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Research Article

Formulation and evaluation of Chlorhexidine gluconate topical gel

Babita*, Pawan Jalwal, Neha, Anu
Baba Mastnath University, Asthal Bohar, Rohtak

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Abstract

Chlorhexidine is an antiseptic effective against a wide variety of gram-negative and gram-positive organisms, facultative anaerobes, aerobes, and yeast. It is used as a topical anti-infective for skin, mucous membranes and as a preservative for eye drops. Chlorhexidine is also used as an antiseptic ingredient used in mouthwash to prevent oral plaque, oral bacteria and in treating gingivitis. Antimicrobial effect Chlorhexidine gluconate is associated with the attractions between Chlorhexidine (cation) and negatively charged bacterial cells. After Chlorhexidine is absorbed onto the organism's cell wall, it disrupts the integrity of the cell membrane and causes the leakage of intracellular components of the organisms.The present study involved the preparation of topical gel of Chlorhexidine. Gel formulations were prepared using Lutrol F-127 (5, 10, 15, 20 and 25%) by using cold process. For the preparation of gels weighed quantity of Lutrol F-127 was placed in the beaker. To that weighed quantity of propylene glycol and Suc-chi was added. Then mixture was kept in an ice bath having temperature ranging from 2-4 oC on magnetic stirrer. Then accurate quantity of pre-cooled distilled water was added and stirred for 30 mins. Then this dispersion was kept in a freezer overnight to remove the air bubble.Topical gel was evaluated for appearance, pH, content uniformity, drug content, spreadibility and in vitro release studies.

Keywords: - : spreadibility, topical gel, invitro release, antiseptic etc.

INTRODUCTION

Chlorhexidine is an antiseptic effective against a wide variety of gram-negative and gram-positive organisms, facultative anaerobes, aerobes, and yeast. It is used as a topical anti-infective for skin, mucous membranes and as a preservative for eye drops. Chlorhexidine is also used as an antiseptic ingredient used in mouthwash to prevent oral plaque, oral bacteria and in treating gingivitis. Antimicrobial effect Chlorhexidine gluconate is associated with the attractions between Chlorhexidine (cation) and negatively charged bacterial cells. After Chlorhexidine is absorbed onto the organism's cell wall, it disrupts the integrity of the cell membrane and causes the leakage of intracellular components of the organisms. Chlorhexidine Gluconate solution is an aqueous solution of 1, 1'-hexamethylenebis [5-(4-chlorophenyl) biguanide] digluconate.

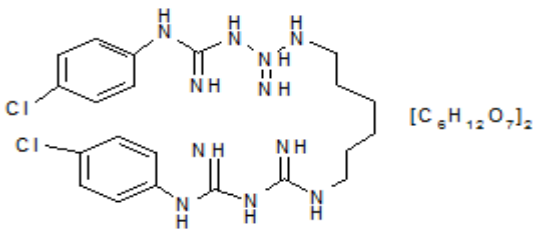

Figure 1: Structure of Chlorhexidine

The molecular weight is 505.46. The melting point is 132-136 °C. The pH of the drug is between 5.5- 7.0, determined in a solution obtained by diluting 5 ml to 100 ml. this drug is under the category of antiseptic, anti-bacterial agents, anti-infective agents, local anti-infective, disinfectants and mouthwashes. It is almost colorless or pale yellowish, clear or slightly opalescent liquid or almost odorless. It is miscible with water, soluble in ethanol (95%) and in acetone. It is store in well closed light resistant containers. The protein binding efficiency of the drug is 87%.

Materials and Methods

Chlorhexidine gluconate was gifted from Dr. Reddy's Pharmaceutical, Hyderabad, India. Sodium hydroxide, acetone, sodium hypochlorite, isopropyl alcohol, succinic anhydride, ethanol, acetic acid, polyethylene glycol 400, sodium acetate, sodium chloride, citric acid and methanol were purchased from Haryana Scientific Emporium. Chitin was gifted from Gadremarine Ratanagiri. Lutrol F-127 was gifted from Dr. Reddy's Pharmaceutical, Hyderabad, India.

Experimental methods

Formulation development of Chlorhexidine gluconate topical gel

Gel formulations were prepared using Lutrol F-127 (5, 10, 15, 20 and 25%) by using cold process. For the It

preparation of gels weighed quantity of Lutrol F-127 was placed in the beaker. To that weighed quantity of propylene glycol and Suc-chi was added. Then mixture was kept in an ice bath having temperature ranging from 2-4 oC on magnetic stirrer. Then accurate quantity of pre-cooled distilled water was added and stirred for 30 mins. Then this dispersion was kept in a freezer overnight to remove the air bubble.

1. Polymer selection

For the preparation of the gel formulation first of all alone succinyl chitosan was used as a gelling agent but the concentration of succinyl chitosan required is so more (up to 10 %) which is not cost-effective. For that a combination of gelling agent were used. In combination with a succinyl chitosan copolymers carbopol- 940, Sodium CMC and Lutrol F-127 in different concentration were used. It was found that out of these three copolymers Suc-chi showed incompatibility with carbopol- 940, Sodium CMC due to their precipitation in the gel formulation. Suc-chi was found compatible with Lutrol F-127; hence it was used as copolymer in gel formulation.

2. Process optimization

Chlorhexidine gluconate gel can be prepared by two methods i.e. hot and cold method. In hot method Lutrol F 127 was dissolved in water at approx. 70 °C. Then Chlorhexidine gluconate was added into propylene glycol and that mixture was then added into the warm aqueous phase to form a homogeneous mass. The gel was form when the solution cools to room temperature. In cold process for the preparation of gels weighed quantity of Lutrol F-127 was placed in the beaker. To that weighed quantity of propylene glycol, a Suc-chi was added. Then mixture was kept in an ice bath having temperature ranging from 2-4 oC on magnetic stirrer. Then accurate quantity of pre-cooled distilled water was added and stirred for 30 mins. Then this dispersion was kept in a freezer overnight to remove the air bubble.

Both methods of preparation will generally yield gels with comparable properties. But it was found that Chlorhexidine is unstable above 70oC and also adding Lutrol F 127 too rapidly to the hot aqueous phase may result in the formation of lumps that will only dissolve after standing for several hours. Hence it was recommended that preferably “cold process” should be used for the preparation of gel.

Evaluation of gels

Gels were evaluated for appearance, consistency, pH, viscosity, spreadability, skin irritation, drug content, content uniformity and in-vitro drug release.

1. Appearance

It was found that gel with 5 and 10 percent concentration of propylene glycol become a clear and transparent while gel with 15 and 20 percent concentration of propylene glycol becomes a whitish in colour. All the gels were smooth in texture and homogeneous in nature.

2.pH

pH of all gel formulation were found to be between 6 to 7 thus indicating suitability for topical application.

3.Speadability

Easy spreadability is one of the important characteristic of any topical preparation as far as patient compliance is concerned. Moreover if gel spreads easily, its application to the concerned area would be more comfortable and also relatively small amount of gel would be required to cover the wounded area. Gel was considered good when it took minimum time to spread on a body surface. It was found that spreadability of formulation C9-C15 were comparatively more than that of the other formulations, which indicate that the concentration of polaxomer affect the spreadability of the gel formulation i.e. as the concentration of polaxomer increases the spreadability gel decreased.

4.Drug content and content uniformity

Drug content and content uniformity of the gel formulations were determined by UV spectrophotometric method and it was found to be within limit except formulation C9, C18, C19 and C20 which deviate from the limit. It was found that such deviations were due to the higher concentration of the polaxomer in the gel, because of that gel became thick which lead to the uneven distribution of drug in the gel, hence show deviation from the limit.

5. In-vitro drug release:

In-vitro release of Chlorhexidine gluconate from gel formulation was studied on Keshary Chien diffusion cell using cellophane membrane. From the result it was found that as the concentration of the polaxomer increase from 10 percent up to 25 percent the drug release from the gel get decrease significantly. Gel formulation C10 show better release than that of the plain Chlorhexidine gluconate gel as well as the marketed gel formulation.

Table 1: Concentration of various ingredients in gel formulation:

Sample ID	Chlorhexidine gluco. Solution (%)	Suc-chi (%)	LutrolF-127	Propylene glycol (%)	Distilled water %)
C9	1	1	15	5	78
C10	1	1	15	10	73
C11	1	1	15	15	68
C12	1	1	15	20	63
C13	1	1	20	5	73
C14	1	1	20	10	68
C15	1	1	20	15	63
C16	1	1	20	20	58
C17	1	1	25	5	68
C18	1	1	25	10	63
C19	1	1	25	15	58
C20	1	1	25	20	53

Table 2: Data of evaluation parameter of gel formulation

Formulation code	Physical appearance	Texture	pH	Spreadability (cm)	Viscosity (in Pascal Second)
C9	Transparent	S	6.91	2.5	0.185663
C10	Transparent	S	6.64	2.9	0.2428
C11	Whitish	S	6.92	3.0	0.2376
C12	Whitish	S	6.74	2.6	0.2812725
C13	Transparent	S	6.69	2.4	0.32467625
C14	Transparent	S	6.91	2.1	0.35479875
C15	Whitish	S	6.38	2.2	0.3470875
C16	Whitish	S	6.81	1.8	0.021816667
C17	Transparent	S	6.85	1.8	0.0983025
C18	Transparent	S	6.74	1.8	0.03315
C19	Whitish	S	6.69	1.9	0.043045333
C20	Whitish	S	6.81	1.9	0.03404225
Plain chlor gel	Transparent	Smooth	6.71	2.3	0.1983
Marketed	Transparent	Smooth	6.65	2.5	0.2143

Table 3: Data of drug content and content uniformity of gel formulation

Parameters / Formulation code	Drug content (µgm/ml)	Content uniformity (%)
C9	16.3589	80.82067
C10	19.9750	99.36583
C11	19.4505	97.057
C12	20.7584	102.1602
C13	19.3189	96.5945
C14	19.5898	97.89733
C15	20.4914	102.6873
C16	20.1741	101.8637
C17	20.6113	102.8438
C18	18.7424	93.654
C19	22.2287	110.8355
C20	25.1153	125.5635
Plain chlor gel	19.3452	96.55717
Marketed	20.4328	101.8498

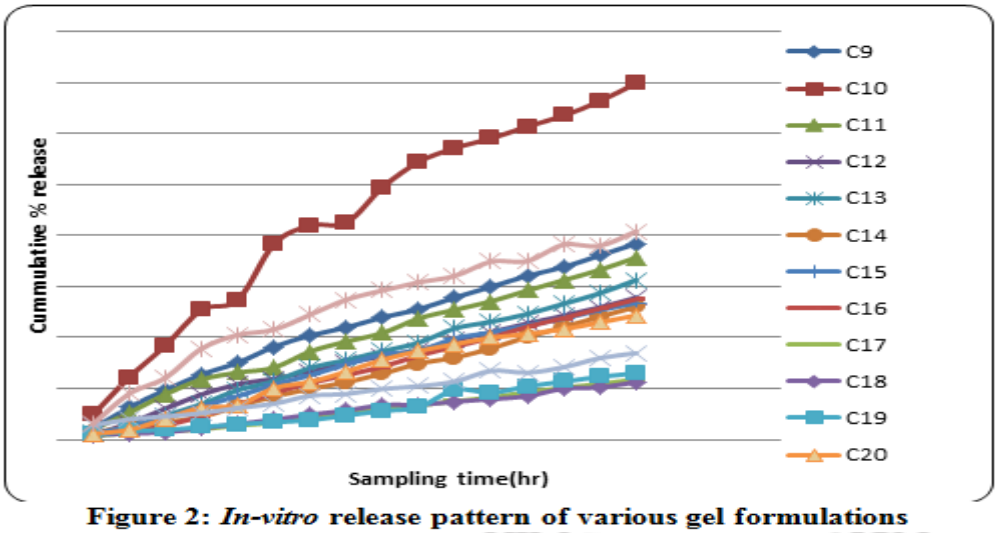

Figure 2: *In-vitro* release pattern of various gel formulations

Summary

Topical therapies present a valuable therapeutic option for Osteoarthritis, Rheumatoid arthritis & ankylosing spondylitis pain management including several other inflammatory diseases. In context with topical application of a drug, critical barrier of epidermal membranes offer several diffusional resistance in the course of skin permeation. Thus, the developments of topical products which allow penetration of compounds into the skin require utilization of several approaches. Chlorhexidine is an antiseptic effective against a wide variety of gram-negative and gram-positive organisms, facultative anaerobes, aerobes and yeast. It is used as a topical anti-infective for skin, mucous membranes and as preservative for eye drops. Chlorhexidine is also used as an antiseptic ingredient used in mouthwash to prevent oral plaque, oral bacteria and in treating gingivitis. For the preparation of the gel formulation succinyl chitosan was used as gelling agent. In the combination with a succinyl chitosan co-polymers such as carbopol-940, sodium CMC and Lutrol F 127 were used. It was found that out of these three co-polymers succinyl chitosan showed incompatibility with carbopol-940, sodium CMC due to their precipitation in the gel formulation. Succinyl Chitosan was found compatible with Lutrol F 127; hence it was used as co-polymer in gel formulation. Polymers were characterized using parameters such as solubility, pH, moisture content, ash content, bulk density, tapped density and angle of repose. Gel formulations were prepared with Lutrol F 127 (5, 10, 15, 20, and 25%) by using cold process. Hot process was not found to be suitable for preparation of the gel as it was found that chlorhexidine is unstable above 70 °C and also adding Lutrol F 127 too rapidly to the hot aqueous phase may result in the formation of lumps that will only dissolve after standing for several hours. Various batches of formulations were prepared and characterized using parameters like appearance, consistency, pH, viscosity, spreadability, drug content, content uniformity and in-vitro drug release. The gels were visually inspected for colour, texture and clearity. It was found that gel prepared with 5 and 10 % concentration of propylene glycol was clear and transparent in appearance while gel with 15 and 20 % concentration of propylene glycols was a whitish in colour. 1g of the prepared gel was mixed with 100 ml of suitable solvent. Aliquots of different concentrations were prepared by suitable dilutions after filtering the stock solution and absorbance was measured. Drug content and content uniformity was calculated using the equation, which was obtained by linear regression analysis of calibration curve. C9, C18, C19, and C20 which deviate from the limit. It was found that such deviations were due to the higher concentration of the polaxomer in the gel, because of the gel become thick which lead to the uneven distribution of drug in the gel; hence show deviation from the limit. Spreadability was expressed in terms of time in seconds taken by two slides to slip off from gel and placed in between the slides under the direction of certain load lesser the time taken for separation of two slides, better the spreadability. It was found that spreadability of formulation C9-C15 were comparatively more than that of the other formulations, which indicate that the concentration of polaxomer affect the spreadability of gel formulation i.e as the concentration of polaxomer increases, the spreadability of gel decreased.

Conclusion

The absorbance maxima of chlorhexidine gluconate were found as 231.5 nm which was selected for UV

analysis. Chlorhexidine gluconate was found to be almost colourless or pale yellowish, clear or slightly opalescent liquid, almost odourless. The melting point of chlorhexidine was found to be 132- 136° C. The molecular weight of chlorhexidine was found to be 505.46 gm. Chlorhexidine gluconate was found to be miscible with water, soluble in ethanol (95%) and in acetone. Chlorhexidine gluconate was prepared by using two methods i.e., hot and cold method. In hot method chlorhexidine is unstable above 70° C and also adding Lutrol F 127 too rapidly to the hot aqueous phase may result in the formulation of lumps that will only dissolve after standing for several hours. Hence, it was recommended that preferably "cold process" should be used for the preparation of gel. Characterization of topical gel was performed on the basis of appearance, consistency, pH, viscosity, spreadability, drug content, content uniformity and in-vitro drug release. Gel formulation with 5 and 10% concentration of propylene glycol became clear and transparent while gel with 15 and 20% concentration of propylene glycol became a whitish in colour. Spreadability of formulation C9-C15 were comparatively more than that of the other formulations, which indicated that the concentration of polaxomer affected the spreadability of the gel formulation i.e., as the concentration of polaxomer increases, the spreadability of gel decreased. It was found that drug content and content uniformity of formulation C9, C18, C20 deviated from the limit which may be due to the higher concentration of the polaxomer in the gel, imparting thickness to the gel which lead to the uneven distribution of drug in the gel, hence showed deviation from the limit. In-vitro release study was done with the help of Keshary Chien Diffusion Cell. Gel formulation C10 showed better release than that of plain chlorhexidine gluconate gel as well as marketed gel formulation.

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Correspondence Address:
Babita
Baba Mastnath University, Asthal Bohar, Rohtak
Email: suhagbabita7@gmail.com
Phone: +91-