Review Of Cetylpyridium Chloride Combination With Azadirachta Indica Extract Antibacterial And Antimicrobial Effervescent Mouthwash

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Abstract:
The objective of present work is to formulate and evaluate mouthwash and to evaluate its effectiveness against microbial load of oral cavity. The plant materials were collected and extracted for water soluble ingredients. Prepared mouthwash was further evaluated for its physicochemical properties and antimicrobial activity. The present mouthwash possesses a good antibacterial property. The results of stability study also confirm the effectiveness of preparation. Present mouthwash is a liquid preparation which normally contains antibacterial and antiseptic agents. These solutions can be used to reduce the microbial growth in the oral cavity Effervescent preparations may enhance absorption and speed up onset of action by increasing gastric pH, therefore hastening the emptying of medication into the small intestine. The carbon dioxide bubbles may also help intestinal absorption by opening up paracellular transport. Extreme bioavailability differences of up to 4-fold have been reported comparing effervescent tablets with ordinary tablets, highlighting the need for extra bioequivalence studies when switching dosage forms.

Keywords: Azadirachta Indica, Antibacterial and Antimicrobial, Effervescent.

1. INTRODUCTION

CPC is a well-known, broad-spectrum antimicrobial agent used in over-the-counter rinses to promote gingival health. It acts by penetrating the cell membrane, causing cell components to leak, which eventually leads to cell death.16 This action can be described to patients using the analogy of puncturing a water balloon. Recently, over-the-counter therapeutic CPC rinses have been introduced in alcohol-free formulations (Crest® PRO-HEALTH™ Mouthwash, Procter & Gamble).[1]

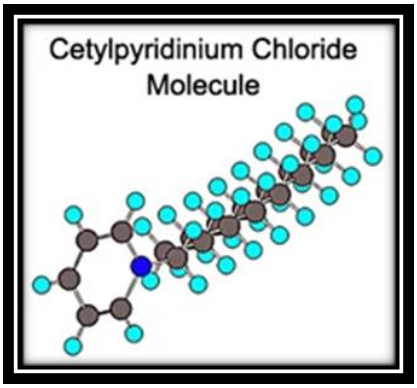

FIG.NO 1 CETYLPYRIDINIUM CHLORIDE MOLECULE

CPC is recognized to be effective against plaque and gingivitis when formulated at concentrations of 0.045% to 0.1% with at least 72% to 77% chemically available cetylpyridinium chloride.7 CPC's efficacy can be affected by other ingredients in the product formulation thus necessitating specific criteria to be established for its concentration and bioavailability.18 Studies have reported formulations with high bioavailable CPC are associated with greater biological activity, consequently indicating an increased probability for clinical efficacy.19 Rinses with lower CPC concentrations or with less chemically available CPC are long standing marketed products identified as cosmetic products used for the temporary control of halitosis.

Numerous 6-month clinical studies have shown statistically significant reductions in plaque and gingivitis for therapeutic CPC rinses relative to negative controls.10,20,21 Reductions ranged from 15% to 24% for gingivitis, 27% to 67% for bleeding, and 16% to 28% for plaque. Other extended use research has shown parity benefits to a positive control rinse.

CPC's safety has been well-documented.24,10,20-23 A small percent of patients may experience temporary taste alteration and/or transient staining as documented with any effective antimicrobial rinse.17 These side effects are usually observed more frequently from the use of prescription rinses (e.g., chlorhexidine) and occur less often in the over-the-

counter formulations. With the 0.07% CPC rinse, (Crest® PRO-HEALTH™ Mouthwash) user acceptability was favorable along with a high patient compliance. This CPC therapeutic mouthrinse has further demonstrated excellent bioavailability success with bacterialcidal activity and antibacterial retention.[2]
Cetylpyridinium chloride (CPC) is a cationic quaternary ammonium compound used in some types of mouthwashes, toothpastes, lozenges, throat sprays, breath sprays, and nasal sprays. It is an antiseptic that kills bacteria and other microorganisms. It has been shown to be effective in preventing dental plaque and reducing gingivitis. It has also been used as an ingredient in certain pesticides. Though one study seems to indicate cetylpyridinium chloride does not cause brown tooth stains, at least one mouthwash containing CPC as an active ingredient bears the warning label "In some cases, antimicrobial rinses may cause surface staining to teeth following a failed classaction lawsuit brought by customers whose teeth were stained. [3]

1.1 Herbs containing Mouthwash

1.1.1 Use of Tulsi (Ocimum sanctum) as a mouthwash

Tulsi is a small plant, sub-shrub which has multiple uses. Ayurveda mentions the importance of medicinal uses of it. The leaves are quite effective for the ulcer and infections in the mouth. A few leaves chewed will cure these conditions. The herb is useful in teeth disorders. Its leaves, dried in the sun and powdered, can be used for brushing teeth. It can also be mixed with mustered oil to make a paste and used as toothpaste. This is very good for maintaining dental health counteracting bad breath and for massaging the gums. It is also useful in pyorrhea and other gum disorders. The anti-inflammatory and anti-infectious properties of tulsi make it a powerful treatment for gum disease (4,5)

1.1.2 Use of neem (Azadirachta indica,

A.indica) as a mouthwash The first known use of neem by the Harrappa culture in ancient India dates back 4500 years. The history of the Neem tree is inextricably linked to the history of the Indian way of life. Today, neem extracts are used to treat various skin diseases, as an antiseptic substance, against endo and ectoparasites or simply as a herbal mouthwash (4). Neem extract has also an excellent effect as a non-toxic repellent, insecticide and pesticide (5). Almost every study of neem notes its antibacterial properties, but the more recent studies typically mention it in passing and emphasize newer discoveries or focus on a more specific use. Most of this work has been done in laboratories because treating bacteria (unlike viruses or cancer) is relatively straight-forward. In test tubes, neem has been shown to have significant effects on both gram-positive and gram-negative organisms and other bacteria that cause a wide array of human and animal diseases including E. coli, streptococcus and salmonella. Some of the more recent work has focused on oral care, a critical issue in both developing countries where professional dental care is limited and in developed nations where populations are aging. Extracts from neem sticks or bark have been shown to inhibit the growth of streptococcus mutans (6). Wolinsky et al have examined the inhibitory effects of aqueous extracts of neem, derived from the bark-containing sticks (Neem stick) of A. indica upon bacterial aggregation, growth, adhesion to hydroxyapatite, and production of insoluble glucan, which may affect in vitro plaque formation. The Neem stick extract and the gallotanninenriched extract from Melaphis chinensis inhibited insoluble glucan synthesis. Incubation of oral streptococci with the Neem stick extract resulted in a microscopically observable bacteria aggregation. These data suggest that Neem stick extract can reduce the ability of some streptococci to colonize tooth surfaces (6). In dentistry, A indica provide abbreviation has also demonstrated a good efficacy in the treatment of periodontal disorders (7). In a small trial from India, it was suggested that a dental gel containing A. indica extract has significantly reduced plaque index and bacterial count as compared to positive controls (chlorhexidine 0.2%). Streptococcus mutans (S. mutans) provide abbreviation in the saliva was found to be reduced significantly (8).The positive effect on dental health has been reported in epidemiological studies such efficacy of the herbal mouthrinses extract and the low dental caries among other natural bioactive products users (9, 10)

1.2 Why oral health important

Oral health is more than dental health. It includes healthy gums, hard and soft palate, linings of the mouth and throat, tongue, lips, salivary glands, chewing muscles, and upper and lower jaws. Good oral health enables us to speak, smile, kiss, breathe, whistle, smell, taste, drink, eat, bite, chew, swallow and express feelings. The oral cavity plays a central role for intake of basic nutrition and protection against microbial infections[4].
The World Health Organization (WHO) defines oral health as ―a state of being free from mouth and facial pain, oral and throat cancer, oral infection and sores, periodontal (gum) disease, tooth decay, tooth loss and other diseases and disorders that limit an individual‘s capacity in biting, chewing, smiling, speaking, and psychosocial wellbeing‖. Oral health is a human right, an integral part of general health and essential for overall wellbeing.
Oral health and general health have close linkages. On the one hand, oral health can be compromised by a number of chronic and infectious diseases which show symptoms in the mouth. On the other hand, oral diseases can lead to infection, inflammation, and other serious impacts on overall health. Thus, maintaining good oral health is crucial to sustain general health and vice versa[5].

Good self-care, such as brushing with fluoride toothpaste, daily flossing and professional treatment, is key to good oral health. There are many products which are used for purpose of oral hygiene such as

- Tooth Pastes
- Tongue Cleaner
- Mouth Gargles
- Mouth Spray
- Mouth Gel
- Tooth Foam
- Dental Cones
- Varnish
- Bio-adhesive Tablets
- Dentifrices
- Flossing Agents
- Mouth Wash
- Chewable tablets

During the past few years, there has been a dramatic increase in the use of mouthwashes. These are perceived by users to maintain oral health and have a fresh ―dental‖ taste (data on file, SmithKline Beecham Consumer Brands). Some health care professionals recommend their use as an adjunct to conventional mechanical removal of plaque'and this advice has been supported by studies which have shown that tooth brushing is only poorly carried out. Mouthwashes have been formulated containing any one of a whole range of different antimicrobials agents such as Bisbiguanides (chlorhexidine), Quaternary am-ammonium compounds [cetylpyridinium chloride (CPC),benzalkonium chloride], detergents (sodium lauryl sulphate),enzymes (mutanase/glucanase, amyloglucosidase/ glucose oxidase), essential oils (thymol, eucalyptol), phenolic compounds (Triclosan), a pyrimidine derivative (hexetidine), metal ions (zinc, copper, stannous) and sanguinarine, a plant extract

1.3 Oral cavity

The oral cavity is the point of entry for digestive and respiratory tracts. The mucous membrane of the mouth consists of squamous epithelium covering vascularized connective tissue. The epithelium is keratinized over the hard palate, lips and gingiva, while elsewhere it is nonkeratinized. Mucous glands (minor salivary glands) are scattered throughout the oral mucosa. Sebaceous glands are present in the region of the lips and the buccal mucosa only. Lymphoid tissue is present in the form of tonsils and adenoids. The oral cavity is the site of numerous congenital and acquired diseases. Besides, many systemic diseases have oral manifestations.

The readily visible components of the oral cavity include the lips (labia), the inside of the cheeks (buccal), the teeth and gums (gingivae), the hard and soft palates, the floor of the mouth, and the tongue (Fig. 1). Not visible, but clearly important, are the muscles, nerves, blood vessels, glands, joints, and especially the bones of the upper (maxilla) and lower (mandible) jaws that provide support for and function with the visible components. The oral cavity begins at the junction of the vermilion border of the lips and the mucosa lining the inside of the lips, and extends posteriorly to the palate glossal folds or arch. Beyond the palatoglossal folds are the palatopharyngeal folds and the beginning of the oropharynx, where the digestive and respiratory tracts come together. The palatine tonsilsare located in the tonsillar fauces between the palatoglossal and palatopharyngeal folds. The lymphoid tissue of the palatine tonsils, along with that of the pharyngeal tonsil (adenoids) and the lingual tonsils, guards the entrance to the oropharynx. Anteriorly, the respiratory tract (nasal cavity) is separated from the oral cavity by the hard palate, and posteriorly by the soft palate. The hard palate has an arch-like shape that varies in width and height among individuals. It also plays an important role in manipulation and mastication of food, and in speech. The soft palate functions to seal the oropharynx from the nasopharynx during swallowing and speech. However, during exhalation, receptor cells that detect odors in the olfactory mucosa are activated by oral vapors moving from the posterior oral to posterior nasal cavity through the nasopharynx, effectively expanding the mouth. It is this retronasal route that gives food and drink the odors that contribute much to flavor perception.

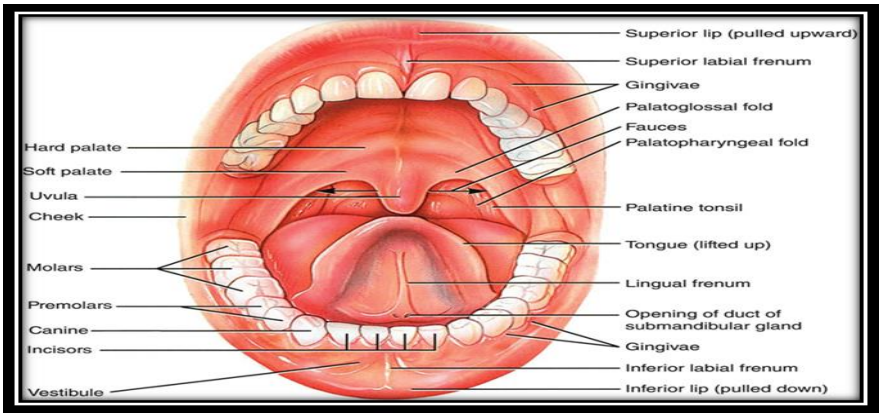

FIG. NO 2; DIAGRAM ILLUSTRATING THE ANATOMY AND MAIN STRUCTURE OF THE ORAL CAVITY.

1.4 Oral mucosa

Mucosa is a wet, soft tissue membrane that lines an internal body space, e.g., the oral cavity, the gastrointestinal, urinary, and reproductive tracts. The oral mucosa consists of three layers: a surface epithelium; a supporting lamina propria consisting of a layer of loose connective tissue (papillary layer) just below the epithelium and a deeper layer of dense irregular connective tissue (reticular layer); and an underlying sub-mucosa consisting of dense irregular connective tissue (Fig. 2). The sub-mucosa frequently contains minor salivary glands, and in some locations may contain adipose tissue. In some regions of the oral cavity, the sub-mucosa may be absent, and the mucosa is bound to either bone or muscle by the lamina propria.

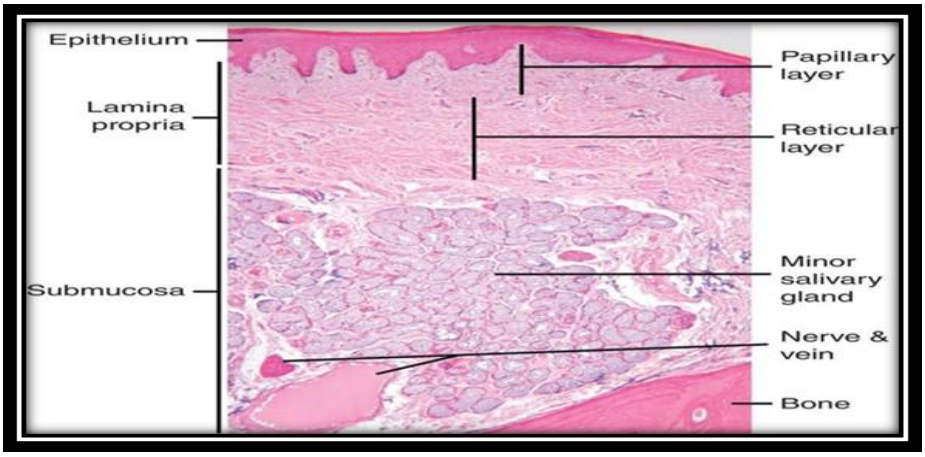

FIG.NO 3: LIGHT MICROGRAPH SHOWING THE LAYERS AND COMPONENTS OF THE ORAL MUCOSA.

A sub-mucosa is not present in all regions of the oral cavity. Three sub-types of mucosa are found in the oral cavity. Lining or moveable mucosa has a stratified squamous non- keratinized epithelium, and is found on the inside of the lips and cheeks, in the vestibules and the floor of the mouth, and on the alveolar processes, the ventral surface of the tongue, and the soft palate. Masticatory mucosa has a stratified squamous keratinized or para-keratinized epithelium, and is found on surfaces subjected to the stresses induced by chewing our food (mastication), the hard palate and the gingivae. Specialized mucosis found on the dorsal surface of the tongue. This mucosa is considered specialized because it forms four different types of papillae, three of which have taste buds through which taste sensations are received. Multiple fungi form papillaedot the dorsal anterior lingual surface, whereas two series of papillae with associated trenches or troughs, the medial circumvallate and lateral foliate papillae are found far posterior near the base of the tongue

1.5 Teeth

The teeth are among the most unique and complex structures of the body. Although they are designed to last a lifetime, teeth can be destroyed or lost in a relatively short time if we fail to take care of them. They consist of three different hard, or mineralized, tissues – dentin, cementum, and enamel– and are supported by a fourth hard tissue –bone (Fig. 3.). The interface between the teeth and the gingivae is the only place in the body where a structure composed of hard tissues breaches a soft tissue covering. This unique anatomic arrangement is the site of significant pathology that can lead to the destruction of the supporting tissues of the tooth (periodontium) and its eventual loss.

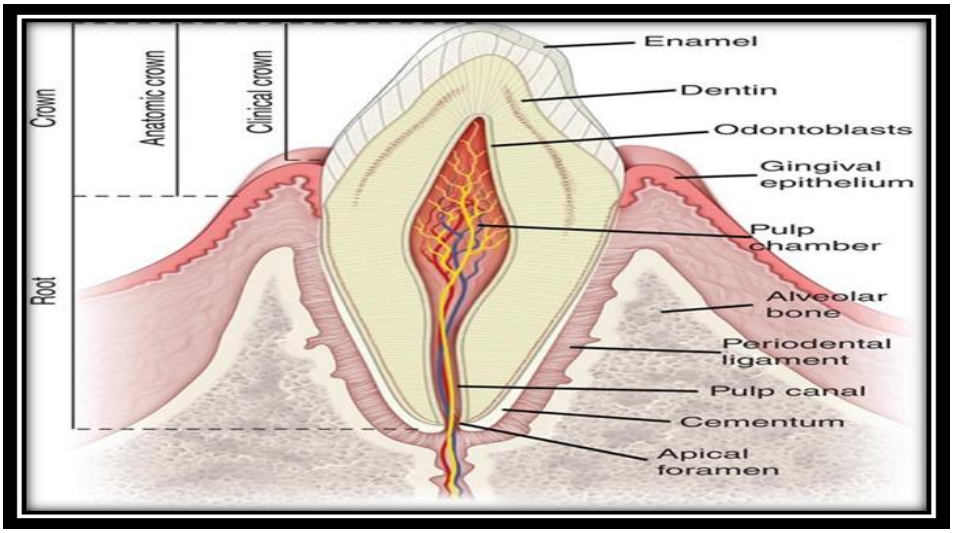

FIG.NO. 4 DIAGRAM ILLUSTRATING THE STRUCTURE OF A TOOTH AND ITS SUPPORTING TISSUES

The teeth are among the most unique and complex structures of the body. Although they are designed to last a lifetime, teeth can be destroyed or lost in a relatively short time if we fail to take care of them. They consist of three different hard, or mineralized, tissues – dentin, cementum, and enamel– and are supported by a fourth hard tissue –bone. The interface between the teeth and the gingivae is the only place in the body where a structure composed of hard tissues breaches a soft tissue covering. This unique anatomic

Supporting tissues of the tooth (periodontium) and its eventual loss. The main tissue of the tooth is dentin. Dentin supports the enamel, which covers the crown, and it forms the root of the tooth. Dentin encloses the pulp, which through its blood and nerve supply and immunologic and regenerative functions maintains the vitality of the dentin and the cells that produce it, odontoblasts. Odontoblasts line the periphery of the pulp and secrete and mineralize the matrix components of dentin, predominantly collagen. Each odontoblast has a long apical or distal cytoplasmic process, the odontoblast process that extends partway through the dentin in a dentinal tubule. The dentinal tubules are created as the dentin is deposited around the odontoblast processes and the odontoblasts gradually move deeper into the pulp. Some of the dentinal tubules also contain nerve endings, which in conjunction with the odontoblasts and other nerve endings associated with the odontoblasts are responsible for the sensation of pain in dentin.

1.6 Disease of oral cavity

♣ Mucocutaneous lesions

Lesions of the oral mucosa occur in many diseases of the skin and they are similar in morphology. Some of these are listed as under:

Lichen planus. Characteristically, oral lichen planus appears as interlacing network of whitening or keratosis on the buccal mucosa but other oral tissues such as gingival, tongue and palate may also be involved.

♣ Vesicular lesions. A number of vesicular or bullous diseases of the skin have oral lesions.

a. Pemphigus vulgaris - Vesicular oral lesions appear invariably in all cases at some time in the course of pemphigus vulgaris. In about half the cases oral lesions are the initial manifestations.
b. Pemphigoid-Vesicles or bullae appear on oral mucosa as well as on conjunctiva in Pemphigoid and are seen more often in older women.
c. Erythema multiforme- Subepithelial vesicles may occur on the skin as well as mucosae.
d. Stevens-Johnson syndrome is a rather fatal and severe form of erythema multiforme involving oral and other mucous membranes occurring following ingestion of sulfa drugs.
e. Epidermolysis bullosa is a hereditary condition having subepidermal bullae on the skin as well as has oral lesions.

1.6.1 Inflammatory diseases

Stomatitis-Inflammation of the mucous membrane of the mouth is called stomatitis. It can occur in the course of several different diseases like

- Aphthous ulcers (Canker sores) is the commonest form of oral ulceration. The etiology is unknown but may be precipitated by emotional factors, stress, allergy, hormonal imbalance, nutritional deficiencies, gastrointestinal disturbances, trauma etc. The condition is characterized by painful oral ulcers, 1 cm or more in size.
- Herpetic stomatitis is an acute disease occurring in infants and young children. The lesions are in the form of vesicles around the lips. Similar lesions may appear on the genital skin. Recurrent attacks occur due to stress, emotional upsets and upper respiratory infections.
- Necrotising stomatitis (Noma or Cancrumoris) occurs more commonly in poorlynourished children like in kwashiorkor; infectious diseases such as measles, immunodeficiency and emotional stress. The lesions are characterised by necrosis of the marginal gingiva and may extend on to oral mucosa

1.6.2 Dental plaque

Dental plaque is made up mainly of microbial masses held together by a mucinous ground substance, and it adheres to tooth surfaces. It varies in color from white to yellowish gray and is referred to as material alba, dentobacterial plaque, gelatinous plaque, microcosm, oral debris, and sordes. Initially it is a soft mass which accumulates within a few days after refraining from tooth brushing. This type of material is termed as soft plaque. It contains in addition to bacteria, a scattering of leukocytes, macrophages, and epithelial cells. Plaque formation is said to occur in two stages: first, an amorphous, nonbacterial layer is laid down (acquired pellicle or cuticle). This is followed by second step of bacterial invasion and subsequent bacterial proliferation. The nature of plaque is variable and dynamic, expressed by constant change in chemical composition and microbial population. Plaque is about 80% water and 20% solids. When it is ―young,‖ the solids fraction contains relatively small amounts of inorganic material (ash). As the plaque ages, the ash content of solid increases, and plaque which is only a few days old can have over 40% ash, based on solids. The nature of microbial population also changes. It has been demonstrated that as plaque ages the proportion of cocci decreases while the proportion of filamentous organism increases. Further evidence for the variability of plaque is the observation that its composition may be different from one site in the mouth to other. Plaque acts as an etiologic agent in several oral diseases mainly because it concentrates large numbers of microorganisms, localizes them to specific areas and protects products of bacterial activity from being readily diluted or dissipated. A mature plaque is essentially a bacterial community. The

metabolic activity of the residents varies with local conditions and can result in the production of many different substances which can markedly affect adjacent tissues. Plaque manifests itself in more than one form, as demonstrated by differences in the nature of the oral hygiene problems it can generate. The course of development of plaque on a freshly cleaned tooth surface will be affected by a myriad of factors in the oral enviromnent of an individual, such as saliva composition, nature of the bacterial flora, dietary habits, the existence of specific disease states and the use of medication for these states, oral hygiene habits, genetic characteristics, etc9

1.6.3 Dental caries

Dental caries is the most common disease of dental tissues, causing destruction of the calcified tissues of the teeth. Dental caries is essentially a disease of modern society, associated with diet containing high proportion of refined carbohydrates. It has been known for almost 100 years that mixture of sugar or bread with saliva in the presence of acidogenic bacteria of the mouth, especially streptococci, produces organic acids which can decalcify enamel and dentin. Caries occurs chiefly in the areas of pits and fissures, mainly of the molars and premolars, where food retention occurs, and in the cervical part of the tooth.

Dental caries is a disease characterised by dissolution of the mineral portion of the tooth. As caries progresses, destruction of tooth enamel and dentine occurs followed by inflammation of pulp and periapical tissues. The mutans streptococci (MS) are a cluster of acidogenic, dental plaqueinhabiting streptococcal species that are considered the principal causative agents of caries. Presently, seven different MS species (known as S. mutans, S. rattus, S. cricetus, S. sobrinus, S. ferns, S. macacae, and S. downei) are recognised. Of these seven species it is mainly S. Mutans and S. Sobrinus that are of significance in terms of human caries.

The gingival tissues tend to recede over time, exposing the tooth root to cariogenic bacteria that can cause root caries. Even the most protective genetic endowment and developmental milieu are unlikely to confer resistance to decay in the absence of positive personal behaviors. These include sound dietary habits and good oral hygiene, including the use of fluorides, and seeking professional care. There are indications, however, that some destructive oral habits are on the rise, such as the use of smokeless (spit) tobacco products by teenage boys. Although the chief concern here lies in the long-term risk for oral cancers, spit tobacco that contains high levels of sugar is also associated with increased levels of decay of both crown and root surfaces.

1.6.4 Calculus

Dental calculus is calcified dental plaque, composed primarily of calcium phosphate mineral salts deposited between and within remnants of formerly viable microorganisms. A viable dental plaque covers mineralized calculus deposits. Levels of calculus and location of formation are population specific and are affected by oral hygiene habits, access to professional care, diet, age, ethnic origin and time since last dental cleaning, systemic disease and the use of prescription medications. In populations that practice regular oral hygiene and with access to regular professional care, supragingival dental calculus formation is restricted to tooth surfaces adjacent to the salivary ducts. Levels of supragingival calculus in these populations are minor and the calculus has little if any impact on oral-health. Subgingival calculus formation in these populations occurs coincident with periodontal disease (although the calculus itself appears to have little impact on attachment loss), the latter being correlated with dental plaque. The composition of calculus and adhesive aspects are influenced by the location of its formation as well as its age. The mineral component of dental calculus predominates in formed, hardened deposits. Minerals found in human calculus are typically calcium phosphate salts, including variable amounts of dicalcium phosphate dehydrate (DCPD), octacalcium phosphate (OCP). Substituted hydroxyapatite (HAP) and magnesium substituted tricalcium phosphate (Whitlockite), Evidence suggests that the proportion of mineral phases is affected by kinetic aspects of calcification initiation and transformation. In addition to mineral components, calculus contains a variety of inorganic and organic species from bacterial, salivary and dietary origin. These can be incorporated either during mineralization or following calcification, as calculus is quite porous. Mineral deposits are found to be distributed both between and within organisms, depending upon deposit age.

It is well-known that the greatest amount of supragingival calculus is present on the lingual surfaces of mandibular anterior teeth and decreases toward the third molars. In the maxilla, supragingival calculus frequently forms on the buccal surfaces of the first molars. In both the mandible and maxilla, these are sites that are close to the orifices of salivary ducts. Subgingival calculus also exhibits site-specificity, although it is much less apparent than that of its supragingival counterpart. It has been reported that the levels of subgingival calculus are significantly higher on the lingual than on the buccal surfaces.

1.6.5 Halitosis (Breath odor)

Halitosis is an unpleasant or offensive odor emanating from the oral cavity, leading to discomfort and psychosocial embarrassment. In approximately 80% of all cases, halitosis is caused by oral conditions, defined as oral malodor. There seems consensus that oral malodor results from tongue coating, periodontal disease, peri-implant disease, deep carious lesions, exposed necrotic tooth pulps, pericoronitis, mucosal ulcerations, healing wounds, impacted food or debris, imperfect dental restorations, unclean dentures and factors causing decreased salivary flow rate. Undoubtedly, the tongue is a major site of oral malodor production, whereas periodontal disease and other factors seem only a fraction of the

overall problem. The oral malodor arises from microbial degradation of organic substrates present in saliva, crevicular fluid, oral soft tissues and retained debris

However, possible non-oral causes of oral malodor should always be considered because of the clinical importance of detecting underlying pathoses. A variety of non-oral conditions may give rise to oral malodor. A variety of non-oral conditions include systemic diseases such as diabetes mellitus, chronic renal failure, cirrhosis of the liver, anaerobic infections, and carcinomas of the lungs and the upper respiratory tract. Oral rinses offer a pleasant, "clean" taste created by essential oils, flavoring agents, and alcohol while they concomitantly reduce malodor because of the antiseptic agents they contain (quaternary ammonium compounds, phenolic derivatives, and other agents). However, without dental treatment and an adequate daily oral hygiene regimen. the problem of halitosis remains largely unsolved.

1.6.6 Salivary flow disturbances

a. Sialorrhoea (ptyalism)-Increased flow of saliva is termed sialorrhoea or ptyalism. It occurs commonly due to: stomatitis, teething, mentally retarded state, schizophrenia, neurological disturbances, increased gastric secretion and sialosis.
b. Xerostomia- Decreased salivary flow is termed xerostomia. It is associated with the following conditions: Sjögren‘s syndrome, sarcoidosis, mumps parotitis, Mikulicz‘s syndrome, megaloblasticanemia, dehydration, drug intake (e.g. antihistamines, antihypertensive, antidepressants)[8].

1.6.7 Periodontal disease

Periodontal disease is a general term used to describe diseases that affect the gingiva and cause damage to the supporting connective tissue and bone which anchor the teeth to the jaws. Periodontal disease is caused by specific bacteria from the biofilm within the periodontal pocket. Periodontitis is also an inflammatory disease resulting from a complex interplay of bacterial infection and host response, but is characterized by attachment and bone loss around the teeth. Most gingivitis does not progress to Periodontitis. Early-onset Periodontitis is a rare form that affects teenagers (juvenile Periodontitis) and young adults (rapidly progressive Periodontitis) and may be associated with specific host factors. As anaerobic infection takes hold, a complex cascade of tissue- destructive pathways is set in motion, triggered by bacterial products and fuelled by inflammatory mediators. The surface area of the mouth affected by periodontal disease can be large, equivalent to the surface area of one to two hand-spans (300 cm2). The infectious and inflammatory burden of chronic periodontitis is thought to have an important systemic impact. periodontitis is associated with an increased likelihood of coronary heart disease and may influence the severity of diabetes.

1.7 Oral diseases specifically caused by anaerobic microorganism

Microbial populations colonizing the teeth are a major source of pathogens responsible for oral and dental infections, including periodontal diseases, gingivitis, pericoronitis, endodontitis, periimplantitis, and post-extraction infections. Each entity has distinct clinical and microbial features. Bacterial species associated with oral infections include Actinobacillus actinomycetemcomitans, Porphyromonasgingivalis, Prevotellaintermedia, Bacteroidesforsythus, Campylobacter rectus, Eubacterium species, Fusobacterium nucleatum, Eikenellacorrodens, and Peptostreptococcus micros. Treponema-pallidum— related spirochetes have been associated with acute necrotizing ulcerative gingivitis. Porphyromonasendodontalis appears to be specifically related to endodontic infections. Oral infections in medically compromised patients, including those with AIDS, are associated with similar species and are usually complicated by superinfection with enteric and Candida species. Table 1 states the names of micro-organisms associated with oral and dental diseases

TABLE 1: MICRO-ORGANISMS ASSOCIATED WITH ORAL AND DENTAL DISEASES

1	Diseases	Micro-organisms
1	Dental carries	Streptococcus mutans
		Campvlo bacterrectust, Fuso bacterium nucleatuni, Peptostrepto coccus micros, Prevotellaintermedia, Eubacteriumtimidum, Eubacteriumalactolyticum,
2	Periodontitis	Fusobacteriumalocis, Selenomonassputigena, Eubacteriumbrachy, Peptostreptococcusanaerobius, Porphyronionasgingivalis, Bacteroidesforsythus, Actinobacilhis, Actinomycetemcomitans.
3	Gingivitis	Streptococcus anginosus, Campylobacter concisus, T. socranskii subspecies paredis, Actinomycesnaeslundii (type III), and S. sanguis
4	Pericoronitis	P. gingivalis and Eubacterium species
5	Endodontic infections	P. gingivalis, P. intermedia, and Porphyromonasendodontalis
6	Peri-implantitis	A. actinomycetemcomitans, P. intermedia, P. gingivalis, Capnocytophaga species, C. rectus, and E. corrodens
7	Actinomycosis	Actinomyces and Arachnia species

1.7.1 Prevention

The varied measures required in the management of oral and dental infections include antimicrobial therapy. Many products containing one or the other antibacterial agents are available in the market which has been used to treat disease caused by the anaerobic micro-organism, e.g. products containing bisbiguanides such as chlorhexidine; phenolic compounds such as β-naphthol, thymol, chlorothymol, amyl-, hexyl-, heptyl- and octylphenol, hexylresorcinol, hexachlorophene, and phenol; quaternary ammonium compounds such as quaternary morpholinium alkyl sulfates, cetylpyridinium chloride, alkyldimethyl benzylammonium chloride, and alkyltrimethyl ammonium halides and miscellaneous antibacterial compounds such as benzoic acid, formaldehyde, potassium chlorate, tyrothricin, gramicidin, iodine, sodium perborate, and urea peroxide.

1.8 Mouthwash concept

Mouthwashes are solutions or liquids used to rinse the mouth for a number of purposes:
(a) to remove or destroy bacteria (b) to act as astringent (c) to deodorize and (d) to have a therapeutic effect by relieving infection or preventing dental caries. Mouthwashes also provide a safe, effective chemical means of reducing or eliminating plaque accumulation. In contradiction to one‘s thinking that mouthwashes are used only for refreshing the oral cavity or just for treatment of dental carries and cleansing the mouth, it has found much use in preventing and treating infection of mouth, treating inflammatory cases like ulcers and relieving the pain related to its etc. Aerosol mouthwash or mouth fresheners are recommended for breath freshening after eating, drinking or smoking and usually contain only flavoring agent, though they may contain antibacterial agents. Products used for freshening breath or cleaning teeth have been in existence for centuries. Water is the simplest mouthwash and aqueous saline is the least complex type of mouthwash. Many of the ancient societies including the Egyptians, Chinese, Greeks and Romans had recipe for such preparations. They used a variety of ingredients; from edible materials like fruit, honey or dried flowers to less appealing compounds such as ground lizard, minced mice or urine. These products were generally ineffective and in some cases were harmful to the sensitive enamel coat each tooth. While tooth cleaning preparation steadily improved over the years, it was not until the early 1800s when the modern toothpaste was developed that truly effective oral products became available. The first mouthwash were basically solution of grain alcohol and were likely developed accidentally during this era. One of the most famous brands, Listerine was developed during the 1800s and is still sold today.

1.8.1 Functions and mechanism of mouthwash

Mouthwash can control the bad breath to a marked degree by one or more of the following mechanism like, Cleaning the teeth and tissue so that fermentative and putrefactive debris is mechanically removed, inhibiting the bacterial enzymatic activity in mouth so that the malodorous end product are not easily formed, using ingredients that modify or eliminate odorous substance by chemical reaction or physical adsorption, substituting pleasant odors for undesirable ones by a masking effect. But the major concern which leads to frequent use of mouthwashes is halitosis. Secondary reason for the use of mouthwash includes control of a plaque and gingivitis when used as an adjunct to mechanical means. The primary function of mouthwash is to freshen the mouth and Breathe by swishing/ swirling the product in the mouth, followed by expectoration. This is achieved by a combination of three factors: the mechanical effect of rinsing debris from mouth, the effect of the flavor, the effect of any agent specifically added to deliver the required end result like antibacterial, astringent, etc.
There is wide latitude in the choice of mouthwash components, depending on the characteristics and end purpose sought. Numerous chemical ingredients can be chosen for their antibacterial effect; the choice of flavor components can often be greatly varied; ingredients for special purposes, such as penetrants, astringents, therapeutic and preventive compounds and deodorants also are subject to great variation.

1.8.2 Types of mouthwashes

Broadly mouthwashes can be classified according to categorical function

- Antiseptic mouthwash. The most common type of mouthwash is antiseptic mouthwash. Typically containing alcohol, antiseptic mouthwash works to halt the growth of bacteria and stave off infection. The most popular brand of antiseptic mouthwash is Listerine.
- Analgesic mouthwash. Commonly used in the ulcerative condition. Triclosan mouthwash will have analgesic effect and can significantly relieve pain, shorten the ulcerative phase.
- Anti-inflammatory mouthwashes. These mouthwashes are used in a specific condition somewhere there is an element of inflammation either as the primary cause of the state or as secondary complication state. These mouthwash contain benzydamine hydrochloride.
- Fluoride mouthwashes are used for the prevention of carries. Stannous fluoride mouthwash produces highly bactericidal effect.
- Salivary substitute mouthwashes: Salivary substitute mouthwashes have been used for the treatment of xerostomia and mainly used for the treatment of dysphagia (difficulty with eating and swallowing) and dysphonia (difficulty in speaking).
- Covering agent are effective in ulcerative conditions. Sucralfate as covering agent used for the mouth that has shown a pain management of mucositis patient.

- Breath freshener mouthwashes are mainly used for the treatment of bad breath. During the day bad breath level inversely related to saliva flow. If saliva flow low then bad breath increases. For the treatment of bad breath used a first marketed preparation Listerine® in 1994.
- Antibacterial rinses have many uses in the oral cavity. For antibacterial rinses to be effective in the oral cavity they need to be bactericidal or bacteriostatic and most of all must have a degree of Substantivity.

1.8.3 In addition to the above classification, mouthwashes may be classified on the basis of the type of product form, such as:

- Liquid mouthwash, ready to use without any dilution.
- Concentrated mouthwashes, prepared and issued in a concentrated form and required to be diluted before use with water.

Tablet preparation, required to be dissolved (or dispersed) in water before use.

- Aerosol mouthwashes, preferably metered aerosol products.

1.8.4 Formulation

Most of mouthwashes contain four basic ingredients: alcohol, flavors, humectants and surfactants, with water and minor ingredients making up the remainder of the product. In addition, depending upon the final use a mouthwash may contain one or more active ingredients like anti-bacterial, astringent, deodorizing, buffering components. An ideal mouthwash contains an astringent, breath freshener, humectant, buffer sweetener, flavor and color besides its active ingredient. It should have long acting pleasant flavor and cooling agent, should remove the fermentative and putrefactive debris and clean teeth and tissue. The actives used in mouthwash should prevent decaying of the teeth and should not impart unwanted color to teeth. Mouthwash should also neutralize the acid produce by microorganism in biofilm.

1.9 Effervescent Tablets

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 (Witzel and Clark, 1978).

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 (Rotthäuser et al., 1998).

Effervescent granules are manufactured in low humidity areas. Effervescent granules are mixed in V-type blender or a ribbon blender. Wet granulation is performed by using 0.1%–1% (weight by weight basis) of water and then immediately, granules are transferred to the drying oven. Care should be taken that all of the equipment used do not contain traces of water or moisture as it can destroy the effervescent mixture. After drying, the granulation is sized, mixing them with watersoluble lubricants, and then compressed into tablets. Strict control of humidity in all of the manufacturing areas is a must [65°F–75°F, 10% relative Humidity (RH)]. Any packaging material used for an effervescent tablet should protect the tablet from external shear as well as entrap little amount of air within it since moisture present in entrapped air can lead to physical and/or chemical degradation of the tablet (Altomare et al., 1997).

Thus effervescent tablets allow for administering a larger amount of dose compared to conventional tablets. There is no need for swallowing, and hence, patient compliance is enhanced in geriatric and pediatric patients. Also, they allow for improved dosing, and due to the evolution of CO2, self-mixing of all ingredients occurs. Along with the characterization

techniques for conventional tablets, effervescent tablets are evaluated for carbon dioxide content, water content, effervescence time, and pH (Tadros, 2010).

1.9.1 Use

In by-mouth medicine

Vitamins may be sold as effervescent tablets. Alka-Seltzer is an antacid and pain reliever sold as an effervescent powder. There are several categories of active ingredients that may be best administered in the form of effervescent preparations:

- Those that are difficult to digest or disruptive to the stomach or esophagus
- Those that is pH–sensitive, such as amino acids and antibiotics.
- Those requiring a large dose.
- Those that are susceptible to light, oxygen, or moisture.
- It is used as a gastrointestinal agent.

Effervescent preparations may enhance absorption and speed up onset of action by increasing gastric pH, therefore hastening the emptying of medication into the small intestine. The carbon dioxide bubbles may also help intestinal absorption by opening up paracellular transport. Extreme bioavailability differences of up to 4-fold have been reported comparing effervescent tablets with ordinary tablets, highlighting the need for extra bioequivalence studies when switching dosage forms.

It is dangerous to swallow an effervescent tablet directly, as the tablet can get stuck in the subglottis and fizzle there. A potentially fatal edema may occur from the irritation. In addition, conventional effervescent tablets contain a significant amount of sodium and are associated with increased odds of adverse cardiovascular events according to an 2013 study. Low or no-sodium formulations exist.

2. SUMMARY AND CONCLUSION

The aim of the present study was to develop Cetylpyridium Chloride Combination with Azadirachta Indica Extract Antibacterial and Antimicrobial Effervescent Mouthwash. 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 factors contributes to non-compliance and inadequate drug release profile. Hence, there is a need to design patient oriented drug delivery system.

Present work lead to the optimization of process for preparation of lyophilize Mouthwas solution and development of effervescent tablet comprising a solid water soluble excipient i.e. glycine, sorbitol, aspartame which dissolve in 160 seconds.

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4. CONFLICTS OF INTEREST

Authors have no conflicts of interest to declare.

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