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Formulation and *In-Vitro* Evaluation of Sublingual Tablet of Montelukast

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ABSTRACT
The aim of this study was to formulate and study the effect of different polymer in Montelukast sublingual tablet using Crospovidone, Croscarmellose Sodium and Sodium starch glycolate as disintegrant polymers. A direct compression technique was employed to prepare nine different formulations of sublingual tablet by varying the concentration of different disintegrant polymers in every formulation containing 10mg of Montelukast, keeping other excipient constant. The powder mixture was evaluated for the pre compression parameters i.e bulk density, tapped density, angle of repose, Carr's index. After the tablets were formulated, the post compression parameters were evaluated i.e., thickness, hardness, weight variation, friability, dispersion time, disintegration time, wetting time, in-vitro dissolution and assay. The prepared sublingual tablets comply all parameter included as per the specification. Among all the formulations, F4 showed better result (i.e., wetting time, dissolution time and assay) in which crospovidone is used as polymer and guar gum and carbopol 934 for sublingual adhesion in comparisions to other polymers.

Keywords: *Montelukast, Sublingual tablets, Disintegating agent, Wetting time, Disintegration, Assay, Dissolution.*

INTRODUCTION

Introduction to Montelukast

Montelukast is a member of Leukotriene receptor antagonist (LRTA) category of drug. And widely used as prophylaxis and chronic treatment of asthma in adult patients and pediatric patients who are 12 months of age and older and also for seasonal allergic rhinitis, and exercise induced bronchitis. Montelukast is in the leukotriene receptor antagonist family of medications. It works by blocking the action of leukotriene D4 in the lungs resulting in decreased inflammation and relaxation of smooth muscle.

Absorption

1) Bioavailability:64%(mean)
2) Peak plasma time: tablet(3-4hr), Chewable tablet (2-2.5 hour), Granules(1-3hr)

Distribution

Protein bound:>99%

Metabolism

Metabolized by CYP3A4 and CYP2C9

Elimination

1) Half-life:2.7-5.5 hours
2) Excretion: feces (86%),urine(0.2%) [1,2,3]

Drug Delivery System

Tablets are solid dosage form manufactured either by dry granulation, wet granulation or direct compression containing medicaments with or without excipients, intended to produce desired pharmacological response. Sublingual tablets are formulated and compressed with sufficient pressure to give desired Sublingual effect administered in sublingual pouch[2].

Drug delivery systems are means of administering drugs to the body in the safe, efficient, reproducible and convenient manner. Medicines are rarely drugs alone, but require additives to make them into dosage form and this in turn introduces the concept of formulation. The 3 major considerations in the design of dosage forms are the physicochemical properties, biopharmaceutical consideration, therapeutic considerations. Tablets are solid dosage forms usually prepared with the aid of suitable pharmaceutical excipients.

They may vary in size, shape, weight, hardness, thickness, disintegration and dissolution characteristics and in other aspects, depending on their intended use and method of manufacture. Drug delivery refers to approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect and minimum adverse effect. The drug should be delivered to its site of action with such rate and concentration to achieve maximum therapeutic effect and minimum adverse effect. There are different types of dosage forms available such as tablets, syrups, suspensions, suppositories, injections, transdermal patches having different drug delivery mechanism. It may involve scientific site targeting within the body, or it might involve facilitating systemic pharmacokinetics; in any case, it is typically concerned with both quantity and duration of drug presence. Drug delivery is often approached via a drug's chemical formulation, but it may also involve medical devices or drug-device combination products [2].

Introduction of Sublingual Tablets

Sublingual administration of the drug means placement of the drug under the tongue and drug reaches directly in to the blood stream through the ventral surface of the tongue and of the mouth. The drug solutes are rapidly absorbed into the reticulated vein which lies underneath the oral mucosa, and transported through the facial veins, internal jugular vein, and brachiocephalic vein and then drained in to systemic circulation. The main mechanism for the absorption of the drug in to oral mucosa is via passive diffusion into the lipoidal membrane [3]. The absorption of the drug through the sublingual route is 3 to 10 times greater than oral route and is only surpassed by hypodermic injection. For these formulations, the small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity [5,6,8].

Statement of Problem

1) Slow absorption
2) Swallowing difficulties in elderly patients and unconscious patients.
3) Slow onset of action

Convenience of administration and patient compliance are gaining significant importance in the design of dosage forms. Recently, more stress is laid down on the development of organoleptically elegant and patient friendly drug delivery system for pediatric and geriatric patients. Many patients, elderly people and person with dysphagia find it difficult to swallow the tablets and hard gelatin capsules and thus do not comply with prescription, which results in high incidence of noncompliance and ineffective therapy [9].

Rational of Study

In order to increase the bioavailability, the sublingual tablet is suitable. Conventional Montelukast tablets available in the market causes gastric irritation and isn't suitable for unconscious and, also, they show poor bioavailability thus sublingual tablets of Montelukast is suitable to relief immediate asthmatic attack and other exercise induced bronchospasm or allergic rhinitis problem because of its highly vascularized supply which leads to greater absorption of drug. Furthermore, Montelukast sublingual dosage form are easy to apply with lower incidence of gastro-intestinal irritation [10].

OBJECTIVES

Specific Objective

The main objectives of this project work are to formulate and perform the *in-vitro* evaluation of sublingual tablet of Montelukast.

General Objectives

The general objectives of this project work are presented below:

1) To carry out the pre-formulation study of powder such as angle of repose, bulk density, tapped density, Hausner ratio and Carr's index.
2) To estimate the drug concentration in prepared formulation (Assay of each batch).
3) To carryout post compression parameters for the developed sublingual tablet such as hardness, friability, thickness and weight variation of each batch.
4) To carry out *in-vitro* release studies using USP Dissolution Apparatus Type-II with paddle assembly and study the drug release.
5) To compare the various formulations using different polymers and choose the best formulation.

REVIEW OF LITERATURE

Introduction

The general background of Sublingual tablets, Montelukast and researches conducted on formulation of various sublingual tablets including Montelukast are presented in this chapter.

Review to Drug Delivery System

Drug delivery refers to approaches, formulations, technologies and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect and minimum adverse effect. The drug should be delivered to its site of action with such rate and concentration to achieve maximum therapeutic effect and minimum adverse effect. There are different types of dosage forms available such as tablets, syrups, suspensions, suppositories, injections, transdermal patches having different drug delivery mechanism. It may involve scientific site-targeting within the body, or it might involve facilitating systemic pharmacokinetics; in any case, it is typically concerned with both quantity and duration of drug presence. Drug delivery is often approached via a drug's

chemical formulation, but it may also involve medical devices or drug-device combination products.

Development of new drug molecule is expensive and time-consuming improving safety efficacy ratio of old drugs has been attempted using different methods such as individualization drug therapy, dose titration and therapeutic drug monitoring [11].

Alternative to Conventional Tablets

Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. It is the most popular route for systemic effects due to its ease of ingestion, pain avoidance, self-medication, versatility and most importantly, patient compliance. Oral route is most popular route but have common drawback of difficulty in swallowing of tablets and capsules. Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available. Because of the increase in the average human lifespan and the decline, with age, in swallow inability, oral tablet administration to patients is a significant problem and has become the object of public attention. Therefore, a lot of research has been done on novel drug delivery systems. Sublingual tablet is a novel approach in drug delivery systems that are now a day's more focused in formulation world, and laid a new path that, helped the patients to build their compliance level with the therapy and ease the administration especially. Quick absorption, rapid onset of action and reduction in drug loss properties are the basic advantages of this dosage form. For the development of a suitable dosage form a thorough study about the physicochemical principles that governs a specific formulation of a drug should be subjected [11].

Review to Sublingual Tablets

Sublingual Drug Delivery is one of the novel drug deliveries which localized the delivery of drug to tissues of the sublingual cavity for treatment of bacterial, fungal infection as well as periodontal disease. Sublingual drug delivery is safer mode of drug delivery system and can be able to remove in case of toxicity and adverse effect. Sublingual mucosa has an excellent accessibility, which leads to direct access to systemic circulation through the internal jugular vein bypasses the drugs from hepatic first pass metabolism. Sublingual tablets are dry dosage forms and it is to be moistened prior to placing in contact with sublingual mucosa. Sublingual tablets are developed by addition of polymers like carbopol, HPMC-K4M, HPMC-K100M, Ethyl cellulose, sodium Carboxymethyl cellulose, sodium alginate, which gives better mucoadhesive property when gets in contact with sublingual lining. The bioavailability of some drugs may be increased due to high blood flow in sublingual area and also due to pre- gastric absorption of saliva containing mucoadhesive drugs. Moreover, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablets [8, 12].

Anatomy of Sublingual Mucosa

The soft tissue of the human oral cavity is covered by a stratifying squamous epithelium. The connective tissue of the lining mucosae is more elastic and flexible than the connective tissue in the masticatory mucosa. The dorsum of the tongue is covered by a specialized epithelium, which can be represented as a mosaic of keratinized end non keratinized epithelium. This epithelium is attached tightly to the muscle of the tongue.

Fig. 1 illustrates diagrammatically the distribution of the different types of mucosa with in the oral cavity. From the measurements made by Collins and Dawes, it can be calculated that the masticatory mucosa represents approximately 25%, the specialized mucosa (dorsum of tongue) approximately 15%, and the lining mucosa approximately 60% of the total surface area of the oral lining. Masticatory mucosa covers the gingiva and hard palate, regions that are subject to mechanical forces of mastication, causing abrasion and shearing. Lining mucosa covers the remaining regions, except for the dorsal surface of the tongue, and provides and elastic, deformable surface capable of stretching with movements such as mastication and speech. It is covered with a stratified squamous epithelium that is non-keratinized and can vary considerably in thickness in different oral results. A specialized mucosa with characteristics both masticatory and lining mucosa, is found on the dorsum of the term. It has a surface consisting of areas of both keratinized and non-keratinized epithelium, these are tightly bound the under-lining muscle of the tongue. Both the structure and the relative area of the different types of mucosa will influence the permeability of the oral lining [13].

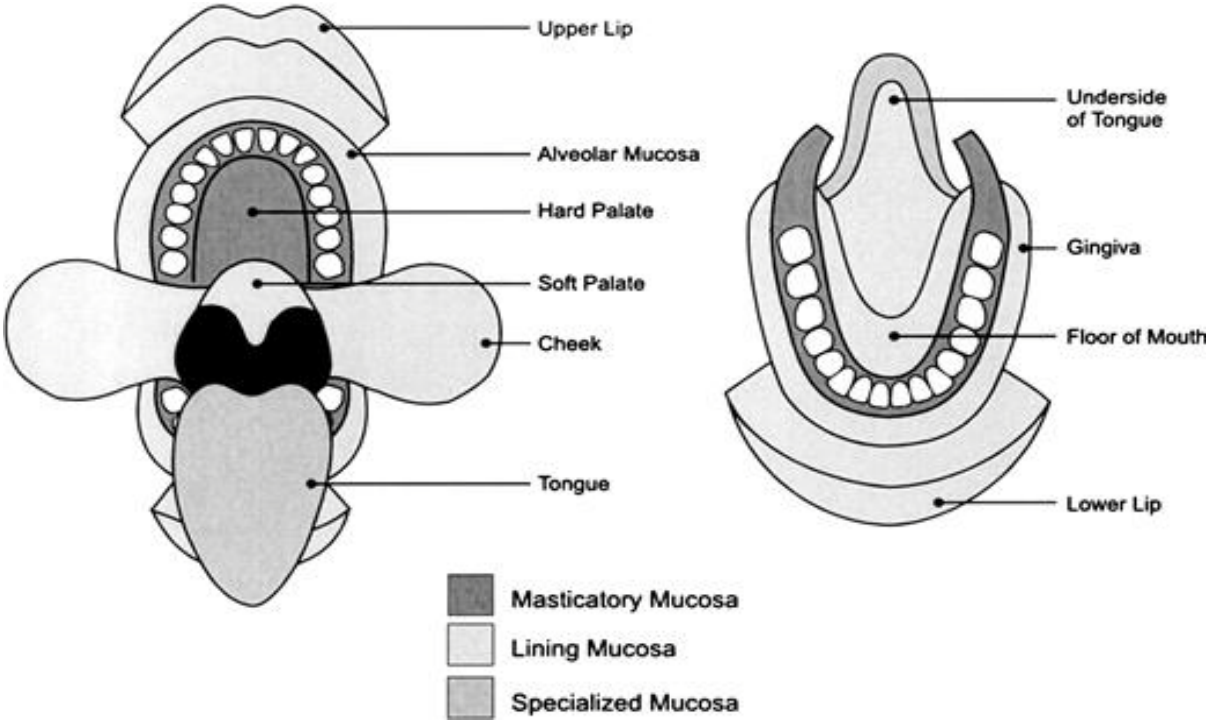


Fig.1. Diagram to show the Anatomic location and extent of masticatory, lining, and specialized sublingual mucosa in the oral cavity.

Advantages of Sublingual Drug Delivery System

The Sublingual forms of the medication have their advantages as the drug can absorb rapidly, it is a significant option during emergencies, while the drug is required to work immediately, like during a heart attack.

1) It quickly disintegrant and small amounts of saliva are usually enough to achieve disintegration of the active pharmaceutical ingredient (API) with improved dissolution and increased bioavailability.

2) It is easy to take for patients, especially the elderly and children who have problems swallowing pills and capsules, no need to swallow, just placed under the tongue or between the cheeks and gum.
3) The two main advantages are that no injections are necessary and treatment can be administered at home
4) The direct compression method is used to manufacture these types of tablets that are simple, cost effective, and efficient process.
5) It reduces interaction with other drugs and foods when compared with liquid dosage forms and solid dosage forms [14].

Ideal Properties of Sublingual tablets

The ideal properties of sublingual tablets are described below:

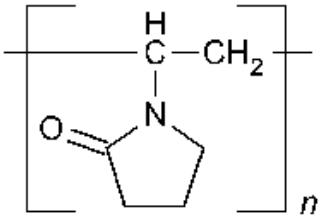
1) They create a pleasant feeling in the mouth and are most suitable for sublingual tablets along with other flavors.
2) The coating of bitter drugs is not an option for drugs to be dissolved in saliva.
3) Sublingual tablets promote rapid absorption and higher bioavailability with an almost instant onset of action.
4) Many drug properties could potentially affect the performance of sublingual tablets,
5) For examples, the solubility, crystal morphology, particle size, hygroscopicity, compressibility and bulk density of drug can significantly affect the final tablets characteristics such as tablet strength and disintegration.
6) Drugs that are unstable in parenteral preparation are suitable for sub-lingual dosage form [15].

Polymers (Super-disintegrant) [16-19]

Disintegrants are agents added to tablet and some encapsulated formulations to promote the breakup of the tablet and capsule “slugs” into smaller fragments in an aqueous environment there by increasing the available surface area and promoting a more rapid release of the drug substance. For many solid dosage forms of disintegration occurs prior to drug substance. For many solid dosage forms disintegration occurs prior to drug dissolution and super disintegrants are now frequently and thus increase the rate of dissolution. Super disintegrants are generally used at a low concentration in the solid dosage form, typically 1-10% by weight relative to the total weight of dosage unit. Their particles are generally small and porous, which allow for rapid tablet disintegration in the mouth without an objectionable mouth feel from either large particles or gelling. The disintegrants are discussed below:

Crosspovidone

Non-proprietary names: BP-Crosspovidone, PhEur-Crosspovidone
USPNF: Crosspovidone.
Synonyms: Crosslinked povidone, E1202, kollidon CL
Chemical name: 1-ethyl-2-pyrrolidinone homopolymer.
Molecular weight: (C6H9NO) n>1000000
Structure:



Functional Category: Tablet Disintegrant

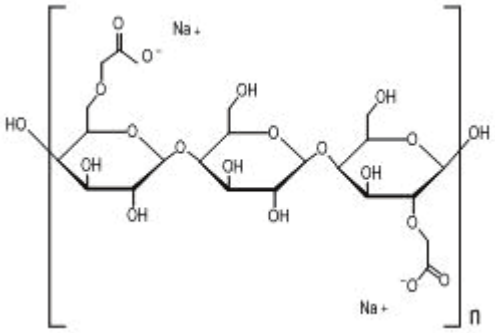
Applications in Pharmaceutical Formulation or Technology: Crospovidone is a water - insoluble tablet disintegrant and dissolution agent used at 2-5% concentration in tablets prepared by direct-compression or wet and dry granulation methods.

Description: Crospovidone is a white to creamy-white, finely divided, free flowing, practically tasteless, odorless and hygroscopic powder.

Stability and storage condition: Since Crospovidone is hygroscopic, it should be stored in structure hydration capacity, with little tendency to form gels. Studies suggests that the particle size of Crosspovidone strongly influences disintegration of analgesic tablets.

Croscarmellose Sodium

Non-proprietary name: USPNF: Croscarmellose sodium.
Synonyms: Ac-Di-Sol, cross-linked Carboxymethyl Cellulose Sodium.
Chemical name: Cellulose, Carboxymethyl ether**,** Sodium salt, crosslinked.
Molecular weight: 90000-700000
Structure:



Functional category: Tablet and Capsule Disintegrant.

Applications: Works as a disintegrant is tablet (wet granulation and direct compression) and capsule formulation in 2-8% concentration.

Description: It occurs as an odorless, white colored powder.

Solubility: Insoluble in water. Although croscarmellose sodium rapidly swells to 4-8 times of its original volume in contact with water.

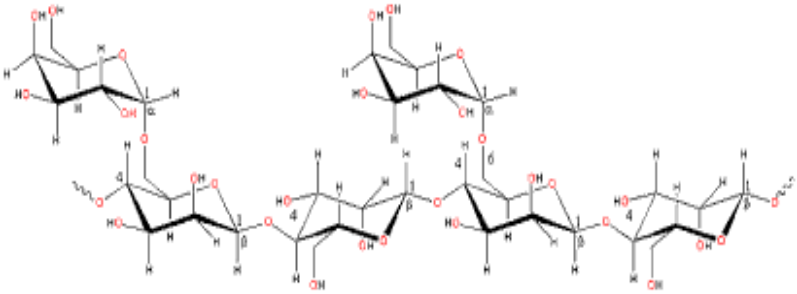
Storage condition: Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by the direct compression, with croscarmellose sodium as disintegrant, showed no significant difference in drug dissolution after storage at 300°C for 14 months.

Incompatibilities: The efficacy of disintegrant, such as Croscarmellose sodium, may be slightly reduced in tablet formulation prepared by wet granulation or direct compression process which contain hygroscopic material such as sorbitol.

Safety: Croscarmellose is mainly used as a disintegrant in a oral pharmaceutical formulations and is generally regarded as an essentially non-toxic and non-irritant material.

Guar Gum [20]

Non- proprietary: Benefiber
Synonyms: Guaran, Clusterbean
Chemical name: Galactomannan [7,18]
Molecular weight: 535.146 g/mol
Molecular formula: $C_{10}H_{14}N_5Na_2O_{12}P_3$
Structure:



Functional category: Natural polymer

Application: As a natural polymer in compression of tablet and a dietary fiber.

Description: It is a natural non-ionic, water-soluble polysaccharide exhausted from the refined endosperm of cluster bean seeds. It occurs as off-whitish and yellowish-white powder consisting of slight odor.

Solubility: Soluble in cold water and insoluble in most of the hydrocarbon solvents.

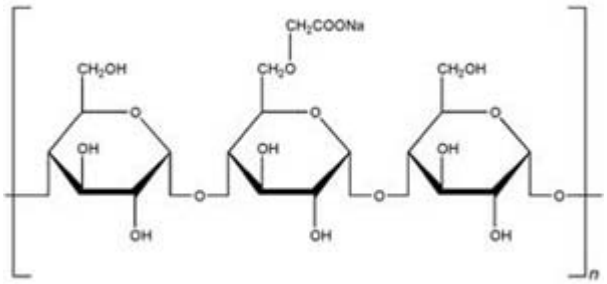
Storage condition: Guar gum property remains unchanged for 12-18 months. A model tablet formulation prepared by direct compression, with Guar gum as polymer, are stored in cool dry place away from heat and sunlight.

Incompatibilities: Guar gum significantly decrease the digestion of starch i.e. act as barrier between starch and starch hydrolyzing enzymes.

Safety: Guar gum is mainly used as polymer in oral pharmaceutical formulations and is generally regarded as an essentially non-toxic and non-irritant material

Sodium Starch Glycolate

Non-proprietary names BP: Sodium Starch Glycolate PHEur: Sodium Starch Glycolate USP-NF: Sodium Starch Glycolate.
Synonyms: Carboxymethyl Starch, Explosol, Glycolys, Primojel, Starchcarboxymethyl ether, sodium salt, Tablo.
C**hemical name and CAS registry name**: Sodium CarboxymethylStarch(9063-38-1)
Molecular weight: 5×10^5-1×10^6
Structural Formula:



Functional group: Tablet and capsule disintegrant.
Application: It is commonly used in tablets prepared by either direct compression or wet granulation process. The used concentration employed in a formulation is between 2% and 8% with the optimum concentration about 4%, although in many cases 2 % is sufficient.

Description: Sodium Starch Glycolate is a white oral most white free flowing very hygroscopic powder.

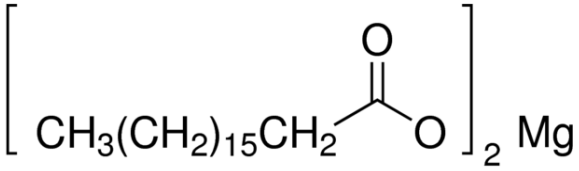
Stability and storage condition: Tablets prepared with sodium starch Glycolate have good storage properties. Sodium Starch Glycolate is a stable although very hygroscopic, and should be stored in a well closed container in order to protect it from wide variations of humidity and temperature which may cause caking.

Incompatibilities: Sodium Starch Glycolate is in compatible with ascorbic acid.

Safety: Sodium Starch Glycolate is in widely used in oral pharmaceutical formulations and is general regarded as a non-toxic and non-irritant material. However, oral ingestion of large quantities may be harmful.

Magnesium Stearate

Structural formula



Non -proprietary name: NF-magnesium stearate, BP/EP- magnesium stearate

Molecular weight: 591.3

Functional category: Tablet and capsule lubricant.

Applications: Tablet and capsule lubricant, glidant and anti-adherent in the concentration range of 0.25 to 2.0%

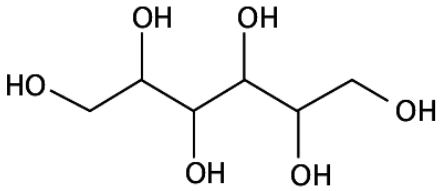
Description: It is a fine white precipitated or milled, impalpable powder of low bulk density, having a faint characteristics odor and taste. The powder is greasy to touch and readily adheres to the skin.

Stability and storage conditions: Stable, non-self-polymerizable. Stored in a cool dry place in a well close container.
Incompatibilities: Incompatible with strong acids, alkali iron salts and with strong oxidizing materials.

Safety: Described as inert dust. Dust clouds of magnesium stearate may be explosive. However, oral consumption of large Quantities may result in some laxative effect or mucosal irritation.

Mannitol

Non-proprietary names: BP, Mannitol, Jp D Mannitol, PHEur, Mannitol USP-NF: Mannitol
Synonyms: Compressol, sugar, Mannit, Dmannite, Mannitolum, Mannogem.
Formula: $C_6H_{14}O_6$
Molar mass: 182.172 g/mole
Structural formula:



Description: It is D-Mannitol. Mannitol occurs as a white, odorless, crystalline powder or free flowing granules. It has a sweet taste approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth. Microscopically it occurs as orthorhombic needles when crystallized from alcohol, mannitol shows polymorphism.

Incompatibilities: Mannitol solution,20% w/v or stronger, may be salted out by potassium chloride or sodium chloride. Precipitation has been reported to occur when 1 25% w/v mannitol solution was allowed to contact plastic.

Talc

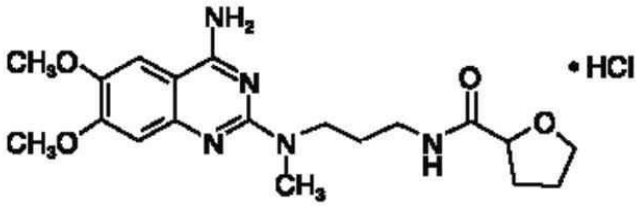
Nonproprietary Names BP: Purified Talc JP: Talc Ph Eur: Talc USP: Talc

Synonyms: Altalc, E553b, hydrous magnesium calcium silicate; hydrous magnesium silicate

Chemical Name and CAS Registry Number: Talc[14807-96-6]

Empirical Formula and Molecular Weight: Talc is a purified, hydrated, magnesium silicate, approximating to the formula Mg_6 (Si2O5)4$(OH)_4$. It may contain small, variable amounts of aluminum silicate and iron.

Structural Formula



Functional Category: Anticaking agent, glidant, tablet and capsule diluents, tablet and capsule lubricant.

Use: It is used as glidant and lubricant in 1-10%
Description: Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

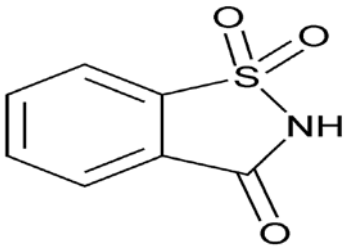
Stability and Storage Conditions: Talc is a stable material and may be sterilized by heating at 1608C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities: Incompatible with quaternary ammonium compounds.

Saccharin

Non-proprietary Names BP: Saccharin JP: Saccharin Ph Eur: Saccharin USP-NF: Saccharin
Chemical Name and CAS Registry Number: 1, 2-Benzisothiazol-3(2H)-one 1,1-dioxide [81-07-2]
Empirical Formula and Molecular Weight:C_7 H $_5$ NO $_3$S183.18

Structural Formula



Functional Category: Sweetening agent

Applications: Saccharin is an intense sweetening agent used in beverages, food products, table-top sweeteners, and oral hygiene products such as toothpastes and mouthwashes. In oral pharmaceutical formulations, it is used at a concentration of 0.02–0.5% w/w. It has been used in chewable tablet formulations as a sweetening agent. Saccharin has been used to form various pharmaceutical co-crystals. Saccharin can be used to mask some unpleasant taste characteristics or to enhance flavor systems. Its sweetening power is approximately 300–600 times that of sucrose.

Description: Saccharin occurs as odorless white crystals or a white crystalline powder. It has an intensely sweet taste, with a metallic or bitter aftertaste that at normal levels of use can be detected by approximately 25% of the population. The aftertaste can be masked by blending saccharin with other sweeteners.

Stability and Storage Conditions: Saccharin is stable under the normal range of conditions employed in formulations. In the bulk form it shows no detectable decomposition and only when it is exposed to a high temperature (1258C) at a low pH (pH 2) for over 1 hour does significant decomposition occur. The decomposition product formed is (ammonium-o-sulfo)benzoic acid, which is not sweet. The aqueous stability of saccharin is excellent. Saccharin should be stored in a well-closed container in a dry place.

Incompatibilities: Saccharin can react with large molecules, resulting in a precipitate being formed. It does not undergo Maillard browning.

Classification of drugs used in Bronchial Asthma [21,22]

A. **Bronchodilator**:

- β2 Sympathomimetics
- Methylxanthines
- Anticholinergic

B. Leukotriene antagonists
C. Mast cell stabilizers
D. Corticosteroids
E. Anti-IgE antibody

Drug Profile: Montelukast [1, 2, 23, 24, 25,26]

Identification of Montelukast

Name	Montelukast
Synonyms	Singulair
IUPAC name	(R,E)-2-(1-((1-(3-(2-(7-Chlorouinolin-2-yl)vinyl)phenyl)-3-(2-(2-hydroxypropan-2-yl)phenyl)propylthio)methyl)cyclopropyl)acetic acid
Trade name	Montair,Monte
Molecular formula	$C_{35}H_{36}ClNO_3S$
Molecular weight	608.2mg
Dose	4-10mg
Type	Small molecule
Groups	Approved, investigation

Pharmacology of Montelukast

Indication	Asthma,exercise induced Bronchospasm, Allergic Rhinitis & Urticaria, treatment of Mastocytosis.
Pharmacodynamics	Montelukast causes inhibition of airway cysteinyl leukotrienereceptors as demonstrated by the ability to inhibit Bronchoconstriction due to inhaled LTD_4 in asthmatics.

Mechanism of action	Montelukast is in the leukotriene receptor antagonist family of medications. It works by blocking the action of leukotriene D4 in the lungs resulting in decreased inflammation and relaxation of smooth muscle.
Absorption	Very quick & high drug level, Bioavailabilty (64%(mean) metabolized by CYP3A4 & CYP2C9 & excreted by feces (86%) & urine (0.2%)
Protein binding	99%
Half life	2.7-5.5 hours
Adverse effect	Abdominal pain, nausea, vomiting, headache, diarrhea, mild fever, rashes. Uncommon ADR are fatigue, malaise, behavioral change, seizures *etc.*
Contraindications	PKU - Phenylketonuria. Increased Eosinophils in the blood. Suicidal thoughts, Depression, inflammation of blood vessels in the skin, anxiety disorder.
Drug interaction	With Amodiaquine and Antimalarial drug increases the plasma concentration of CYP28 substrate(26).

Structure of Montelukast

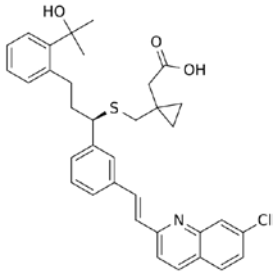


Fig. Structure of Montelukast

In this section, researches conducted on the formulation of Sublingual tablets are presented.

Genedy *et al*, have prepared HHC rapidly disintegrating sublingual tablets of higher absorption rate, short onset of action, and higher bioavailability for rapid control on blood pressure (BP) in hypertensive emergencies especially preeclampsia using starch sodium glycolate and Pharmaburst as super disintegrants at three different levels by direct compression and were subjected to full *in vitro* evaluation; the drug bioavailability from the optimized sublingual tablet formula was assessed in comparison to conventional oral tablets in rabbits, and the clinical efficacy on controlling BP in induced preeclampsia like mouse model was also studied. Sublingual tablet formula containing Pharmaburst (7%) that showed fastest disintegration (21 seconds) and 100% drug release within 5 minutes was selected for further bioavailability and pharmacodynamic studies. The drug bioavailability was significantly increased in comparison to conventional oral tablets. Results of pharmacodynamic studies proved significant rapid control on both systolic and diastolic BP to normal values within only 30 minutes without any significant difference from intravenous data. These results confirm the suitability of the prepared HHC sublingual tablets for use in rapid control on hypertensive crisis especially in pregnant women as an alternate to parenteral administration [6].

Sudarshan K. Singh *et al,* have formulated and evaluated directly compressed tablet of Lisinopril was formulated using Mannitol, Micro Crystalline Cellulose and Kyron T-314 as super disintegrant and was observed that concentration of Micro Crystalline Cellulose, Kyron T-314 has significant effect on the disintegration time of Lisinopril sublingual tablet formulation. The present approach of formulating sublingual tablet of Lisinopril would definitely improve bioavailability leading to reduced conventional dose of this drug. The administration of sublingual tablet becoming easy and it will improve patient compliance to therapy for hypertension for pediatrics, geriatric and bed ridden patient [27].

Ranjeev Soni *et al,* have attempt to develop and evaluate muco adhesive bilayered buccal patches to ensure satisfactory unidirectional release of Montelukast sodium (MS). The patches were designed to release the drug for a prolonged period of time so as to reduce the frequency of administration of the available conventional dosage forms of MS. Experimental design was built to investigate the effect of two factors sodium Carboxymethylcellulose (NaCMC) and Carbopol 974P (CP 974P), each at three levels, as independent variables on mucoadhesion strength and invitro residence time as dependent variables. The patches were prepared by solvent casting method and also evaluated for key test parameter such as in vitro drug release. The impermeable backing layer prepared was of ethyl cellulose based to ensure unidirectional drug release. Efficiency of impermeable backing membrane found suitable for mucoadhesive dosage form was also evaluated. After 8 hours the drug lost from ethyl cellulose based backing membrane [3].

ZiyaBayraka *et al,* have formulated and studied, zolmitriptan sublingual tablets by direct compression method using different mucoadhesive polymers such as hydroxypropyl methyl cellulose, Chitosan and Sodium Carboxy methyl cellulose at a concentration range of 0.5–5% to reduce flushing action of saliva and provide enough time for drug to be absorbed. The tablets disintegrantd rapidly, and dissolution tests revealed that Zolmitriptan was dissolved from the formulation within the compendial limits. This especially showed us that the concentration range of polymers is in acceptable limit. As a result, sublingual tablet administration of Zolmitriptan formulated with appropriate excipients and especially with chitosan seems promising alternative to traditional routes [18].

Chauhan Vishakha *et al,* have formulated and evaluated Venlafaxine hydrochloride as sublingual formulations as it is very patient friendly compared to the conventional tablets. Sublingual tablet formulation was proposed to be developed for Venlafaxine hydrochloride to enhance the bioavailability by avoiding first pass effect. Crospovidone and sodium starch Glycolate used as superdisintegrants. Lactose was used as glidant and mannitol as directly compressible filler. Microcrystalline cellulose used as tablet disintegrant. Direct compression method found best and easy for preparing the sublingual tablets and it can be concluded that the superdisintegrants increased the solubility and in vitro drug release of Venlafaxine hydrochloride. Sublingual formulation (tablets) increased the onset of action and bioavailability of Venlafaxine Hydrochloride and prevent them from extensive first-pass effect [14].

Yasser q. almajidi1 *et al*, have formulated and evaluated, Montelukast sodium (MS) nanoemulsions (NEs) by ultra-sonication using different surfactants (tween 20, tween 60 and tween 80) in different surfactant: co-surfactant (ethanol) ratios (Smix). The prepared NEs were evaluated for different parameters including droplet size (DS) using zetasizer as a

function of ultra-sonication time, dispersibility, phase separation, conductivity, percent transmittance, optical transparency, in vitro release in addition to morphology using transmission electron microscopic (TEM) and result of this study is the formulation of a stable oral NE containing MS which presents new easily swallowed dosage form that may enhance drug permeability as well as it may reduce drug metabolism leading to improving bioavailability for asthmatic patients [16].

Muhammad TalhaUsmani1 *et al,* have designed an orally disintegrating Montelukast sodium tablet (ODT) that disintegrants in the oral cavity leaving an easy-to-swallow residue especially for pediatric and elderly patients who have difficulty swallowing tablets by direct compression method, using microcrystalline (Avicel PH-102), mannitol, sodium bicarbonate, crospovidone and magnesium stearate as key excipients, and with cherry flavor and aspartame as flavor and sweetener, respectively. These formulations were then evaluated using pharmacopoeial and non-pharmacopoeial physical and chemical tests. Dissolution and assay tests were performed using USP apparatus II and ultraviolet (UV) spectrophotometry, respectively. Formulations with better results were further subjected for optimization study using central composite design method and the formulations were further evaluated for three and six months under accelerated conditions to ascertain their stability. Conclusion: The results obtained demonstrate the suitability of the formulation as an ODT for convenient delivery of Montelukast sodium for asthmatic patients. However, clinical studies are required to confirm this [23].

Andrzej Emeryketal *et al*, In pediatrics, acceptability has emerged as a key factor for compliance, and consequently for treatment safety and efficacy. Polyvalent mechanical bacterial lysate (PMBL) in 50-mg sublingual tablets is indicated in children and adults for the prophylaxis of recurrent respiratory tract infections. This medication may be prescribed in children over 3 years of age; the appropriateness of this sublingual formulation should thus be demonstrated amongst young children. Using a multivariate approach integrating the many aspects of acceptability, standardized observer reports were collected for medication intake over the course of treatment (days 1, 2, and 10) in 37 patients aged 3 to 5 years, and then analyzed in an intelligible model: the acceptability reference framework. According to this multidimensional model, 50-mg PMBL sublingual tablets were classified as “positively accepted” in children aged 3 to 5 years on all three days of evaluation. As the acceptability evaluation should be relative, we demonstrated that there was no significant difference between the acceptability of these sublingual tablets and a score reflecting the average acceptability of oral/buccal medicines in preschoolers. These results highlight that sublingual formulations could be appropriate for use in preschoolers [11]..

Sheetal Sem *et al*, have formulated a sublingual tablet of antiemetic drug. Doxylamine succinate is an antihistaminic commonly used for the prevention and treatment of nausea and vomiting. Oral bioavailability of doxylamine succinate is low and shows extensive hepatic metabolism. The Objective of the present research is to formulate doxylamine succinate sublingual tablet to avoid hepatic first pass metabolism and to improve its bioavailability. Sublingual route not only overcome the problem of dysphagia but also giving the rapid onset of action by enhancing permeability through site of administration [17].

Shailesh T Prajapati *et al*, have prepared Sublingual tablets using ispaghula husk powder, gellan gum, sodium alginate as super disintegrating polymers and citric acid, tartaric acid and camphor as permeation enhancers by direct compressible technique and evaluated for weight variation, thickness, friability, content uniformity, hardness, disintegration time, wetting time, in-vitro drug release, in-vitro and ex-vivo permeation study. Stability study of optimized formulation was performed as per ICH (International Conference on Harmonisation) guideline.The sublingual tablet formulation gives better results using natural super disintegrant for fast onset of action [18].

Satyajit Sahoo *et al*, have formulated and evaluated sublingual tablets of Enalapril maleate for rapid management of Hypertension. The metallic taste of Enalapril maleate was masked by using Kyron T-114 in 1:2 ratio. The Drug-Resin Complex was formulated as sublingual tablets using Cross Povidone (X1) and Avicel PH102 (X2) by direct compression method. In this study, the fast release of tablets depends on the concentration of Cross Povidone (X1) and Avicel PH102 (X2). The selected formulation showed the fastest release of the tablets in 45 s. Stability study was performed by taking an optimized formulation and it was observed stable. The sublingual tablets showed acceptable results in all studies. The results indicate that the formulation can be used for rapid management of Hypertension. Also, Enalapril maleate's bioavailability may be increased by selecting sublingual route of administration [28].

MATERIALS AND METHODS

Materials

The following materials of Pharmaceutical grade or the best possible Laboratory Reagent (LR) were used as supplied by the manufacturer. The distilled water was used in all experiments.

Table. 1: List of Chemicals Used with Supplier

S.N.	MATERIALS	SOURCE
1.	Montelukast	Gifted by Deurali-Janata Pharmaceutical Pvt. LTD.
2.	Carbopol-934	Gifted by CTL Pharmaceutical Pvt. LTD
3.	Mannitol	Gifted by CTL Pharmaceutical Pvt. LTD
4.	Gaur gum	Gifted by CTL Pharmaceutical Pvt. LTD
5.	Croscarmellose sodium	Gifted by CTL Pharmaceutical Pvt. LTD
6.	Magnesium stearate	HIMEDIA
7.	Talc	LOBA CHEMIE Pvt. LTD.
8.	Sodium Saccharin	HIMEDIA
9.	Cross-povidone	Gifted by CTL Pharmaceutical Pvt. LTD
10.	Sodium starch glycolate	Gifted by CTL Pharmaceutical Pvt. LTD
11.	MCC	Gifted by LOMUS Pharmaceutical Pvt. LTD

Equipment /Instrument

The equipment used in this project are presented in Table 3.2.

Table 2: List of equipment, instrument and machineries used.

S. No.	Instrument	Manufacturer
1	Dissolution Test Apparatus	Aastha International/PDA-65
2.	Digital Electronic balance	Kern &Sohn GmbH/D- 72335

3.	Friability test apparatus	Dica India® /FTA-23/D
4.	Tablet hardness tester	Monsanto type
5.	UV spectrophotometer (double beam)	ELICO®/SL210UV SPECTROPHOTOMETER
6.	Disintegration test apparatus	EI/1209578
7.	pH Meter	Simtronics®
8.	Bulk density apparatus	Dica India
9.	Digital Vernier caliper	Stainless Hardened
10.	Glass wares	Borosilicate Grade
11.	8 station rotatory tablet punching machine	Cemech machineries Ltd/R & D labpress
12.	Digital ultrasonic mixture	Ambalacantt India

Pre-formulation Study

Pre-formulation studies relates to pharmaceutical and analytical investigation carried out proceeding and supporting formulation development efforts of the dosage form of the drug substance. It gives information needed to define the nature of drug substance and provide framework for the drug combination with pharmaceutical excipients in the dosage form. Hence, following pre-formulation studies were performed.

Physical Appearance and Determination of Solubility

Physical appearance test was preformed manually.

The solubility of Montelukast was performed in solvents water, methanol, acetone, chloroform, Ethanol.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9

Determination of Wavelength (λ_{max})

A solution of Montelukast containing concentration 20µg/ml was prepared in methanol and UV spectrum was taken using spectrophotometer respectively. The solution was scanned in the range of 200-400 nm.

Preparation of Standard Calibration Curve for Montelukast

Accurately weighed 25mg of Montelukast was dissolved in methanol and volume was made up to 250 ml methanol which is the stock solution containing 100µg/ml concentration. Similarly, from the Stock solution different aliquot of 10, 20, 30, 40 and 50 ppm were prepared respectively. Then, the absorbance was measured at 285 nm using UV Spectrophotometer. The standard curve was obtained by plotting absorbance versus concentration in ppm.

Formulation Development

Montelukast sublingual tablets were manufactured in nine formulations F1 to F9 using the ingredients mentioned in the Table keeping the total weight (310 mg) of the tablet constant in all the formulations by direct compression method. An excipient; lubricant (magnesium stearate and talc) was passed through sieve no 80#, polymers were passed through sieve no. 40#, filler was passed through sieve no. 40#, sweetner like sodium saccharin was passed through sieve no. 80#, solubilizing agent was passed through sieve no. 30# and active drug

was passed through the sieve no.60#. All the above ingredients were properly mixed together (in an air tight plastic container). All tablets were punched through size 10.5mm. Sublingual tablet containing an Montelukast drug were prepared by this procedure.

Formulation of Montelukast
Nine batch of Montelukast tablets were prepared using the formulation shown in Table 3.

Formulation chart of Montelukast sublingual Tablets. (F1-F9)
Evaluations of Sublingual Tablet [18, 29, 30]
Pre- Compression Parameters
The following pre-compression evaluation were performed.

Angle of Repose
The powder mixture was taken in a funnel. The height of the funnel was adjusted at definite height in such a way that the tip of the funnel just touches the apex of the heap of blend. The drug blend was allowed to flow through the funnel freely on to the surface. The diameter of the powdered cone was measured and the angle of repose was calculated using the following equation;

$\tan \theta = 2h/D$

Where, θ = Angle of repose
h = height of the cone
D = Diameter of the cone

The angle of repose and corresponding types of flow is shown in Table 3.4. Angle of Repose less than 30 shows the free flowing of the material.

Table 3. Angle of Repose and powder flow properties.

S. No.	Angle of Repose	Type of Flow
1	25-30	Excellent
2	31-35	Good
3	36-40	Fair
4	41-45	Passable
5	46-55	Poor
6	56-65	Very poor

Bulk Density (D_b)
It is the ratio of total mass of powder to bulk volume of powder. It is expressed in g/ml. This was determined by pouring an accurately weighed quantity of blend into a graduated cylinder and then the volume and weight was measured.

$$D_b = M / V_b$$

Where, D_b = bulk density, M = Weight of powder, V_b = bulk volume of the powder

Tapped Density (D_t)
It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 100 times in a bulk density apparatus) and tapped volume is noted. It is expressed in g/ml and given by,

$$D_t = M/V_t$$

Where M is the mass of powder, Vt is the tapped volume of the powder.

Where, D_b = bulk density, M = Weight of powder, V_b = bulk volume of the powder

Tapped Density (D_t)

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Montelukast	10	10	10	10	10	10	10	10	10
Sodium Starch Glyconate	5	10	15	-	-	-	-	-	-
Crospovidone	-	-	-	5	10	15	-	-	-
Croscarmellose Sodium	-	-	-	-	-	-	5	10	15
Carbopol -934	0.5	1	1.5	2	2.5	3	3.5	4	4.5
Guargum	0.5	1	1.5	2	2.5	3	3.5	4	4.5
Mannitol	130	130	130	130	130	130	130	130	130
Sodium saccharin	1	1	1	1	1	1	1	1	1
Talcum	10	10	10	10	10	10	10	10	10
Magnesium stearate	10	10	10	10	10	10	10	10	10
Microcrystalline cellulose	143	137	131	140	134	128	137	131	125
Total weight	310	310	310	310	310	310	310	310	310

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 100 times in a bulk density apparatus) and tapped volume is noted. It is expressed in g/ml and given by,

$$D_t = M/V_t$$

Where M is the mass of powder, Vt is the tapped volume of the powder.

Carr's Index

The compressibility index of the granules was determined by Carr's compressibility index. Grading of the powders for their flow properties according to Carr's Index is shown in below Table 3.5.

Table 4. Carr's Index Flow Property

Compressibility	Flow ability
5-12	Excellent
12-16	Good
18-21	Fair Passable
23-25	Poor
33-38	Very poor
>40	Very very poor

Hausner's Ratio

Hausner's ratio is an indirect index of ease of powder flow. The Hausner's ratios of prepared mucoadhesive dry powder blends were determined by following formula.

Hausner's ratio = Tapped density / poured density

According to specifications values less than 1.25 indicate good flow (=20% of Carr's index), whereas greater than 1.25 indicates poor flow (=33% of Carr's index). Between 1.25 and 1.5, added glidant normally improves flow.

Post – Compression Parameter [31]

Weight variation: The tablets were then weighed individually using a digital balance to determine the weight of each tablet. The tablets were subjected to weight variation by individually weighing 20 randomly selected tablets. Such determinations were carried out for each formulation.

Tablet thickness: The thickness of tablet was measured by placing the tablet between two arms of the digital vernier caliber.

Tablet hardness: The tablet hardness, which is the force required to break a tablet in diametric compression force. The hardness tester used in the study was Monsanto hardness tester, which applies force to the tablet diametrically with the help of an inbuilt spring.

Friability Test: The friability of the tablets was measured in a Roche friabilator. Tablets of a known weight (W_o) or a sample of 20 tablets are deducted in a drum for a fixed time (100 revolutions) and weighed (W1) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1%.

$$\text{Friability (\%)} = \frac{\text{Initial weight(Wo)} - \text{Final weight(W1)}}{\text{Inital weight(Wo)}} \times 100\%$$

Wetting Time

10ml water containing Eosin, water soluble dye, was added to petri dish. A tablet was placed carefully on the surface of the plate. The time required for water to reach upper surface of the tablet was noted as wetting time.

Dispersion time

Tablet was added to15 ml of water and time required for complete dispersion was measured. Three tablets from each formulation were randomly selected and dispersion time was performed.

Palatability test

The test was conducted in three volunteers. One tablet of each formulation batch was given to test to all volunteer and their response was noted.

Disintegration time

The test was carried out on six tablet using tablets disintegration tester, distilled water at 25°C±2°C was used as a disintegration media and the time taken for complete disintegration of the tablet with no passable mass remaining in the apparatus was measured in seconds.

Assay [32, 33, 34, 36, 37]

Preparation of Standards: Accurately 20 mg standard Montelukast was weighed and transferred to 100 ml volumetric flask (VF). Drug was dissolved in methanol and volume was made up to the 100ml with methanol. From this stock solution 1ml was taken and transferred to 10ml volumetric flask and volume was maintained and volume was made up to mark.

Preparation of sample: 5 Tablets were then weighed accurately, and then powdered in motar and pestle. Tablet drug powder equivalent to 20mg of drug was taken in 100ml

volumetric flask which was first dissolved in methanol and volume was maintained upto mark with methanol. From this stock solution 1ml was withdrawn and volume maintained upto 10ml with methanol in volumetric flask. Then this solution was filtered, diluted properly and analyzed spectrophotometrically at 285 nm.

Procedure: The absorbance was measured at 285 nm to find out the content of Montelukast. Content of Montelukast in tablet in percentage was calculated by using following formula.

$$(\%) = \frac{\text{absorbance of sample}}{\text{absorbance of standard}} \times \frac{\text{weight of standard}}{\text{weight of sample}} \times \text{dilution} \times \frac{\text{average weight}}{\text{label claim}} \times 100\%$$

***In-vitro* Drug release [32, 33, 35, 36, 37]**

Preparation of Standard: [16, 17] Accurately 22 mg standard Montelukast was weighed and transferred to 1000 ml volumetric flask (VF). Drug was dissolved in distilled water and sonicated for 15min and volume was made up to the 1000ml. 500ml of stock solution is taken in another 1000ml VF and diluted by distilled water up to mark.

Preparation of Sample: *In-vitro* drug release of the samples was carried out using USP – type II dissolution apparatus (paddle type). The dissolution medium, 900 ml of distilled water, was placed into the dissolution flask maintaining the temperature of 37±0.5ºC and of 50 RPM. Tablets were placed in each flask of dissolution apparatus. Accurately 10mg tablet was taken in 900ml buffer solution. The apparatus was allowed to run for 30 min. Samples measuring 10 ml were taken out in 5,10 15 and 30 minutes which was filtered. The collected samples were analyzed at 285 nm using dissolution medium as blank. The percentage drug release was calculated. The details of the in-vitro dissolution study are presented in Table 3.6.

Table 5. *In-Vitro* Dissolution Studied Detail

Apparatus used	USP type II dissolution apparatus
Dissolution medium	Distilled
Dissolution medium volume	900 ml
Temperature	37±0.5ºC
Speed of paddle	50 rpm
Sample withdrawn	10 ml
Wavelength	285nm

RESULTS

Authentication of Drugs

Physical appearance and Determination of Solubility

Physical appearance of Montelukast was white in color and powder was Amorphous. Solubility study were carried out in different solvents and observations are presented in Table 4.1.

Table 6. Solubility Profile of Montelukast

Solvent	Solubility
Water	Soluble

Ethanol	Freely Soluble
Methanol	Freely Soluble
Acetone	Soluble
chloroform	Soluble

Determination of λmax of Montelukast in methanol

Determination of λmax

The different concentrations were prepared using methanol and Montelukast. λmax was found to be 285 nm. The result is plotted as shown in Figure 4.1

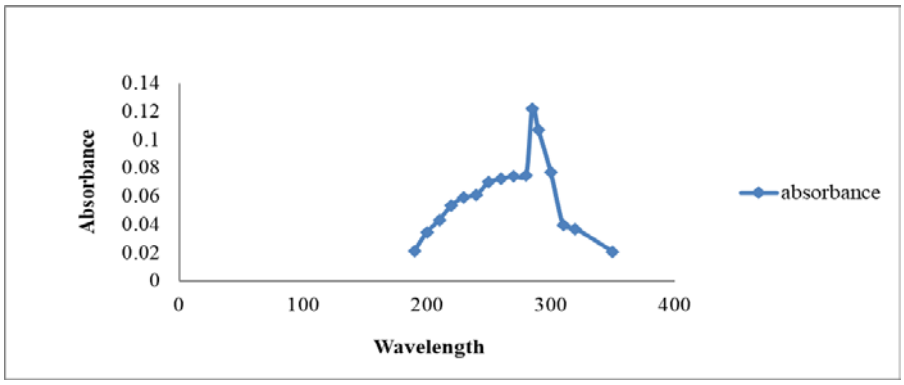


Fig. 2. λ_{max} of Montelukast in methanol

Standard Calibration Curve for Montelukast and Methanol: A Standard Calibration Curve for Montelukast was obtained by measuring absorbance at 285 nm and by plotting graph of absorbance versus concentration. The absorbance reading of Montelukast and methanol in different concentrations were showed in Table 4.3.

Table 7. Absorbance Values of Montelukast in methanol

S. N.	Concentration (ppm)	Absorbance (285 nm)*
1.	0	0
2.	10	0.3766
3.	20	0.6614
4.	30	0.8710
5.	40	1.0569
6.	50	1.2176

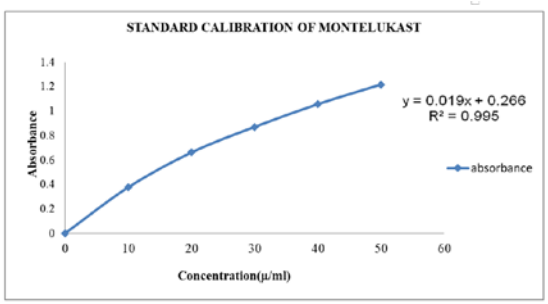


Fig. 3. Standard Calibration Curve of Montelukast in methanol

Pre-Compression Parameter of Sublingual Tablet Montelukast

Pre-compression parameter including bulk density, tapped density, compressibility index, angle of repose and Hausner ratio are presented in Table 4.3.

Table 8. Pre-Compression Parameters.

S. N.	Formulation code	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Compressibility index (%)	Angle of repose(θ)	Hausner ratio
1	F1	0.588	0.667	11.84	36	1.13
2	F2	0.555	0.625	11.20	37.74	1.12
3	F3	0.555	0.667	16.79	35.53	1.20
4	F4	0.555	0.625	11.20	39.70	1.12
5	F5	0.526	0.625	15.84	38.48	1.18
6	F6	0.526	0.588	10.54	39.60	1.11
7	F7	0.526	0.625	15.84	37.70	1.18
8	F8	0.500	0.666	24.92	37.56	1.20
9	F9	0.500	0.625	20.00	37.70	1.18

Post-Compression Parameters of Sublingual Tablets of Montelukast

Thickness, Hardness, Friability, Weight variation.

Table 9. Table Showing Post Compression Parameters

S.N	Formulation code	Thickness (mm) n=3	Hardness (Kg/cm^2) n=3	Weight variation n=20	Friability (%) n=20	Wetting time(sec) n=3	Disintegration time (sec) n=6
1	F1	3.68	3.58	312 ±1.45	0.70	43	22
2	F2	3.56	3.70	311.2±1.56	0.59	48	27
3	F3	3.62	3.64	312.75±1.56	0.54	54	24
4	F4	3.57	3.52	312.1±1.56	0.37	45	19
5	F5	3.62	3.82	312.85±1.56	0.43	47	13
6	F6	3.63	3.88	312.7±1.53	0.30	62	15
7	F7	3.54	3.76	312.5±1.56	0.47	113	30
8	F8	3.55	3.58	312.65±1.56	0.48	62	29
9	F9	3.56	3.48	313.2±1.56	0.45	107	32

n= No. of samples

Palatability test

Volunteers	V1	V2	V3
F1	3	4	3
F2	4	4	4
F3	3	3	4
F4	4	5	4
F5	4	3	4
F6	3	4	3
F7	4	3	3
F8	4	4	4
F9	3	4	4

1 = Bitter; 5 = Sweet

Assay of Formulated Batches

Table 10.. Table for Assay

S. No.	Formulation code	Assay (%)
1.	F1	100.30
2.	F2	97.19
3.	F3	99.85
4.	F4	100.99
5.	F5	98.98
6	F6	97.80
7	F7	97.80
8	F8	97.55
9	F9	95.76

Figure 4.7 Assay for Different Formulations

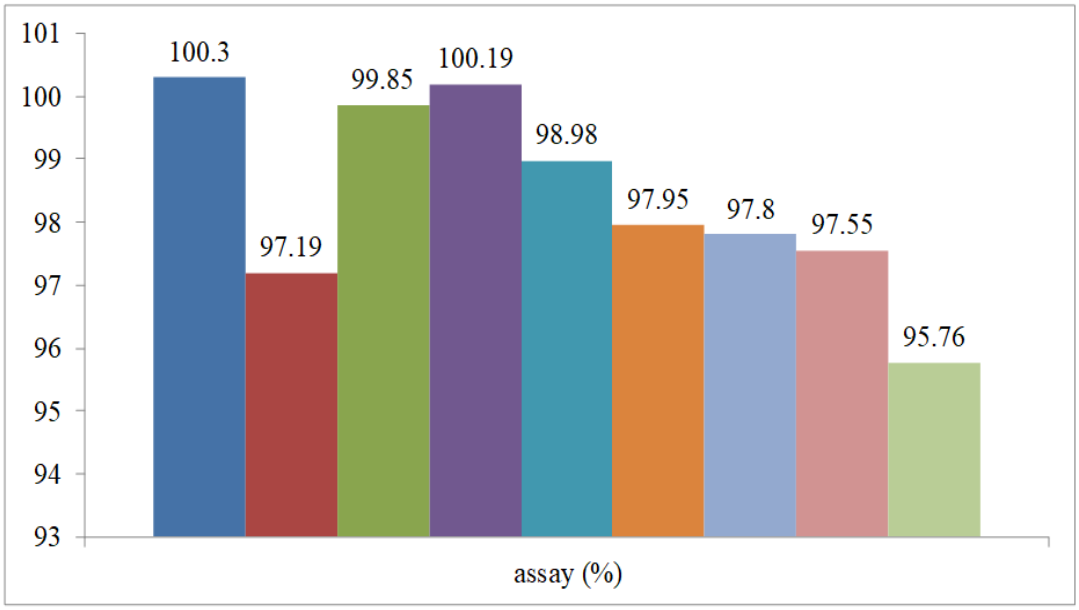


Fig.4. 4.8 % Drug release for different formulation.

***In-Vitro* Drug Release**

Table 11. Cumulative Drug Release

Formulation code	Time			
	5min	10min	15min	30min
F1	87.34%	90.92%	95.75%	100.53%
F2	84.38%	87.27%	99.29%	102.12%
F3	85.83%	91.37%	95.15%	100.88%
F4	83.78%	91.97%	102.12	102.50%
F5	87.38%	92.61%	98.65%	101.76%
F6	80.99%	95.30%	100.10%	102.57%
F7	78.62%	92.82%	98.69%	99.92%
F8	90.60%	93.56%	99.32%	101.37%
F9	60.78%	84.41%	85.51%	99.64%

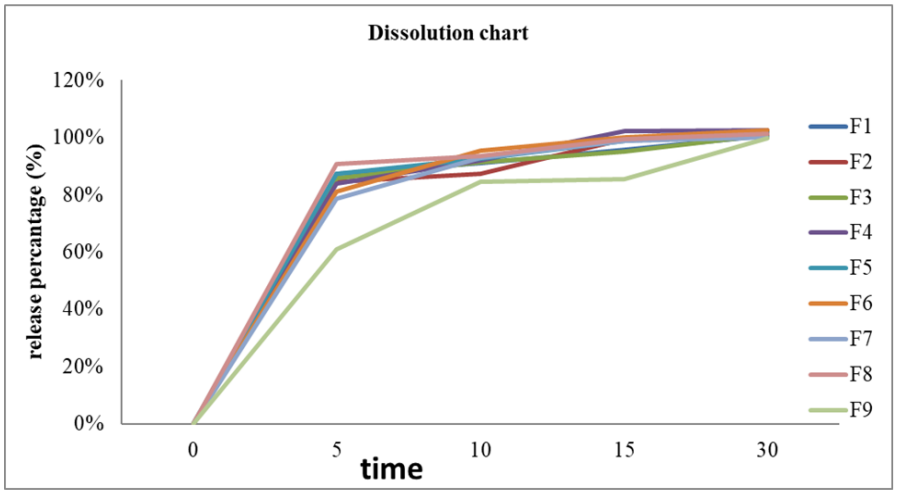


Fig. 5. Time vs percentage drug release chart

Comparison of Best Formulation (F4) with Marketed Product

Test	Best Formulation (F4)	Marketed product
Thickness	3.57	3.69
Disintegration time	45 sec	9 min 45 sec
Dissolution in 15 minutes	102.12%	83.67%

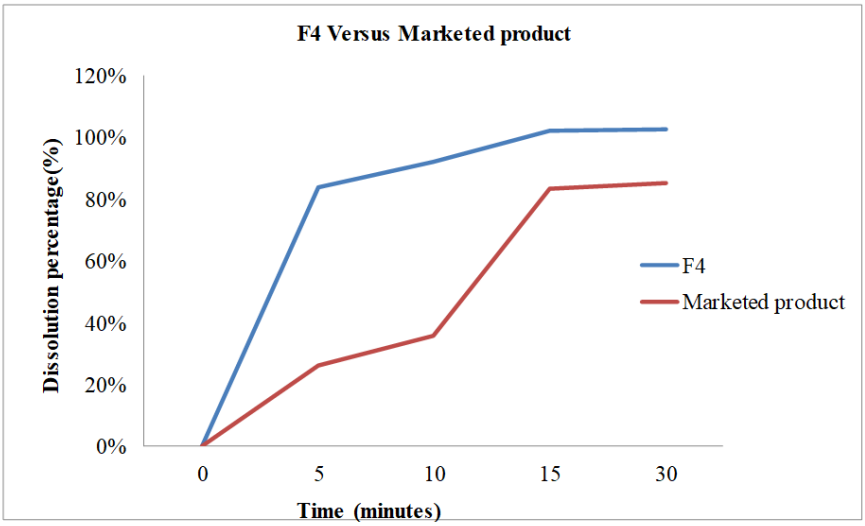


Fig.6. Comparison between Best Formulation (F4) and Marketed Product

DISCUSSION

Pre-Compression Parameters

Pre compression parameters play an important role in improving the flow properties of pharmaceuticals especially in tablet formulation. These include angle of repose, bulk density, tapped density, Hausner ratio and CARR'S index. Before formulation of tablets the drug was evaluated for all the above said parameters and it was found that all the observations were within the prescribed limits of IP.

1) **Angle of Repose:** The data obtained from angle of repose for all the formulations were found to be within the range of 35.5 to 39.7 which reveals flow property of powder between good to fair.
2) **Bulk Density:** The bulk density of the powder primarily depends on particle size distribution, particle shape, and the tendency of particle to adhere together. The value of bulk density of all formulation prepared fall within the range of 0.500-0.588 g/cm³.
3) **Tapped Density:** It was found that the value of tapped density of all the formulation range from 0.588-0.667 g/cm^3.
4) **Carr's Index/ Compressibility Index:** The compressibility index of the powder was found to be within the range of 10.54 to 24.92. This shows good to fair passable flow ability and compressibility of powder prepared.
5) **Hausner ratio:** The Hausner ratio of the powder was found to be within the range of 1.20-1.11. This shows good flow ability of the powder prepared.

Post Compression Parameters

1) **Weight Variation:** The result obtained shows that there is not much variation in weight of tablet. Weight variation range falls between 5%.
2) **Tablet Thickness:** The thickness of all formulated tablet falls within the range of 3.54 to 3.68 mm.
3) **Hardness:** Hardness of tablet was found to be 3.48 to 3.88 kg/cm^2.
4) **Friability:** Friability indicates the ability of tablet to withstand mechanical shocks while hand. The friability range was found to be 0.30 to 0.70 %. which indicates that all formulation batches can withstand mechanical shock while handling before administration.
5) **Palatability Test:** Palatability test shows that F4 has nice palatability then other formulation.
6) **Comparison of Best Formulation (4) with Marketed Product:** Dissolution of F4 formulation is more than the dissolution of marketed product in 15 minutes.
7) **Assay:** The result obtained shows that all formulation contains Montelukast not less than 95.76% and not more than 100.30 %. This indicates uniformity of dose in each batch and therapeutically equivalent.

***In Vitro* Dissolution Study**

After getting all the physical parameters satisfactory, the dissolution for all the batches was tested. The dissolution study was carried out as per the procedure mentioned in the methodology chapter. Among all the formulation the batch containing Crospovidone and guar gum, F4 showed the release of 102.50% of drug in 30 minutes.

CONCLUSION

Based on our laboratory, studies the following conclusions can be drawn. The sublingual tablet of Montelukast were successfully prepared by using different polymer agent namely Carbopol, Croscarmellose Sodium, Guar gum, Crospovidone and Sodium starch Glycolate. All samples of different formulation were subjected to pre-compression and post-compression evaluations. The result indicates that although all formulations are in required criteria, F4 was the best formulation among the all formulation developed for sublingual tablets. The *in-vitro* dissolution studies for tablets were carried out and tablet of formulation F4 containing 1.6% Crospovidone released 102.12% during 15 minutes which is fast release as compared to Croscarmellose sodium and Sodium starch Glycolate containing formulation.

Comparision of F4 formulation with marketed product shows, F4 have better dissolution than marketed product. From the above, concluded that the fast-dissolving tablets of Montelukast prepared with Crospovidone showed better dissolution time profile and assay as compared to other polymers.

SUMMARY

Solid dosage form is popular because of the ease of administration, accurate dose, self-medication, pain avoidance, and most importantly the patient compliance. Tablets and capsules are the most popular solid dosage form. However, many patient groups such as the elderly, children and patient who are mentally retarded, uncooperative on reduced liquid intake/diets have difficulties swallowing these tablets and hard gelatin capsules. Thus, these conventional dosage form results in high incidence of non-compliance and ineffective therapy with respect to swallowing specially in the case of pediatric, geriatric, or any mentally retarded persons. The concept of formulating sublingual tablet containing montelukast offers suitable and practically approach in serving such patients with characteristic increases bioavailability and patient compliance.

In the present work, an effort is made to formulate and evaluate sublingual tablets of Montelukast. The polymers such as Carbopol, Guar gum and were used along with sweetener *i.e.,* Saccharin to impart better mouth feel in developing sublingual tablets. Prior to the formulation development, Pre formulation studies were conducted for drugs compatibility by taking infrared spectrum to determine any interaction between the components for sublingual tablets. Pre-compression parameters were carried out to determine the flow properties of powder blend. Angle of repose, Bulk density, and Tapped density, Hausner ratio and also Carr's Index were determined for all the formulations, which showed good results indicating good flow properties. Post-compression parameters were conducted for the tablets. The results of the evaluation parameters demonstrate that it is possible to design and develop sublingual tablets of Montelukast by using different polymers. Among the polymer used showed better disintegration property and dissolution profile compared to other polymers along with swelling index.

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