



Formulation Development and Evaluation of Dynamic Effervescent Antimicrobial Mouthwash.

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Abstract: Oral health is over dental health. It includes healthy gums, hard and lip, linings of the mouth and throat, tongue, lips, salivary glands, chewing muscles, and upper and lower jaws. Good oral health enables us to talk, smile, kiss, breathe, whistle, smell, taste, drink, eat, bite, chew, swallow and express emotion. The rima plays a central role for intake of basic nutrition and protection against microbial infections. The World Health Organization (WHO) describes oral health as a state of being free from mouth and facial pain, mouth and throat cancer, oral infection and sores, periodontal (gum) disease, caries, tooth loss and other diseases and disorders that limit an individual's capacity in biting, chewing, smiling, speaking, and psychosocial wellbeing. Oral health could be a right, an integral a part of general health and essential for overall wellbeing. Oral health and general health have close linkages. On the one hand, oral health may be compromised by variety of chronic and infectious diseases which show symptoms within the mouth. On the opposite hand, oral diseases can cause infection, inflammation, and other serious impacts on overall health. Thus, maintaining good oral health is crucial to sustain general health and vice versa. Good self-care, like brushing with fluoride toothpaste, daily flossing and professional treatment, is essential to good oral health. There are many products which are used for purpose of oral hygiene like.

KEYWORDS- Chlorhexidine, Effervescent, Antimicrobial, Mouthrinses.

1. INTRODUCTION

Effervescent or carbon tablets are tablets which are designed to dissolve in water, and release carbon dioxide. They are products of compression of component ingredients in the form of powders into a dense mass, which is packaged in blister pack, or with a hermetically sealed package with incorporated desiccant in the cap. To use them, they are dropped into water to make a solution. The powdered ingredients are also packaged and sold as effervescent powders or may be granulated and sold as effervescent granules. Generally powdered ingredients are first granularized before being made into tablets.

Effervescent medicinal beverages date back to the late 1800s and originally arose to mask the taste of bitter waters taken as curatives, during the water cure craze of that era.

Effervescent tablet formulations generally include an agent that is capable of releasing CO₂ (sodium carbonate and sodium bicarbonate) and an agent that induces releases of CO₂ (adipic acid, malic acid, tartaric acid, ascorbic acid, fumaric acid, maleic acid, succinic acid, or citric acid). API is either present in the effervescent granule mixture, or if it is having poor solubility, then it is converted into the salt form during the dissolution process. Effervescent tablets are formulated by mixing these agents along with binders, diluents, and lubricants, and then compressing them into tablets. Water-soluble lubricants are used such as sodium benzoate, polyethylene glycol, and adipic acid. Magnesium stearate, the most commonly used lubricant, is insoluble in water and thus it will interfere with the process of effervescence. Effervescent tablets do not need disintegrants incorporated into their formulations as the evolution of in situ CO₂ facilitates the disintegration process.

The rate of effervescence can be modified with the use of a plasticizer. Basically, increasing the amount of plasticizer prolongs the rate of effervescence. Also, by controlling the hydrophobicity and hydrophilicity of binders used in the hot melt extrusion process, one can modify the effervescence. Increasing hydrophobic binder amounts reduces the rate of effervescence. Also, if a slight excess of either acidic or alkaline agents is used, they will enhance the effervescence rate compared to both the agents used in the same quantity. Further, these effervescent tablets can be coated to have drug release at the desired site in GIT.

2. NEED

The literature reveals the wide applicability of chlorhexidine gluconate in several fields mentioned elsewhere. One among its applications is that the chlorhexidine gluconate act as an antimicrobial agent. At physiologic pH, chlorhexidine salts dissociate and release the charged chlorhexidine cation. The bactericidal effect may be results of the binding of this cationic molecule to charged bacterial cell walls. At low concentrations of chlorhexidine, this leads to a bacteriostatic effect; at high concentrations, membrane disruption ends up in death, facultative anaerobes, aerobes, and yeasts. Hence this phenomenon can provide an aerobic environment in mouth when formulation of chlorhexidine gluconate solution is swished within the rima oris. The aerobic environment in mouth will inhibit the expansion of anaerobic micro-organisms which causes variety of diseases within the rima. It was found in literature that chlorhexidine absorbed to the tooth surface instead of its oral retention or initial bactericidal effect thereby inhibit the bacterial plaque and helps to forestall inflammation of the gingiva and decay. Chlorhexidine molecule attaches to pellicle by one cation, leaving the opposite absolute to interact with bacteria attempting to colonise the tooth surface. the method of plaque prevention would therefore occur at the tooth surface itself by tooth bound chlorhexidine. Further, Chlorhexidine gluconate is use in disease ascribe to some pathological conditions characterized by degeneration and inflammation of gums, periodontal ligaments, alveolar bone, and dental cementum. it's a localized inflammatory reaction caused by bacterial infection of a periodontal pocket accompanying with sub-gingival plaque. Additionally, a dosage form like mouthwash can control the bad breath to a marked degree by one or more of the subsequent mechanism like, cleansing the teeth and tissue in order that fermentative and putrefactive debris is mechanically removed, inhibiting the bacterial enzymatic activity in mouth so the malodourous end products aren't easily formed, using ingredients that modify or eliminate odorous substance by chemical action or physical adsorption, substituting pleasant odors for undesirable ones by a masking effect or using any agent specifically to deliver the desired effect like antibacterial, astringent, etc. Other reason for the mouthwash includes control of plaque and gingivitis when used as an adjunct to mechanical means. The dosage forms during which chlorhexidine is being delivered at various sites are; solution, gel, toothpaste, ointment, cream, tablets etc. But, chlorhexidine in liquid forms poses stability problems and like requires stringent conditions to be stored in. So, if possible, solid dosage form will always be preferred and thus promoting a thought of tablet for mouthwash.

2.1 AIM

Formulation Development and Evaluation of Dynamic Effervescent Antimicrobial Mouthwash.

2.2 OBJECTIVE

- i. To lyophilize the chlorhexidine gluconate solution and analysis of the content.
- ii. To formulate fast dissolving mouthwash tablet by direct compression method.
- iii. Optimization of fast dissolving mouthwash tablet.
 - To find the formula with least time of disintegration.
 - Has pleasant mouth feel and also pleasant flavor.
- iv. Evaluation of fast dissolving mouthwash tablet.
 - Pre-compression parameter.

- Post compression parameter.
- Reconstitution study

3. PLAN OF WORK

1. Literature survey
2. Procurement of raw material
3. Lyophilize the chlorhexidine gluconate solution
4. Characterization and evaluation of Lyophilized mixture.

a. Analysis of the content

b. FTIR

5. Formulation design of fast dissolving tablet of lyophilized mixture.
6. Evaluation of fast dissolving tablet
 - a. Appearance
 - b. Thickness and diameter
 - c. Hardness
 - d. Friability
 - e. Disintegration time
7. Reconstitution study
 - a. Drug content analysis

4. DRUG PROFILE

4.1 Chlorhexidine gluconate solution

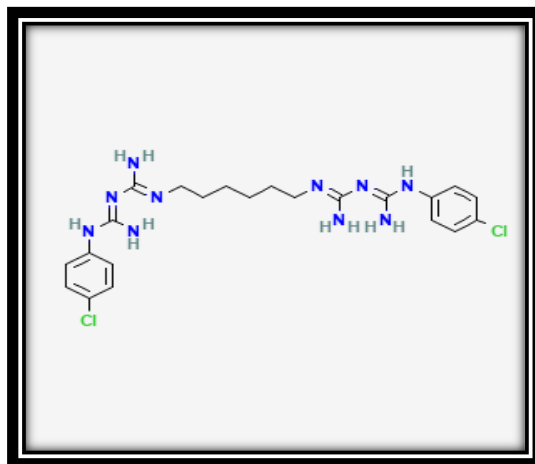


Fig.No 1: Structure of chlorhexidine gluconate.

Chlorhexidine Gluconate Solution is an aqueous solution of 1, 1'-hexamethylenebis [5- (4-chlorophenyl) biguanide] digluconate.75

5. EXCEPIENT

| Excepiant | Category |
|----------------------------|--------------------|
| Sodium Bicarbonate | Effervescent Agent |
| Citric Acid (Monohydrate), | Effervescent Agent |
| Tartaric Acid, | Effervescent Agent |
| PEG 6000, | Thickeners |
| Glycine | Bulking Agent |
| Sodium Benzoate, | Preservative |
| Manitol, | Sweetener |
| Menthol | Cooling Agent |
| Aspartame | Sweetning Agent |
| brilliant blue | Coloring Agent |
| Orange Peel | Flavouring Agent |

Table-1. Excepiant Use in Mouthwash Tablet Formulation

6. EXPERIMENTAL WORKS

6.1 Lyophilize the chlorhexidine gluconate solution

Chlorhexidine gluconate solution (IP) was dried using freeze dryer (lyophilizer). Take a chlorhexidine gluconate solution 100 ml and add sorbitol 80 gm. as bulking agent. These mixture thoroughly mix then transfer into a lyophilization tray. This lyophilization tray placed in an exceedingly lyophilization shelf chamber also temperature probe was kept in this lyophilization trays properly. the most stage within the lyophilization is ready a correct lyophilization cycle and ramping rate. within the opening within the lyophilization is freezing the chlorhexidine and sorbitol mixture below at -40oC. Then freezing material placed under

vacuum and increase the temperature gradually to deliver enough energy for the ice to sublime. Finally allows the upper vacuum for the extraction of bound water at above zero temperature.

| Sr. No. | Lyophilized mixture composition | Quantity |
|---------|----------------------------------------|----------|
| 1 | Chlorhexidine gluconate solution (20%) | 100 ml. |
| 2 | Sorbitol | 80 gm. |

Table 2: Lyophilized mixture composition

6.2 Characterization and Evaluation of lyophilized mixture

6.2.1 Fourier Transform Infra-Red Spectroscopy

FTIR spectrum of lyophilized blend was obtained by scanning over a range of 4000- 400 cm⁻¹ and spectrum was recorded.

6.2.2 Content analysis (Assay %)

The analysis of content of the lyophilized blend of chlorhexidine gluconate was carried out utilizing IP assay of chlorhexidine gluconate solution by High Performance Liquid Chromatography method (HPLC).

6.2.3 HPLC assay method:

Mobile phase:

Prepare by dissolving 2 gm. of sodium octanesulphanate in a mix of 120 ml of glacial acetic acid, 270 ml of water and 730 ml of methanol.

Solution (1):

Dilute correctly about 5 gm. of sample with mobile phase to make 100 ml solution in a volumetric flask.

Solution (2):

Dissolve 0.1 gm. of chlorhexidine acetate WS in the water to make 50 ml. pipette out 2 ml and dilute to 50 ml with mobile phase in another volumetric flask.

Calculation:

$$\text{Assay, \% of LC} = (TA \times W1 \times 100 \times 2 \times 1.775 \times P \times \text{Sp. gr.}) \div (SA \times W2 \times 50 \times 50 \times 1.238 \times 0.2)$$

Equation 1: HPLC assay calculation formula of chlorhexidine.

Where,

TA= Average area of sample peaks.

W1= Weight of working standard taken.

W2= Weight of sample taken.

P= potency of working standard.

Sp.gr. = specific gravity of the sample.

SA= Average area of standard peaks.

6.3 Formulation studies

6.3.1 Selection of process

Method of direct compression was selected for the Formulation of reconstituted fast dissolving tablet.

6.3.2 Mixing and Blending

All the components were weighed and triturated in glass mortar in ascending order of their amounts and were taken in an air tight sealable poly bag and mixed for 5-6 minutes.

6.3.3 Evaluation of tablet blend

The evaluation of tablet blends for dissimilar flow properties study as given below all the components were weighed and triturated in glass mortar in ascending order of their amounts and were taken in an air tight sealable poly bag and mixed for 5-7 minutes.

6.3.3.1 Angle of repose

The frictional forces in a loose powder or granules can be measured by the angle of repose. Angle of repose was measure by funnel method. The blend was poured through a funnel which raise vertically until a maximum cone height (h) was obtained. Radius of the heap (r) measured and angle of repose (θ) calculated by using the formula:

$$\tan\theta = \left(\frac{h}{r}\right)$$

Equation 2: Angle of repose

Where, θ is the angle of repose h is the height r is the radius

| Angle of repose (θ) | Flowability |
|------------------------------|-------------|
| < 25 | Excellent |
| 25-30 | Good |
| 30-40 | Passable |
| > 40 | Very Poor |

Table 3: Relationship between angle of repose (θ) and flowability

6.3.3.2 Bulk density (Db)

It is the ratio of total mass of the powder to the bulk volume of powder. It was measure by pouring the weight powder (passed through standard sieve # 44) into a measuring cylinder and preliminary volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$Db = M/Vb$$

Equation 3: Bulk density

Where, M is the mass of powder

Vb is the bulk volume of the powder

6.3.3.3 Tapped density (Dt)

It is the proportion of total mass of the powder to the tapped volume of the powder. Bulk was measured by tapping the powder for 100 times and the tapped volume was noted if the difference between these 2 volumes is less than two%. If it is more than two%, tapping is constant for some times and tapped volume was noted. Tapping was continued until the successive volume is less than two% (in a bulk density apparatus). It is expressed in g/ml and is given by

$$Dt = M/V$$

Equation 4: Tapped density

Where, M is the mass of powder

V_t is the tapped volume of the powder.

6.3.3.4 Carr's index

The simple method of measurement of free flow of powder is the compressibility, an sign of the ease with which material can be induced to flow is given by compressibility index (I) which his considered as follows.

$$\text{Carr's index} = \frac{D_t - D_b}{D_t} \times 100$$

Equation 5: Carr's index

Where, D_t is the tapped density of the powder.

D_b is the bulk density of the powder.

| Carr's index (%) | Type of Flow | Hausner's Ratio |
|------------------|----------------|-----------------|
| ≤10 | Excellent | 1.00-1.11 |
| 11-15 | Good | 1.12-1.18 |
| 16-20 | Fair | 1.19-1.25 |
| 21-25 | Passable | 1.26-1.34 |
| 26-31 | Poor | 1.35-1.45 |
| 32-37 | Very poor | 1.46-1.59 |
| >38 | Extremely poor | >1.60 |

Table 4: Flow properties according to Carr's index and flowability

6.3.3.5 Hausner's ratio

This is an indirect ratio for ease of powder flow. It was considered by the following formula:

$$\text{Hausner's ratio} = \frac{D_t}{D_b}$$

Equation 6: Hausner's ratio

Where, D_t is tapped density and D_b is bulk density.

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

6.3.4 Tableting

The resulting constant blends of composition per tablet were compressed on 12 stations compression machine using 8 mm flat faced tooling.

6.3.5 Tablet batches

The conclusion of glycine was studied at 3 levels (-1, 0, +1), amount of rest of the components were fixed. At the level of (-1), glycine concentration of 2%, at level (0), Glycine concentration 4%, at level (+1), Glycine at concentration of 6% of that of the tableting mass were taken.

6.3.5.1 Preformulation

Firstly, the formulations were made up in the different stoichiometric ratios from tartaric acid, citric acid and sodium bicarbonate based on below reactions. According to materials of each one preparation were weighed and then mg of Active was additional to each formulation. Finally, after preparation of proper mixture, the lubricants including 30 mg of PEG 6000 and 10 mg of sodium benzoate were added the blend and then the tablets compressed by using a single-punch press machine. For next stages, the well stoichiometric ratios were selected with regard to 3 factors: solubility, effervescence time.

| Formulations | Tartaric acid | Citric acid | Na bicarbonate | Effervescent time(s) | pH | *Solubility |
|-----------------|---------------|-------------|----------------|----------------------|------------|-------------|
| S ₁ | - | 0.5 | 0.5 | 105 ± 2.08 | 5.9 ± 0.05 | 3 |
| S ₂ | - | 0.5 | 1 | 40 ± 1.52 | 6.2 ± 0.1 | 3 |
| S ₃ | 1 | 0.5 | 1 | 39 ± 1.51 | 6.1 ± 0.04 | 1 |
| S ₄ | 0.5 | 1 | 1 | 36 ± 2 | 6.1 ± 0.05 | 2 |
| S ₅ | - | 1 | 1 | 50 ± 2.13 | 5.9 ± 0.06 | 5 |
| S ₆ | 1 | 1 | 1 | 48 ± 2.01 | 6.1 ± 0.06 | 2 |
| S ₇ | 1.5 | 0.5 | 1 | 52 ± 1.8 | 6.1 ± 0.1 | 2 |
| S ₈ | 2 | 0 | 1 | 55 ± 1.83 | 6.1 ± 0.08 | 1 |
| S ₉ | - | 1 | 1.5 | 43 ± 1.51 | 6.1 ± 0.7 | 4 |
| S ₁₀ | - | 1 | 0.5 | 30 ± 3.11 | 5.6 ± 0.4 | 4 |
| S ₁₁ | - | 1.5 | 1.5 | 25 ± 2.13 | 5.6 ± 0.05 | 5 |
| S ₁₂ | - | 1.5 | 1 | 49 ± 1 | 5.6 ± 0.04 | 4 |
| S ₁₃ | - | 2 | 2 | 20 ± 2.07 | 5.5 ± 0.06 | 4 |

*Solubility was defined by Likert Scale from 1= very poor, 2 = poor, 3 = average, 4 = good and 5 = excellent

Table. 5. Composition of preliminary formulations (ratio) with their effervescence time, pH and solubility (Mean ± SD).

6.3.5.2 Methods of Anti-Microbial Effervescent Tablets Production

a. Direct Compression

According to Table 2, raw materials of each formulation were weighed and were mixed in a tumbling cubic blender for 15 minutes.

| Ingredients (mg) | Formulations | | | | | |
|-----------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| | F ₁ | F ₂ | F ₃ | F ₄ | F ₅ | F ₆ |
| K citrate | 2700 | 2700 | 2700 | 2700 | 2700 | 2700 |
| Citric acid | 570 | 850 | 850 | 850 | 850 | 850 |
| Na bicarbonate | 500 | 750 | 750 | 750 | 750 | 750 |
| Mannitol | - | - | 60 | 120 | - | 60 |
| Sorbitol | - | - | - | - | 60 | - |
| Aspartame | - | - | - | - | - | 1.5 |

Table 6 Different components of prepared tablets from the direct compression (D) and fusion (f) methods.

After the preparation of the first powder mixtures, sweeteners including aspartame, sorbitol, mannitol and fruit flavoring agents were added to the acceptable mesh and were added to the powders and these were mixed altogether for five minutes. Finally, the selective lubricants including benzoate of soda (10 mg) and PEG 6000 (30 mg) were added and again mixed for about 2-5 minutes with other material. Then, the powders were compressed into tablets by employing a single-punch press machine with 25 mm punch set. Weight of every tablet was considered about 4.5 g. At the end, the tablets were dry in an oven with air passage at 54°C for 1 hr. and after cooling were filled in plastic tubes

b. Fusion Method

According to the formulations which are shown in Table 2, amounts of acid, bicarbonate of soda, Active and mannitol (sorbitol) were weighted accurately and were mixed for about quarter-hour in a very tumbling cubic blender. Then, the obtained blend was placed in an oven at 54 °C. The powder was mixed regularly until the crystallization water of acid was released as binder factor (approximately 30 minutes). After obtaining an appropriate pasty mass, this wet mass was more experienced sieve No. 20 and also the obtained granules were dried in an oven at 54 °C for 1 hr. After drying, for second times the granules were more established sieve No. 20. within the next stage, sweeteners and flavors were added with the granule mass and mixed for five minutes with other material. At last, the lubricants including benzoate (10 mg) and polyethylene glycol 6000 (30 mg) were added and mixed for 2-5 minutes with other material. The granule mixtures compressed into tablets by a single-punch press machine with 25 mm punch set. Finally, they were dried and filled with the previous methods.

c. Wet granulation Method

Wet granulation was done on F5 and F6 formulations. First, acid and saleratus and Active were milled by using miller in order that all powders were saw sieve No. 35 and were blended for 10 minutes. Then 9.5 % w/v PVP solution in absolute ethanol was added with the mixture, so white pasty mass was formed. This wet mass was undergone sieve No. 20 and therefore the granules were dried in an oven at 54 °C for 75 minutes. So, the dried mass was more established sieve No. 20 and therefore the other ingredients were added to them like as fusion method. The granule mixtures were compressed into tablets by employing a single-punch press machine with 25 mm punch set. Prepared tablets were dried in an oven with air circulation at 54 °C for 90 minutes, then were wrapped in foil and were packaged in plastic tubes.

6.3.6 Evaluation of tablet

6.3.6.1 Appearance and shape

The general appearance of the tablet includes the morphological characteristics like size, shape, color, odor, etc.

6.3.6.2 Uniformity of thickness and diameter

The uniformity of the diameter and thickness was measured using vernier micrometer. the common thickness of the 20 tablet was calculated. The test was positive if none of the individual thickness value deviated by $\pm 5\%$ of the common.

6.3.6.3 Hardness

Hardness of the tablet was tested by Monsanto Hardness tester which measures the diametrical crushing strength of the tablets. The tablet to be verified was placed in among the fixed and movable jaw after adjusting the reading to zero. By moving the screw knob the force on the tablet was steadily increased until the tablet breakdowns. The pressure required in kg to interrupt the tablet was noted from the dimensions on the tester. The hardness of the tablet depends on weight of the fabric used and compression force applied during compression.

6.3.6.4 Friability

Tablets require certain quantity of strength or hardness and resistance to friability. it's necessary or important to face up to mechanical shocks of handling while manufacturing, packaging and shipping. This test was performed by using Roche Friabilator. Six tablets were weighed and tumbled at rate of 25 rpm for 4 min. the tablets were weighed and percent friability was calculated by the subsequent formula.

$$\text{Friability} = \frac{(\text{initial wt.} - \text{final wt.}) \times 100}{\text{initialwt}}$$

Equation 7: Friability

Where, W_0 = initial weight of six tablets.

W = final weight of six tablets.

6.3.6.5 Disintegration test

The disintegration test was done by insertion one tablet in 15 ml water. The time mandatory for the complete disintegration noted as disintegration time.

6.3.6.6 Reconstitution study

6.4 Content analysis (Assay %)

The examination of content of the batch F1, F2 and F3 reconstructed solution of chlorhexidine gluconate tablet was carried out utilizing IP assay of chlorhexidine gluconate solution by High Performance Liquid Chromatography method (HPLC).

HPLC Method

Mobile phase: Make by dissolving 2 gm. of sodium octanesulphanate in a blend of 120 ml of glacial acetic acid, 270 ml of water and 730 ml of methanol.

Solution (1): Dilute accurately about 5 gm. of sample with mobile phase to make 100 ml solution in a volumetric flask.

Solution (2): Dissolve 0.1 gm. of chlorhexidine acetate WS in the water to make 50 ml. pipette out 2 ml and dilute to 50 ml with mobile phase in another volumetric flask

Calculation:

$$\text{Assay, \% of LC} = \frac{(\text{TA} \times \text{W1} \times 100 \times 2 \times 1.775 \times \text{P} \times \text{Sp.gr.})}{(\text{SA} \times \text{W2} \times 50 \times 50 \times 1.238 \times 0.2)}$$

Where,

TA= Average area of sample peaks.

W1= Weight of working standard taken.

W2= Weight of sample taken.

P= potency of working standard.

Sp.gr. = specific gravity of the sample.

SA= Average area of standard peaks.

7. RESULT AND DISCUSSION

7.1 Lyophilize the chlorhexidine gluconate solution

Chlorhexidine gluconate solution and Sorbitol were taken a 100ml (20%), 80 gm. at an optimized ratio respectively.

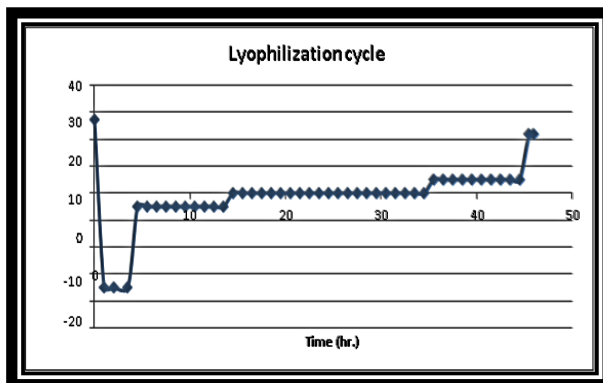


Fig.No 2: Lyophilization Cycle Of Chlorhexidine Gluconate Solution

| Parameter | Segment 1 | | | | Segment 2 | | | | | | | | | |
|-----------|-----------|-----|-----|-----|-----------|-----|-----|-----|-----|-----|------|------|------|------|
| | 0 | 1 | 2 | 3.5 | 4.5 | 5.5 | 6.5 | 7.5 | 8.5 | 9.5 | 10.5 | 11.5 | 12.5 | 13.5 |
| Temp.(°C) | 27 | -35 | -35 | -35 | -5 | -5 | -5 | -5 | -5 | -5 | -5 | -5 | -5 | -5 |

Table 7: Time and temperature for segment 1 and segment 2

| Parameter | Time (hr.) | Temperature (°C) |
|-----------|------------|------------------|
| Segment 3 | 14.5 | 0 |
| | 15.5 | 0 |
| | 16.5 | 0 |
| | 17.5 | 0 |
| | 18.5 | 0 |
| | 19.5 | 0 |
| | 20.5 | 0 |
| | 21.5 | 0 |
| | 22.5 | 0 |
| | 23.5 | 0 |
| | 24.5 | 0 |
| | 25.5 | 0 |
| | 26.5 | 0 |
| | 27.5 | 0 |
| | 28.5 | 0 |
| | 29.5 | 0 |
| | 30.5 | 0 |
| 31.5 | 0 | |
| 32.5 | 0 | |
| 33.5 | 0 | |
| 34.5 | 0 | |

Table 8: Time and temperature for segment 3

| Parameter | Segment 4 | | | | | | | | | | Segment 5 | |
|------------------------|-----------|------|------|------|------|------|------|------|------|------|-----------|----|
| | 35.5 | 36.5 | 37.5 | 38.5 | 39.5 | 40.5 | 41.5 | 42.5 | 43.5 | 44.5 | 45.5 | 46 |
| Time(hr.) | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 22 | 22 |
| Temp.(^o C) | | | | | | | | | | | | |

Table 9: Time and temperature for segment 4 and segment 5

7.2 Characterization and evaluation of lyophilized mixture

7.2.1 Fourier Transform Infra-Red Spectroscopy

IR spectrum of chlorhexidine lyophilized mixture showing following characteristics peaks confirming its structure

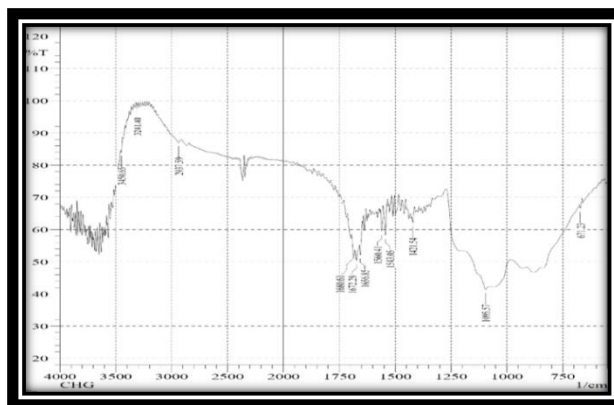


Fig. No 3: FT-IR Spectrum Of Chlorhexidine Gluconate Lyophilized Mixture.

| Sr. no. | Particular | Standard range(cm ⁻¹) | Observed value(cm ⁻¹) |
|---------|---------------------------|-----------------------------------|-----------------------------------|
| 1. | 2° Amine (-NH-) | 3200-3400 | 3241.40 |
| 2. | Hydroxyl group (-OH) | 3300-3500 | 3450.65 |
| 3. | Chlorine group (-Cl) | 600-800 | 671.23 |
| 4. | Carbonyl group (>C=O) | 1680-1740 | 1680.61 |
| 5. | Aromatic C-H (stretching) | 2900-3100 | 2937.29 |
| 6. | Aromatic C-H (bending) | 1475-1575 | 1543.05 |

Table 10: FT-IR Assignment For Chlorhexidine Gluconate

7.2.2 Content analysis (Assay %)

Content analysis of the chlorhexidine gluconate lyophilized mixture by using HPLC assay IP method.

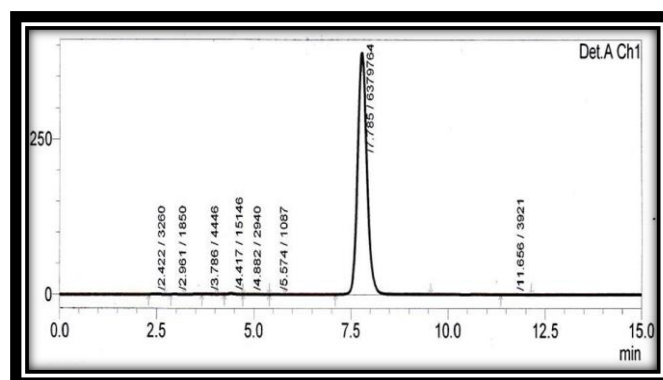


Fig. No 4: HPLC Chromatogram Of Standard Chlorhexidine Acetate WS

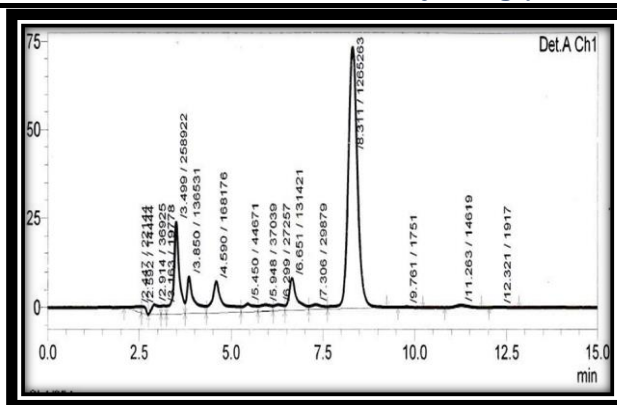


Fig. No 5: HPLC Chromatogram of Lyophilized Mixture Of Chlorhexidine Gluconate

Run average solution six times and test solution in duplicate. By using standard Average peak area and test sample peak area calculate the content of lyophilized mixture. Content analysis of the lyophilized mix was found to be 20.49% within the definite limit as per I.P.

| Lyophilized mixture | Assay (%) |
|------------------------------------|-----------|
| Chlorhexidine gluconate + Sorbitol | 20.49 % |

Table 11: Content Analysis Of Lyophilized Mixture

7.3 Formulation studies

7.3.1 Excipients

The prerequisite for selection of the excipients for preparation of a fast dissolving tablet was reconstituted as the ultimate goal was to develop a mouthwash with water as the final vehicle. So with a view to formulate a mouthwash, excipient chosen were glycine as disintegrant, menthol as a flavoring agent, Ecocool as cooling agent, ribitol and aspartame used as sweetening agent, brilliant blue as coloring agent and PEG 6000 as lubricant

7.3.2 Selection of process

Method of direct compression was selected for the preparation of fast dissolving tablet.

7.3.3 Evaluation of tablet blend

The prepared blend was subjected for the study of different micromeritics properties. The result for analysis of F1, F2 and F3 batches were summarized in the table 17. The analysis result of tablet blend indicates that all the batches possess good flowability and compressibility.

7.3.4 Tablet Evaluation parameter

7.3.4.1 Appearance and shape

All the tablets of design batches were having light blue color uniformly distributed, 8 mm in diameter with circular curved surface.

7.3.4.2 Thickness

Excessive variation in tablet thickness can result in problem with packaging as well as consumer acceptance. There was no marked variation in thickness of tablet within each formulation (5%) indicating uniform behavior of blend throughout the compression process. Thickness of design batches were found in range of 2.46 to 2.48 mm.

7.3.4.3 Friability

Friability of the tablet is measure of the tablet strength. Tablets with friability less than 1% of their weight are acceptable. The friability of the design batches were in the range of 0.34 to 0.79.

7.3.4.4 Disintegration test

Fast dissolving tablets are expected to disintegrate within 3 min. The disintegration time of optimized batch was found to be 160 seconds.

| Batch Code | Bulk Density (gm/cm ³) | Tapped Density (gm/cm ³) | Carr's Index (%) | Hausner's Ratio | Angle of Repose (°) |
|------------|------------------------------------|--------------------------------------|------------------|-----------------|---------------------|
| F1 | 0.4873 ± 0.010 | 0.6137 ± 0.012 | 20.59 ± 3.354 | 1.25 ± 0.027 | 30.11 ± 1.12 |
| F2 | 0.4529 ± 0.008 | 0.5406 ± 0.005 | 19.36 ± 1.215 | 1.19 ± 0.044 | 29.24 ± 1.40 |
| F3 | 0.430 ± 0.012 | 0.493 ± 0.010 | 12.92 ± 2.231 | 1.14 ± 0.033 | 28.31 ± 1.23 |

all the reading taken in replicate represented as mean ± SD

Table 12: Evaluation Of Tablet Blend

| Batch Code | Diameter (mm) | Thickness (mm) | Friability (%) (n=3) | Hardness (kg/cm ²) |
|------------|---------------|----------------|----------------------|--------------------------------|
| F1 | 8 | 2.46 ± 0.029 | 0.34 | 3.1 ± 0.287 |
| F2 | 8 | 2.48 ± 0.017 | 0.79 | 3 ± 0.268 |
| F3 | 8 | 2.48 ± 0.023 | 0.44 | 3.1 ± 0.290 |

Table 13: Evaluation Tablets Properties

| Batch Code | Disintegration time (sec.) |
|------------|----------------------------|
| F1 | 195 |
| F2 | 180 |
| F3 | 160 |

Table 14: Formulation Characteristics of Tablets

7.4 Reconstitution study

7.4.1 Content analysis (Assay %).

The analysis of content of the batch F1, F2 and F3 reconstituted solution of chlorhexidine gluconate tablet was carried out utilizing IP assay of chlorhexidine gluconate solution by High Performance Liquid Chromatography method (HPLC). Run standard sample six times and test sample duplicate.

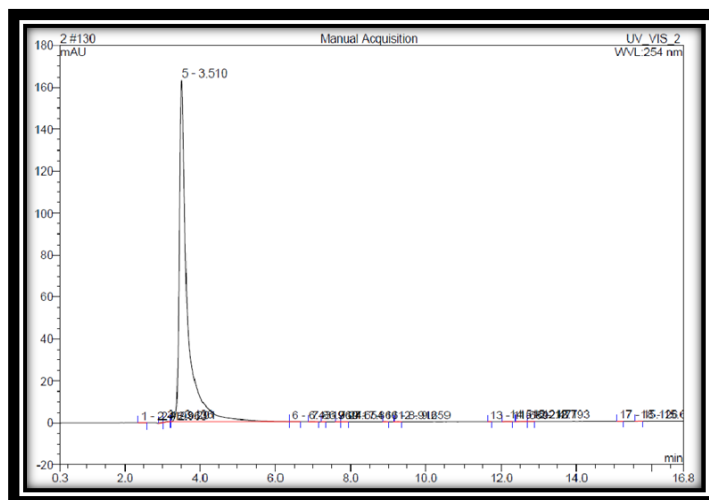


Fig. No 6: HPLC Chromatogram of Standard Chlorhexidine Acetate WS.

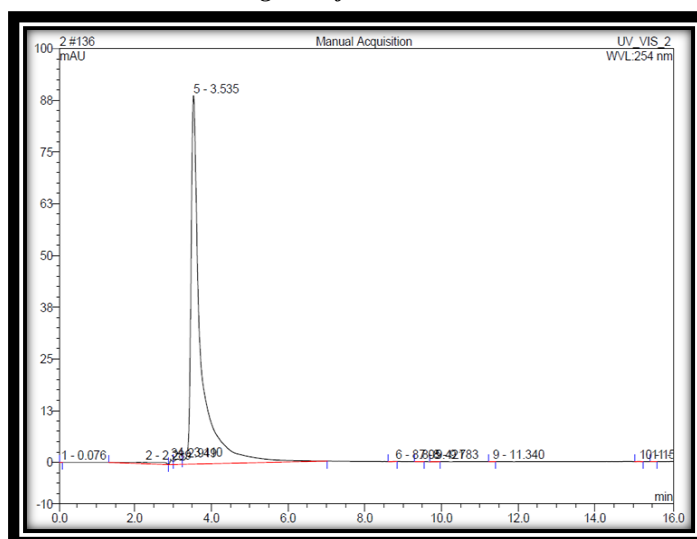


Fig.No 7: HPLC Chromatogram of Batch F1 Chlorhexidine Gluconate

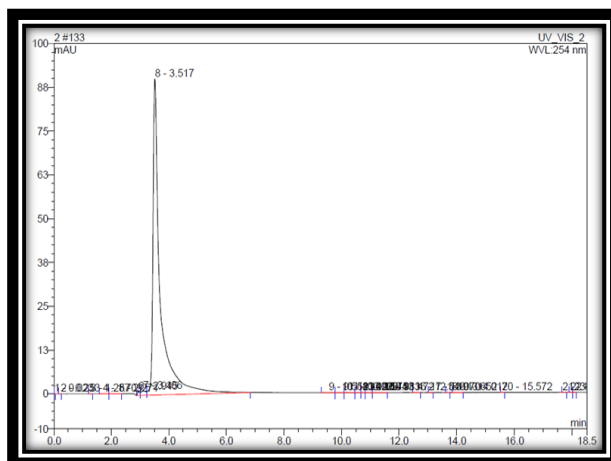


Fig.No 8: HPLC Chromatogram of Batch F2 Chlorhexidine Gluconate

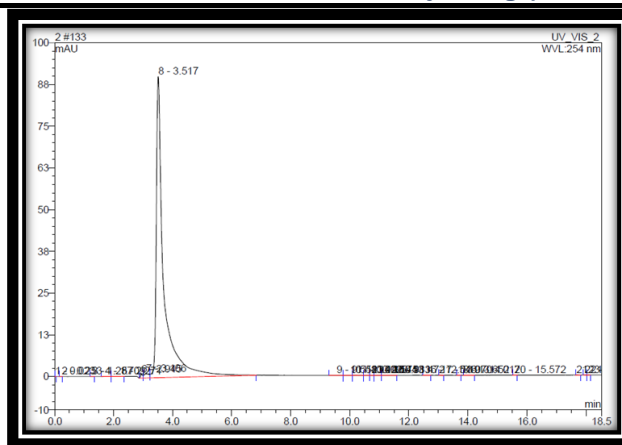


Fig.No 9: HPLC Chromatogram of Batch F3 Chlorhexidine Gluconate.

Chlorhexidine acetate WS standard solution average area was found to be 41.3316 mAU and test solution of chlorhexidine mouthwash tablet formulation F1, F2 and F3 average area was found to be 34.64 mAU, 34.47 mAU and 35.17 mAU respectively. By using the average sample peaks of standard solution and test formulation calculate content in the formulation batch F1, F2 and F3 (Table 20).

| Batch code | Average peaks of sample (mAU) | Average peaks of standard (mAU) | Assay (%) |
|------------|-------------------------------|---------------------------------|--------------|
| F1 | 34.64 | 41.3316 | 98.20 |
| F2 | 34.47 | 41.3316 | 97.70 |
| F3 | 35.17 | 41.3316 | 99.68 |

Table 15: Reconstituted Formulation Batches Content Analysis (Assay %)

7.5 Optimized batch

F3 batch was selected as optimized batch amongst design batches for the reconstitution of mouthwash tablet. Depending upon the evaluation of the tablet blend, tablet properties like hardness, friability, disintegration time. Also reconstitution study of the F3 batch assay within the specified limit as per I.P.

8. CONCLUSION

Recent trends of patient oriented practice demands design of patient oriented dosage form to achieve patient compliance and better therapeutic profile. The number of formulation related aspects contributes to non-compliance and insufficient drug release profile. Hence, there is a necessity to design patient oriented drug delivery system.

Present work lead to the optimization of process for preparation of lyophilize chlorhexidine gluconate solution and development of effervescent tablet comprising a solid water soluble excipient i.e. glycine, ribitol, aspartame which dissolve in 160 seconds. Formulation being a solid dosage form, the predicted stability of chlorhexidine gluconate is more, as chlorhexidine gluconate is available in liquid form and possesses stability problems if not stored at low temperature. Further a fast dissolving tablet strip will always be preferred by an end user over a liquid mouthwash bottle. The said formulation will be widely useful for a traveler, tourist or a camper, as it is difficult to carry liquid mouthwash bottle with him because of weight, fragility or bulk hence offering patient compliance and also solving the problem of shelf space at the retail outlet and home.

Formulation had a pleasant mouth feel with long lasting cooling effect. Formulation passed test within specified limits

Thus, attempt to develop a fast dissolving tablet for mouthwash was feasible with added advantage mentioned above.

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