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DEVELOPMENT AND EVALUATION OF TROCHES CONTAINING CHLORHEXIDINE HCL AND TRIAMCINOLONE FOR TREATMENT OF DENTAL PLAQUE, GINGIVITIS AND MOUTH ULCERS

***PATEL MANISHA R, Dr. SK JAIN, PRAVEEN TAHILANI, HARISHANKAR PANCHAL**

Sagar Institute of Research and Technology-Pharmacy, Ayodhya Bypass Road, Bhopal, M.P.

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Corresponding Author

Ms. Patel Manisha

Sagar Institute of Research and Technology-Pharmacy, Bhopal.

Abstract

The mouth of human body provides non-shedding surfaces (teeth) for natural microbial colonization. This can result in the accumulation of large masses of bacteria and their products at stagnant sites. Dental plaque and gingivitis are some of this type of conditions, which can develop due to microbial accumulation on teeth. And mouth ulcers are small, painful sores on the inside lining of the mouth. Chlorhexidine is widely used antimicrobial drug in treatment of dental plaque and gingivitis and triamcinolone is used as anti ulcerative as well as anti-inflammatory. A troche is a lozenge designed to deliver medications directly to the mucus membranes of the mouth by dissolving slowly when placed between the tongue and gums. Validated HPLC method was developed for quantitative estimation of Chlorhexidine HCl and Triamcinolone in dosage forms. Optimized mobile phase for these two drugs was 2.0 g of sodium octane sulphonate in a mixture of 120 ml of glacial acetic acid, 270 ml of water and 730 ml of methanol, and retention time was found as 9.8 and 4.2 minutes respectively for Chlorhexidine HCl and Triamcinolone.

Troches were formulated using sugar base mannitol, binder Avicel 102, sweetener- stavioside 80%, sodium saccharine, flavor-strawberry and ecocool. These were prepared using direct compression tablet technology. Use of ecocool imparted additional cooling effect and can increase patient compliances. Formulated troches were evaluated for weight variation, crushing strength, friability, thickness, taste, dissolution time, %assay and content uniformity. Crushing strength of optimized troches was found between 11-12 kg/cm. Antimicrobial study was performed on *staphylococcus mutans* and results revealed that Chlorhexidine HCl have antimicrobial effect. Troches containing combination of Chlorhexidine HCl and Triamcinolone were prepared.

INTRODUCTION

Chlorhexidine Hydrochloride (CHX) is recognized as the primary agent for chemical plaque control. It is effective in reducing gingivitis and potent chemotherapeutic agents against mutans streptococci and caries. It is effective on both gram-positive and gram-negative bacteria, although it is less effective with some gram-negative bacteria. It has both bactericidal as well as bacteriostatic mechanisms of action, the mechanism of action being membrane disruption, not ATPase inactivation as previously thought. It is also useful against fungi and enveloped viruses, though this has not been extensively investigated. Chlorhexidine's antimicrobial effects are associated with the attractions between Chlorhexidine HCL (cation) and negatively charged bacterial cells. After Chlorhexidine HCL is absorpted 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 major advantage of CHX over most other compounds lies in its oral substantively, because it is a cationic substance that binds to soft and hard tissues of the mouth as well as to bacterial cell walls. However, when formulations are prepared the availability of CHX can be impaired. While dentifrices are considered inappropriate vehicles to deliver CHX because of the detrimental interactions between CHX and the foaming and abrasive

agents used. Because CHX has an extremely bitter taste, it is often necessary to flavor and sweeten the products. Saccharin is considered compatible with CHX and has been used in any preparations. Sodium saccharine was used as 0.2% because as its concentration increases beyond 0.5%, antimicrobial activity of CHX decreases. 0.2% of sodium saccharine was not able to mask the bitter taste of CHX, so stavioside 80%, a natural sweetener was used to mask the bitter taste. This compound range in sweetness from 40 to 300 times sweeter than sucrose.

Triamcinolone and its derivatives are synthetic gluco corticoids used as anti inflammatory or immunosuppressive agents. Triamcinolone has little mineralo corticoid activity and is therefore not used to manage adrenal insufficiency unless a more potent mineralo corticoid is administered concomitantly. Topical triamcinolone preparations are considered medium or high potency. Corticosteroids exhibit anti-inflammatory, anti pruritic, and vaso constrictive properties. At the cellular level, corticosteroids induce peptides called lipocortins. Lipocortins antagonize phospholipase A^2, an enzyme which causes the breakdown of leukocyte lysosomal membranes to release arachidonic acid. This action decreases the subsequent formation and release of endogenous inflammatory mediators including prostaglandins, kinins, histamine, liposomal enzymes and the complement system. Early anti-inflammatory effects of topical corticosteroids include the inhibition of macrophage and leukocyte movement and activity in the inflamed area by reversing vascular dilation and permeability. Later inflammatory processes such as capillary production, collagen deposition, keloid (scar) formation also are inhibited by corticosteroids. Clinically, these actions correspond to decreased edema, erythema, pruritus, plaque formation and scaling of the affected skin.

There were no interactions found in our database between Chlorhexidine HCL topical and nystatin/triamcinolone topical.

The mouth of human body provides non-shedding surfaces (teeth) for natural microbial colonisation. This can result in the accumulation of large masses of bacteria and their products at stagnant sites. The types of mouth bacteria depend on the

environmental conditions inside the mouth. Acidity, alkalinity, temperature, host diet, and other factors affect the types of bacteria colonizing the mouth.[1]

Dental plaque forms naturally on teeth and acts as part of the defense of the host by helping to prevent colonization by exogenous and often pathogenic microorganisms. However, if plaque is allowed to accumulate beyond levels that are compatible with health, then disease can occur. Plaque is associated with two of the most prevalent diseases affecting industrialized societies, namely dental caries and periodontal diseases. Dental plaque has been defined as the diverse microbial community found on the tooth surface embedded in a matrix of polymers of bacterial and salivary origin. Plaque that becomes calcified is termed calculus or tartar. The resident plaque micro flora consists of a wide range of gram-positive and gram-negative bacteria, including facultative anaerobic and obligatory anaerobic species. The composition of plaque varies at different sites over the tooth surface due to differences in their local biological properties.[3]

Gingivitis is an apparently non-specific inflammatory response to dental plaque growth around the gums (gingival margins). If good oral hygiene is restored, gingivitis is usually eradicated and the gingival tissue becomes clinically normal again. Gingivitis is associated with an increase in plaque mass around the gingival margin. This leads to a shift in the composition of plaque away from a streptococci dominated micro flora towards higher levels of Actinomyces sp. and an increase in the isolation of Capnophilic and Obligatory anaerobic gram-negative bacteria. The micro flora increases in diversity during the development of gingivitis, but no particular group of bacteria is uniquely associated with disease. It is still not clear whether gingivitis is a prerequisite for the development of more advanced forms of periodontal disease but, perhaps significantly, it has been reported that some species that predominate in chronic periodontitis, but which are not detectable in the healthy gingival crevice, are also found as a small percentage of the flora in gingivitis.[5]

Mouth ulcers are small, painful sores on the inside lining of the mouth. They usually develop on the inside of the lips and cheeks

and on the underneath and edge of the tongue. Ulceration is a breach in the oral epithelium, which typically exposes nerve endings in the underlying lamina propria, resulting in pain or soreness, especially when eating spicy foods or citrus fruits. Patients vary enormously in the degree to which they suffer and complain of soreness in relation to oral ulceration. It is always important to exclude serious disorders such as oral cancer (Part 9) or other serious disease, but not all patients who complain of soreness have discernible organic disease. Conversely, some with serious disease have no pain. Even in those with detectable lesions, the level of complaint can vary enormously. Some patients with large ulcers complain little; others with minimal ulceration complain bitterly of discomfort. Sometimes there is a psychogenic influence. Mouth ulcers cannot be passed from person to person. For example, you cannot get an ulcer from kissing someone, or from sharing a glass, or cutlery.[6] The three main types of mouth ulcer are:

Minor ulcer: This is the most common type of ulcer. It account for 80% of all mouth ulcers. They are small (2-8mm in diameter) and normally heal naturally within 10-14 days. A minor ulcer will not cause any scarring.

Major ulcer: This type of ulcer is deeper and larger than a minor ulcer, and usually has a raised or irregular border. A major ulcer is usually 1cm or more in diameter. This type of ulcer will heal more slowly, over a period of several weeks, and can cause scarring. Approximately 10% of mouth ulcers are major.

Herpeti form ulcers: These ulcers form as multiple, pinhead sized sores. The number of ulcers can range from 5-100. These tiny ulcers often fuse together to form larger, irregular shaped sores which are extremely painful. Approximately 5-10% of mouth ulcers are herpetiform.

A troche is a lozenge designed to deliver medications directly to the mucus membranes of the mouth by dissolving slowly when placed between the tongue and gums. While placed in the mouth, these lozenges are not designed to be swallowed. They may be flavoured to make taking the medication more pleasant. Two types of lozenge bases have gained wide usage because of their ready adaptation to

modern high-speed methods of product manufacture. These two lozenge forms include hard (or boiled) candy lozenges and compressed tablet lozenges (troches). The term for this form of medication delivery is derived from the Greek word for "wheel" and troches are traditionally round in shape. The size of the medication can vary, depending on what is being delivered. This form of delivery is used when medications cannot be ingested because the digestive juices will damage or compromise the medication. An alternative to a troche might be a medication rubbed on the mucus membranes of the mouth, or a Trans dermal patch applied to the skin. As the troche breaks down in the mouth, the medication seeps through the porous mucus membranes in the mouth and rapidly enters the bloodstream. This allows for extremely rapid delivery of medications, which can be useful with medications like analgesic drugs. The blood levels of the medication will rise rapidly and then stabilize. Depending on the medication, doses can be repeated at varying levels to keep the level as stable as possible.[13]

Troches, with the desired area of activity on the mucous membrane of the mouth and pharynx, are usually large-diameter tablets (5/8 to 3/4 in.), compressed in a weight range of 1. 5- 4.0 g and formulated with a goal of slow, uniform, and smooth disintegration or erosion over an extended time period (5-10 min). In the case of the troches is on the slow, uniform release of medicament directly onto the affected mucous membrane. This attribute enhances the patient acceptance and desire to hold the tablet in the mouth until it is completely dissolved. The troches should erode (not disintegrate) while in the oral cavity, as the presence of particulate matter can be extremely disconcerting to the patient. For maximum drug efficacy the product must not be chewed.

MATERIALS & METHODS

MATERIALS

Mannitol: It is d-mannitol; Hexahydric alcohol related to mannose and is isomeric with sorbitol. It is commercially prepared by the catalytic or electrolytic reduction of monosaccharides such as mannose and glucose.

Stavioside 80%: The steviol glycosides are responsible for the sweet taste of the

leaves of the stevia plant (Stevia rebaudiana Bertoni). These compounds range in sweetness from 40 to 300 times sweeter than sucrose.

Magnesium stearate: Magnesium stearate is a compound of magnesium with a mixture of solid organic acids and consists chiefly of variable proportions of magnesium stearate and magnesium palmitate. This is prepared either by the interaction of aqueous solutions of magnesium chloride with sodium stearate, or by the interaction of magnesium oxide with stearic acid at elevated temperature. It is widely used in cosmetics, foods and pharmaceutical preparations, as a lubricant in capsule and tablet manufacture at concentrations between 0.25-5.0percent.

Microcrystalline cellulose (Avicel): Purified, partly depolymerised cellulose prepared by treating alpha-cellulose, obtained as a pulp from fibrous plant material, with mineral acids. It is used as binder/diluents in oral tablet and capsule formulations. It also has some lubricant and disintegrates properties that make it useful in tablet. It acts as spheronizing aid in preparation of pellets.

Sodium saccharin: Saccharin is produced by the oxidation of o-toluene sulfonamide by potassium permanganate in a solution of sodium hydroxide. Acidification of the solution precipitates saccharin, which is then dissolved in water at 50°C and neutralized by addition of sodium hydroxide. Saccharin sodium is an intense sweetening agent used in beverages, food products, table-top sweeteners and pharmaceutical formulations such as tablets, powders, medicated confectionery, gels, suspensions, liquids, and mouthwashes. Its sweetening power is approximately 300–600 times that of sucrose.

Ecocool: products are designed for immediate & extended cooling effect to the various formulations. The product benefit is that it prolongs cooling effect. It's used for flavoured drinks, ice-creams, fruit juices, health supplements, chewing gums, anti-dandruff shampoos, creams, flavoured mouth fresheners, shaving creams, lotions, tooth paste, mouth wash, prickly heat powder, pain balm, dry syrup & suspensions.

The products are designed to be available in the form of pellets, granules & solutions. The service support is provided as per the customer's requirement.

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Strawberry flavor: Strawberry got its name from the straw that farmers used to mulch the berry beds. Whatever you call it, the strawberry has become a well known addition to American desserts, including the very popular strawberry shortcake.

Strawberry Powder is used for making Ice-cream, Desserts, Dairy products, Bakery products, Jam, Jelly, Strawberry Milk Shake can also be prepared by blending sugar and cold milk to the powder.

Dosage: 0.2-0.5%

METHOD

Preformulation

Melting point of drug samples was determined by melting point apparatus, Rolex India.

Solubility analysis was done by the drugs were dissolved in different solvent and test its solubility in the dissolution medium which was to be used.

The partition coefficient (P) is defined as the ratio of the equilibrium concentrations (ci) of a dissolved substance in a two-phase system consisting of two largely immiscible solvents. In the case n-octanoland water.

Po/w = n-octanol /water.

And it is found out by shake flask method.

The pH is measured using a pH meter of a glass electrode by making 1% solution of samples.

The FT-IR spectrum of the sample of drug were taken and compared with the standard FT-IR spectra of the pure drug. The infrared absorbance spectrum of Chlorhexidine HCL and triamcinolone were recorded using a Brukar FT-IR Spectrophotometer over the range of 600 – 4000 cm-1 at a resolution of 4 cm-1.

UV–Vis spectrophotometer: absorption spectra were recorded in a wavelength range of 190–400 nm in a 10 mm quartz cell, by a Jasco V-530 (Jasco, Japan)

Spectrophotometer, in the following conditions: scan rate 100 nm min−1; time response: 1 s; spectral band 1 nm. For spectral acquisition and elaboration of the data obtained with V-530 Spectrometer (Jasco, Japan) the software Spectra Manager for Windows (Jasco) was used.

Bulk Density was determined by weighing accurately 10 g of drug, which was previously passed through #20 sieves and transferred in 25 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume (v0) and wt of powder was divided by bulk volume.

Tapped Density was determined by weighing accurately 10 g of drug, which was previously passed through #20 sieve and transfer in 25 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14± 2 mm at a nominal rate of 300 drops per minute. tap the cylinder for 50 times initially and measure the tapped volume (v1-7.8 ml) to the nearest graduated units, repeat the tapping an additional 75 times and measure the tapped volume (v2-7.8 ml) to the nearest graduated units. if the difference between the two volumes is less than 2% then final the volume (v2). And wt of powder was divided by tapped volume.

Carr's index was determined by Carr's compressibility index. it is a simple test to evaluate the BD and td of a powder and the rate at which it packed down. The formula for Carr's index is as below:

Carr's index= [(TD-BD)*100]/ TD

Hausner's ratio is a number that is correlated to the flow ability of a powder or granular material.

Hausner's ratio = TD/BD

Angle of repose was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured. And angle of repose was calculated using the following equation.

tan = h / r

Drug-Drug and Drug-Excipient compatibility study carried out by FT-IR spectroscopy. The FT-IR spectra of drug with excipients were compared with the standard FT-IR spectrum of the pure drug. The mixture of drug and excipients in selected ratio were prepared and initial spectra were taken. Then the mixture were kept in 40 0 c for 1 month and after 1 month FT-IR spectra were taken.

Optimized chromatographic condition was

System: Shimadzu LC-2010 C HT

Column: Water C18, 5µ (250 X 4.6mm id)

Detection Wavelength: 254 nm

Flow rate: 1 ml/min

Column Temperature: 25°C

Injection volume: 20 µl

Mobile Phase : Glacial acetic acid: Water: MeOH (10:30:75%v/v)

Operating pressure: 205kgf (± 1)

FORMULATION

Preparation of mannitol granules: first prepared solution of 20% PVP K-30 in APA.

Preparation of Troches by Direct compression method: The flow chart for direct compression method is as follows:

Weighing, Shifting, mixing, Lubrication, Compression

EVALUATION

Weight Variation Test: Twenty troches were randomly selected form prepared batches and individually weighed. The average weight and standard deviation of 20 troches was calculated. The batch passes the test for weight variation test if not more than two of the individual troche weight deviates from the average weight by more than the percentage according to USP limits shown in table and none deviate by more than twice the percentage shown.

Crushing Strength of Troches: Crushing strength of the troches was determined by using Monsanto crushing strength tester. Twenty troches were taken randomly from prepared batches. The force required to break the troches is recorded. The unit is kg/cm2.

Diameter and Thickness of Troches: The diameter and thickness of the troches were measured by using digital vernier caliper.

Twenty troches from prepared batches were randomly selected and diameter and thicknesses were measured.

Friability: 10 troches were weighed and placed in the Roche Friabilator. The apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were deducted and weighed again. The percentage friability was measured using the formula,

$$\%F = \frac{Wo - W}{Wo} \times 100$$

Where, % F = friability in percentage,

Wo = initial weight of troches

W = weight of troches after revolution

Assay of Prepared Troches: The prepared troches were tested for their drug content. The assay was carried out using HPLC method. Ten troches were finely powdered and 750 mg powder was transferred to a 100 ml of volumetric flask. Shake with 20 ml methanol. Then the volume was made up to 100 ml mark with the same solvent. Pipette out 10 ml of this solution and diluted up to 100 ml with phosphate buffer (pH-6.8) +10% tween-20 solutions. Solution was then filtered using a whatman filter paper. Sample was evaluated in HPLC and found out area under curve (AUC) and from that concentration of drugs in each troche was found.

Content Uniformity: The test for uniformity of content of single dose preparation is based on the assay of the individual contents of active substances of a number of single dose units to determine whether the individual contents are within limits set with reference to the average content of the sample.

Take 10 troches from prepared batches and performed the assay of each individual troche. All troches were crushed and 1 gm of cruse powder was dissolved in 100 ml of methanol. Pipette out 10 ml of this solution and diluted up to 100 ml with phosphate buffer (pH-6.8) +2% tween-20 solutions. Sample was evaluated in HPLC and found out area under curve (AUC) and from that concentration of drugs in each troche was found. The preparation complies with the test if individual drug content is in between 85 – 115 % of the average content.

In-Vitro Dissolution Study: The in-vitro release study of drug from troches of all

formulations was performed in triplicate using USP apparatus type II (paddle type). The following conditions were followed to study the in-vitro dissolution study of medicated troches. Dissolution medium about 5 ml was withdrawn at specified interval. The volume withdrawn was replaced by volume of fresh dissolution medium. The filtered samples of troches were analyzed by HPLC method.

Antimicrobial Study: Test organism: Streptococuss mutants

Medium: Soya-bean Casein Digest Agar Medium (SCDA)

Incubation time: 24-48 hours

Inoculation of one loop culture in 10-15 ml of 95% saline solution and take dilution which was given 100-150 CFU/ml.

Then transfer 1 ml of it to sterile petriplates and after that pour SCDA medium (20ml) in to petriplates and mix properly.

Then 2 wells were cut out in the agar layer of each plate with an aluminium bore of 5mm diameter to contain equal volume of standard drug solution and mixture of two standard drugs solution. All the work was carried out under strict aseptic conditions.

The plate were kept in fridge for 30 minutes after addition to allow diffusion of the solution into the medium and then incubated at 37°C for 24-48 hrs. After the incubation period the diameter of zone of inhibition in mm obtained around the well was measured.

Stability Study: The purpose of stability testing is to provide evidence on how the quality, efficacy

And safety of a drug substance or drug product varies with time the time under the influence of a variety of environmental factors such as temperature, humidity and light and to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions.

Acceptance criteria for Stability study at the point of data submission: In general, “significant change” for a drug product is defined as:

1. A 5% change in assay from its initial value; or failure to meet the acceptance criteria for potency when using biological or immunological procedure.

2. Any degradation product's exceeding its acceptance criterion.

3. Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., colour, phase separation, resuspendibility, caking, hardness, dose delivery per actuation); however, some changes in physical attributes (e.g., softening of suppositories, melting of creams) may

be expected under accelerated conditions; and, as appropriate for the dosage form.

4. Failure to meet the acceptance criterion for pH.

5. Failure to meet the acceptance criteria for dissolution for 12 dosage units.

Methodology: The optimized batch of troche was subjected to accelerated studies at the condition of 40°C/75% RH in the stability chamber. . Troches were packed in alu-alu strip packaging for 6 months.

The samples were collected at the end of 3 month and 6 month. Troches were tested for the physical appearance, hardness, thickness, friability, % assay, dissolution profile. All above test results were compared to Initial data as well as standard stability requirements.

Drug Characterization was determined with different parameters such as: melting point, partition coefficient, pH ect. and result were obtained as below

FT-IR Spectroscopy of Chlorhexidine HCL and Triamcinolone: FTIR spectrum of Chlorhexidine HCL complies with its chemical structure 1,1'-(hexane-1,6-diyl)bis[5-(4-chlorophenyl)biguanide] dihydrochloride since the characteristic bands for functions such as -NH, -CH,C-Cl, Ar C-N was observed. FT-IR spectrum of Triamcinolone complies with its chemical structure 2,4,4'-trichloro-2'-

hydroxy-diphenylether since the characteristic bands for functions such as C=O, C=H.

FORMULATION STUDIES

Evaluations of Preliminary Batches of Troches were carried out and observe the readings.

For taste

score: 1=poor, 2=average, 3=good, 4=very good, 5= excellent

Evaluation of 32 Factorial Design Optimization Batches of Troches were carried out and observe the batch no 6 were good in all parameters so batch no 6 had taken as optimized final batch.

RESULTS AND DISCUSSION

In-vitro dissolution study: of factorial batches were carried out and note down the % cumulative amount of the drugs.

Stability Study: of optimized formulation were carried out by storing the product for 3 months and 6 months

CONCLUSION

Chlorhexidine HCL is widely used antimicrobial drug in treatment of dental plaque and gingivitis and triamcinolone is used as anti ulcerative as well as anti-inflammatory. Combination of Chlorhexidine HCL and Triamcinolone has antimicrobial and anti ulcerative effect on dental plaque, gingivitis and mouth ulcers.

Troches of Chlorhexidine HCL and Triamcinolone combination were prepared by direct compression technique with excipients like mannitol, stavioside, Avicel, sodium saccharine, flavour and ecocool. Here, Chlorhexidine HCL is compatible with triamcinolone.

Compatibility of Chlorhexidine HCL and Triamcinolone was found out by FTIR spectroscopy.

As sweetener sodium saccharin and stavioside was used as a flavour strawberry flavour was used. Sodium saccharin was used in concentration of 0.4% as the concentration increases up to 0.5%, it decreases antimicrobial effect of Chlorhexidine HCL Addition of sweetener and flavour masked the bitter taste of drug Chlorhexidine.

Mannitol was used as a base. It has negative heat of solution sweetness and mouth feel. Use of ecocool imparted cooling effect which can increase patient acceptability. Mannitol was in powder form. So, granules of mannitol were prepared by PVP K30 in IPA as a binding agent. Only use of base has not imparted sufficient crushing strength. So, Avicel 102 was added as a binder.

Validated HPLC method was developed for quantitative estimation of Chlorhexidine HCL and Triamcinolone in dosage forms.

Optimized mobile phase for these two drugs was 2.0 g of sodium octane sulphonate in a mixture of 120 ml of glacial acetic acid, 270 ml of water and 730 ml of methanol, and retention time was found as 9.8 and 4.2 minutes for Chlorhexidine HCL and Triamcinolone respectively.

For further optimization 32 factorial designs was applied. Concentration of Stavioside 80% and eco-cool were used as critical parameters. From factorial design it was concluded that the optimized concentration of Stavioside 80% and eco-cool were 1% and 0.6% respectively.

Antimicrobial study was performed on staphylococcus mutans and results revealed that combination of Chlorhexidine HCL have antimicrobial effect.

It can be concluded that concentration of Avicel gave positive effect on crushing strength and drug release. Troches containing combination of Chlorhexidine HCL and Triamcinolone were prepared successfully

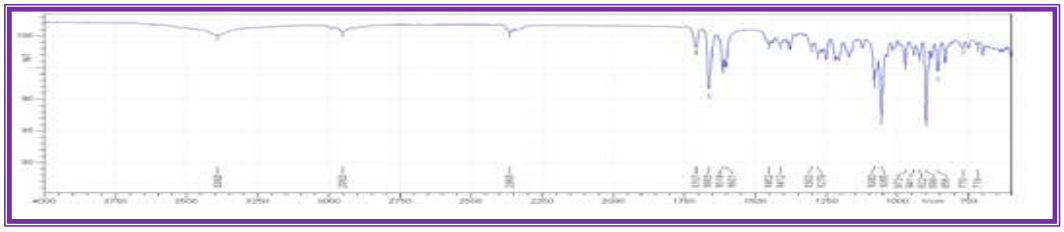


Figure 1 FT-IR Spectra of Chlorhexidine HCL was taken by Brukar FT-IR Spectrophotometer over the range of 600 – 4000 cm-1 at a resolution of 4 cm-1.

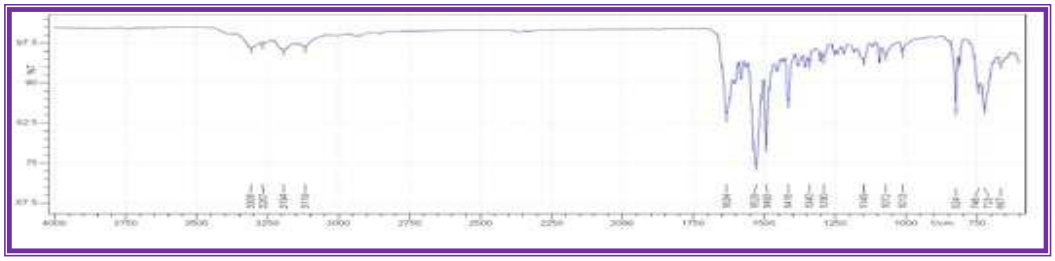


Figure 2 FT-IR Spectra of Triamcinolone was taken by Brukar FT-IR Spectrophotometer over the range of 600 – 4000 cm^{-1} at a resolution of 4 cm^{-1}.

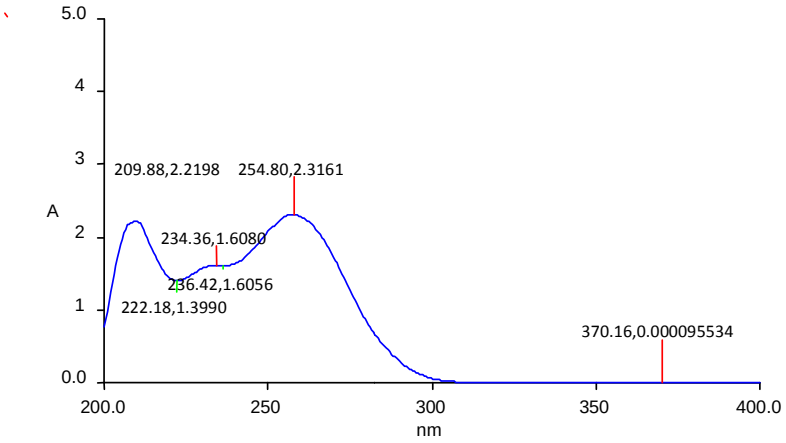


Figure 3 UV spectra of Chlorhexidine HCL 20 ppm were recorded in a wavelength range of 190–400 nm in a 10 mm quartz cell, by a Jasco V-530 (Jasco, Japan) Spectrophotometer.

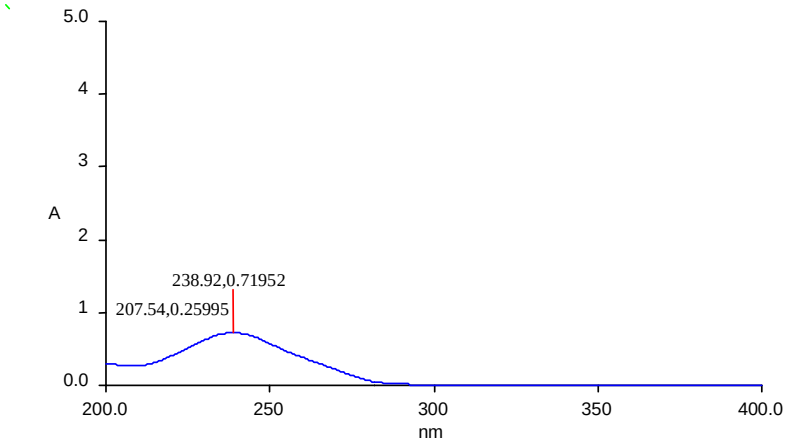
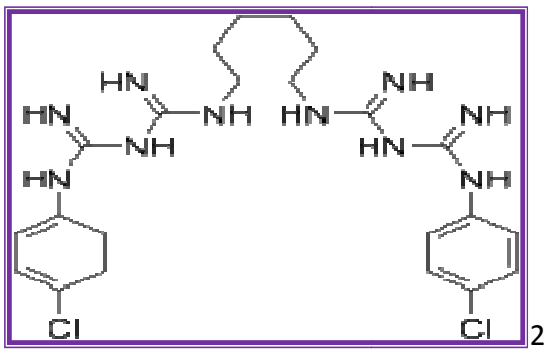


Figure 4 UV spectra of Triamcinolone 50 ppm were recorded in a wavelength range of 190–400 nm in a 10 mm quartz cell, by a Jasco V-530 (Jasco, Japan) Spectrophotometer.



2HCL

Figure 5(A) Structure of Chlorhexidine HCL

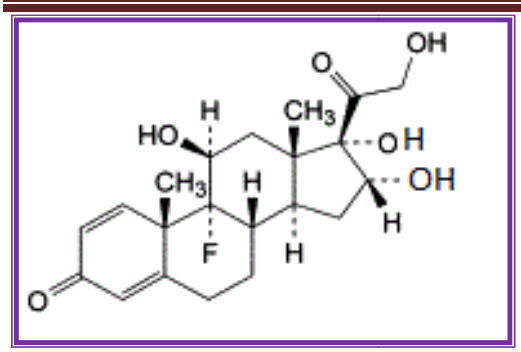


Figure 5(B) Structure of Triamcinolone

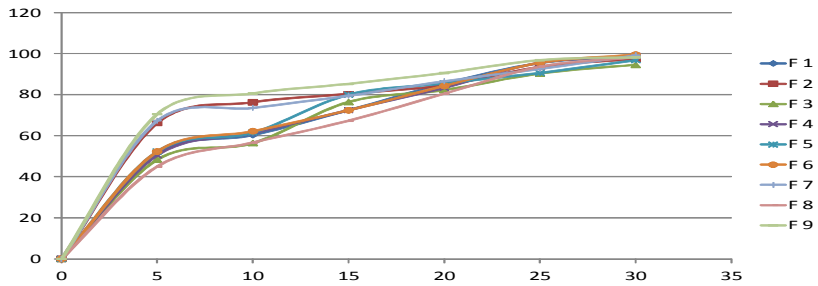


Figure 6 Drug release of Chlorhexidine HCL

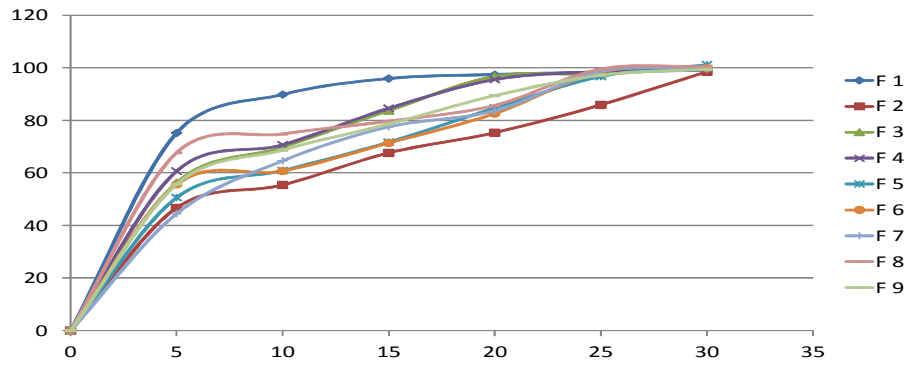


Figure 7 Drug release of Triamcinolone

Table 1

Weight variation limit according to USP

AVERAGE WEIGHT OF TABLET (MG)	PERCENTAGE DEVIATION
130 or less	10
130-324	7.5
More than324	5

Table 2

Observation readings of melting point, partition coefficient, and PH.

SR. NO.	PARAMETER	CHX	TRI
1	Melting point	255 - 265^{0}C	294-296^{0}C
2	Partition coefficient	2.85	1.2
3	pH	6.6	6.7

Table 3

Dissolution study parameter

SR. NO.	PARAMETER	CONDITION
1	USP dissolution apparatus	Type 2 (paddle method)
2	Volume of dissolution medium	250 ml
3	Speed of rotation	50 rpm
4	Temperature	37±0.5ºC
5	Dissolution medium	Phosphate buffer pH-6.8+10%tween-20
6	Sampling interval	5, 10, 15, 20, 25, 30 minutes

Table 4

The recommended storage test condition for different types of stability Studies

STUDY	INTENDED STORAGE CONDITION OF FINISHED PRODUCT			MINIMUM PERIOD COVERED BY DATA AT SUBMISSION
	GENERAL CASE, NONAQUEOUS, SOLVENTBASED PRODUCTS.	**REFRIGERATOR**	**FREEZER**	
Long term	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	5°C ± 3°C	-20°C± 5 °C	12 months
Intermediate Stability	30°C ± 2°C/65% RH ± 5% RH	25°C± 2°C/60% RH ±5% RH	-	6 months
Accelerated Stability	40°C ± 2°C/75% RH ± 5% RH	-	-	6 months

Table 5

Absorption bands observed in FT-IR spectra of the Chlorhexidine HCL and Triamcinolone

SR. NO.	CHLORHEXIDINE HCL		TRIAMCINOLONE	
	ABSORPTION BANDS (CM-1)	ATTRIBUTED TO	ABSORPTION BANDS (CM-1)	ATTRIBUTED TO
1	3308	-NH	1707	Ketone C=O
2	1634	Aromatic C=C	1663	Aromatic C=C
3	3119	Aromatic C-H	1080	Aromatic C-OH
4	1529	N-H bend	922	Alkenes C-H
5	1290	Aromatic C-N		
6	1072	Aliphatic C-N		
7	1149	C-Cl		

Table 6

Observation readings of flow property

FLOW PROPERTY	CHX	TRI
Angle of repose (^{0})	29^0	32^0
Bulk density (gm/cm3)	0.980	0.961
Tapped density (gm/cm3)	1.282	1.219
Carr's index	23.55	21.16
Hausner's ratio	1.3081	1.2684
Flow pattern	Passable flow	Passable flow

Table 7

Observation of FTIR spectra of Drug-Drug and Drug-Excipients Compatibility Spectra

SR. NO.	NAME	INITIAL SPECTRA		AFTER 1 MONTH	
		DESCREPTION	IR BANDS	DESCREPTION	IR BANDS
1	Chlorhexidine HCL+ Triamcinolone	White in color, power form	1493cm	White in color, power form	No change
2	Chlorhexidine HCL+ Mannitol granules	White in color, granular form	9820cm 15905cm	White in color, granular form	No change
3	Chlorhexidine HCL+ Stavioside 80%	White in color, power form	1529cm	White in color, power form	No change
4	Chlorhexidine HCL+ Eco-cool	White in color, power form	1493cm	White in color, power form	No change
5	Chlorhexidine HCL+ Sod. Saccharine	White in color, power form	1531cm	White in color, power form	No change
6	Chlorhexidine HCL+ Mg. stearate	White in color, power form	2916cm 1574cm	White in color, power form	No change
7	Chlorhexidine HCL+ Avicel(MCC)	White in color, power form	1057cm 1032cm	White in color, power form	No change
8	Chlorhexidine HCL+ Flavor	Reddish white color, power form	1529cm	Reddish white color, power form	No change
9	Triamcinolone + Mannitol granules	White in color, granular form	1078cm 1018cm	White in color, granular form	No change
10	Triamcinolone + Stavioside 80%	White in color, power form	1070cm 1034cm	White in color, power form	No change
11	Triamcinolone + Eco-cool	White in color, power form	1637cm 1057cm	White in color, power form	No change
12	Triamcinolone + Sod. Saccharine	White in color, power form	1080cm	White in color, power form	No change
13	Triamcinolone + Mg.	White in color,	2916cm	White in color,	No change

	stearate	power form	1574cm	power form	
14	Triamcinolone + Avicel(MCC)	White in color, power form	1055cm	White in color, power form	No change
15	Triamcinolone + Flavor	Reddish white color, power form	1030cm 1080cm	Reddish white color, power form	No change

Table 8

Evaluations data of Preliminary Batches of Troches

SI N.	PARAMETERS	FORMULATION BATCHES (%)							
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
1	Taste	1	1	1	2	2	3	4	3
2	Weight Variation Test	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS
3	Crushing strength (kg/cm)	12	11.5	12	12.5	11.7	12	12.2	11
4	Diameter & Thickness(mm)	4-5	4-5	4-5	4-5	4-5	4-5	4-5	4-5
5	Friability (%)	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS
6	Observation during manufacturing	More friable	More Friable	Some bitter taste	Cooling Effect	More cooling effect	Effective cooling effect	No bitter taste,some grittiness	Weight variation problem

SR. NO.	PARAMETERS	FORMULATION BATCHES (%)							
		F9	F10	F11	F12	F13	F14	F15	F16
1	Taste	3	4	4	4	4	4	5	5
2	Weight Variation Test	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS
3	Crushing strength (kg/cm)	10.8	11	11.8	12	11.8	12.2	11	12
4	Diameter & Thickness (mm)	4-5	4-5	4-5	4-5	4-5	4-5	4-5	4-5
5	Friability (%)	FAIL	PASS	PASS	PASS	PASS	PASS	PASS	PASS
6	Observation during Manufacturing	Weight variation problem	Gritty	Gritty	Gritty	Gritty	Less gritty	Good appearan	Good appearance and taste

Table 9

Evaluation of factorial batches of troches

SR. NO.	PARAMETERS	FORMULATION BATCHES (%)								
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	Taste	2	3	3	2	4	5	2	4	3
2	Weight Variation Test	749.5 mg	749.6 mg	750.7 mg	749 mg	750.5 mg	750 mg	749.1 mg	748.9 mg	751 mg
3	Crushing Strength(kg/cm)	12	12	12	12	12	12	12	12	12
4	Diameter & Thickness (mm)	4-5	4-5	4-5	4-5	4-5	4-5	4-5	4-5	4-5
5	Friability (%)	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS
6	Assay-Chlorhexidine HCL	98.21	97.88	99.33	98.65	98.44	99.77	97.66	97.45	98.11
7	Assay-Triamcinolone	98.92	96.45	97.45	98.99	99.22	99.95	98.33	97.55	97.34
8	Content uniformity	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS

Table 10

Chlorhexidine HCL drug release study of factorial batches

SR. NO.	TIME (min)	FORMULATION BATCHES								
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	5	51.4	66.2	48.3	50.5	52.3	52.3	67.3	45.0	70.5
2	10	60.3	76.3	56.4	61.3	61.5	62.2	73.6	56.7	80.6
3	15	72.4	80.4	76.4	72.5	80.01	72.4	79.5	67.3	85.3
4	20	85.4	84.6	82.2	83.4	85.5	84.3	86.6	80.5	90.6
5	25	95.4	93.5	90.3	95.6	90.6	95.5	92.6	93.6	96.8
6	30	98.7	97.4	94.5	98.9	96.8	99.5	99.2	98.2	98.2

Table 11

Triamcinolone drug release study of factorial batches

SR. NO.	TIME (min)	FORMULATION BATCHES								
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	5	75.2	46.7	56.3	60.7	50.6	55.6	44.5	67.7	55.7
2	10	89.8	55.4	69.8	70.7	60.9	60.7	64.6	74.8	68.7
3	15	95.9	67.6	83.7	84.6	71.7	71.4	77.5	79.7	78.6
4	20	97.4	75.3	96.7	95.5	84.7	82.6	83.6	85.7	89.4
5	25	98.3	85.9	97.6	98.6	96.7	98.4	98.6	99.5	97.2
6	30	99.1	98.5	100.2	99.7	101.2	99.9	99.6	100.4	99.4

Table 12

Observation readings of stability study.

SR. NO.	TEST	INITIAL	3MONTH	6MONTH
1	Description	White color	White color	White color
2	Hardness(kg/cm)	12	12	12
3	Thickness (mm)	4.5	4.5	4.5
4	Friability	Pass	Pass	Pass
5	% Assay of Chlorhexidine HCL	99.77	99.77	99.77
6	% Assay of Triamcinolone	99.95	99.95	99.95
7	Dissolution Time require for 95% drug release.	25 min	25 min	25 min

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