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DEVELOPMENT AND VALIDATION OF ANALYTICAL METHODS FOR ANTIBACTERIAL DRUGS – A REVIEW

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ABSTRACT

Skin and Soft skin infections are been reported widely across various region. Topical medications are key agents in treating a range of skin conditions. Topical antibacterial are commonly used for superficial pyodermas such as impetigo and treatment or prevention of infections following minor cuts, abrasions, burns, and surgical wounds and other skin infections. Several antibiotics and antiseptics are available for used in skin disease such as bacteria causes cellulitis, impetigo and staphylococcal infections. In this review article, we have compared multiple antibiotics and antiseptics simultaneously or individually for their respective reported analytical methods along with patents. The main objective of the review article is to provide a detailed study of antibacterial drugs along with reported analytical methods and patent search of these drugs which may serve the purpose of summarised data of antibacterial drugs using a common review article.

Keywords: Analytical method validation, Antibiotic, Antiseptic, Antibacterial resistance, Skin infections, High Performance Liquid Chromatography, Stability Indicating method, UV visible spectroscopy

INTRODUCTION

The first line of protection against a variety of bacterial invaders is the skin. The skin's natural defence deteriorates when its integrity is intentionally or unintentionally violated, which is when anti-bacterial come into play **[1]**. The topical route of administration has a number of benefits above systemic administration, including avoiding widespread toxicity and side effects reducing the generation of bacterial resistance, and concentrating high amount of antibacterial agent at a source of transmission **[1]**.

Normal, healthy skin acts as a strong natural defence against disease invasion. An individual might become more vulnerable to infection if this barrier is compromised **[2]**. Therefore, cutaneous bacterial infections can result from physical damage such as wounds, burn, scars, and skin irritation as well as existing dermatoses associated with compromised membrane state, nutritional deficiencies, diabetes mellitus, and other inherited and congenital immunodeficiency disorders **[3]**.

Skin infections are frequently prevented and treated using topical antibiotics. Additionally, topical anti-bacterial are used to treat acne vulgaris, which aetiology involves bacterial infection **[3]**.

TYPES OF ANTIBACTERIAL DRUGS:

ANTISEPTICS: Antiseptics are cleaning solvents that have the potential to kill or suppress bacteria on exposed skin and in some open wounds. Antiseptics frequently have several different modes of motion, a wide range antibacterial persistent antibacterial activities effects **[4]**.

ANTIBIOTICS: In order to conduct this review, an antibiotic is broadly specified as any real (made by microbes) or artificial material that can either kill or limit the growth of pathogens in low concentrations. They often have a restricted spectrum of activity and one single cell target **[4]**.

ETIOPATHOGENESIS OF ANTI-BACTERIAL SKIN INFECTIONS

The skin is thought to serve as very effective defence towards penetration and subsequent bacterial illnesses, even though numerous other bacterial species come into touch with it or may be present there **[5]**.

PRIMARY BACTERIAL SKIN INFECTIONS

Common skin bacterial infections are typically started by a single organism, occurring most frequently on healthy skin and showing a distinctive shape and course. Streptococcus pyogenes, Staphylococcus aureus, and occasionally coryneform bacteria are the pathogens most frequently linked to this kind of infection **[6]**.

SECONDARY BACTERIAL SKIN INFECTIONS

A variety of bacterial species might flourish and induce secondary cutaneous illnesses on account of the damp, injured skin. Intertrigo and toe web infectious diseases are a couple of the prevalent examples **[6]**.

TREATMENT:

The type and severity of the infection will determine how it is treated. Several viral skin infections often heal on their own in a period of days or weeks **[7]**.

Oral antibiotics or topical antibiotics given directly to the skin are frequently used to treat bacterial infections. If the bacterium strain is difficult to treat, curing the disease can necessitate intravenous antibiotics given in a medical facility. Antibiotics given by mouth, such as penicillin, can cure

the infection. Cold packs and drugs for pain may relieve discomfort **[7]**.

Symptoms of a skin infection can be managed at home. The following may be provided as home care: **[7]**

- Apply cold compresses to your skin several times a day to reduce itching and inflammation.
- Take over-the-counter antihistamines (e.g. Chlorpheniramine) to decrease itching.
- Use topical creams (e.g. Fusidic Acid & Betamethasone Dipropionate Cream)and ointment (e.g. Neosporin)to reduce itching and discomfort.
- Depending on the cause of the infections, syrups and injections are also used to treat it.

MECHANISM OF THE SKIN AND SOFT SKIN INFECTIONS:

Figure 1 revels the mechanism of the bacterial infections into the skin tissues by the genetic disorders or the environmental factors **[7]**.

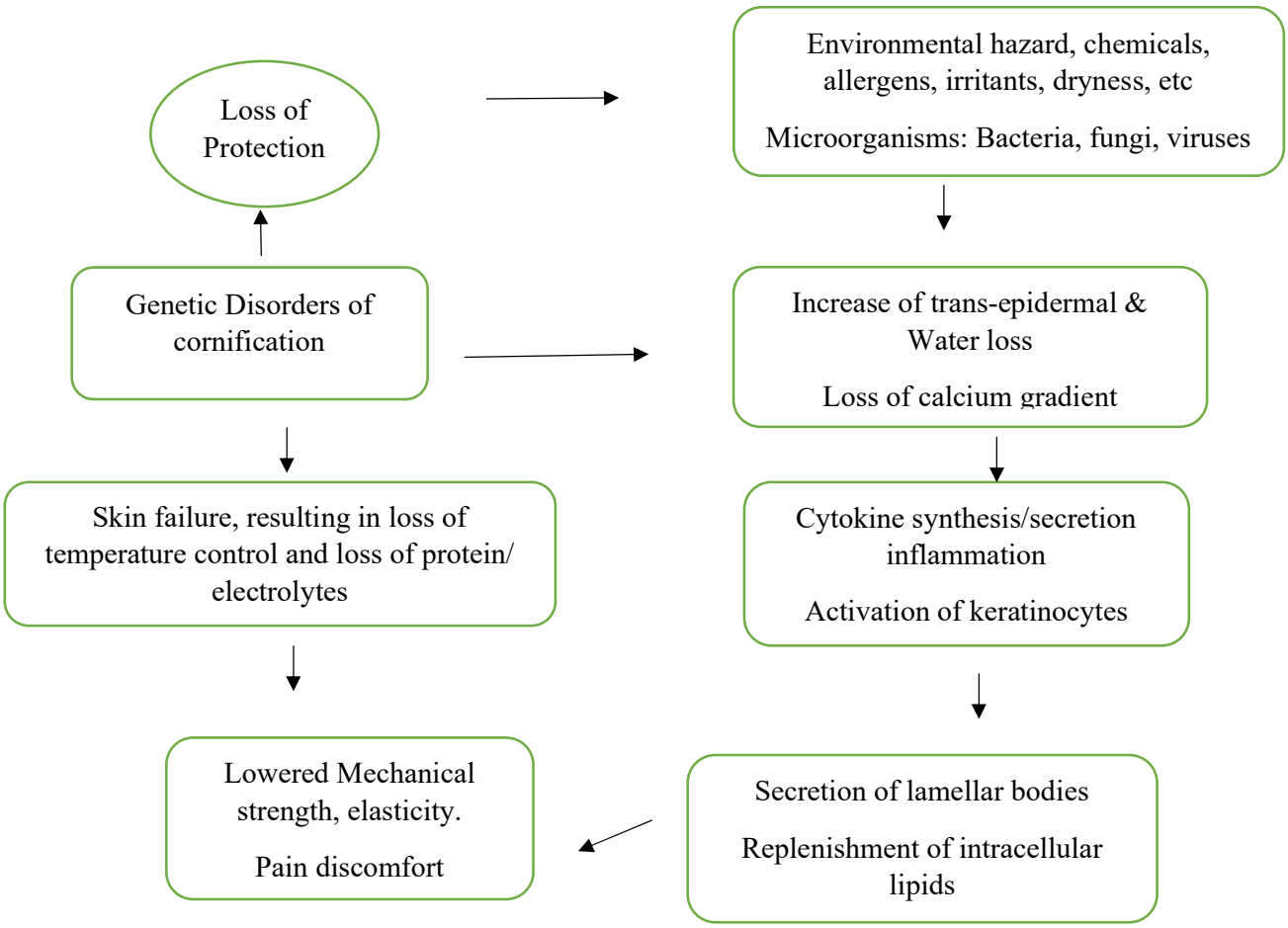

Figure 1: Genetic Disorders and Environmental Factors affect Skin Infections

PATENT SEARCH FOR ANTI-BACTERIAL DRUGS

Over the years there has been many research done on antibacterial drugs and many patents that can be beneficial for research purposes, **Table 1** represents a list of patent search for antibacterial drugs.

LIST OF ANALYTICAL METHODS OF ANTIBACTERIAL DRUGS:

Analytical techniques must be validated before being used for regular analysis. As per the ICH Q2(R1) guidelines also mention that analysis must be carried out according to the protocol and acceptance criteria must be followed. **Table 2** represents the reported methods such as LC-MS, RP-HPLC, UPLC, and UV spectrophotometry for assessment of anti-bacterial drugs.

Table 1: Patent of Antibacterial Drugs

Sr no	Patent Application No	Patent Title	Summary
1.	CN112315904A	Vancomycin hydrochloride solution and preparation method thereof [8]	The cosolvent and organic acid are combined to improve the stability of vancomycin hydrochloride solution, the stability problem of the vancomycin hydrochloride solution preparation is solved [8].
2.	CN106963939A	Vancomycin hydrochloride medicine composition and method for preparing vancomycin hydrochloride medicine composition [9]	The method has the advantages that components in the vancomycin hydrochloride medicine composition are easily matched with one another, and medicines are high in stability [9].
3.	CN107118129A	Antibacterial pharmaceutical Composition, method of preparation, and application [10]	Antibacterial medicament contents provided by the invention can be used for the preparation of an antibacterial medicine [10].
4.	CN107325159A	Vancomycin derivatives, preparation method thereof, pharmaceutical composition and application [11]	An application of the compound to prepare a medicine for treating and/or preventing bacterial infectious diseases, especially infectious diseases caused by gram-positive bacteria [11].
5.	CN101991557A	Liquid vancomycin capsule and preparation method thereof [12]	The liquid vancomycin hydrochloride capsule that has the benefit of quick effect-taking performance, low side effect, & attractive appearance [12].
6.	CN107595782A	Linezolid dry suspension and preparation method thereof [13]	The linezolid dry suspension provided by the invention has the dosage form advantages, and thus achieves the effects that the transportation is convenient; the long-time storage stability is high [13].
7.	CN104586768A	Linezolid-containing anti-infection pharmaceutical composition and preparation method thereof [14]	The pharmaceutical composition contains 1.0-5.0% (g/ml) of linezolid and is composed of an ethosome drug-loading system and a hydrogel system; and the pharmaceutical composition can be prepared into a linezolid-ethosome gel spray [14].
8.	CN111686072A	Linezolid injection and preparation method thereof [15]	The preparation method of the linezolid injection comprises the steps of weighing, preparation, filtration, encapsulation and sterilization, and nitrogen filling protection is carried out on liquid medicine [15].
9.	US10933019B2	Liquid formulations of daptomycin [16]	Provided formulations including daptomycin, a single polar protic solvent, or a combination of polar protic solvents. Formulations made in a calcium source or a polar aprotic solvent may also be included in line with the present invention. [16].
10.	CN114344447A	Daptomycin for injection and preparation method [17]	Injection is prepared by sequentially separating and purifying through ion exchange resin, macro porous adsorption resin, polymer resin and C18 resin, and then crystallizing, redissolving, desalting [17].
11.	CN108743552A	Compound sulfamethoxazole tablet and preparation method thereof [18]	The compound sulfamethoxazole tablet takes sulfamethoxazole and trimethoprim as the main drugs, and is added with a filler a lubricant, a

			surfactant, an adhesive, a disintegration agent, and a coating agent [18].
12.	**CN113952296A**	**Preparation method of compound sulfamethoxazole injection [19]**	**The ratio of sulfamethoxazole to trimethoprim is 5: 1, and in addition, the ethanolamine, propylene glycol, ethyl alcohol, sodium pyro-sulphite and water for injection are added as auxiliary materials [19].**
13.	**CN106727618A**	**Compound sulfamethoxazole oral suspension and preparation method thereof [20]**	**The preparation method is simple, the process is controllable, the compatible stability is high for composition medicine, and the component efficacy is high in preservation degree [20].**
14.	**CN101555215A**	**Preparation technology of doxycycline hydrochloride for injection [21]**	**The injection-grade doxycycline hydrochloride can be used for preparing medical preparation for intravenous injection, such as the doxycycline hydrochloride powder injection, lyophilized powder injection and injection liquid for in vivo injection [21].**
15.	**CN105267977A**	**Dissolvable doxycycline powder and preparation method thereof [22]**	**The dissolvable doxycycline powder is prepared by a saturated water solution method, the preparation method is simple in technological process, and the dosage form of the dissolvable doxycycline powder is powder [22].**
16.	**CN103083264A**	**Doxycycline tablet and preparation method thereof [23]**	**The doxycycline tablet comprises, by weight, 10 to 50% of doxycycline and 50 to 90% of one or more pharmaceutic adjuvants, wherein the one or more pharmaceutic adjuvants are selected from a disintegrating agent [23].**
17.	**CN103263391A**	**Doxycycline hydrochloride dry suspension and preparation method thereof [24]**	**The doxycycline hydrochloride dry suspension disclosed by the invention is relatively high in settling volume and capable of realizing improving dispersing stability during a taking process [24].**
18.	**CN104095809A**	**Pharmaceutical composition of clindamycin phosphate injection and preparation method [25]**	**The pharmaceutical composition of the clindamycin phosphate injection comprises clindamycin phosphate, a complexing agent, a bacteriostat, a pH adjusting agent and water for injection [25].**
19.	**CN101780032A**	**Clindamycin phosphate injection preparation and prepar ation method thereof [26]**	**The clindamycin phosphate injection preparation comprises clindamycin phospha te, a cosolvent, a metal ion complexing agent, a solvent of raw materials and auxiliary materials [26].**
20.	**CN113768866A**	**Clindamycin phosphate suppository and preparation method thereof [27]**	**The clindamycin phosphate suppository is prepared from 4-5 parts by weight of clindamycin phosphate and 55-135 parts by weight of semi-synthetic fatty acid glycerine [27].**
21.	**CN105640898A**	**Dalbavancin pharmaceutical com position for injection. [28]**	**The dalbavancin pharmaceutical composition mainly comprises an active component dalbavancin, mannitol, and sodium hydroxide [28].**
22.	**WO2006078277A2**	**Dalbavancin Compositions in order to treat bacterial infections [29]**	**The administration of dalbavancin medicines, specifically a Gram-positive antibiotic, for the cure of bacterial illnesses bacterial infection of skin and soft tissue, is one of the invention's methods. [29].**
23.	**CN108926706A**	**Pharmaceutical composition for infection treatment and preparation method thereof [30]**	**A pharmaceutical composition for infection treatment, wherein the pharmaceutical composition comprises medicinal active ingredients of a glycopeptide antibacterial drug [30].**
24.	**CN113520994A**	**Mupirocin ointment preparation [31]**	**The ointment preparation specifically comprises mupirocin, polyethylene glycol 400, polyethylene glycol 3350 and a cellulose derivative, the obtained preparation can solve the stability problem of mupirocin ointment [31].**
25.	**WO2020141482A1**	**Pharmaceutical Compositions Comprising Mupirocin [32]**	**A pharmaceutical composition meant for administering to mucosal surface comprising mupirocin or a pharmaceutical acceptable salt thereof and a process for its preparation [32].**
26.	**WO2007075794A2**	**Oral Formulations Comprising Tigecycline [33]**	**Pharmaceutical mixtures that contain tigecycline for oral use. Tigecycline with at least single enteric coating may be included in the mix. [33].**

27.	**CN105079816A**	**Tigecycline pharmaceutical composition and preparation method thereof [34]**	**Relates tigecycline pharmaceutical composition and a preparation method thereof, particular to stable tigecycline pharmaceutical composition [34].**
28.	**CN102138925A**	**Tigecycline composition and preparation method thereof [35]**	**The composition available by the innovation is adding one or more selected from Vitamin C or pharmaceutically acceptable salts thereof and amino acids [35].**
29.	**CN103120692A**	**Preparation method for injection cefoperazone sodium tazobactam sodium composition [36]**	**The preparation method comprises the following steps of: crushing the cefoperazone sodium and the tazobactam sodium; and mixing the cefoperazone sodium and the tazobactam sodium in a weight ratio of 4:1; and separately packaging, pressing and capping the mixture [36].**
30.	**WO2014146775A1**	**Fluoroquinolone Antibacterial Agent and Method for Its Preparation in a Pharmaceutical Composition [37]**	**The current invention relates to a stable pharmaceutical formulation for orally administered that contains an appropriate salt of the antibacterial fluoroquinolone or a therapeutically effective amount of it [37].**
31.	**CN103830240A**	**Fluoroquinolone medicine composition [38]**	**The fluoroquinolone medicine composition provided by the invention has the advantages that the content of the fluoroquinolone medicine is greatly increased and the treating effect of one-time administration is greatly improved [38].**

Table 2: Reported Method for Assessment of Anti-bacterial Drug

Sr No.	Title	Description
1.	**Vancomycin HPLC method development and validation, and application in a pharmacokinetic study [40]**	**Column: Nucleosil 120 C_{18}, 5 µm, Mobile phase: 0.05M $NH_4H_2PO_4$– Acetonitrile (92:8, v/v) Detection: UV at 220nm [40].**
2.	**A Rapid and Efficient HPLC Method for Vancomycin Therapeutic Monitoring [41]**	**Column: C18 silica-based, 2.7µm Mobile phase: Ammonium acetate/formic acid buffer (pH 4.0): methanol 88;12(v/v) Detection: UV at 240nm [41].**
3	**Development and validation of the LC-MS/MS technique for the detection of vancomycin and polymyxins in rat plasma [42]**	**Column: C18 5µm 300 Å 50 mm × 2mm Mobile phase: pH-2.8 Detection: At UV 240nm [42].**
4.	**Application to investigations on the pharmacokinetics and biodistribution of vancomycin in rat plasma, skin, and lymph nodes using a sensitive HPLC-UV technique [43]**	**Column: cortecs C18 [4.6 × 150mm, 2.7µm particle size] Mobile phase: phosphate buffer contains 0.5% v/v of triethyl-amine and mixture of methanol-acetonitrile (70:30 v/v) Detection: UV at 215nm [43].**
5.	**By using reversed-phase high-performance liquid chromatography, linezolid can be identified in plasma. [44]**	**Column: Reversed-phase (C8, 4.6×150mm,5µm) Mobile phase: 20% Acetonitrile in Water Detection: UV at 251nm [44].**
6.	**Linezolid concentrations in several biomatrices can be found using a basic isocratic HPLC assay for in vivo and in vitro research [45]**	**Column: Reversed-phase C8 column Mobile phase: Water and acetonitrile (80:20% v/v) Detection: UV at 251nm [45].**
7.	**Developing a Validated Stability-Indicating LC Assay and Studying Linezolid Stress Degradation in Tablets [46]**	**Column: Reversed phase on RP-18 Mobile phase: 1% Acetic acid: methanol: Acetonitrile (50:25:25, v/v/v) Detection: UV at 251nm [46].**
8.	**A stability-indicative agar diffusion assay has been created and validated to assess the effectiveness of linezolid in tablets in the existence of photodegradation products. [47]**	**Column: Symmetry Waters C18 column, 5µm, 250mm × 4.6mm Mobile phase: Aqueous 1% acetic acid: methanol: acetonitrile (50:25:25, v/v/v) Detection: UV at 254nm [47]**

9.	**Linezolid Estimation Using a Validated Stability Indicating Rp-HPLC Method in a Pharmaceutical Dosage Form [48]**	**Column: C18 Mobile phase: Water: methanol (50:50 v/v) Detection: UV detected at 254nm [48].**
10.	**An ultra-performance liquid chromatography-tandem mass spectrometry method for measuring the amount of daptomycin in human plasma has been developed and validated. [49]**	**Column: C18 (100mm × 2.1mm,1.7µm) Mobile phase: Gradient with 0.1% formic acid and acetonitrile with 0.1% formic acid Detection: UV at 262nm [49].**
11.	**For the purpose of detecting daptomycin in rabbit plasma, a UPLC-UV technique has been developed and validated. [50]**	**Column: C18 Mobile phase: Gradient elution using 0.1% aqueous Trifluoroacetic acid and methanol Detection: UV at 262nm [50].**
12.	**In comparison to reference mass spectrometry, a new, validated HPLC-UV approach for therapeutic evaluation of daptomycin [51]**	**Column: C18 (250×4.6mm,5µm) Mobile phase: isocratic consisted of acetonitrile buffer KH2PO4 pH= 3.2 Detection: UV at 262nm [51].**
13.	**Daptomycin injectable form determination using a stability-indication LC-UV approach that has been developed and validated, together with a kinetic analysis in an alkaline medium [52]**	**Column: C18, 250mm × 4.6mm, 5µm Mobile phase: Methanol-acetonitrile-buffer (pH 2.2) Detection: Photodiode array at 223nm [52].**
14.	**Doxycycline Hyclate Quantification in Tablets Using the HPLC-UV Method [53]**	**Column: 250 × 4.6mm, 5.0 µm particle size Mobile phase: Water + 0.1% TFA-acetonitrile with 0.1%TFA, 60:40v/v Detection: UV at 360nm [53].**
15.	**Development of an HPLC technique for measuring doxycycline in human seminal fluid [54]**	**Column: Reversed- phase C18 column Mobile phase: Acetonitrile and water buffered at pH 2.5 with a concentrated Orthophosphoric acid in the volume ratio of 20:80 v/v Detection: UV at 350nm [54].**
16.	**Liquid chromatography with UV detection and liquid chromatography-tandem mass spectrometry were used to determine the presence of doxycycline in chicken fat. [55]**	**Column: Luna C8 analytical column and for LC-MS/MS analysis Mobile phase: Solution of oxalic acid (pH 4.0) and ethyl acetate Detection: UV at 350nm [55].**
17.	**An improvement to the analytical process for a medical countermeasure (MCM) medicine, doxycycline Hyclate, was developed and validated using an ultra-performance liquid chromatography (UPLC) approach. [56]**	**Column: Acquity BEH C18 (2.1 × 50mm, 1.7µm) column Mobile phase: 75mM ammonium acetate, 4mM EDTA (pH 8.8) and acetonitrile (97:3) Detection: UV at 270nm [56].**
18.	**Doxycycline Hyclate and Curcumin Simultaneous Estimation by RP-HPLC Method: Quality by Design Approach [57]**	**Column: C8 Column with dimension of 250 × 4.6mm, particle size 5.0µm Mobile phase: 30 volumes of potassium dihydrogen phosphate buffer Detection: UV at 400nm [57].**
19.	**HPLC Thermostability Testing and Doxycycline Degradation Profiles in Bulk, Tablets, and Capsules [58]**	**Column: µ- Bondapak C8 column (4.6 × 150mm, 5µm particle size Mobile phase: Acetonitrile with THF, adjusted pH 2.5 with 1.0M HCL Detection: UV at 350nm [58].**
20.	**Application in a preclinical pharmacokinetic investigation of a sensitive analytical technique to measure**	**Column: Gradient using a reverse phase C18 column Mobile phase: mixture of 1% formic acid in water and 1% formic acid in acetonitrile Detection: At 214nm [59].**

	clindamycin in plasma and micro dialysate samples [59]	
21.	**An innovative tablet formulation's clindamycin and related components were measured using a gradient HPLC method that was developed and validated. [60]**	**Column: Waters Xterra RP18 column (4.6mm × 100mm, 3.5µm) Mobile phase: pH 10.5, 10mM carbonate buffer and acetonitrile Detection: UV at 214nm [60].**
22.	**Reversed-phase high-performance liquid chromatography with a UV detector is a simple approach for measuring clindamycin in human plasma. [61]**	**Column: Reverse phase cyano (CN) column Mobile phase: Acetonitrile distilled water 7-6mm tetra-methylammonium chloride, adjusted to pH 3.2 Detection: UV at 204nm [61].**
23.	**Clindamycin determination in human plasma using coupled columns and high-performance liquid chromatography [62]**	**Column: Reverse-phase Nucleosil 100 C18 HD column Mobile phase: 80% acetonitrile-0.01% trifluoroacetic acid Detection: UV at 204nm [62].**
24.	**Dalbavancin Quantification in Human Plasma Using a New Liquid Chromatography Coupled to Mass Spectrometry (HPLC-MS) Method: Validation and Clinical Application [63]**	**Column: Atlantis T3 5µm 4.6 × 150mm column Mobile phase: MP-A, 0.05%v/v formic acid in HPLC-grade H2O and B MP-B 0.05%v/v formic acid Detection: At 300nm [63].**
25.	**The development and validation of a liquid chromatographic technique for the measurement of mupirocin in vitro in both skin layers and percutaneous penetration tests [64]**	**Column: Chromatographed on 250mm ×4mm C8 Lichrospher select B (5µm) Mobile phase: Mixture of acetonitrile ammonium acetate 0.05M adjusted to pH 6.3 with acetic acid Detection: UV at 228nm [64].**
26.	**Development and validation of a stability-indicating RP-HPLC technique for determining Mupirocin calcium in bulk and pharmaceutical formulation [65]**	**Column: PrincetoneSPHER-100-C8 (250×4.6mm,5µm) column Mobile phase: Methanol and Water (75:25 v/v) pH adjusted to 4 with acetic acid Detection: UV at 221nm [65].**

CONCLUSION:

Skin and Soft skin infections are been reported widely across various region. Topical medications are key agents in treating a range of skin conditions. The present review focuses on how antibacterial drugs affects the bacterial infection and their management for skin and soft skin tissues. This review works on the mechanism of the genetic disorders and environmental factors affects the skin infections. The review also represents the already reported various analytical methods for antibacterial drugs along with their patent search. The current review can be a guidance for development of any new antibiotic formulation and analytical method for the same.

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[11] Vancomycin derivatives, preparati on method thereof, pharmaceutical compositi on and application CN107325159A

[12] Liquid vancomycin hydrochloride capsule and preparation method thereof CN101991557A

[13] Linezolid dry suspension and preparation method thereof CN107595782A

[14] Linezolid-containing-anti-infection pharmaceutical composit ion and preparation method thereof CN104586768A

[15] Linezolid injection and preparation method thereof CN111686072A

[16] Liquid formulations of daptomycin US10933019B2

[17] Daptomycin for injection and preparation method CN114344447A

[18] Compound sulfamethoxazole table t and preparation method thereof CN108743552A

[19] Preparation method of compound sulfamethoxazole inject ion CN113952296A

[20] Compound sulfamethoxazole oral suspension and preparation method thereof CN106727618A

[21] Preparation technology of doxycycline hydrochloride for injection CN101555215A

[22] Dissolvable doxycycline powder and preparation method thereof CN105267977A

[23] Doxycycline tablet and preparation method thereof CN103083264A

[24] Doxycycline hydrochloride dry suspension and preparation method thereof CN103263391A

[25] Pharmaceutical composition of clindamycin phosphate injection and preparation method CN104095809A

[26] Clindamycin phosphate injection preparation and preparati on method thereof CN101780032A

[27] Clindamycin phosphate suppository and preparation method thereof CN113768866A

[28] Dalbavancin pharmaceutical comp osition for injection CN105640898A

[29] Dalbavancin Compositions for Treatment of Bacterial Infections WO2006078277A2

[30] Pharmaceutical composition for infection treatment and preparation method thereof CN108926706A

[31] Mupirocin ointment preparation CN113520994A

[32] Pharmaceutical Compositions Comprising Mupirocin WO2020141482A1

[33] Oral Formulations Comprising Tigecycline WO2007075794A2

[34] Tigecycline pharmaceutical compo sition-and preparation method thereof CN105079816A

[35] Tigecycline composition and preparation method thereof CN102138925A

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