising anionic colorant (Abstract: "an anionic tinting agent") and a non-ionic, polymer or copolymer with polar binding sites wherein the polar site has a nitrogen carrying a positive charge and an oxygen carrying a negative charge (Abstract: "a film forming polymer"; para [0024] "The film forming polymer may be selected from acrylate polymers, such as acrylamide polymers"; para [0025] "Example acrylate polymers include...DERMACRYL 79P (2-propenoic acid, 2-methyl-, 2-methylpropyl ester, polymer with 2-propenoic acid and N-(1,1,3,3-tetramethylbutyl)-2-propenamide"); the N-(1,1,3,3-tetramethylbutyl)-2-propenamide section of the copolymer has the description described, see PubChem article 'N-Tert-Octylacrylamide' (a synonym of N-(1,1,3,3-tetramethylbutyl)-2-propenamide) figure 1.1 that shows the polar structure of this section as well as the amide group), and a lower alcohol-based solvent (Abstract: "The solvent is preferably ethanol, isopropanol, and n-propanol.").

As the shared technical features were known in the art at the time of the invention, they cannot be considered special technical features that would otherwise unify the groups. Therefore, Groups I-II lack unity under PCT Rule 13.

Item 4 (contd.): Claims 4-17 have been found to be unsearchable because they are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 20/53173

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-17
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
(see supplemental Box)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3, 18

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.