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Formulation and Eveluation of Buccal Mucoadhesive Tablet Diltiazem HCL

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I. INTRODUCTION:-

The adminisration of drug through oral route is considered as most convenient and cost effective way in human and is prefered by patient. The drug is the most important part in the formulation and it has to be developed into satisfactory dosage form. Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of administration problems such as high first pass metabolism, drug degradation in harsh gastro intestinal environment can be circumvented by administering a drug via buccal route. More over buccal drug absorption can be terminated promptly in case of toxicity by removing the dosage form from the buccal cavity. It is also possible to administer the drug to patients who cannot be dosed orally to prevent accidental swallowing. Therefore, mucoadhesive dosage forms were suggested for oral drug delivery which include adhesive tablets, adhesive gels, adhesive patches.

Diltiazem is antianginal drug (calcium channel blocker), which has been used in the treatment of various cardiovascular disorders, particularly angina pectoris and systemic hypertension. It has a short biological half-life of about 3.5 hr and is rapidly eliminated. The oral bioavailability of diltiazem is 40 % in humans. Diltiazem was selected as a model drug for investigation because of its suitable properties like shorter half-life, optimum partition coefficient (158) and molecular weight (450.98) make it suitable for administration by buccal route. A suitable buccal drug delivery system should posse's good bioadhesive properties. The buccal mucoadhesive drug can be retained in oral cavity for desired duration and localize the dosage form in a specific region and control release rate of drug.

MUCOADHESIVE DRUG DELIVERY SYSTEM.

Mucoadhesive drug delivery systems interact with the mucus layer covering the mucosal epithelial surface, and mucin molecules and prolongs the residence time of the dosage form at the site of application. Bio adhesion may be defined as the state in which two materials, at least one of which is of a biological nature, are held together for extend periods of time by interfacial forces. Buccal mucosa is the preferred site for both systemic and local drug action. The mucosa has a rich blood supply and it relatively permeable. Buccal trans mucosal delivery helps to bypass first-pass metabolism by allowing direct access to the systemic circulation through the internal jugular vein. Mucoadhesive drug delivery systems can be delivered byvarious routes:

- Buccal delivery system
- Oral delivery system
- Vaginal delivery system
- Rectal delivery system
- Nasal delivery system
- Ocular delivery system

Mucoadhesive Oral Drug Delivery Systems:

Oral route is the most preferred route for the delivery of any drug. Drug delivery via the membranes of the oralcavity can be subdivided as:

1. Sublingual delivery:
This is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth.

2.Buccal delivery:
This is drug administration through the mucosalmembranes lining the cheeks (buccal mucosa).

Advantages of Oral Mucoadhesive Drug Deliver Systems:

1. Prolongs the residence time of the dosage form at the site of absorption, hence increases the bioavailability.
2. Excellent accessibility, rapid onset of action.
3. Rapid absorption because of enormous blood supply and good blood flow rates.
4. Drug is protected from degradation in the acidicenvironment in the git.
5. Improved patient compliance.

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 # Disadvantages of Mucoadhesive Drug DeliverSystems:

1. Occurrence of local ulcerous effects due to prolonged contact of the drug possessing ulcerogenic property.
2. One of the major limitations in the development of oral mucosal delivery is the lack of a good model for in vitro screening to identify drugs suitable for such
administration.
3. Patient acceptability in terms to taste and irritancy.
4. Eating and Drinking is prohibited.

 # Structure and Function of Oral Mucosal

- **Membrane:**

The outermost layer of oral mucosa is stratified squamous epithelium and below it, there is a basementmembrane called lamina propria which is followed by the sabmucosa. It also contains many sensory receptors including the taste receptors of the tongue. Laminapropria, consist of collagen fibers a supporting layer ofconnective tissues, blood vessel and smooth muscles. The epithelium may consist of a single layer (stomach, small and large intestine, bronchi) or multiple layers (esophagus, vagina). The upper layer contains goblet cells, which secrete mucus components directly onto the epithelial surface. Tissue have moist surface due to mucus which is a, viscous, gelatinous secretion and this mucus composed of glycoproteins, lipids, inorganic salts, and up to 95% water. Mucin (Glycoproteins) are the most important components of mucus and it is also responsible for gelatinous structure, cohesion, and antiadhesive properties. Mucin consist of three-dimensional network with large number of loops. The main functions of the mucus are to protect and lubricate the supporting epithelial layer.

- **Permeability:**

The permeability of the buccal mucosa is estimated to be 4-4000 times greater than the skin. In general, the permeabilities of the oral mucosa decrease in the order of sublingual greater than buccal, and buccal greater than palatal. This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized. The permeability barrier property of the oral mucosa is predominantly due to intracellular materials derived from the so called – "membrane coating granules"(MCGS). Recent evidence has shown that passive diffusion is the primary mechanism for the transport of drugs across the buccal mucosa while carrier mediated transport has been reported to have a small role. In buccal mucosa two routes of passive transport are found one involves the transport of compounds through the intercellular space between the cells (paracellular) and other involves passage into and across the cells (transcellular). Another barrier to drug permeability across buccal epithelium is enzymatic degradation.

- **Role of Saliva:**

a) Protective fluid for all tissues of the oral cavity.
b) Continuous mineralization / demineralization of the tooth enamel.
c) To hydrate oral mucosal dosage forms.

- **Role of Mucus:**

a) Made up of proteins and carbohydrates.
b) Cell-cell adhesion
c) Lubrication
d) Bioadhesion of mucoadhesive drug delivery systems

 # Buccal Drug Delivery and Mucoadhesive Property:

For the development of Buccal drug delivery systems, mucoadhesion of the device is the important criteria. For proper and good mucoadhesion, mucoadhesivepolymer have been utilized in many different dosages form suchpolymer as tablets, patches, tapes, films, semisolids and powders. Many studies showed that addition of various polymers to drug delivery systems such as gums, increased the duration of attachment of the formulations to the mucous surface and also increased the efficacy.

The polymers should possess following general physiochemical features so as to serve as mucoadhesive polymers:

1. Predominantly anionic hydrophilicity with numerous hydrogen bond-forming groups.
2. Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.
3. Should have good spreadability, wetting, swelling
and solubility and biodegradability properties.
4. P H should be biocompatible and should possess

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good viscoelastic properties.
5. Should possess peel, tensile and shear strengths at the bioadhesive range

 # Theories of Mucoadhesion:
There are six general theories of adhesion, which have been adapted for the investigation of mucoadhesion:

1) **The electronic theory:** suggests that electron transferoccurs upon contact ofadhering surfaces due to differences in their electronic structure. This is proposed to result in the formation of an electrical double layer at the interface, with subsequent adhesion due to attractive forces.

2) The wetting theory: Is primarily applied to liquid systems and considers surface and interfacial energies. It involves the ability of a liquid to spread spontaneously onto a surface as a prerequisite for the development of adhesion. The affinity of a liquid for a surface can be found using techniques such as contact angle goniometry to measure the contact angle of the liquid on the surface, with the general rule being that the lower the contact angle, the greater the affinity of the liquid to the solid.

3) The adsorption theory:Describes the attachment of adhesives on the basis of hydrogen bonding and van der Waals' forces. It has been proposed that these forces are the main contributors to the adhesive interaction. A subsection of this, the chemisorptions theory, assumes an interaction across the interface occurs as a result of strong covalent bonding.

4) The diffusion theory: Describes interdiffusion of polymers chains across an adhesive interface. This process is driven by concentration gradients and is affected by the available molecular chain lengths and their mobilities. The depth of interpenetration depends on the diffusion coefficient and the time of contact. Sufficient depth of penetration creates a semi-permanent adhesive bond.

5) The mechanical theory:Assumes that adhesion arises from an interlocking of a liquid adhesive (on setting) into irregularities on a rough surface. However, rough surfaces also provide an increased surface area available for interaction along with an enhanced viscoelastic and plastic dissipation of energy during joint failure, which are thought to be more important in the adhesion process than a mechanical effect.

6) The fracture theory:Differs a little from the other five in that it relates the adhesive strength to the forces required for the detachment of the two involved surfaces after adhesion.

 # Mechanisms of Mucoadhesion:
The mechanism of mucoadhesion is generally divided in two steps,
1. Contact stage
2. Consolidation stage

Fig : Mechanism of mucoadhesion

The first stage is characterized by the contact between the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer. In some cases, such as for ocular or vaginal formulations, the delivery system is mechanically attached over in other cases, the deposition is promoted by the aerodynamics of the organ to the membrane, the system is administered, such as for the nasal route. In the consolidation step, the mucoadhesive materials are activated by the presence of moisture.
Moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak van der Waals and hydrogen bonds.

Essentially, there are two theories explaining the consolidation step:
1. The diffusion theory
2. The dehydration theory.

According to diffusion theory, the mucoadhesive molecules and the glycoproteins of the mucus mutually interact by means of interpenetration of their chains and the building of secondary bonds. For this to take placethe mucoadhesive device has features favouring both chemical and mechanical interactions.

According to dehydration theory, materials that are able to readily gelify in an aqueous environment, when placed in contact with the mucus can cause its dehydration due to the difference of osmotic pressure.

 # Mechanism to Increase Drug Delivery Through Buccal Route:
Absorption enhancer: The epithelium that lines the buccal mucosa is a very effective barrier to the absorption of drugs. Sub-stancesthat facilitate the permeation through buccal mucosa arereferred as absorption enhancers. As most of theabsorption enhancers were originally designed forincrease the absorption of drug and improved efficacy and

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reduced toxicity. However, the selection of enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other excipients. In some cases, usage of enhancers in combination has shown synergistic effect than the individual enhancers.

The efficacy of enhancer in one site isnot same in the other site because of differences in cellular morphology, membrane thickness, enzymatic activity, lipid composition and potential protein interactions are structural and functional properties. The most common absorption enhancers are azone, fatty acids, bile salts and surfactants such as sodium dodecyl sulfate. Solutions/gels of chitosan were also found to promote the transport of mannitol and fluorescent-labelled dextrans across a tissue culture model of the buccal epithelium while Glyceryl monooleates were reported to enhance peptide absorption by a co-transport mechanism.

Mechanism:

Mechanisms by which penetration enhancers are thought to improve mucosal absorption are as follows.

1) Changing mucus rheology:

Mucus forms viscoelastic layer of varying thickness that affects drug absorption. Further, saliva covering the mucus layers also hinders the absorption. Somepermeation enhancers' act by reducing the viscosity of the mucus and saliva overcomes this barrier.

2) BY overcoming enzymatic barrier:

These acts by inhibiting various peptidase and proteases present within buccal mucosa, thereby overcoming the enzymatic barrier. In addition, changes in membrane fluidity also alter the enzymatic activity indirectly.

3) Increasing the thermodynamic activity of drug:

Some enhancers increases the solubility of the drug and there by alters the partition coefficient. This leads to in-creased thermodynamic activity resulting better absorption

Surfactants such as anionic, cationic, non-ionic and bile salts increases permeability of drugs by perturbation of intercellular lipids whereas chelators act by interfering with the calcium ions, fatty acids by increasing fluidity of phospholipids and positively charged polymers by ionic interaction with negative charge on the mucosal surface. Chitosan exhibits several favorable properties such as biodegradability, bioavailability, antifungal/antimicrobial properties in addition to its potential bioadhesion and absorption enhancer.

Examples of some of permeation enhancers:
1 Cyclodextrin
2 Lauric acid
3 Polyoxyethylene
4 Polysorbate 80
5 Sodium glycodeoxychlorate
6 Sodium lauryl sulphate
7 Sodium taurochlorate

 # Formulation of Buccal Drug Delivery System

Formulation Design:

a) General criteria for selection of drug candidate:

Buccal adhesive drug delivery systems with the size 1–3 cm^2 and a daily dose of 25mg or less are preferable. The maximal duration of buccal delivery is approximately 4–8 hr. Drug must undergo first pass effect or it should have local effect in oral cavity. Drugs with biological half life 2-8 hr will in general be good candidates for sustained release dosage forms. Local drug irritation caused at the site of application is to be considered while selecting the drug.

b) Pharmaceutical Considerations:

Great care needs to be exercised while developing a safe and effective buccal adhesive drug delivery device. Factors influencing drug release and penetration through buccal mucosa, organoleptic factors, and effects of additives used to improve drug release pattern and absorption, the effects of local drug irritation caused at the site of application are to be considered while designing a formulation.

c) Buccal adhesive polymers:

Is a generic term used to describe a very long molecule consisting of structural units and repeating units connected by covalent chemical bonds. The term is derived from the Greek words: polys meaning many, and meros meaning parts.

The key feature that distinguishes polymers from other molecules is the repetition of many identical, similar, or complementary molecular subunits in these chains. These subunits, the monomers, are small molecules of low to moderate molecular weight, and are linked to each other during a chemical reaction called polymerization.

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Instead of being identical, similar monomers can have varying chemical substituent. The differences betweenmonomers can affect properties such as solubility, flexibility, and strength. The term buccal adhesive polymer covers a large, diverse group of molecules, including substances from natural origin to biodegradable grafted copolymers and thiolated polymers. Bioadhesive formulations use polymers as the adhesive component. These formulations are often water soluble and when in a dry form attract water from the biological surface and this water transfer leads to a strong interaction. These polymers also form viscous liquids when hydrated with water that increases their retention time over mucosal surfaces and may lead to adhesive interactions. Bioadhesive polymers should possess certain physicochemical features including hydrophilicity, numerous hydrogen bondforming groups, flexibility for interpenetration with mucus and epithelial tissue and viscoelastic properties.

d) Ideal characteristics:

Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.Should have good spreadability, wetting, swelling and solubility and biodegradability properties.pH should be biocompatible and should possess good viscoelastic propertiesShould adhere quickly to buccal mucosa and should possess sufficient mechanical strength. Should possess peel, tensile and shear strengths at the bioadhesive range. Polymer must be easily available and its cost should not be high. Should show bioadhesive properties in both dry and liquid state.Should demonstrate local enzyme inhibition and penetration enhancement properties. Should demonstrate acceptable shelf life.Should have optimum molecular weight.

Buccal mucoadhesive dosage forms may be classified into three types, a single layer device with multidirectional drug release.An dosage form with impermeable backing layer which is superimposed on top of an drug loaded bioadhesive layer, creating a double layered device and preventing loss from the top surface of the dosage form into the oral cavity. Unidirectional release device, the drug is released only from the side adjacent to the buccal mucosa.

 # Characterization of Tablet:

1) Particle Size Distribution:

The particle size distribution can be measured by sieving method.

2) Angle of Repose:

Angle of repose can be measured by fixed funnel method. It determines flow property of the powder. It is defined as maximumangle formed between the surface of the pile of powder and the horizontal plane. The powder was allowed to flow through the funnel fixed to a stand at definite height (h). By measuring the height and radius of the heap of powder formed (r), angle of repose can be calculated by using formula,

Tan Ø=h/r

Where,

h and r are the height and radius of the powder cone.

3) Moisture Sorption Capacity:

All disintegrates have capacity to absorb moisture from atmosphere which affects moisture sensitive drugs. Moisture sorption capacity can be performed by taking 1g of disintegrate uniformly distributed in Petri-dish and kept in stability chamber at 37±1°C and 100% relative humidity for 2 days and investigated for the amount of moisture uptake by difference between weights.

4) Density:

Bulk density can be determined by tapping method. It is determined by pouring the weighed powder (sieve #20) into a measuring cylinder and initial weight was noted and the initial volume of powder is called bulk volume. The bulk density is expressed in terms of g/mL and calculated by formula,

DB = W/ VB

Where,

W is the weight of the powder

VB is the bulk volume of the powder

 # Evaluation of Tablet:

1) Tablet Thickness and Size:

Thickness and diameter of tablets are important foruniformity of tablet size. Thickness and diameter can be measured by venire caliper.

2) Tablet Hardness:

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each

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formulation was measured by Monsanto hardness tester. The hardness can be measured as kg/cm2.

3) Friability:

Friability can be measured as tablet strength. Friabilityof tablet can be determined by using friabilator (Aarson). It is expressed in percentage (%). The tablets are subjected into a plastic chamber revolving at 25rpm for 4 minutes or run upto 100 revolutions by dropping a tablet at height of 6 inches in each revolution. Pre weighed tablets were placed in friabilator and subjected for 100 revolutions. It is measured by % loss = [(Initial weight of tablets –Final weight of tablets)/Initial weight of tablets] × 100.

4) Uniformity of Weight:

The weight of the tablet being made can be routinely determined to ensure that a tablet contains the properamount of drug. Twenty tablets selected randomly were weighed individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit.

5) Dissolution Studies:

Dissolution rate of the tablets can be studied using dissolution test apparatus USP II employing a paddle stirrer at 50rpm and at 37°± 1°C. Phosphate buffer of pH 6.8 (500ml) was used as a dissolution fluid. Samples of 5 ml each, were withdrawn at 0, 0.25, 0.5, 1, 2, 4, 6, 8 hrs and the samples were assayed. And the cumulative amount of drug release is calculated using standard calibration curve. Each sample withdrawn was replaced with an equal amount of drug free dissolution fluid.

II. MATERIAL AND METHOD

Materials:

Diltiazem HCL.,Carbapol 934P, hydroxy propyl methyl cellulose, mannitol and Mg Stearate was received as a gift simple form arrochem Products, Mumbai. Other chemical used were of analytical grade.

Method:

Mucoadhesive matrix tablets of 100mg each containing 30mg of diltiazem HCL were prepared by conventional direct compression method. Diltiazem HCL was mixed manually with different ratios ofHPMC,carbapol934p mannitol, blend was lubricated with the magnesium stearate for 4-5 min then compressed into tablet by direct compression method using 3mm concave punch. The mass of tablet were determined by using digital balance and thickness of tablet with digital screw guage.

Sr. No	Formulation Ingredients	Quantity
1	Diltiazem HCL	30mg
2	HPMC	15mg
3	Carbapol934p	15mg
4	Mannitol	40mg
5	Magnesium stearate	1mg

III. RESULTS:-

Preformulation parameter

A batch of 20 tablet were prepared by using direct compression method. The preformulation studies were performed on the powder blend of 20 tablets as follows-

1) Total weight of powder blend for 20 tablet= 2.020gm
2) Bulk volume= 5.5ml
3) Bulk density= 0.3672gm/ml
4) Tapped volume= 3.2ml
5) Tapped density= 0.6312gm/ml
6) Compressibility index= 41.82
7) Hausner's ratio= 1.72
8) Angle of repose= 42.92°
9) Flow of powder blend= passable

Evaluationparameterfortablet:

Various evaluation test was done for each tablet as follows:

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1) **Hardness test:-** the hardness of tablet was determined using Monsanto hardness tester and was found to be 6N/cm. The force required to break the tablet was measured.

2) **Thickness test:-** the thickness of tablet was mostly related to hardness can be used as initial control parameter. tablet thickness was found to be 1mm which is measured using vernier calliper.

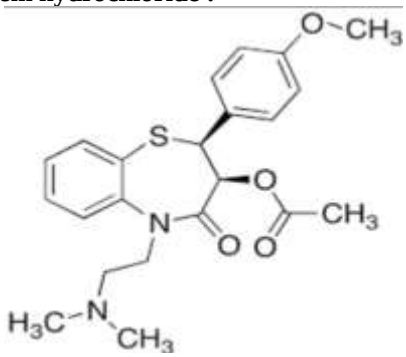
3) **Friabilitytest**:- friability is measured by using rochefriabilator. The 6 pre-weighed tablet were placed in friabilator which was operated for 100rpm, then dusted and reweighed. The percentage variation was found to be 0.98.

4) **Weightvariation test**:- the weight of individual 20 tablet was noted. Average weight was calculated from the total weight of all tablets. The individual weight of tablet were compared with average weight. The tablet should lie in the range 94.31mg-109.59mg. out of 20 tablet only 1 tablet vary from the given range of tablet.

5) **Swelling index**:-the swelling rate of tablet is evaluated using pH 6.4 phosphate buffer. The tablet placed in the phosphate buffer and removed at different time interval (1,2,3 hrs.) blotted with filter paper and reweighed and It was found to be 88.35%.

MONOGRAPH

Diltiazem hydrochloride :-



$C_{22}H_{26}N_2O_4S,HCl$

Diltiazem hydrochloride is **cis-(+)-[2-(2-Dimethylaminoethyl)-5-(4-methoxyphenyl)-3-oxo-6-thia-2-azabicyclo[5.4.0]undeca-7,9,11-trien-4-yl]ethanoate**

It contains not less than 98.5%and not more than 101.4%of $C_{22}H_{26}N_2O_4S,HCl$ calculated on dry basis.

CATEGORY :-Antianginal (calcium channel blocker)

DESCRIPTION:- A white crystalline powder or small crystals.

IDENTIFICATION:-

A.Determine by infrared absoption spectrophotometry.comppare the spectrum with that obtained with diltiazem hcl IPRS or with reference spectrum of diltiazem hydrochloride

B.In the assay, the principal peak in chromatograph obtained with test solution corresponds to the principal peak in chromatogram obtained with reference solution.

C.A 5% w/vsolution gives reactions of chloride

TESTS

Specific otical rotation $+110.0^0$-116.0^0 determined in a1.0%w/v solution

RELATED SUBSTANCES:

DETERMINE BY liquid chromatography.

Test solution:dissolve 0.12g of substance under examination in methanol and dilute 100ml with methanol.

Reference solution(a) :a0.12% solution of diltiazem hydrochloride IPRS in methanol

Reference solution (b):a solution containing 0.0012%w/v each of diltiazem hydrochloride IPRSa and desacetyl diltiazem hydrochloride IPRS methanol.

Chromatographic system

-a stainless steel column 30 cm x 3.9 mm, packed with octadecylsilane bonded to porous silica (5 um),

- mobile phase: a mixture of 50 volumes of a buffer solution containing 0.116 per cent w/v of d-10-camphorsulphonic acid in 0.1 M sodium acetate, adjusted to pH 6.2 with acetonitrile 0.1 M sodium hydroxide, 25 volumes of and 25 volumes of methanol,

- flow rate: 1.6 ml per minute,

spectrophotometer set at 240 nm,

injection volume: 10 µl.

The relative retention time with reference to diltiazem for desacetyl diltiazem is about 0.65

Inject reference solution(a). The test is not valid unlewss the resolution between the peaks due tp desacetyl diltiazem and diltiazem is not less than

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3, the coloumn effiency is not less than 1200 theoritical plates and the relative standards deviation for replicate injections is not more than 10% for diltiazem peak.

Inject reference solution(b) and the test solution in the chromatograph obtained with test solution, the area of any peak corresponding desacetyl dilitiazem is not more t han 0.5 times the area of coresponding peaks in chromatogram obtained with reference solution(b) (0.5%), the area of any other secondary ppeak is not more than area of principle peak in chromatogram obtained with reference solution(b) (1.0%). Ignore any peak with an area less than 0.05 times the area of principle peak in chromatogram obtained with reference solution (b) (0.05%)

Heavy metals -1.00g complies with limit test for heavy metals method (a)(20ppm)
Sulphated ash-not more than 0.1%
Loss on drying- not more than 0.5%,determined by drying in oven at 105^{o} for 2 hours.
Assay- determine by liquid chromatography as described under related substances using the folloeing methods.
Inject reference solution(a). the test is not valid unless the reletive standards deviation for repllicate injections is not more than 2.0%.
Inject reference solution(a) and the test solution.
Calculate the test content of $C_{22}H_{26}N_2O_4S,HCl$

STORAGE Store protected from light.