FORMULATION AND EVALUATION OF MONTELUKAST SODIUM CHEWABLETABLETS BY DIRECT COMPRESSION METHOD

Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

Chennai - 32

In partial fulfillment for the award of the degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

Reg. No. 26113007

DEPARTMENT OF PHARMACEUTICS

J.K.K. NATTRAJA COLLEGE OF PHARMACY

KOMARAPALAYAM - 638183

TAMILNADU

APRIL-2013

I. INTRODUCTION

FORMULATION AND EVALUATOIN OF MONTELUKAST SODIUM CHEWABLE TABLETS BY DIRECT COMPRESSION METHOD

1. Introduction

A tablet is a compressed solid unit dosage form containing medicaments with or without excipients. According to the Indian pharmacopoeia, pharmaceutical tablets are solid flat or biconvex dishes prepared by compressing a drug or a mixture of drugs, with or without excipients[1,2]. They vary in shape and differ greatly in size, shape and weight, depending on the amount of medicinal substances and the intended mode of administration. It is most popular dosage form and 70% of the total medicines are dispensed in the form of tablets. Tablets offer advantages over both patient and manufacturers.

Tablets are most popular dosage form due to their simplicity and economy of the manufacture, relative stability and convenience in packaging, shipping and storage. For the patients, ease of manufacturing convenience in administration, accurate dosing and stability compared to oral liquids, tamper proofness compared to capsules, safe compared to parentral dosage forms make it a popular and versatile dosage form[3].

1.1 Properties of tablets[4]

- Should be elegant product having its own identity while being free of defects such as chips, cracks, discoloration and contamination.
- Should have strength to withstand the rigors of shocks encountered in its production, packing, shipping and dispensing.
- Should have the physical stability to maintain its physical attributes over time.
- Must be able to release the medicament agent(s) in the body in a predictable and reproducible manner.
- Must have suitable chemical stability over time so as not to allow alteration of medicinal agent(s).

1.2 Tablet is one of the most popular oral dosage forms due to the following potential advantages[5,6,7]

- ❖ They are unit dosage form and they offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
- ❖ Cost is lowest of all oral dosage forms.
- ❖ Lighter and most compact.
- ❖ Easiest and cheapest to package and transport.
- ❖ Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face.
- ❖ Easy to swallow with least tendency for hang-up.
- ❖ Objectionable odor and bitter taste can be masked by coating techniques.
- ❖ Suitable for large scale production.
- ❖ Greatest chemical and microbial stability over all oral dosage form.

1.3 Disadvantages compared to other dosage forms[8]

- ❖ Difficult to swallow in case of children and unconscious patients.
- ❖ The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
- ❖ The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.

1.4 Pharmaceutical excipients used in tablets and capsules [9,10]

The pharmaceutical industry is ever thirsty to satisfy patient's therapeutical needs and apart from active ingredients, excipients play a major role in formulation development.

In addition to transporting the active drug to the site in the body where the drug is intended to exert its action, excipients play an important part in the manufacturing process. They may also be important for keeping the drug from being released too early in the assimilation process in places where it could damage tender tissue and create gastric irritation or stomach upset.

Disintegrant helps the drug to disintegrate into particles small enough to reach the blood stream more quickly and few excipients protect the product's stability so it will be at maximum effectiveness at time of use. In addition, some excipients are used to aid the identification of a drug product.

Some excipients are used simply to make the product taste and look better. This improves patient compliance, especially in children. Although technically "inactive" from a therapeutic sense, pharmaceutical excipients are critical and essential components of a modern drug product. In many products, excipients make up the bulk of the total dosage form. Apart from the drug's active ingredient, other essential components include diluents or fillers, binders, disintegrants, lubricants, coloring agents and preservatives. Diluents or fillers are inert ingredients that can significantly affect the chemical and physical properties of the final tablet thus affecting the biopharmaceutical profile.

One classic example of this is calcium salts, which can be utilized as fillers, which interfere with the absorption of tetracycline from the gastrointestinal tract. This example emphasizes that excipients may not always be inert, as they may be perceived. Usually tablets are designed so that the smallest tablet size which can be conveniently compressed is formed. Thus, if the dose is small more diluents are required and if the dose is high less diluents are required as not to increase the tablet size, which might make it difficult to swallow.

Diluents selection should be made carefully as physical-chemical changes might render the product unstable and might cause problems in manufacturing. Binders are added to tablet formulations to add cohesiveness to powders thereby providing the necessary bonding to form granules which under compaction form a compact mass as tablet. In other words, binders are essential to achieve the "hardness" of the tablet.

Binders are usually selected on basis of previous experience, particular product needs, literature or vendor data or the preference of individual scientists or manufacturing unit. The primary criterion when choosing a binder is its compatibility with other tablet components. It must add sufficient cohesion to the powders to allow for normal processing yet allow the tablet to disintegrate and the drug to dissolve upon ingestion, releasing the active ingredients for absorption. Disintegrant facilitate the breakup of a tablet after oral administration.

They can be added prior to granulation or during the lubrication step prior to compression or at both processing steps. The effectiveness of many disintegrants is affected by their position within the tablet. Since disintegration is the opposite operation to granulation (agglomeration) and the subsequent formation of strong

compacts, one must carefully weigh these two phenomena when designing a tablet. Lubricants prevent sticking of the tablets to the tablet punches during the compression phase of the tablet manufacturing process.

When lubricants are added to a powder mass, they form a coat around individual particles which remains more or less intact during compression. Lubricants are mostly hydrophobic. The presence of lubricant coating may cause an increase in the disintegration time and a decrease in drug dissolution rate. The choice of a lubricant may depend upon the type of tablet being manufactured, dissolution, flow characteristics and requirements of the formulation in terms of hardness, friability and compatibility.

Glidants are the materials that have good flow properties and poor lubrication properties. Glidants improve the flow of powder into the tableting machines for compaction. They act to minimize the tendency of a granulation to separate or segregate due to excessive vibration. High speed tablet machine require smooth even flow of material to die cavities (tablet mold). The uniformity of tablet weights directly depends on how uniformly the die cavity is filled. In general many materials commonly referred to as lubricants possess only a minimal lubricating activity and are better glidants or anti-adherents.

Thus a blend of two or more materials may be necessary to obtain these properties. Pharmacists should be familiar with the components of pharmaceuticals products, beyond their active ingredients. In order to educate pharmacists on excipients that are routinely used in the pharmaceutical industry, we decided to examine the top 200 prescription, tablets and capsules products of 2003 and find out how many or which excipients are used in each product.

The selection will cover both brand and generic drugs. Out of the 200 prescription drugs, the total numbers of inactive excipients used except for coating and coloring agents were only 94. Although the list is composed on the top 200 drugs of 2003, very few blockbusters has been launched since then and still the excipients in all remains the same.

Table No: 1 Pharmaceutical excipients used in tablets and capsules

No	Excipients	No. of times used out of 200 formulations	Use
1	Acacia	2	Emulsifying agent, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent
2	Alginate	1	Binder
3	Alginic Acid	1	Stabilizing agent, suspending agent,tablet binder, Tablet disintegrant, Viscosity-increasing agent
4	Aluminum Acetate	1	Antiseptic
5	Benzyl Alcohol	2	Antimicrobial preservative, disinfectant,solvent
6	Butyl Paraben	1	Antimicrobial preservative
7	Butylated Hydroxy Toluene	1	Antioxidant
8	Citric acid	1	Disintegrant
9	Calcium carbonate	1	Tablet and capsule diluents, therapeutic agent
10	Candelilla wax	4	Binder
11	Croscarmellose sodium	22	Tablet and capsule disintegrant
12	Confectioner sugar	1	Sugar coating adjunct, sweetening agent
13	Colloidal silicone dioxide	22	Adsorbent,anticaking agent,emulsionstabilizer, glidant,suspending agent,tablet disintegrant, thermal stabilizer, viscosity-increasing agent
14	Cellulose	19	Adsorbent, suspending agent, tablet and capsule diluents, tablet disintegrant, Adsorbent, glidant, suspending agent, tablet and capsule diluents, tablet disintegrant
15	Plain or anhydrous calcium phosphate	3	Diluent
16	Carnuba wax	12	Binder
17	Corn starch	17	Binder

No	Excipients	No. of times used out of 200 formulations	Use
18	Carboxymethyl cellulose calcium	3	Stabilizing agent, suspending agent, tablet and capsule disintegrant, viscosity-increasing agent, water-absorbing agent
19	Calcium stearate	5	Tablet and capsule lubricant
20	Calcium disodium EDTA	1	Chelation
21	Copolyvidone	1	Film-former, granulating agent, tablet binder
22	Castor oil hydrogenated	4	Extended release agent, stiffening agent,tablet and capsule lubricant
23	Calcium hydrogen phosphate dihydrate	1	Diluent
24	Cetylpyridine chloride	1	Antimicrobial preservative, antiseptic, cationic surfactant, disinfectant, solubilizing agent, wetting agent
25	Cysteine HCL	1	Reducing Agent
26	Crosspovidone	20	Tablet disintegrant
27	calcium phosphate di or tri basic	7	Anticaking agent, buffer, nutrient, dietary supplement, Glidant
28	Dibasic Calcium Phosphate	9	Diluent
29	Disodium hydrogen phosphate	1	Buffering agent
30	Dimethicone	1	Antifoaming agent, Emollient
31	Erythrosine Sodium	2	Color
32	Ethyl Cellulose	3	Coating agent, flavoring fixative, tablet binder, tablet filler, viscosity-increasing agent
33	Gelatin	14	Coating agent, film-former, gelling agent, suspending agent, tabletbinder, viscosity-increasing agent

No	Excipients	No. of times used out of 200 formulations	Use
34	Glyceryl monooleate	2	Non-ionic surfactant
35	Glycerin	3	Antimicrobial preservative, Emollient, humectants, plasticizer, Solvent, sweetening agent, tonicity Agent
36	Glycine	1	Tonicity agent
37	Glyceryl monostearate	1	Emollient, emulsifying agent, solubilizing agent, stabilizing agent,sustained-release ingredient
38	Glyceryl behenate	1	Coating agent, tablet binder, lubricant
39	Hydroxy propyl cellulose	25	Coating agent, emulsifying agent, suspending agent, thickening agent,viscosity-increasing agent
40	Hydroxyl propyl methyl cellulose	45	Coating agent, film-former, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, viscosity-increasing agent
41	Hypromellose	7	Coating agent, film-former, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent
42	HPMC Pthalate	1	Coating agent
43	Iron oxides or ferric oxide	15	Color
44	Iron oxide yellow	5	Color
45	Iron oxide red or ferric oxide	6	Color
46	Lactose hydrous or anhydrous or monohydrate or spray dried	77	Binding agent, diluent for dry-powder inhalers, lyophilization aid, tablet binder, tablet and capsule diluent.(lactose nhydrous) Binding agent, diluent for dry-powder inhalers,tablet binder, tablet and capsule diluents(lactose monhydrate), Binding agent, diluent for dry-powder inhalations, tablet and capsule diluents,

No	Excipients	No. of times used out of 200 formulations	Use
			tablet and capsule filler(lactose spray dried)
47	Magnesium stearate	108	Tablet and capsule lubricant
48	Microcrystallin e cellulose	61	Adsorbent, suspending agent, tablet diluents, tablet disintegrant
49	Mannitol	4	Sweetening agent, diluents, tonicity agent, vehicle (bulking agent) for lyophilized preparations
50	Methyl cellulose	3	Coating agent, emulsifying agent, suspending agent, tablet and capsule disintegrant, tablet binder, viscosity-increasing agent
51	Magnesium carbonate	2	Diluents
52	Mineral oil	3	Emollient, lubricant, oleaginous vehicle, solvent
53	Methacrylic acid copolymer	5	Coating
54	Magnesium oxide	2	Diluents
55	Methyl paraben	5	Antimicrobial preservative
56	Povidone or PVP	36	Disintegrant, dissolution aid, suspending agent, tablet binder
57	PEG	40	Ointment base, plasticizer, solvent, suppository base, tablet and capsule lubricant
58	Polysorbate 80	19	Solubilizer
59	Propylene glycol	10	Antimicrobial preservative, disinfectant,humectants, plasticizer, Solvent, stabilizer for vitamins, water-miscible cosolvent
60	Polyethylene oxide	3	Mucoadhesive, tablet binder, thickening agent
61	Propylene paraben	4	Antimicrobial preservative
62	Polaxamer 407 or 188 or plain	3	Dispersing agent, emulsifying and coemulsifying agent, solubilizing agent, tablet lubricant, wetting agent

No	Excipients	No. of times used out of 200 formulations	Use
63	Potassium bicarbonate	1	Alkalizing agent, therapeutic agent
64	Potassium sorbate	1	Antimicrobial preservative
65	Potato starch	1	Binder
66	Phosphoric acid	1	Acidifying agent
67	Polyoxy140 stearate	1	Emulsifying agent, solubilizing agent, wetting agent
68	Sodium starch glycolate	20	Tablet and capsule disintegrant
69	Starch pregelatinized	21	diluents, disintegrant,binder (starch pregelatinized Glidant (starch , potato, corn , wheat, rice)
70	Sodium crossmellose	1	Disintegrant
71	Sodium lauryl sulfate	13	Anionic surfactant, detergent, emulsifying agent, skin penetrant, lubricant, wetting agent
72	Starch	19	Glidant, diluents, disintegrant binder.(starch , potato, corn , wheat, rice)
73	Silicon dioxide	14	Same as colloidal silicon dioxide
74	Sodium benzoate	2	Antimicrobial preservative, lubricant
75	Stearic acid	12	Emulsifying agent, solubilizing agent, lubricant
76	Sucrose	9	Base for medicated confectionery, granulating agent, sugar coating adjunct, suspending agent, diluents, sweetening agent, viscosity-increasing agent
77	Sorbic acid	3	Antimicrobial preservative
78	Sodium carbonate	1	Carbonating agent
79	Saccharin sodium	1	Sweetening agent
80	Sodium alginate	1	Stabilizing agent, suspending agent, disintegrant, binder, viscosity-increasing agent
81	Silica gel	1	Adsorbant
82	Sorbiton monooleate	1	Solubilizer

No	Excipients	No. of times used out of 200 formulations	Use
83	Sodium stearyl fumarate	4	Tablet and capsule lubricant
84	Sodium chloride	3	Tablet and capsule diluents, tonicity agent
85	Sodium metabisulfite	1	Antioxidant
86	Sodium citrate dihydrate	1	Alkalizing agent, buffering agent, emulsifier, sequestering agent
87	Sodium starch	1	Binder
88	Sodium carboxy methyl cellulose	1	Disintegrant, binder, stabilizing agent, suspending agent, viscosity-increasing agent, Water-absorbing agent.
89	Succinic acid	1	Acidity
90	Sodium propionate	1	Antimicrobial preservative
91	Titanium dioxide	49	Coating agent, opacifier, pigment
92	Talc	20	Anticaking agent, glidant, diluents, lubricant
93	Triacetin	6	Humectant, plasticizer, solvent
94	Triethyl citrate	3	Plasticizer

In the tablet formulation, a range of excipients materials is normally required along with the active ingredient in order to give the tablet the desired properties. For example the reproducibility and dose homogeneity of the tablets are dependent on the properties of the powder mass. The tablet should also be sufficient strong to withstand handling, but should disintegrate after intake to facilitate drug release. The choice of excipients will affects all these properties.

1.4.1 Filler

Fillers are used to make the tablets of sufficient for easy handling by the patient and to facilitate production. Tablets containing a very potent active substance would be very small without additional excipients. Good fillers will have good compact ability and flow properties, acceptable taste will be non-hygroscopic and good compact ability chemically inert. It may also be advantageous to have filler that fragment easily, since this counteracts the negative effects of lubricant additions to the formula.

1.4.2 Binder

A material with a high bonding ability can be used as a binder to increase the mechanical strength of the tablet. A binder is usually a ductile material prone to undergo plastic deformation. Typically binder is polymeric material often with disordered solid state structures. Of special importance is the deformability of the peripheral parts of the binder particles. Thereby this group of materials has the capacity of reducing interparticulate distance within the tablet, improving bond formation. If the entire bulk of the binder particle undergoes extensive plastic deformation during compression, the interparticulate voids will at least partly be filled and the tablet porosity will decrease. This increase the contact area between the particles which promote the creation of interparticulate bonds subsequently increases the tablet strength. However, the effect of the binder depends on the both its own properties and those of the other compounds within the tablet. A binder is often added to the granulation liquid during wet granulation to improve the cohesiveness and compactability of the powder particles, which assists formation of granules. It is commonly accepted that binder added in dissolved form, during a granulation process is more effectives than used in dry powder form during direct compression.

1.4.3 Disintegrating agent

A disintegrants are normally added to facilitate the rupture of bonds and subsequent disintegration of tablets. This increases the surface area of the drug exposed to the gastrointestinal fluids incomplete disintegration can result in incomplete absorption or a delay in the onset of action of the drug. There are several types of disintegrations acting with different mechanisms

a) Promotion of the uptake of aqueous liquids by capillary forces.
b) Swelling in contact with water
c) Release if gases when in contact with water
d) Destruction of the binder by enzymatic action.

Starch is a traditional particles swells moderately in contact with water and tablets disrupts so called superdisintegrants they are now commonly used since these are primarily by extensive swelling they are effective in only small quantities. Cross linked sodium carboxymethyl cellulose which is effective in concentrations of 2-4%.

Larger particles of disintegrates have been found to swell to a greater extent and with faster rate than finer particles resulting in more effectiveness disintegration.

1.4.3.1 Super Disintegrants[11,12,13]

Super disintegrants were increased demands for faster dissolution requirements, there are now available. The major groups of compounds which are used as superdisintegrants in many solid-dosage forms are as follows.

1.4.3.1.1Microcrystalline cellulose (Avicel)

Apart from its use in direct compression, microcrystalline cellulose is used as a diluent in tablets prepared by wet granulation, as filler in capsules and for the production of spheres. MCC tablets when exposed to increased humidity (75 %,one week) resulted in a softening and swelling of plain microcrystalline cellulose tablets. This change disappeared on removal of humid condition.

Table No: 2 Comparative properties of various grades of Avicel

AvicelGrade	Features
pH-101	Most widely used for direct compression tabletting and wet granulation
pH-102	Larger particle size, Compression properties similar to pH-101.
pH-103	Reduced moisture content and ideal for moisture-sensitive materials
pH-105	Finest particle size and may be used in direct compression of coarser or granular or crystalline materials. It can be admixed with pH-101 to achieve specific flow and /or compression properties
pH -200	Larger particle size which offers increased flowability within minimum effect on compression characteristics. It can be used to reduce tablet weight variation and to improve content uniformity. Higher lubricant sensitivity and lower carrier capacity
pH-301	Higher density than its particle size equivalent, pH-01, providing increased flowability, greater tablet weight uniformity
pH-302	Density characteristics similar to pH-102, pH-302. Offers increased flowability, greater tablet weight uniformity and potential for smaller tablets.

1.4.4 Glidants, Anti-adherents and Lubricants

Glidants are added to increase the flow ability of the powder mass reduce interparticular friction and improve flow in the hopper shoe and die of the tablet machine. Anti-adherents can be added to decrease sticking of powder to the faces of the punches and die walls during compaction and lubricants is added to decrease friction between powder and die. Facilitating ejection of the tablet from the die however addition of lubricants can have negative effect on tablet strength, since they often reduces the creation of interparticular bond space. Further lubricants can also slow the drug dissolution process by introducing hydrophobic films around drug and excipients particles. These negative effects are especially pounced when long mixing times are required. Therefore the amount of lubricants should be kept relatively low and the mixing procedure kept short to avoid a homogenous distribution of lubricant throughout the powder mass. An alternative approaches could then be to admix granulated qualities of lubricant.

1.4.5 Flavor, sweetener and colorants

Flavor and sweeteners are primarily used to improve or mask the taste of the drug with subsequent improvement in patient compliance. Coloring tablets has aesthetic value that can improve tablet identification especially when patients are taking number of different tablets at once.

1.5 Manufacturing

1.5.1 Tablet manufacturing methods[14-24]

Tablets are the unit solid dosage forms meant for oral use and are manufactured by using tablet compression machines. The tabletting mixture that is going to be compressed can be prepared by either of the three techniques- Wet granulation, Dry granulation or direct compression. Each of the individual technique mentioned above has their own advantages and disadvantages respectively.

(a.)Methods for tablet preparation

1. Granulation method.

a. Wet granulation.

b. Dry granulation.

2. Direct compression method.

(b.) Steps involved in these methods

Wet granulation	**Dry granulation**	**Direct compression**
Blending	Blending	Blending
Wet massing and screening Slugging/roller compaction	-	Drying
-	-	Dry screening
Blending(with lubricant)	Blending (with lubricant)	Blending (with lubricant)
Compaction	Compaction	Compaction

1.5.1.1 Wet granulation

Wet granulation is the process in which a liquid binder is added to a powder in a vessel equipped with any type of agitation that will produce agglomeration or granules these granules after drying are compressed to tablet form.

1.5.1.2 Dry granulation

In this technique, there is no use of liquid. The process involves the formation of flugs. Then these flugs are screened or milled to produce granules. The granules formed are then compressed into tablet forms.

1.5.1.3 Direct compression

In general direct compression method involves the direct compaction of tabletting mixture without the step of granulation, provided the tabletting mixture should have enough flow properties and should form a robust tablet. For suppose, if the tabletting mixture is not having good flow properties, we can either use direct compression vehicles (DCV) for improving the flow and compatibility of tabletting mixture or by subjecting the mixture for granulation process (wet or dry granulation).

The invention of direct compression had increased the production of tablets enormously all over the world due to its advantages over the other two techniques. The main focus that must be kept in direct compression technique is about the use of direct compression vehicle (DCV). Drugs must have good flow properties to be suitable for direct compression along with good compaction properties. By using DCVs, the flow properties of the drugs with poor flow can be improved and

hence can be manufactured by direct compression technique. Drugs with minute doses (potent drugs) as well as drugs with large doses are not suitable for direct compression due to segregation problems and large tablet sizes respectively. Here we mainly focused on the advantages and disadvantages of the direct compression technique, essential properties of DCVs, some of the examples of DCVs and the drugs that are suitable for direct compression technique.

Advantages of Direct compression

- **Cost Effectiveness:** The prime advantage of direct compression over wet granulation is economic since the direct compression requires fewer unit operations. This means less equipment, lower power consumption, less space, less time and less labor leading to reduced production cost of tablets.
- **Stability:** Direct compression is more suitable for moisture and heat sensitive APIs, since it eliminates wetting and drying steps and increases the stability of active ingredients. Changes in Dissolution profiles are less likely to occur in tablets made by direct compression on storage than in those made from granulations.
- **Faster Dissolution:** Disintegration or dissolution is the rate limiting step in absorption in case of tablets with poorly soluble API prepared by wet granulation. The tablets prepared by direct compression disintegrate into API particles instead of granules that directly come into contact with dissolution fluid and exhibits comparatively faster dissolution.
- **Less wear& tear of punches:** The high compaction pressure involved in the production of tablets by slugging or roller compaction can be avoided by adopting direct compression. The chances of wear and tear of punches and dies are less.
- **Other advantages:** As ingredients are processed for a shorter period of time, the chance for contamination is low. Due to fewer unit operations, the validation and documentation requirements are reduced and will become easier. Due to the absence of water in granulation, chance of microbial growth is minimal in case of tablets prepared by direct compression.

Limitations of Direct compression

- **Segregation:** Direct compression is more prone to segregation due to the difference in density of the API and excipients. The dry state of the materials during mixing may induce static charges and lead to segregation. This may lead to the problems like weight variation and content non-uniformity.
- **Cost:** Directly compressible excipients are the speciality products produced by spray drying, fluid bed drying, roller drying or co-crystallization. Hence, the products are relatively costly than the respective raw materials.
- **Low dilution potential:** Most of the directly compressible materials can accommodate only 30-40 % of the poorly compressible active ingredients like acetaminophen that means the weight of the final tablet to deliver the 500 mg of acetaminophen would be more than 1300 mg. The large tablets may create difficulty in swallowing.
- **Lubricant sensitivity:** Lubricants have more adverse effect on the filler, which exhibit almost no fracture or shear on compression (e.g. starch 1500). The softening effects as well as the hydrophobic effect of alkaline stearates can be controlled by optimising the length of blending time to as little as 2-5 min.
- **Variation in functionality:** There is a lack of awareness in some situations that the excipients behave differently, depending upon the manufacturer so much so that substitution from one source to that of another is not possible. Hence, there is a need for greater quality control in purchasing of raw materials to assure batch uniformity.

1.5.2 General formula for direct compression includes the following ingredients

1. Binder-Filler (DC-vehicles)

These DC vehicles (either binders or fillers) play an important role as that of API in this method. In general, the terms binder and filler are always confusingly used in direct compression. But, the major difference between these two is their Dilution capacities. (Dilution capacity is the maximum proportion of the API that can be compacted into an acceptable compact by the binder or filler.)Binders have high dilution capacity as these are more compactible where fillers have less dilution capacity due to their less compatibility nature. But, these values vary depending upon the compacting ability of the API used. In general, dilution capacity values of

binders and fillers are determined by using some reference materials which are difficult to compact. Eg: ascorbic acid.

Based upon the solubility and disintegration properties of the Binders, these can be classified as-

1. Binders

i. **Soluble Binders:** These are always non- disintegrating. Some of the examples are Sugars, Ploy hydric alcohols etc.

ii. **Insoluble Binders:** These insoluble binders are again of two types-

a. Disintegrating (MCC, starch etc.)

b. Non-disintegrating (DCP)

When we use soluble filler, there will be rapid release of API from the tablet, but the problem is that soluble erosion and release profile dominates the disintegration and release profile. (We observed faster release patterns in case of MCC tablets whencompared with similar formula where lactose is used instead of MCC).

Factors influencing the selection of optimum DC- vehicle

- Properties of Powders. (particle size, shape, density, solubility)
- Properties of compacts. (flow, compatibility)
- Stability factors. (temperature and moisture effects)
- Others. (cost, availability etc.)

2.Disintegrants

In general, we use less concentration of disintegrants in DC method when compared with the wet granulation method which are nothing but super disintegrants. This can be explained by following reasons-To minimize the softening and flow properties of the tabletting mixture. The required uniform particle size of API upon disintegration can be achieved only if the disintegrant used is uniformly distributed in the tablet, which may be difficult when high loadings of API are used. Also when we use soluble fillers, erosion followed by dissolution occurs instead of disintegration, which can be avoided if we use more concentration of disintegrant or super disintegrants. Some of the examples of super disintegrants are sodium starch glycollate, crosspovidone, crosscarmellose etc. Though starch is not a super disintegrant, we use it in DC because it can also be used as DC filler.

3. Lubricants

We prefer hydrophilic lubricants over the hydrophobic ones in case of DC method. This is because, hydrophobic ones (magnesium stearate) may form a film around other ingredients used in the formula which may results in the decrease of tablet hardness.

This problem can be overcome by following by –

- Blending the tableting mixture (excluding lubricant) by high shear mixtures and then adding the lubricant to this main blend with low shear mixing.
- By carefully controlling the particle size and surface area of the lubricant used.
- Use of hydrophilic lubricants such as stearic acid, stearyl fumerate, hydrogenated vegetable oils etc.

Some works showed that ejection force, hardness, disintegration and dissolution times of MCC and lactose tablets were adversely effected depending upon the lubricant mix time. Also the type of blender used effects the crushing strength of the tablets. For example, crushing strength is much decreased for large industrial mixers compared with small laboratory blenders when same concentration of lubricant is used in both cases.

1.5.3 General requirements for Direct compression

Vehicles

In order to perform direct compression without any problems, we need to consider certain parameters which are to be maintained in optimum range and are as follows

- Compactability
- Flow properties

1. Compactability: In general, a good conventional tablet must have enough hardness to withstand various stages of stress and must disintegrate and dissolve in almost 60 minutes. So for the tablet to have enough hardness, it should have enough compaction properties. If the API dose is low, then required compactability can be achieved by using DC- filler.But if the API loadings are high with poor compaction profile, then we must use a DC-binder to achieve a strong compact. (MCC is the best DC- binder but can't be used in case of low levels of insoluble API because the drug may get encased in the MCC aggregates formed upon disintegration and the

dissolution may become slower. In this case we can use soluble filler (Lactose) with a superdisintegrant.) When we use more than one compactable agent (binders) then we can expect both additive (MCC and lactose) and antagonistic effects.(cellulose or starch with fast dissolving sugars like dextrose, sucrose and the result is poorer compactability with long disintegration times). Also, as the crystal properties of tabletting mixture increase, its compactability decreases. So, pure crystals are generally inferior in terms of compactability. So, by increasing the amorphous nature either by spray drying or co-crystallization we can improve the compactability.

Eg: Spray drying of lactose results in small alpha monohydrate crystals that are held together by amorphous glass. These agglomerates are superior to normal crystals in terms of flow and compactability. Also, spray drying of acid hydrolyzate of cellulose (MCC), agglomeration of starch and partially hydrolyzed starch, Co-crystallization of sucrose with modifieddextrins.

2. Flow properties: "No flow, no tablets." It is required in each and every step of tablet preparation. Poor flow may result in difficulties for the compression mix to flow from hopper to the die cavity which may cause weight variation problems. Granulation step increases the flow in case of wet granulation method but in case of DC we must use DC grade excipients for better flow. Proper flow can be attained by using Glidiants at levels of 0.1-0.2%. Also if the flow exceeds the optimum range, it may results in segregation of tablet ingredients, this will leads to content uniformity problems.

Preparation of DC-vehicles

As we have already discussed that DC excipients are speciality products prepared by modification of normal ingredients, these modification can be done in two ways

- **Chemical modification**

  Ethyl cellulose, Methyl cellulose, HPMC, Na-CMC, Cyclodextrins etc.

- **Physical modification**

  Dextrates or compressible sugars, sorbitol, DCP etc.

- **Spray drying**

  MCC, Emdex, Spray dried Lactose etc.

- **Crystallization**

  Dipac etc.

- **Granulation**

  Tabletose (granulated lactose) etc.

- **Co-processing**

  Cellactose : MCC, Lactose

  Ludipress : Lactose, PVP, Crosspovidone

  Starlac : Lactose, Maize starch

  Celocol : MCC, Calcium phosphate

1.6 Chewable Tablet [25-32]

Tablet is most popular among all dosage forms existing today because of convenience of self administration, compactness and easy manufacturing.[25] Many patients express difficulty in swallowing tablets and hard gelatin capsules, resulting in noncompliance and ineffective therapy.[26]

To overcome this weakness, scientists have developed innovative drug delivery systems known as fast dissolving tablets[27]. United States Food and drug administration (FDA) defined fast dissolving tablet (FDT) as "a solid dosage form containing medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed up on the tongue".[28] Their characteristic advantages such as administration without water, patient compliance, rapid onset of action, increased bioavailability and good stability make these tablets popular as a dosage form of choice in the current market.[29]

Montelukast sodium is a leukotriene receptor antagonist (LTRA) used in maintenance treatment of asthma and to relieve symptoms of seasonal allergies. It is usually administered orally. Montelukast sodium is freely soluble in ethanol, methanol and water and practically insoluble in acetonitrile and its bioavailability is 63%.[30,31]

In the present study an attempt had been made to prepare chewable tablets of Montelukast sodium in the oral cavity with enhanced dissolution rate and hence improved patient compliance. The basic approach used in the development of Montelukast sodium chewable tablets by using co-processed super disintegrants containing croscarmellose sodium was studied. The concept of formulating tablets (FDT) of Montelukast sodium using co-processed superdisintegrants helps to

increase the water uptake with shortest wetting time and thereby decrease the disintegration time of the tablets by simple and cost effective direct compression technique. These systems may offer superior profile with potential mucosal absorption, thus increase the drug bioavailability.

These systems are also called mouth dissolving tablets, melt-in-mouth tablets, Reprimelts, porous tablets, Oro dispersible, quick dissolving or rapidly disintegrating tablets. Montelukast (sodium salt) is potent, selective CysLT1 receptor anatagonist. It is indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients. The drug is commercially available in various forms of once- daily oral dosage formulations including oral granules.

In addition to the therapeutic ingredients of pharmaceutical tablets (commonly referred to as "actives"), materials inert and non-reactive with respect to the actives (commonly referred to as "excipients") are added to the tablet formulation to confer specific properties not related to the activity of the therapeutic agents. Excipients such as diluents, binders, glidants, and lubricants are added as processing aids to make the tableting operation more effective.

Other excipients such as microcrystalline cellulose are also added to improve the compression of the tablets. Still other types of excipients added to pharmaceutical tablets are those which enhance or retard the rate of disintegration of the tablet in the patient, improve the taste of the tablet, (for example sweetening agents), or impart a color to the tablets. In some instances such materials will provide more than one of these benefits to the finished tablet. Although excipients are classified as inert materials, they are only inert in the sense that they are not pharmaceutical actives and do not provide a therapeutic effect in themselves, but they make delivery of the therapeutic agent in the most effective manner possible.

Chewable tablets, regardless their geometry, represent a particular form of oral dosage; they are intended to be chewed in the mouth by the patient and are not intended to be swallowed intact. Many chewable formulations are intended to be used to provide a known dosage of active to children or the people who either will refuse to swallow an intact tablet or may have difficulty doing so. Such tablets are often used to administer analgesics, antacids, antibiotics, anticonvulsants, vitamins, and laxatives, for example. In addition to the foregoing, chewable tablets have several advantages which make them the method of choice in delivering certain

types of therapeutic agents to an even greater population. One such advantage is that certain types of tablets, because of the large size of the dosage, must be unusually large and, therefore, difficult to swallow. In some cases the effectiveness of the therapeutic agent is improved by the reduction in size that occurs during mastication of the tablets before swallowing. Furthermore, patient compliance with the prescribed therapy, such as antacid treatment, is enhanced by the use of smaller, more convenient tablets which may be consumed when it is inconvenient to swallow pills, for example, in the workplace. This is particularly true when the therapy would otherwise involve a liquid suspension of the therapeutic agent which would be inconvenient to transport, for example in chewable antacid tablets.

Excipients when added to chewable tablets must not only be inert in respect of the active, preferably they provide pleasant mouthfeel and/or prevent tooth packing, grittiness, and the like, without imparting any unpleasant characteristics to the tablets as they are chewed. Microcrystalline cellulose in various forms.

Aggregates of coprocessed microcrystalline cellulose and guar, by which these aggregates may be made and their physical and organoleptic properties. The aggregates are disclosed as being useful as fat replacements in such food applications as low-fat salad dressings and frozen dessert products. In this patent a brief mention is made of several other possible uses for these materials including controlled release agents, tableting excipients, flavor carriers, or bonding, bulking, or encapsulating agents. Except for this mention, there is no enabling disclosure directed toward their use as excipients nor suggestion that they possess unique properties that might suit them for use in pharmaceutical tablets nor any indication that they might provide extraordinary properties to a particular type of pharmaceutical tablet, for example "chewable" tablets[32].

1.7 Asthma[33-37]

Asthma is a most common chronic inflammatory disease of the airways, characterized by hyper responsiveness to a variety of stimuli. The role of circadian rhythms in the pathogenesis and treatment of asthma indicates that airway resistance increases progressively at night in asthmatic patients. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours. The worsening of asthma at night, commonly referred to as nocturnal asthma (NA). A drug delivery system administered at bedtime. Asthma is chronic respiratory

disorder that causes difficulty in breathing when the airways become inflamed and narrow. It is usually caused by allergies. The condition can be managed by medication but sometimes, severe asthma attacks can be fatal. Oral administration could be useful for the treatment of certain diseases, such as asthma, gastric ulcer, hypertension, ischemic heart disease, arthritis, etc., which exhibit circadian rhythms. Oral drug delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, most convenient and an economical method of drug delivery having the highest patient compliance.

1.7.1 Causes

In most cases of asthma in children, multiple triggers or precipitants exist, and the patterns of reactivity may change with age. Treatment can also change the pattern. Certain viral infections, such as respiratory syncytial virus (RSV) bronchiolitis in infants, predispose the child to asthma.

- **Respiratory infections:** Most commonly, these are viral infections. In some patients, fungi (eg,allergic bronchopulmonary aspergillosis), bacteria (eg, mycoplasmata, pertussis) or parasites may be responsible. Most infants and young children who continue to have a persistent wheeze and asthma have high immunoglobulin E(IgE) production and eosinophilic immune responses (in the airways and in circulation) at the time of the first viral (Upper Respiratory tract infection). They also have early IgE-mediated responses to local aeroallergens.
- **Allergens:** In patients with asthma, 2 types of bronchoconstrictor responses to allergens exist.
- **Early asthmatic** responses occur via IgE-induced mediator release from mast cells within minutes of exposure and last for 20-30 minutes.
- **Late asthmatic** responses occur 4-12 hours after antigen exposure and result in more severe symptoms that can last for hours and contribute to the duration and severity of the disease. Inflammatory cell infiltration and inflammatory mediators play a role in the late asthmatic response. Allergens can be foods, household inhalants (eg, animal allergens, molds, fungi, cocroach allergens, dust mites), or seasonal outdoor allergens (eg, mold spores, pollens, grass, trees).

- **Irritants:** Tobacco smoke, cold air, chemicals, perfumes, paint odors, hair sprays, air pollutants, and ozone can initiate BHR by inducing inflammation.
- **Weather changes:** Asthma attacks can be related to changes in atmospheric temperature, barometric pressure, and the quality of air (eg:humidity, allergen and irritant content).
- **Exercise:** Exercise can trigger an early asthmatic response. Mechanisms underlying exercise-induced asthmatic response remain somewhat uncertain. Heat and water loss from the airways can increase the osmolarity of the fluid lining the airways and result in mediator release. Cooling of the airways results in congestion and dilatation of bronchial vessels. During the rewarming phase after exercise, the changes are magnified because the ambient air breathed during recovery is warm rather than cool.
- **Emotional factors:** In some individuals, emotional upsets clearly aggravate asthma.
- **Gastroesophageal reflux(GER):**The presence of acid in the distal esophagus, mediated via vagalor other neural reflexes, can significantly increase airway resistance and airway reactivity.
- **Allergic rhinitis, sinusitis, and chronic URTI:** Inflammatory conditions of the upper airways (eg, allergic rhinitis, sinusitis, or chronic and persistent infections) must be treated before asthmatic symptoms can be completely controlled.
- **Nocturnal asthma:** Multiple factors have been proposed to explain nocturnal asthma. Circadian variation in lung function and inflammatory mediator release in the circulation and airways (including parenchyma) have been demonstrated. Other factors, such as allergen exposure and posture-related irritation of airways (eg, GER, sinusitis) can also play a role. In some patients, abnormalities in CNS control of the respiratory drive may be present, particularly in patients with a defective hypoxic drive and obstructive sleep apnea.

1.7.2 Signs and Symptoms

Asthma is characterized by recurrent attacks of dyspnea, cough, and expectoration of tenacious mucoid sputum, and usually wheezing. Symptoms may be mild and may occur only in association with respiratory infection, or they may occur in various degrees of severity to the point of being life-threatening.

Classic allergic (atopic) asthma usually begins in childhood and becomes progressively more severe throughout life, although spontaneous remissions may occur in adulthood. Hay fever often accompanies atopic asthma.

The acute attack is characterized by dyspnea usually associated with expiratory wheezing that may be heard without a stethoscope. Cough may be present but is usually not the predominant symptom. There is a small group of patients with asthma in whom paroxysmal cough may be the predominant symptom. When asthma becomes prolonged, with severe intractable wheezing, it is known as status asthmaticus.

1.7.3 Essentials of Diagnosis

- Recurrent acute attacks of dyspnea, cough, and mucoid sputum, usually accompanied by wheezing.
- Prolonged expiration with generalized wheezing and musical rales.
- Bronchial obstruction reversible by drugs.

1.7.4 Laboratory Studies

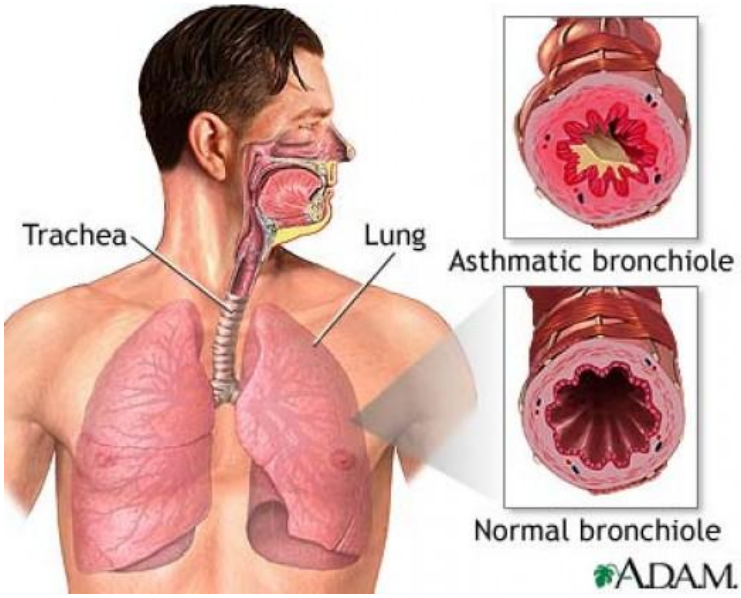
The sputum is characteristically tenacious and mucoid, containing "plugs" and "spirals." Eosinophils are seen microscopically. The differential blood count may show eosinophilia. In severe, acute bronchospasm, arterial hypoxemia may be present as a result of disturbed perfusion/ventilation relationships, alveolar hypoventilation, or functional right-to-left shunts.

1.7.4.1 X-Ray Findings

Chest films usually show no abnormalities. Reversible hyper expansion may occur in severe paroxysms, or hyper expansion may persist in long-standing cases. Transient, migratory pulmonary infiltrations may be present. Severe attacks are sometimes complicated by pneumothorax.

1.7.4.2 Differential Diagnosis

Distinguish wheezing from that due to other disorders such as bronchitis, obstructive emphysema and congestive heart failure.



Picture:1 Chronic Asthamatic Bronchiole.

1.7. 5 Treatment of the patients

Medications used to treat asthma are generally divided into 2 main categories: relievers and controllers. Relievers are best represented by the inhaled short-acting β2-agonists. These quick-acting bronchodilators are used to relieve acute intercurrent asthma symptoms, only on demand and at the minimum required dose and frequency.

Inhaled ipratropium bromide is less effective, but is occasionally used as a reliever medication in patients intolerant of short-acting β2-agonists. Controllers (or preventers) include anti-inflammatory medications, such as inhaled (and oral) glucocorticosteroids, leukotriene-receptor antagonists, and anti-allergic or inhaled nonsteroidal agents, such as cromoglycate and nedocromil. These agents are generally taken regularly to control asthma and prevent exacerbations. Inhaled glucocorticosteroids are the most effective agents in this category.

The controller group also includes some bronchodilators that are taken regularly in addition to inhaled gluco-corticosteroids to help achieve and maintain asthma control. These include the long-acting inhaled β2-agonists salmeterol and formoterol, which are the first choice in this category, as well as theophylline and ipratropium. The β2-agonists and ipratropium are considered of no significant benefit in reducing airway inflammation.

There is some evidence that theophylline may have immunomodulatory effects, but the clinical significance of this remains to be demonstrated. Asthma drugs are preferably inhaled, because this route minimizes systemic absorption and, thus, improves the ratio of the therapeutic benefit to the potential side-effects. The patient must have repeated instruction on how to use the inhaled medication. The recently developed oral leukotriene-receptor antagonists have good safety and tolerance profiles and are taken orally, which may help certain patients comply with treatment.

Asthma medications should be used at the minimum dose and frequency required to maintain acceptable asthma control; they should not be used as a substitute for proper control of the environment. Asthma medications are considered to be safe over many years when used appropriately. The participants in the asthma consensus conference have reviewed the role of each category of medication. In the following sections they describe briefly the mode of action, pharmacologic and clinical profile, mode of administration and potential side-effects of these drugs.The treatment may be divided into 2 phases: treatment of the acute attack and interim therapy, which is aimed at preventing further attacks.

1.7.6 Asthma management

- For all patients with asthma, monitoring should be performed on a continual basis based on the following parameters, which helps in the overall management of the disease.
- Monitoring signs and symptoms of asthma: Patients should be taught to recognize inadequate asthma control, and providers should assess control at each visit.
- Monitoring pulmonary function: Regularly perform spirometry and peak-flow monitoring.
- Monitoring quality of life and functional status: Inquire about missed work or school days, reduction in activities, sleep disturbances, or change in caregiver activities.
- Monitoring history of asthma exacerbations: Determine if patients are monitoring themselves to detect exacerbations and if these exacerbations are self-treated or treated by health care providers.

- ❖ Monitoring pharmacotherapy: Ensure compliance with medications and usage of short-acting beta-agonists.
- ❖ Monitoring patient-provider communication and patient satisfaction.

1.7.7 Drug Category

- ❖ Bronchodilators

  Albuterol, Levalbuterol, Salmeterol, Ipratropium And Theophylline
- ❖ Leukotriene Receptor Antagonists

  Montelukast (Singulair), Zafirlukast
- ❖ Corticosteroids

  Fluticasone, Triamcinolone, Beclomethasone ,Prednisone, Budesonide
- ❖ Mast Cell Stabilizers

  Cromolyn
- ❖ Combination Beta-Agonist/Corticosteroid

  Salmeterol/Fluticasone
- ❖ 5-Lipoxygenase Inhibitors

  Zileuton

1.8 General guidelines for collection stability data[38-40]

In general case stability are defined in three types. The conditions are given in the table that covered storage condition and time period of the study. Accelerated study was done at 40^{o}C+/- 2^{o}C/75% RH+/- 5%RH, to know the results of the study in short duration of time. The results of accelerated stability were then extrapolated to know the\e stability at ordinary conditions. Long term study in mainly done at 25^{o}C +/- 2^{o}C/60^{o}C RH +/- 5% RH, and the results are collected after 12 months. Sometimes intermediate stability studied at 30^{o}C+/- 2^{o}C/60% RH+/- 5%RH, done and data is collected after 6 months.

Table No: 3 ICH Guidelines

Study	Storage condition	Minimum time period covered by data at submission
Long term	25°C +/- 2°C/60°C RH +/- 5% RH or 30°C +/-2°C/65°C RH +/- 5% RH,	12 months
Intermediate	30°C +/- 2°C/65°C RH +/- 5% RH,	6 months
Accelerated	40°C +/- 2°C/75°C RH +/- 5% RH,	6 months

- It is up to the applicant to decide whether long term 25°C +/- 2°C/60°C RH +/- 5% RH or 30°C +/- 2°C/65°C RH +/- 5% RH is to be performed.
- If 30°C +/- 2°C/65°C RH +/- 5% RH is long term there is no intermediate condition.

1.8.1 Stability guidelines for different climatic zones

For convenience in planning and storage and for stability studies international practice identifies four climatic zones, where are described in the united states Europe and Japan are characterized by zones I and II. The values in are based on observable temperature and relatively humidity's both in and outside in the rooms from which mean kinetic temperature and average humidity values are calculated. Derived values are based on inspections of data of individual cities and on allowances for a margin of safety in assignment of theses specified conditions.

2. LITERATURE REVIEW

Chewable tablet dosage forms continued to draw attention in the search for improved patient compliance and decreased incidence of adverse drug reaction. Many drugs exhibit bitter taste when orally administered and the bitter taste often causes non-compliance of patients because of the discomfort. Therefore, suppression of the bitter taste has been an important subject for chewable tablets with simultaneous improvement in oral feeling.

- **Priyanka *et al*[41]**., has formulated and evaluated montelukast sodium chewable tablets by wet granulation method using microcrystalline cellulose, croscarmellose sodium, mannitol, magnesium stearate, hydroxypropyl cellulose, ferric oxide. The compatability studies were carried out by mixing definite proportion of Montelukast sodium and microcrystalline cellulose, croscarmellose sodium, mannitol, magnesium stearate, hydroxypropyl cellulose, ferric oxide and cherry flavour, 1:1,1:2.5,1:3,1:5,1:10 and kept in glass vials which has stored at 50°C (three weeks). Based on the optimization of parameters concluded that chewable tablet of Montelukast sodium can be prepared by wet granulation method using croscarmellose sodium as a superdisintegrants.
- **Kaur Harbir *et al*[42]**., has reported pharmaceutical tablets can produced three methods viz. direct compression, dry granulation and wet granulation. Out of three methods, direct compression is most convenient and cheaper method.
- **Swati J *et al*[43]**., designed and evaluated chewable tablet of levamisole (used in treatment of worm infestations). As an anthelmintic, it probably works by targeting the nematode nicotinergic acetylcholine receptor. In the market, levamisole tablets are available in the form of tablets. The chewable tablets of levamisole were prepared by using lactose or mannitol along with sodium starch glycolate in concentration ratios especially for paediatric use. Sodium saccharin and vanilla were used as sweetening agent and flavouring agent respectively. It was observed that the formulation containing lactose shows less disintegration time than formulation containing mannitol.
- **Kanaka *et al*[44].,** formulated and evaluated montelukast sodium chewable tablets by different techniques. Montelukast sodium is used for prophylaxis and chronic treatment of asthma. Montelukast sodium chewable tablets (5 mg) were prepared

and evaluated for the parameters such as average weight, hardness, tensile strength, friability, *in vitro* dissolution, and assay. The study on the dissolution profile revealed that product prepared from direct compression method had faster dissolution rate while compared to remaining batches and marketed product. Assay values were within the limits of 95 to 105%.

- **Kathiresan K *et al*[45].**, formulated and evaluated 5 batches of loratadine chewable tablets. Loratadine, H_1 receptor antagonist used in the treatment of allergic rhinitis and urticaria. Results showed that thickness, weight variation, friability, hardness, and content uniformity of all 5 formulations were within the acceptance limits. But in the *in-vitro* dissolution study, formulations 1, 2, and 5 demonstrated better cumulative drug release than formulations 3 and 4. However, cumulative drug release of formulation 5 was comparable with innovator than formulations 1 and 2. Hence the study concludes that loratadine chewable tablet formulated using avicel CE 15 and starch paste showed better characteristics of chewable tablets.
- **Hiroyuki S *et al*[46].,** developed oral acetaminophen chewable tablets with inhibited bitter taste. Various formulations with some matrix bases and coregents' were examined for development of oral chewable tablets which suppressed the bitter taste of acetaminophen, often used as an antipyretic for infants. Corn starch/lactose, cacao butter and hard fat (Witepsol H-15) were used for matrix bases, and sucrose, cocoa powder and commercial bitter-masking powder mixture made from lecithin (Benecoat BMI-40) were used for corrigents against bitter taste. For the tablets made of matrix base and drug, Witepsol H-15 best inhibited the bitter taste of the drug, and the bitter strength tended to be suppressed with increase in the Witepsol H-15 amount. When the inhibitory effect on the bitter taste of acetaminophen solution was compared among the corrigents, each tended to suppress the bitter taste; especially, Benecoat BMI-40 exhibited a more inhibitory effect. Further, chewable tablets were made of one matrix base and one corrigent, and of one matrix base and two kinds of corrigents, their bitter taste intensities after chewing were compared. As a result, the tablets made of Witepsol H-15/Benecoat BMI-40/sucrose, of Witepsol H-15/cocoa powder/sucrose and of Witepsol H-15/sucrose best masked the bitter taste so that they were tolerable enough to chew and swallow. The dosage forms best masking bitter taste showed good release of the drug, indicating little change in bioavailability by masking.

➢ **Maddi SS *et al*[47].,** designed sodium fluoride chewable tablets for dental caries. Chewable tablets containing low dosage fluoride content were prepared using two varities of celluloses and their *in vitro* parameters were evaluated. An eighteen month clinical trial revealed that both these formulations were effective in controlling the caries. However, ethyl cellulose is proved to be superior to methylcellulose as a controlled release matrix material in controlling caries. Thus this study recommends ethyl cellulose matrix tablets containing low fluoride content is an efficacious and cost effective drug device in controlling dental caries.

➢ **Shajan *et al*[48].,** studied Montelukast sodium and Doxofylline bilayer tablet by using disintegrant such as HPMC, Crosscarmellose sodium. The sustained release layer of doxofylline HCl was developed by wet granulation technique using polymers HPMC K100M and eudragit RL100 and the immediate release layer of montelukast sodium by direct compression method using superdisintegrant crosscarmellose sodium. The tablets were evaluated for their physical parameters. All the values were found to be within acceptable limits. The *in vitro* release was carried out using USP Type II apparatus. The optimized batch was subjected to stability studies for 6 months at 40˚C ± 2 ˚C/ 75 % RH ± 5 % RH. The results suggested that the developed bilayer tablets can be used as an alternative to the conventional dosage form

➢ **Ganji Amarnath Reddy *et al*[49].,** studied oral fast disintegrating tablet of Amlodipine Besylateusing different combination of superdisintegrants like Croscarmellose sodium (Ac-Di-Sol), Sodium Starch Glycolate (Primogel), Cross Povidone (Polyplasdone) and got better bioavailability within a short duration of time with different formulations. For the masking of bitter taste we used aspartame as sweetening agent. In this study instead of drug we prepared drug solid dispersion so that drug's solubility was enhanced.

➢ **Errolla Mahesh *et al*[50].,** has prepared and studied fast dissolving tablets of Montelukast sodium by using novel co-processed superdisintegrants consisting of crospovidone and sodium starch glycolate in the different ratios (1:1,1:2 & 1:3) in vice versa. Montelukast sodium is a drug of choice in treatment of asthma and allergic rhinitis. Drug compatibility with excipients was checked by FTIR studies. After examining the flow properties of the powder blends the results were found to be within prescribed limits and indicated good flowing property and it was subjected

to tablet compression. All the formulations were subjected to post compression parameters like hardness and friability (≤1%), indicated that tablets had a good mechanical strength and resistance. Drug content was found to be in the range of 93.51 to 98.79%. The wetting time is an important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water were found to be in the range of 20 to 55 sec.

- **Mahalaxmi Rathnanand *et al*[51],** has formulated and evaluated chewable Tablet of Metformin HCl using Stevia by different techniques. The variation in the dissolution rate of Metformin chewable tablets made by different techniques were in the following order, direct compression < non-aqueous granulation < aqueous granulation. Various evaluation parameters like thickness, hardness, friability, weight variation and drug content of the formulations were found to be satisfactory. Chewable immediate release metformin tablets DSC (Differential scanning calorimetry) and IR (Infra-red) studies showed no interaction between drug and excipients in optimized formulation. The optimized tablets found to be stable under accelerated conditions for a period of one month.
- **M. Rajesh *et al*[52]** has formulated and characterized Albendazole chewable tablets Albendazole (ABZ) is a benzimidazole derivative that has been widely used in the treatment of worm infestations in both humans and animals. Albendazole chewable tablets were prepared by wet granulation method using superdisintegrants such as croscarmellose sodium and sodium starch glycolate. The formulations were prepared and the granules were evaluated for pre-compression parameters such as angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The results showed that all the physical parameters were within the acceptable limit. The stability study for the formulations showed no significance change in disintegration time, drug content and percentage drug release after stored at 40°C±2°C/75%± 5% RH for the period of 30 days.
- **Mohd Abdul Hadi *et al*[53].,** has developed sustained release tablets of Montelukast sodium by direct compression method using various polymers. The drug excipient mixtures were subjected to pre-formulation studies. The tablets were subjected to physicochemical studies, *in- vitro* drug release, kinetic studies and stability studies. FTIR and DSC studies shown there was no interaction between drug and polymers. The physicochemical properties of tablets were found within the

limits. Montelukast sodium is a leucotriene receptor antagonist used for the maintenance treatment of asthma. The drug release from formulations was extended for a period of 12 hrs. The kinetic treatment showed that the release of drug follows first order models. The optimized formulations were subjected to stability studies and shown there were no significant changes in drug content, physicochemical parameters and release pattern. Results of the present study indicated the suitability of the above mentioned polymers in the preparation of sustained release formulation of Montelukast sodium.

- **Janugade *et al*[54].,** was prepared oral press-coated tablet by using direct compression and wet granulation methods to achieve the predetermined lag time. This press-coated tablet containing montelukast sodium in the inner core was formulated with an outer barrier layer by different compositions of hydrophobic polymer ethylcellulose and hydrophilic polymer low-substituted hydroxypropylcellulose. The effect of formulation composition on the barrier layer comprising both hydrophobic and hydrophilic excipients on the lag time of drug release was investigated.
- **Halder A *et al*[55].**, has prepared Loperamide Hydrochloride chewable tablets by wet granulation technique by using croscarmellose sodium, microcrystalling cellulose, lactose monohydrate, magnesium stearate and SLS..etc. It has been found that the prepared tablets showed good physical characteristics, drug content and percentage of drug release.the present work aimed to prepare Loperamide Hydrochloride chewable tablets in combined with simethicone and develop a new sensitive and specific analytical procedure by HPLC suitable for application in a drug quality control.the method of non-aqueous granulation and adsorption of simethicone to dry powder blend improved hardness and provides good physical appearance.

3. AIM AND OBJECTIVE

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site of the body, to achieve promptly and then maintain the desired therapeutic drug concentration that elicits the desired pharmacological action and to minimize the incidence and the severity of unwanted adverse effects.

For many decades, treatment of an acute disease or a chronic illness has been mostly accomplished by delivering drugs using various pharmaceutical dosage forms, including tablets, capsules, pills, suppositories, ointments, creams, liquids, aerosols, and injectables as carriers. Amongst various routes of drug delivery, oral route is perhaps the most preferred to the patients. The oral route of drug administration is the most important method of administering drugs for systemic effects. Nevertheless, it is probable that at least 90% of all drugs used to produce systemic effects are administered by oral route. It is very popular and successfully used for delivery of drugs because of convenience and ease of administration, greater flexibility in dosage form design, and ease of production and low cost of such a system.

Chewable tablets are intend to be chewed in the mouth prior to swallowing and are not intended to be swallowed intact. The purpose of chewable tablet is to provide a unit dosage form of medication which can be easily administered to children or to the elderly, who may have problem in swallowing a tablet intact. It is also recommended to achieve rapid onset of action. Chewable tablets are preferred for the drugs having high dose, the tablets of which cannot be swallowed.

Conversely, many patients are not able to tolerate the taste of many drugs when formulated as liquid dosage forms, thus leading to poor patient compliance in those cases. Lately recent developments in dosage form technology are concentrating on presenting the patient with variable dosage alternatives which provide good palatability and ease of administration at same time. This is especially valid when the preparation is to be administered to an infant or to an elderly patient.

Hence it was decided to formulate Montelukast chewable tablets to improve the compliance in children and elderly patients. Additionally, chewable tablet facilitate more rapid release and hence more rapid absorption of active ingredients and provide quick onset of action.

Montelukast sodium is a Leucotriene receptor antagonist used for the treatment of asthma. Montelukast blocks the action of Leucotriene D4 on the cysteinyl Leucotriene receptor in the lungs and bronchial tubes by binding to it. Its biological half life 2.7 to 5.5 hrs.

The main objective of the present study was to formulate and evaluate Montelukast chewable tablets dosage form at the dose of 5 mg and to study the various formulation variables that affect the drug release by using the following exicipients like Mannitol, Microcrystalline cellulose, Croscarmellose sodium, Aspartame, Magnesium stearate, Cherry black, Euroxide and Red iron oxide .

4. PLAN OF WORK

Preformulation studies

Design and development of chewable tablet by direct compression method using superdsintigrants in different concentration. Prepared Chewable tablets of Montelukast sodium will be subjected for the following evaluation parameters.

I. Pre-compression parameters

1. Angle of repose
2. Bulk density
3. Tapped density
4. Carr's index
5. Hausner ratio
6. Compatibility study

II. Post-compression parameters

1. Appearence
2. Thickness
3. Hardness test
4. Friability test
5. Weight variation test
6. *In-vitro* dissolution studies
7. Stability studies

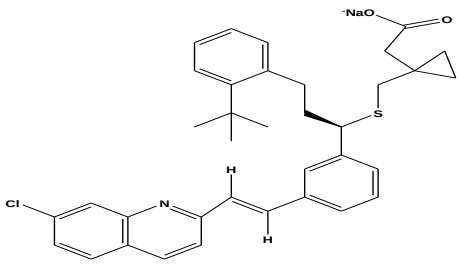
5. DRUG AND EXCIPIENTS PROFILE

1. Montelukast sodium[56-60]

Montelukast is a Leucotriene Receptor Antagonist (LTRA) used for the maintenance treatment of asthma and to relieve symptoms of seasonal allergies. It is usually administered orally.

Montelukast blocks the action of leukotriene D4 on the cysteinyl leukotriene receptor CysLT1 in the lungs and bronchial tubes by binding to it. This reduces the bronchial constriction caused by the leucotriene and results in less inflammation. Because of its method of operation, it is not useful for the treatment of acute asthma attacks. Again because of its very specific locus of operation, it does not interact with other allergy medications such as theophylline.

Structure



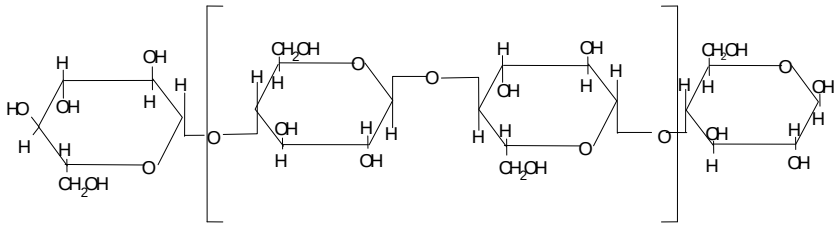
IUPAC Name: 2-[1-[[(1R)-1-[3-[(E)-2-(7-chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(2-hydroxypropan-2-yl)phenyl]propyl]sulfanylmethyl]cyclopropane]acetate.

Physical and chemical properties

Description	**:**	Hygroscopic, white to off-white powder
Empirical formula	**:**	$C_{35}H_{36}ClNO_3S$
Molecular weight	**:**	586.18324 g/mol (608.17 sodium salts)
Category	**:**	Antihistaminic
Chemical nature	**:**	Montulukast sodium is an sulfanylmethyl] cyclopropyl]acetic acid
Solubility	**:**	Freely soluble in ethanol, methanol, water. Practically insoluble in acetonitrile

2. Microcrystalline Cellulose (Avicel)

Structural formula



Microcrystalline Cellulose

Physical and chemical properties

Description : **W**hite, odourless, tasteless, crystalline powder composed of porous particles.

Empirical formula : $(C_6H_{10}O_5)n$, n=220

Molecular weight : 36,000(approx)

Functional Category: Tablet and capsule diluent, tablet disintegrant, suspending and/or viscosity increasing agent.

Solubility : Insoluble in water, dilute acids and most organic solvents, slightly soluble in 5% w/v NaOH solution.

Synonyms : Cellulose gel, Crystalline cellulose, Avicel PH101, 102, **Density** : Apparent density - 0.28g/cm^3

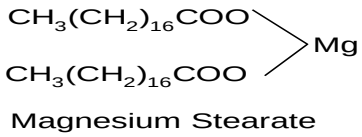
Tap density - 0.43g/cm^3

Applications:

Tablet binder/diluent (wet or dry granulation)	:	5 to 20%
Tablet disintegrant	:	5 to 15%
Tablet glidant	:	5 to 15%
Antiadherent	:	5 to 20%

3. Magnesium Stearate

Structural Formula



Magnesium Stearate

Physical and chemical properties

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

Empirical formula **:** $C_{36}H_{70}MgO_4$

Molecular weight **:** 591.3

Functional category **:** Tablet and capsule lubricant.

Solubility **:** Practically insoluble in ethanol, ethanol (95%), ether and water, slightly soluble in benzene and warm ethanol (95%).

Synonyms **:** Metallic stearic; Magnesium salt.

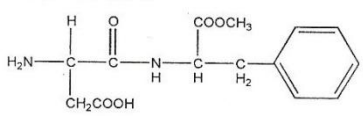
Density **:** Bulk volume : 3.0-8.4 ml/g

Tapped volume : 2.5-6.2 ml/g

Applications **:** Tablet and capsule lubricant, glidant and antiadherent in the concentration range of 0.25 to 5.0%.

4. Aspartame

Structural Formula



N-a-L-Aspartyl-L-phenyialanine 1-methyl ester

Physical and chemical properties

Description **:** Aspartame occurs as an off white, almost odorless crystalline powder with an intensely sweet taste

Empirical Formula **:** $C_{!4}H_{18}N_2O_5$

Molecular Weight **:** 294.31

Functional Category: Sweetening agent.

Solubility **:** Soluble in water and organic solvents

Synonyms **:** 3-Amino-N-(a-carboxyphenethyI)succin amicacid IV-merhyl ester, 3-amino-N-(a-methoxycarbonyl phenethyl) succinamic acid Aspartyl phenylamine methyl ester methyl N-a-L-aspartyl-l.-henylalaninate

Applications in Pharmaceutical Formulation or Technology

Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets, powder mixes, and vitamin preparations, it enhances flavour systems and can be used to mask some unpleasant taste.The approximate sweetening power is 180-200 times that of sucrose.Therapeutically, aspartame has also been used in the treatment of sickle cell anemia.

Table No 4: Pharmacopeia Specifications.

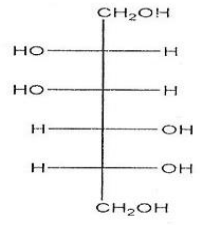
Test	PhEur2005	USPNF23
Characters	+	-
Identification	+	+
Appearance of solution	+	-
Conductivity	≤ 30μS/cm	-
Specific optical rotation	+14.5-+16.5	+14.5-+16.5
Related substances	+	-
Heavy metals	≤ 10ppm	≤ 0.001%
Loss on drying	≤ 4.5%	≤ 4.5%
Sulfoted ash	≤ 0.2%	≤ 0.2%
Im purl lies	+	-
Transmittance	-	+
Limit of 5-benzyl-3,6-dioxo-2-piperazineacetic acid	-	≤ 1.5%
Organic volatile impurities	-	+
Assay	98.0-102.0%	98.0-102.0%

+ indicates Presents, -- indicates Absent

5. Mannitol

Structural Formula

D-Mannitol



Physical and chemical properties

Description

Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol. 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 appears as orthorhombic needles when crystallized from alcohol. Mannitol shows polymorphism.

Empirical Formula	**:**	$C_6H_{14}O_6$
Molecular Weight	:	182.17
Functional Category	**:**	Diluent,diluent for lyphilizcd preparations, Sweetening agent, tablet and capsule diluents, tonicity agent.
Synonyms	**:**	Cordycepic acid,manna sugar, D-mannite, mannite, Mannogem, Pearlitol

Applications in Pharmaceutical Formulation or Technology

Mannitol is widely used in pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10-90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus it is used with moisture-sensitive active ingredients.

Mannitol may be used in direct-compression tablet applications for which the granular and spray-dried forms are available, or in wet granulations. Granulations containing mannitol have the advantage of being dried easily. Specific tablet applications include antacid preparations, glyceryl trinirrate tablets, and vitamin preparations. Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of

solution, sweetness, and 'mouth feel'. In lyophilized preparations, mannitol (20-90% w/w) has been included as a carrier to produce a stiff, homogeneous cake that improves the appearance of the lyophilized plug in a vial. A pyrogen-free form is available specifically for this use.

Mannitol has also been used to prevent thickening in aqueous antacid suspensions of aluminum hydroxide (<7% w/v). It has been suggested as a plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulations, and as a carrier in dry powder inhalers. It is also used as a diluent in rapidly dispersing oral dosage forms. It is used in food applications as a bulking agent.

Therapeutically, mannitol administered parenterally is used as an osmotic diuretic, as a diagnostic agent for kidney function, as an adjunct in the treatment of acute renal failure, and as an agent to reduce intracranial pressure, treat cerebral edema, and reduce intraocular pressure. Given orally, mannitol is not absorbed significantly from the GI tract, but in large doses it can cause osmotic diarrhea.

Typical properties

Bulk Density **:** 0.430g/cm^3 for powders
0.7g/cm^3 for granules

Tapped density **:** 0.734g/cm^3 for powders
0.8 g/cm^3 for granules

Table No 5: Pharmacopeial specification for mannitol

Test	JP 2001	Ph Eur2005	USP28
Characters	-	+	+
Identification	+	+	+
Appearance of solution	+	+	-
Melting range	166-169 ^oC	165-170 ^oC	164-169 ^oC
Conductivity	-	≤ 20µS/cm	-
Specific optical rotation	$+137^o$ - $+145^o$	$+23^o$ - $+25^o$	$+137^o$ - $+145^o$
Related substances	-	≤ 0.1%	-
Heavy metals	≤ 5ppm	-	-
Loss on drying	≤ 0.3 %	≤ 0.5 %	≤ 0.3 %
Acidity	+	-	+

Test	JP 2001	Ph Eur2005	USP28
Assay	≥ 98.0 %	98.0-102.0%	96.0-101.5 %
Sulfate	≤ 0.01%	-	≤ 0.01%
Arsenic	≤ 1.3 ppm	-	≤ 1 ppm
Lead	-	≤ 0.5 ppm	-
Nickel	+	≤ 1 ppm	-
Chloride	≤ 0.007 %	-	≤ 0.007 %
Reducing Sugars	+	≤ 0.2%	+
Residue on ignition	≤ 0.1%	-	-
Bacterial endo toxins	-	≤ 4 IU/g[(a)]	-
Microbial contamination	-	≤ 100/g	-

6. Croscarmellose Sodium

Description

Croscarmellose sodium is a cross linked polymer of carboxymethyl cellulose sodium. Cross linking makes it an insoluble, hydrophilic, highly absorbent material, resulting in excellent swelling properties and its unique fibrous nature gives it excellent water wicking capabilities. Croscarmellose sodium provides superior drug dissolution and disintegration characteristics, thus improving bioavailability of formulations.

Empirical Formula

Percentage of sodium chloride : 584.4VN/[(100–b)W]

Percentage of sodium glycolate :12.9w/[(100–b)W]

Degree of acid carboxymethyl substitution(A) : 1150M/(7102–412M–80C)

Degree of sodium carboxymethyl substitution(S) :(162+58A)C/(7102–80C).

Functional category : Disintegrant for Capsules, Tablets and Granules

Solubility : It is easily dispersed in water to form colloidal solutions.

Insoluble in alcohol, in ether, and in most other organic solvents.

NF category: Coating agent, suspending and/or viscosity-increasing agent,wet binder, film-forming agent, release-modifying agent, disintegrant.

Synonyms **:**Croscarmellose sodium, modified,
croscarmellose natrium,
Cross-linked carboxymethylcellulose sodium

Applications

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for Capsules, Tablets and Granules. In tablet formulations, Croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations the Croscarmellose sodium is best added in both the wet and dry stages of the process (intra- and extra granularly) so that the wicking and swelling ability of the disintegrant is best utilized. Concentrations of up to 5% w/w of Croscarmellose sodium may be used as a tablet disintegrant although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

Table no:6 Croscarmellose sodium phycio-chemical properties

Croscarmellose Sodium	
Identification	
A	Methylene blue - Blue fibrous mass
B	1-Nepthol - Red-purple colour at interface
C	K-Antimonate-Sodium test positive
Ph	5.0 - 7.0
Loss on Drying, NMT %	10
Sodium Chloride and Sodium Glycollate, sum NMT %	0.5
Heavy Metals, NMT %	0.001
Degree of Substitution	0.60 - 0.85
Content of Water Soluble Material, %	1.0 - 10.0
Settling Volume, ml	10.0 - 30.0
Organic Volatile Impurities	Meets the requirement

7. Euroxide Red Iron Oxide

Ferric oxide red is used in oral pharmaceutical formulations to impart a distinctive appearance to the tablet of capsule. It is also useful in identification of products with different strengths and aesthetic appearance etc.

8. Cherry Flavour

Cherry flavour functions as aflavour for improving the palatability of the chewable tablet formulation. It also acts as a taste masking agent.

6. MATERIALS AND METHODS

6.1 Source of data

The Physicochemical properties of drug will be collected from the national and international journals, Internet facilities, Related articles, and Standard books from library of the college.

6.2 Procurement of Drug and Excipients

The following materials and instruments used in the experiment are of laboratory grade.

Table No 7: Details of Materials used

Sl. No.	Materials	Grade	Supplier
1.	Montelukast sodium	Pharma	Shasun Drugs and Pharmaceuticals limited
2.	Mannitol	Pharma	Roquette Freres
3.	Microcrystlline cellulose	Pharma	FMC Biopolymer
4.	Croscarmellose sodium	Pharma	FMC Biopolymer
5.	Aspartame	Pharma	The Nutra Sweet Company
6.	FLV ART Cherry 501027APO551	Pharma	The Sensient PharmaChem Technology
7.	Euroxide Red *Iron oxide (E7016)*	Pharma	The Sensient PharmaChem Technology
8.	Magnesium stearate	Pharma	Peter Greven Netherland

6.3 Instruments and Equipments used

Table No 8: Details of equipments used

Sl. No.	Instruments	Manufacturer/ Suppliers
1.	FTIR Spectrophotometer.	Shimadzu 1800
2.	Rotary Compression machine	Clit Pilot press Chamnnda
3.	Dissolution test Apparatus	Electrolab, USP TDT 06P
4.	Disintegration Tester	Electro lab
5.	Hot air Oven	Lawrence & Mayo
6.	Friability Tester	Electro lab, USP EF 2
7.	Hardness Tester	Monsanto
8.	Bulk density Apparatus (digital)	KE India
9.	Digital pH meter	Hanna instrument
10.	Vernier calliper	Pico India Ltd
11.	Digital Analytical balance	Mettle Toledo
12.	HPLC	Shimadzu

7. EXPERIMENTAL WORK

7.1 Method of collection of data

- To develop the formulation and estimation of Montelukast Sodium in suitable pH solution.
- Preformulation studies including solubility, compatibility with the excipients.
- To evaluate the physical properties of powder blend of tablet batches such as angle of repose, bulk density, tapped density, compressibility index and hausner's ratio.
- Evaluation of Montelukast Sodium chewable tablets for the parameters such as description, hardness, friability, thickness, disintegration time, drug content, drug release and uniformity of weight.
- *In vitro* release characteristics of Montelukast Sodium from the chewable tablets by dissolution test.
- Short term stability studies of prepared formulations as per ICH guidelines.
    - **Controlled room temperature**: 25°C ± 2°C/60% RH ± 5% RH
    - **Accelerated conditions**: 40°C ± 2°C/75% RH ± 5% RH
    - **Stress testing** is conducted on a single batch of the tablets. The study includes testing the effect of temperature at 50°C, 60°C, etc. and humidity at 75% RH or greater as the drug is heat sensitive.
    - **Packing system**; The stability studies will be conducted on the drug substance packaged in a container.

7.2 Physico-chemical properties of Montelukast Sodium

7.2.1 Appearance

The sample of Montelukast Sodium is white or almost white, odourless crystalline powder.

7.2.2 Solubility

Montelukast sodium is freely soluble in water. The solubility in water is 8.553 mg/mL. The aqueous solubility as a function of pH at 37°C is studies at various pH and the data presented in table.

Table No: 9 Solubility of Montelukast sodium in various media

Medium used	pH of Media	Solubility (mg/mL)	Solubility (mg/250 mL)
Water	6.80	8.553	2138.25
0.5% SLS in water	6.00	15.114	3778.5
0.001N HCl	6.56	Insoluble	Insoluble
0.01N HCl	2.95	Insoluble	Insoluble
0.1N HCl	1.25	Insoluble	Insoluble
pH 2.50 phosphate buffer	2.50	Insoluble	Insoluble
pH 3.00 Phosphate buffer	3.00	Insoluble	Insoluble
pH 3.50 Phosphate buffer	3.50	Insoluble	Insoluble
pH 4.00 Phosphate buffer	4.00	Insoluble	Insoluble
pH 4.50 Phosphate buffer	4.50	Insoluble	Insoluble
pH 5.00 Phosphate buffer	5.00	Insoluble	Insoluble
pH 5.50 Phosphate buffer	5.50	Insoluble	Insoluble
pH 6.00 Phosphate buffer	6.00	Insoluble	Insoluble
pH 6.50 Phosphate buffer	6.50	Insoluble	Insoluble
pH 7.00 Phosphate buffer	7.00	Insoluble	Insoluble
pH 7.50 Phosphate buffer	7.50	Insoluble	Insoluble
pH 8.00 Phosphate buffer	8.00	0.001	0.001
SIF	6.80	Insoluble	Insoluble
SGF	1.20	Insoluble	Insoluble
pH 4.5 Acetate buffer	4.50	Insoluble	Insoluble

7.2.3 Water content

Montelukast sodium drug substance was reported to be hygroscopic and the water content was found to be 5.48%.

7.2.4 Hygroscopicity Study

1 gm of the drug was kept in pre-weighed petridish in duplicate and was exposed to humidity condition of 40°C and 75% RH in order to assess the moisture uptake tendency. The moisture gain was calculated from the weight gained by the drug after periodic interval.Many compounds and salts are sensitive to the presence

of water vapour or moisture when compounds interact with moisture, they retain the water by either bulk or surface adsorption, capillary condensation, chemical reaction and, extreme cases a solution (deliquescence).

Moisture is also an important factor that can affect the stability of the drugs and their formulations. Absorption of water molecules into a drug (or excipient) can obtain includes hydrolysis.The influence that moisture has on stability depends on how strongly it is bound, that is, it depends on whether the moisture is in a free or bound state.

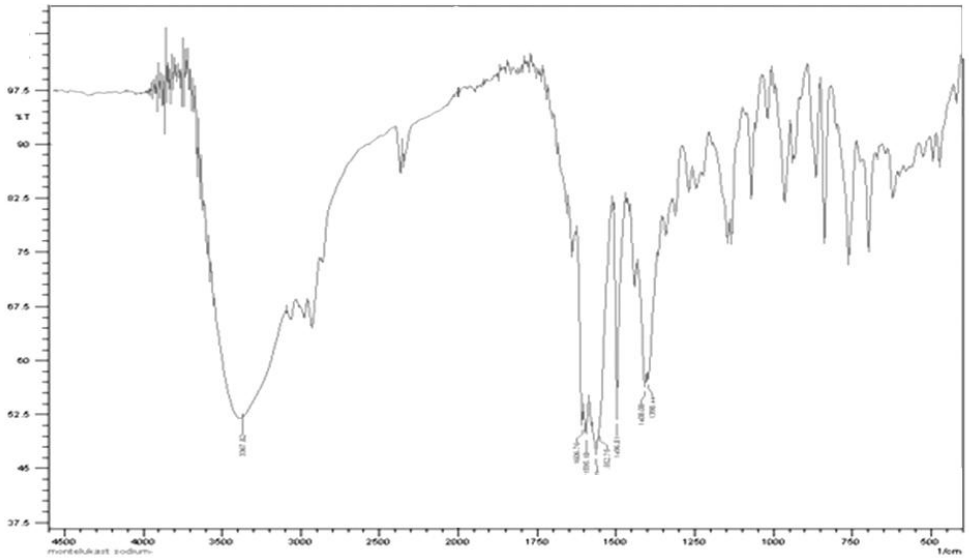
Table No:11 Hygroscopicity Classifications

S.No.	Class	Type	Remarks
1	Class1	Non-hygroscopic	Essentially no moisture increase occur at RH below 90%
2	Class2	Slightly hygroscopic	Essentially no moisture increase occur at RH below 80%
3	Class3	Moderately hygroscopic	Moisture content does not increase more than 5% after storage for one week at RH below 60%
4	Class4	Hygroscopic	Moisture content increase may occur at RH as low 40 to 50%

If a compound is very hygroscopic, proper care should be taken to process it in such a way to minimize the effect of moisture.

7.2.5 Identification of Montelukast sodium by IR

Chemical interactions between the drug and excipients may change the potency and therapeutic efficacy of the drug. To investigate the possibilities of chemical interaction between drug and excipients. FTIR spectra of pure drug and optimized formulation were analyzed over the range 400-4000cm^{-1}.



Picture:2 IR spectrum of Montelukast sodium

7.3 Drug and Excipient Compatibility Studies [54,55]

A drug excipient compatability study was performed to evaluate compatibility of Montelukast sodium drug substance with different excipients. Excipients were individually combined with the drug substance and exposed to solid-state stress conditions (heat, light, heat/high humidity).

The compatibility of various drug substance / excipient combinations was studied for all excipeints which were considered to find potential use in Montelukast chewable tablet formulation. The table below summarizes the compatability study results for the various excipients proposed to be employed in the formulation of Montelukast chewable tablets.

Table No:10 Drug and Excipient Compatibility Studies

Sample	Interval/ condition	Assay (%)	Water content (%)
Montelukast sodium	Appearance	White powder	
	Initial	99.52	6.46
	14 Days -40°C/75% RH	99.47	7.58
	14 Days – 60°C	99.46	7.25
	28 Days – 40°C/75% RH	99.38	8.22
	28 Days – 60°C	99.28	7.00

Montelukast sodium + Microcrystalline cellulose PH 102	Appearance	White powder	
	Initial	99.59	6.18
	14 Days – 40°C/75%RH	99.39	7.17
	14 Days – 60°C	91.25	6.05
	28 Days – 40°C/75% RH	99.12	6.91
	28 Days – 60°C	87.10	6.32
Montelukast Sodium + Mannitol	Appearance	White powder	
	Initial	98.42	0.85
	14Days – 40°C/75%RH	99.36	1.11
	14 Days – 60°C	99.00	0.74
	28 Days – 40°C/75% RH	98.60	1.24
	28 Days – 60°C	99.24	0.92
Montelukast Sodium +Croscarmellose sodium	Appearance	White powder	
	Initial	99.58	1.97
	14 Days – 40°C/75%RH	99.54	3.54
	14 Days – 60°C	99.35	3.47
	28 Days – 40°C/75% RH	99.49	4.64
	28 Days – 60°C	99.07	4.75
Montelukast sodium + Aspartame	Appearance	White powder	
	Initial	99.60	3.10
	14 Days – 40°C/75%RH	99.35	4.79
	14 Days – 60°C	97.98	3.69
	28 Days – 40°C/75% RH	99.25	3.60
	28 Days – 60°C	97.26	4.28
Montelukast sodium +Red ferric oxide	Appearance	Pink colored powder	
	Initial	99.59	6.17
	14 Days – 40°C/75%RH	99.51	7.28
	14 Days – 60°C	99.47	5.84
	28 Days – 40°C/75% RH	99.41	7.47
	28 Days – 60°C	99.29	5.69
Montelukast sodium +Cherry Flavor	Appearance	White powder	
	Initial	99.48	5.64

	14 Days – 40°C/75%RH	99.38	7.58
	14 Days – 60°C	98.50	6.32
	28 Days – 40°C/75% RH	99.26	6.29
	28 Days – 60°C	99.41	5.89
Montelukast sodium +Magnesium stearate	Appearance	White powder	
	Initial	99.41	6.40
	14 Days – 40°C/75%RH	99.36	7.27
	14 Days – 60°C	99.15	7.59
	28 Days – 40°C/75% RH	99.24	7.74
	28 Days – 60°C	99.01	7.80

All the powder characteristics were good and satisfied according to pharmacopeia.

A physical compatibility study was designed to determine the interaction of the drug with various excipients. The samples that is drug alone and homogeneous mixture of drug and each excipients were kept at accelerated conditions of 40^{o}C in sealed glass vials, and 40^{o}C /75% RH in open and closed glass vials (punctured to enable exposure to RH conditions for four weeks).These samples were then periodically examined against a control sample kept at 4^{o}C

25°C, 75% : Sealed vials

40°C, 75% RH (open) : Punched vials

40°C 75% RH (closed) : Sealed vials

60°C (close) : Sealed vials

The ratio for physical mixture of drug and the excipients was selected based on the probable concentration of the excipients in stable formulation.

7.4 Pre-compression parameters for powder blend

7.4.1 Flow Properties

The flow properties of powder are critical for an efficient tabletting operation. Interparticulate interactions that influence bulking properties of the powder are also interaction that interferes with flow of powder. A comparison of

bulk density and tapped density gives a measure of relative importance of these interactions in a given powder.

7.4.2 Bulk Density

Calculated amount of the model drug was introduced in a 100ml graduated cylinder. Powder level was noted without compacting shows in table-19, Bulk density was calculated using the following equation:

Bulk density = M/V_o

M =Mass of the test sample

V_o =Unsettled apparent volume

7.4.3 Tapped Density

Calculated amount of the model drug was introduced in a 100ml graduated cylinder. Mechanically the cylinder was tapped using the tapped density apparatus by raising the cylinder and allowing it to drop under its own weight that provides a fixed drop of 14+_2 mm at a normal rate of 250 drops per minute. The cylinder was tapped 1250 times initially and tapped volume measured. Tapped density was calculated using the following equation:

Tapped Density = (M)/Vf

M= Mass of test sample

Vf = Final tapped volume

Since the interparticulate interaction that influence the bulking properties of a powder causing interactions that interfere with powder flow, a comparison of the bulk and tapped densities indicate a measure of the relative importance of these interaction in a given powder. Such a comparison is often used as an index of ability of the flow of property.

7.4.4 Compressibility Index (Carr's index)

This parameter is the measure of propensity of powder to be compressed and reflect the relative importance of interparticulate interaction shows in table-19.

$$\text{Carr's Index} = \frac{100(TD - BD)}{TD}$$

7.4.5 Hausner Ratio

The **Hausner ratio** is a number that is used to correlate the flow ability of drug substance.

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Table No: 11 Flow ability of powder on the basis of Carr's index and Hausner Ratio

Carr's Index	Flow character	Hausner ratio
<10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>32	Very, very poor	>1.60

The powder flow properties of API were studied to evaluate compressibility of the drug since it is formulated as tablet. The result of various parameters of flow properties of the API are shown in table.

7.4.6 Angle of Repose (θ)

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose.

$\tan \theta = h / r, \quad \theta = \tan^{-1} (h/r)$

Where, θ is the angle of repose,

h is height of pile

r is radius of the base of pile

Different ranges of flow ability in terms of angle of repose are given in table no. 8.

Table No :12 Relationship between Angle of Repose (θ) and flow properties.

Angle of Repose (θ) (degrees)	Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Method

A funnel was filled to the brim and the test sample was allowed to flow smoothly through the orifice under gravity. From the cone formed on a graph sheet was taken to measure the area of pile, thereby evaluating the flowability of the granules. Height of the pile was also measured.

7.5 Optimization of diluents, disintegrant and lubricant concentration:

Microcrystalline cellulose is a versatile ingredient playing multiple roles in the formulations. Depending on the concentrations used, it can act as a diluent or disintegrant. It aids in flow of the blend and is also an important ingredients in direct compression techniques for tabletting. The optimization of microcrystalline cellulose for Montelukast sodium chewable tablets 5 mg was done by varying the concentrations of microcrystalline cellulose i.e 0 %, 5 %, 10 %,20 % and 27 %.

Croscarmellose sodium is used as a disintegrant in tablets and capsules formulations. Three different trials were taken with various concentrations of Croscarmellose sodium i.e. 0.5 %, 1% and 3 % in the formulation of Montelukast sodium chewable tablets.

Magnesium stearate is used as a lubricant in tablets and capsules formulations. Three different trials were taken with various concentrations of magnesium stearate i.e. 1.25 %, 1.50 % and 1.75 % in the formulation of Montelukast sodium chewable tablets.

Table No: 13 Percentage concentration of excipients used in the various formulations

Name of ingredients	**% F1**	**% F2**	**% F3**	**% F4**	**% F5**	**% F6**	**% F7**	**% F8**	**% F9**	**% F10**
Montelukast sodium	1.73	1.73	1.73	1.73	1.73	1.73	1.73	1.73	1.73	1.73
Mannitol	91.87	87.07	82.12	72.12	65.00	89.57	89.07	87.07	87.32	86.82
MCC(Diluent)	0.00	5.00	10.00	20.00	27.00	5.00	5.00	5.00	5.00	5.00
CCS (Disintegrant)	3.00	3.00	3.00	3.00	3.00	0.50	1.00	3.00	3.00	3.00
Aspartame	0.50	0.50	0.50	0.50	0.50	0.50	1.00	1.00	1.00	1.00
Cheery Black	1.00	1.00	1.00	1.00	1.00	1.00	0.50	0.50	0.50	0.50
Euroxide iron oxide	0.40	0.20	0.15	0.15	0.15	0.60	0.20	0.20	0.20	0.20
Magnesium stearate	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.25	1.75
Total tablet weight	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

7.6 Formulation design

The formula for preparation of Montelukast sodium chewable tablets by direct compression

Table No: 14 Qualitative and quantitative composition

Name of ingredients	**Quantity in mg/ tablet and percentage**									
	F 1	**%**	**F 2**	**%**	**F 3**	**%**	**F4**	**%**	**F 5**	**%**
Montelukast sodium	5.20	1.73	5.20	1.73	5.20	1.73	5.20	1.73	5.20	1.73
Mannitol	275.6	91.87	261.2	87.07	246.35	82.12	216.35	72.12	195.00	65.00
Microcrystalline cellulose	0.00	0.00	15.00	5.00	30.00	10.00	60.00	20.00	81.35	27.00
Croscarmellose sodium	9.00	3.00	9.00	3.00	9.00	3.00	9.00	3.00	9.00	3.00
Aspartame	1.50	0.50	1.50	0.50	1.50	0.50	1.50	0.50	1.50	0.50
Cheery Black	3.00	1.00	3.00	1.00	3.00	1.00	3.00	1.00	3.00	1.00
Euroxide iron oxide	1.20	0.40	0.60	0.20	0.45	0.15	0.45	0.15	0.45	0.15
Magnesium stearate	4.50	1.50	4.50	1.50	4.50	1.50	4.50	1.50	4.50	1.50
Total tablet weight	**300**	**100**	**300**	**100**	**300**	**100**	**300**	**100**	**300**	**100**

Continued…..

Name of ingredients	Quantity in mg/ tablet and percentage									
	F 6)	**%**	**F 7**	**%**	**F 8**	**%**	**F 9**	**%**	**F 10**	**%**
Montelukast sodium	5.20	1.73	5.2	1.73	5.2	1.73	5.20	1.73	5.20	1.73
Mannitol	268.7	89.57	267.2	89.07	261.20	87.07	261.95	87.32	260.45	86.82
Microcrystalline cellulose	15.00	5.00	15.0	5.00	15.00	5.00	15.00	5.00	15.00	5.00
Croscarmellose sodium	1.50	0.50	3.00	1.00	9.00	3.00	9.00	3.00	9.00	3.00
Aspartame	1.50	0.50	3.00	1.00	3.00	1.00	3.00	1.00	3.00	1.00
CherryBlack	3.00	1.00	1.50	0.50	1.50	0.50	1.50	0.50	1.50	0.50
Euroxide red iron oxide	0.60	0.60	0.60	0.20	0.60	0.20	0.60	0.20	0.60	0.20
Magnesium stearate	4.50	1.50	4.50	1.50	4.50	1.50	3.75	1.25	5.25	1.75
Total tablet weight	**300**	**100**	**300**	**100**	**300**	**100**	**300**	**100**	**300**	**100**

7.7 Direction compression process [56]

Tablets was decided to prepared by either Direct compression method.

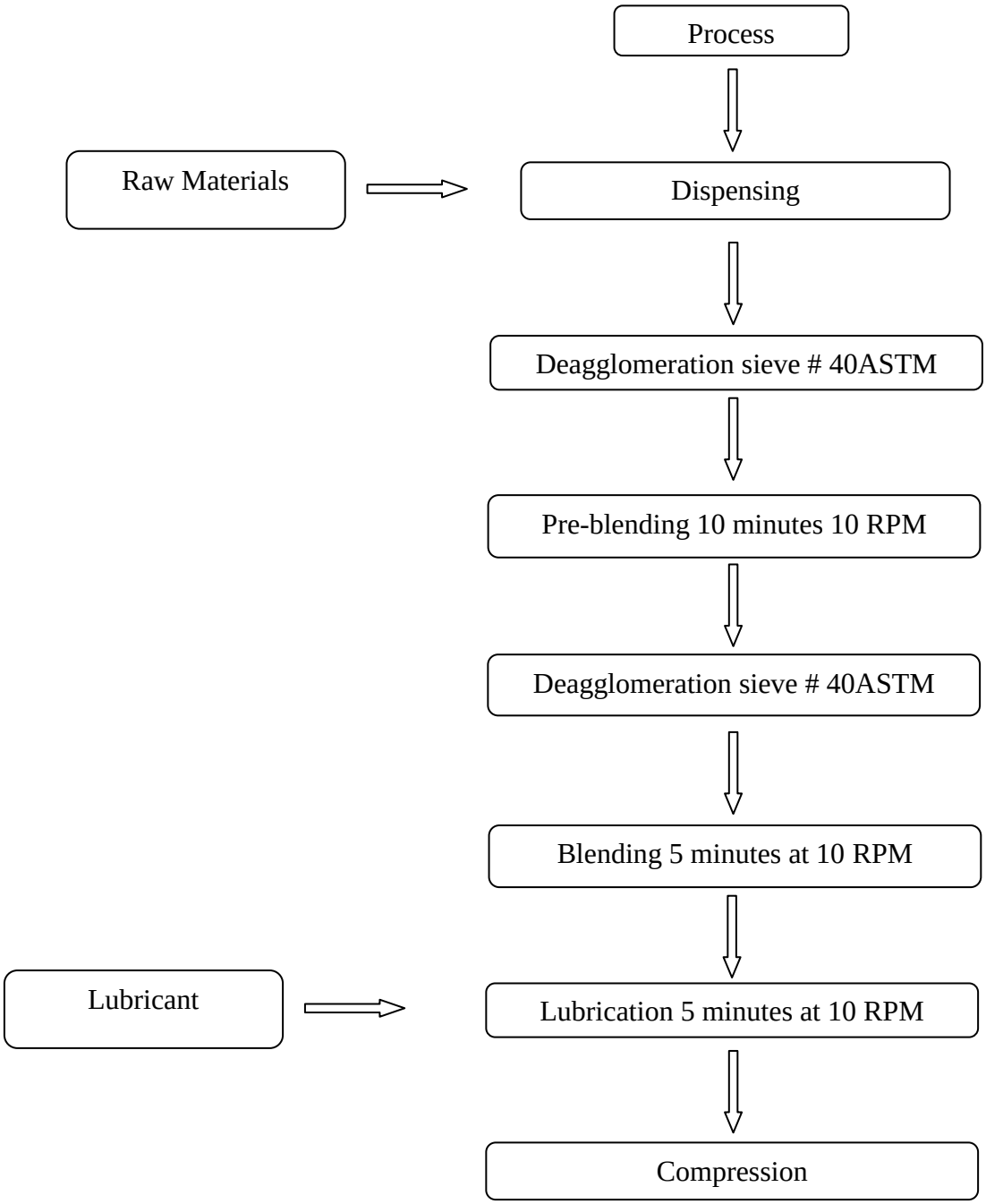
Table No: 15 Composition of Core Tablet

Materials	%w/w of the total weight of the Tablets	Mg/tablet	Function
Montelukast Sodium	1.73	5.20	API
Mannitol	87.1	261.20	Diluent
Microcrystalline cellulose	5.0	15.00	Diluent
Croscarmellose sodium	3.0	9.00	Disintegrant
Aspartame	1.0	3.00	Sweetening Agent
Magnesium Stearate	1.5	4.5	Lubricant
Cherry Black	0.5	1.5	Flavouring agent
Euroxide Red Iron Oxide	0.2	0.6	Colorant
Total Tablet Weight	100	300	--

All ingredients should be taken within the limits

7.8 Manufacturing process of Montelukast chewable Tablets

Flow diagram of the manufacturing process



7.9 Evaluation of Tablets

7.9.1 Shape and colour[58]

Uncoated tablets were examined under a lens for the shape of the tablet and colour was observed by keeping the tablets in light.

7.9.2 Thickness[59]

The crown thickness of individual tablet may be measured with a vernier caliper, which permits accurate measurements and provides information on the variation between tablets. Other technique employed in production control involves placing 5 or 10 tablets in a holding tray, where their total crown thickness may be measured with a sliding caliper scale. The tablet thickness was measured using vernier caliper.

7.9.3 Hardness test [60]

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

7.9.4 Friability test[61]

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The percentage friability was then calculated by,

$$F = \frac{W(initial) - w(final)}{W(initial)} \times 100$$

% Friability of tablets less than 1% is considered acceptable.

7.9.5 Weight variation test[62]

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The percentage deviation in weight variation is shown in table no 10.

Table No :16 Percentage deviation in weight variation

Average weight of a tablet	Percentage deviation
130 mg or less	10
More than 130 mg and less than 324 mg	7.5
324 mg or more	5

In all the formulations the tablet weight was more than130mg and less than 324 mg, hence 7.5% maximum difference allowed.

7.9.6 In-*vitro* disintegration time

The process of breakdown of a tablet into smaller particles is called as disintegration. The *in-vitro* disintegration time of a tablet was determined using disintegration apparatus as per I.P. specifications.

Method

For a drug to be absorbed from a solid dosage form after oral administration, it must first be in solution, and the first important step toward this condition is usually the break-up of the tablet, a process known as disintegration. The disintegration time of chewable tablets was determined in accordance with the official "United status of pharmacopoeia Chewable tablets" stating a maximum disintegration time of 5 minutes (USP 36).

One tablet in each of the 6 tubes of the basket is to be placed and the apparatus subjected to run. The assembly should be raised and lowered between 50 cycles per minute. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

Disintegration or more specifically dispersion times were measured in 900 ml purified water according to the I.P. method without using disc at room temperature (25°C ± 2°C)

7.9.7 *In-vitro* dissolution studies[63]

In vitro release studies were carried out using tablet USP <711> dissolution test apparatus. Two objectives in the development of *in-vitro* dissolution tests was to show that,

i) Release of the drug from the tablet is as close as possible upto 100% and

ii) Rate of drug release is uniform from batch to batch and is the same as the release rate from those proven to be bioavailable and clinically effective.

Summary of general *in-vitro* dissolution conditions employed throughout the study to determine the *in-vitro* dissolution rate for all the formulation is given in table No 14.

Table No: 17 Summary of general dissolution conditions

Sl. No.	Parameter	Specifications
1.	Dissolution medium	900 ml of 0.5%sodium dodecyl sulphate
2.	Temperature	37°C ± 5°C
3.	Rotation speed	50 rpm
4.	Volume withdrawn	10 ml sample at 5,10,15,20 and 30 minutes
5.	Wavelength	220 nm

7.9.8 Dissolution by HPLC

Mobile phase

Solution A: Add 1.0 ml of ortho phosphoric acid (85% or 88%) in 1000 ml of water and mix. Filter and degas.

Solution B: Acetonitrile

Mix the solution A & B in the ratio 40:60 and degas.

Dissolution medium preparation: 0.5 % sodium dodecyl sulphate

Chromatographic condition

Flow rate : 1.5 ml/minute

Injection volume: 50µl

Run time : 6 minutes

Wavelength : 220 nm

Standard and sample preparation

28.6 mg of Montelukast sodium which is equivalent to 27.5 mg of Montelukast, transfer to 50 ml volumetric flask. Add 30 ml of methanol sonicate for 3 minutes to dissolve. Dilute the volume with methanol and mix. Further dilute 5 ml to 50 ml with dissolution medium and mix. Further dilute 5 ml to 50 ml with dissolution medium.

Calculation:

$$\% \text{ Dissolved} = \frac{A_{Spl}}{A_{Std}} \times \frac{\text{Std. wt}}{\text{Std. dilution}} \times \frac{\text{Spl dilution}}{\text{Spl. weight}} \times \frac{\% \text{ purity}}{100} \times \frac{100}{LC} \times \frac{585.18}{608.18}$$

7.9.9 Assay

Standard preparation

Weighed 52 mg of Montelukast sodium standard which is equivalent to 50 mg of Montelukast and transfer into a 100ml volumetric flask. Add about 70 ml of mobile phase and sonicate for 5 minutes to dissolve and make up with mobile phase. Dilute 10 ml of stock solution to 50ml and mix.

Sample preparation

Weighed 10 tablets, transfer into 200 ml volumetric flask and add 150 ml methanol, shake it for 2 mins and mechanically shake for about 20 minutes. Further sonicate for 10 minutes with intermittent shaking and make up with mobile phase. Further dilute 10 ml to 50 ml.

Calculation

$$\% \text{ Dissolved} = \frac{A_{Spl}}{A_{Std}} \times \frac{\text{Std. wt}}{\text{Std. dilution}} \times \frac{\text{Spl dilution}}{\text{No. of tabs}} \times \frac{\% \text{ purity}}{100} \times \frac{100}{LC} \times \frac{585.18}{608.18}$$

7.10 Stability Studies

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications.

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of

environmental factors such as temperature, humidity and light and enables recommended storage conditions, re-test periods and shelf lives to be established.

In the present study, the Montelukast Sodium Chewable Tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

(1) 25 ± 2°C/60±5%RH

(2) 40 ± 2°C/75±5%

The tablets were withdrawn after period of 1, 2 and 3Months and analyzed for physical characterization (Appearance, hardness, friability, disintegration, dissolution etc) and drug content.

8. RESULT AND DISCUSSION

8.1 Solubility of Montelukast Sodium

Highest dose (5.2 mg of Montelukast sodium equivalent to 5 mg of Montelukast) is insoluble over the entire pH range except in water and water containing 0.5% SLS. The highest dose of 5.2 mg of Montelukast Sodium is soluble in 5200 ml which is more than 250 ml. Montelukast sodium is considered as a low soluble drug.

The solubility determination at various time intervals was not feasible as the drug is insoluble in other pH except water and water containing 0.5 % SLS.

Table: 18 Solubility of Montelukast sodium in various media at different time interval

Medium used	pH of Media	Solubility (mg/ml) (Initial)	Solubility (mg/ml) (12^{th} hour)	Solubility (mg/ml) (24^{th} hour)
Water	6.80	8.553	7.361	6.510
0.5% SLS in Water	6.00	15.114	15.083	15.000

8.2 Evaluation of Precompression Parameters

Table: 18 Powder characterization of formulations (F1- F10)

Formulation code	Bulk density (gm/ml) (± SD)	Tapped density (gm/ml) (± SD)	Carr's index (%) (± SD)	Hausner's ratio (± SD)	Angle of repose (± SD)
F1	0.526±0.094	0.666±0.120	21.02±0.03	1.26	29.56±0.04
F2	0.555±0.089	0.666±0.91	16.6±0.074	1.20	26.21±0.079
F3	0.588±0.074	0.714±0.069	17.64±0.065	1.21	27.89±0.051
F4	0.526±0.101	0.666±0.034	21.02±0.094	1.26	29.19±0.067
F5	0.476±0.093	0.588±0.113	19.04±0.093	1.23	27.97±0.084
F6	0.526±0.099	0.666±0.074	21.02±0.099	1.26	25.86±0.044
F7	0.50±0.107	0.558±0.07	14.9±0.107	1.17	25.52±0.021
F8	0.476±0.112	0.555±0.108	14.23±0.034	1.16	27.61±0.099
F9	0.50±0.094	0.625±0.043	20.0±0.0102	1.25	24.12±0.042

Formulation code	Bulk density (gm/ml) (± SD)	Tapped density (gm/ml) (± SD)	Carr's index (%) (± SD)	Hausner's ratio (± SD)	Angle of repose (± SD)
F10	0.501±0.086	0.625±0.09	20.03±0.065	1.25	25.86±0.042

Mean±SD,(n=3)

For the all powder blend of the all formulated batches, the angle of repose was found to be in the range of, thus indicating that the flow properties were fair. Hausner's ratio was less than1.26 for the all batches indicating good flow properties.

8.3 Evaluation of Tablets

Table: 19 Physical Evaluation of Montelukast Chewable Tablets

Parameter	Weight (mg)	Thickness (mm)	Hardness (kp)	Disintegration time(mins' and sec'')	Friability (%)
F1	301-304	4.38-4.32	8-9	3'18''-3'42''	0.18
F2	299-303	4.36-4.39	8-9	43''-50''	0.18
F3	297-303	4.36-4.42	9-11	1'06''-1'20''	0.08
F4	298-303	4.30-4.34	8-9	51''-1'05''	0.01
F5	301-306	4.12-4.4	8-9	50''-57''	0.14
F6	299-301	4.31-4.35	8-9	2'05''-2'27''	0.25
F7	299-301	4.35-4.37	8-10	1'17''-1'25''	0.18
F8	299-303	4.36-4.39	8-9	43''-50''	0.18
F9	301-304	4.39-4.43	8-9	38''-44''	0.13
F10	300-303	4.38-4.39	8-9	47''-53''	0.25

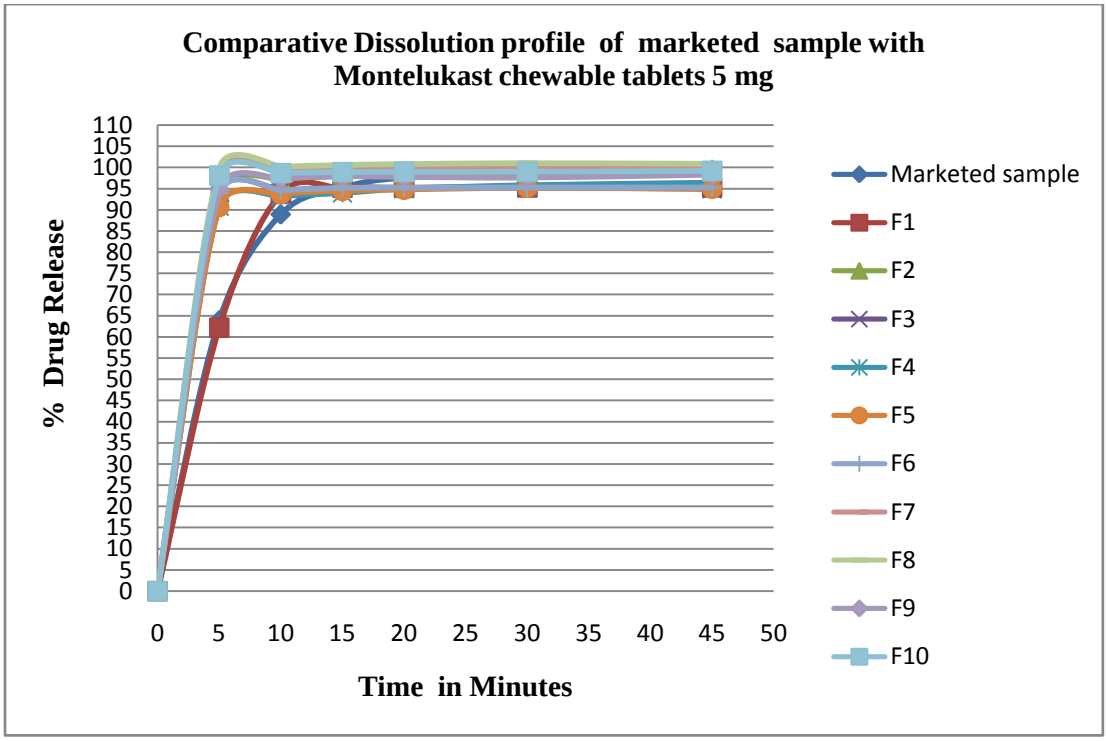
Mean±SD,(n=3)

8.4 Dissolution Profile of Marketed Tablets Vs Montelukast Chewable Tablets.

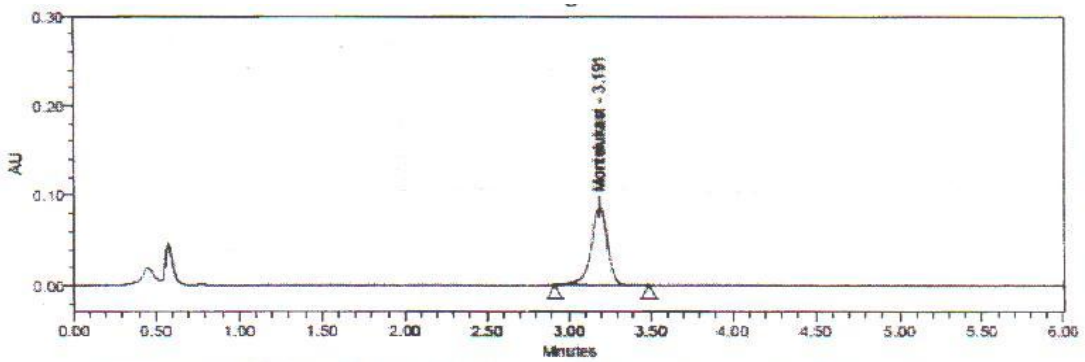
Table: 20 Dissolution Profile of Marketed Tablets Vs Montelukast Chewable Tablets

Percentage of Drug Release at various time points						
Time	**5Minutes**	**10Minutes**	**15Minutes**	**20Minutes**	**30Minutes**	**45Minutes**
Marketed Drug	63.9	88.9	95.2	97.6	98.8	99.3
F1	62.2	93.8	95.2	95.2	95.3	95.3
F2	94.2	97.2	98.0	98.7	99.0	99.6
F3	94.0	94.6	95.2	95.2	95.3	95.0
F4	90.8	93.2	94.0	95.0	95.8	96.4
F5	90.7	93.7	94.5	94.8	95.2	95.0
F6	94.0	94.6	95.2	95.2	95.3	95.3
F7	98.8	99.7	99.9	99.9	100.3	100.2
F8	99.8	100.2	100.6	100.8	101.0	100.9
F9	94.9	97.3	97.9	97.8	97.6	98.3
F10	98.1	98.7	98.9	99.0	99.0	99.2

Comparative dissolution profile of marketed tablets Vs Montelukast Chewable Tablets 5 mg (F1 – F10)



Dissolution: HPLC Chromatogram



	Sample Name	Name	Retention Time (min)	Area (µV*sec)	USP Tailing	USP Plate Count	injection	Vial	Int Type
1	Standard 5mg	Montelukast	3.191	603879	0.9	5331	1	1:2	BB

Stability studies

Table No: 21 Stability data of final formulation-F8 (Accelerated studies)

Storage Condition: Accelerated (40°±2°C/75±5%RH)				
Parameters	Limits	1 month	2 month	3 months
Appearance	Pink coloured, round shaped biconvex tablets	Complies	Complies	Complies
Hardness	8-9 kp	8.5	8.4	8.5
Friability	NMT 1%	0.18	0.19	0.18
Disintegration time	5 minutes	48''	51''	49''
Dissolution	Q=80% at 20 min	99%	95%	98%
Assay	90% - 110%	103%	103.6%	102.8%

Table No: 22 Stability data of final formulation-F8 (Controlled Room Temperature)

Storage Condition: Controlled Room Temperature (25°±2°C/60±5%RH)			
Parameters	Limits	Initial	3 month
Appearance	Pink coloured, round shaped biconvex tablets	Complies	Complies
Hardness	8-9 kp	8.3	8.4
Friability	NMT 1%	0.18	0.19
Disintegration time	5 minutes	50''	51''
Dissolution	Q=80% at 20 min	99%	98%
Assay	90% - 110%	102%	102.3%

Discussion

The formulations were evaluated for pre-compression, post-compression parameters and the values were found to be prescribed limits for all formulations. The angle of repose indicates passable to good flow properties for all the formulations. The results were presented in Table 18.

The compressed tablets were evaluated for various physical parameters such as description, weight variation, thickness, hardness, friability, disintegration time and *in-vitro* dissolution test. The results were presented in Table 19. Weight variation was found in the range of 297 mg to 306 mg, Thickness was found in the range of 4.12 mm to 4.42 mm, Hardness was found in the range of 8 to 11 kp for the all the formulations indicating good mechanical strengths. The percentage friability of all formulations were found in the range of 0.01% to 0.25%, and the value the below 1% is an indication of tablet with good mechanical resistance. The disintegration time of all formulations were found to be in the range of 38 seconds to 3 minutes 42 seconds. The drug content of the all tablets was found in the range of 95.2 % to 101 % of Montelukast sodium, which was with the acceptance criteria.The results were presented in Table 20.

Montelukast sodium chewable tablets from all formulations and marketed sample was subjected to *in-vitro* release studies. The formulation F1- F5 were Prepared with MCC (0 %, 5%, 10%, 20% &27%), CCS (3%) and magnesium stearate (1.5%). The release of the Montelukast sodium from formulations F1- F5 was 95.3%, 99.0%, 95.3%, 95.83% and 95.2 % respectively in 30 minutes.

The formulation F6- F8 was prepared with MCC (5%), CCS (0.5 %, 1 % and 3%) and magnesium stearate (1.5%). The release of the Montelukast sodium from formulations F6- F8 was 95.3%, 100.3% and 101 % respectively in 30 minutes.

The formulation F9- F10 was prepared with MCC (5%), CCS (3%) and magnesium stearate (1.25 % and 1.75 %). The release of the Montelukast sodium from formulations F9- F10 was 97.6% and 99 % respectively in 30 minutes.

The drug release datas of the all formulations were compared with marketed sample of Montelukast sodium. The release of the Montelukast sodium from the Marketed sample was 98.8% at 30 minutes. From the above results of all formulations were well within the limit (Q=80% at 30 minutes as per USP <711>, 2013).

The formulation F8 was stored at 40°C±2°C/75 ± 5%RH, 25°C±2°C/60± 5%RH for 3 months and evaluated for any changes in the Physical appearance, hardness, friability, disintegration time, *in-vitro* dissolution and Assay. The results revealed that there was no significance change in the appearance, hardness, friability, disintegration time, *in-vitro* dissolution and Assay after 3 months. The stability study results were presented in Table 21 and 22.

9. SUMMARY AND CONCLUSION

From the above compiled data it was concluded that pharmaceutical tablets Can be produced by three methods viz, direct compression, dry granulation and wet granulation. Out of these three methods direct compression is the most convenient and cheaper method.

Based on the optimization of the parameters concluded that chewable tablets of Montelukast sodium can be prepared by direct compression method using croscarmellose sodium as superdisintegrants. Chewable tablet of Montelukast sodium with 3% of croscarmellose sodium and 5% of microcrystalline cellulose shown better drug release of 101.0% at 30 minutes. The stability study of Formulation F8 revealed that the drug was stable under accelerated and long term stability conditions for 3 months. Hence the Formula F8 containing Montelukast sodium 5 mg has been formulated as a chewable tablet by direct compression method, which satisfied all the criteria for chewable tablets.

10. BIBLIOGRAPHY

1. Kaur Harbir., Processing Technologies for Pharmaceutical Tablets. International Research Journal of Pharmacy, 2012, 3(7), ISSN: 2230-8407.
2. Rudnic E M and Schwartz J D., Oral Dosage forms Remington. The science and Practice of Pharmacy Gennaro AR (Eds), Lippincott Williams and Wilkins, USA:858.
3. Gohel M C., A Review of co-processed directly compressible excipients. Journal of Pharm. Pharmaceutical sciences, vol.8 :76-93.
4. Lechman L., Liberman H A., Kanig J L., The Theory and Practice of Industrial Pharmacy, 3rd Ed,Varghese Publishing House, Bombay, 1987: 313- 315.
5. Rawlins E A., Bently's text book of pharmaceutics., Eighth edition ELBS.
6. Notari R., BioPharmaceutics and Clinical Pharmacokinetics. 3rd Edn, Marcel Dekker Inc. New York, 1980:152-54.
7. Banker G S and Rhodes C T., Modern pharmaceutics, 3rd Edn. Newyork, Marcel Dekker, INC,1996:205.
8. Rubinstein M H and Aulton M E., Pharmaceutics, The Sciences of dosage form design, Churchill Livingstone Edinburgh London Melbourne and new York:305.
9. Raymond C Rowe., Sheskey., Paul J and Owen Sian C., Hand book of Excipients, 5th edition, 2006 :132-703.
10. Http://drugtopics.modernmedicine.com/drug-topics/news/modernmedicine/modern-medicine-news/overview-pharmaceutical-excipients-used-tablets.
11. Michael E Alton., Pharmaceutical Science of dosage form design, 4th Edn, page 404- 407.
12. Raymond C R., Paul G S., Paul J W., Hand book of pharmaceutical excipients.
13. Banker G S and Rhodes C T., Modern Pharmaceutics, 3rd edn, Newyork, Marcel Dekker, 1996:205.
14. Gowtham Kumar., Dokala C H., Pallavi., Direct Compression-An Overview., International Journal of Research in Pharmaceutical and Biomedical Sciences, Vol. 4 (1), 2013,ISSN: 2229-3701.
15. Herbert A., Liberman., Leon Lachman., Pharmaceutical dosage forms(Tablets), Vol 1, 2nd edition.

16. Khan K A., Rhodes C T., The Production of Tablets by Direct Compression, Can. J. Pharm. Sci.1973, 8: 1-5.
17. Shangraw R F., Demarets D A., Survey of Current Particles in the Formulation and Manufacture of tablets and Capsules, Pharm. Technol 1993, 17: 32-44.
18. Robertson M I., Regulatory Issue with Excipients., International Journal of Pharmacy,1999, 197: 273-276.
19. Gonnissea Y., Remona J P., Vervaet C., Pharmaceutical excipients having improved compressibility, European Journal of Pharmacy 2007, 67: 220-226.
20. Jogani P D., Gohel M C., Review of co-processed Direct Compression of Excipients, Journal of Pharmaceutical Sciences 2005, 8(1): 76-3.
21. Gonul N., The Consolidation and compressibility property of some novel directly compressible Binders & fillers, Ankara University, Acta. Pol. Pharm.2000, 57(4): 311-317.
22. Parot E L., Lachman L., Liberman H A., Kanig J L., Eds Lea and febiger, Theory and Practice of Industrial Pharmacy,1986, 3: 21-46.
23. Fiese E F., Hagen T A., Lachman L., Liberman HA., Kaninig J L., Eds Lea and Febiger, Theory and Practice of Industrial Pharmacy,1986, 3:171-194.
24. Aulton M E., Rowe R C., Weller PJ., Hand book of Pharmaceutical Excipients, The Pharmaceutical Press, UK, 2003:112-114.
25. Rajkumar Gopal., Satyendra Singh Baghel., Ashish Pathak., Kshamashill Sharma., Gourav Tiwari and Rituraj Shihare, A Review on formulation and evaluation of orodispersible tablets (Fast Dissolving tablets),WJPR,2012:1(30).
26. Kanakadurga N., Devi A., Prameela Rani B., Sai Mrudula., Formulation and evaluation of oral disintegrating tablets of Montelukast sodium effect of functionality of superdisintegrants, J P R, 2010, 3(4):803-08.
27. Dineshmohan S., Vanitha K., Ramesh A., Srikanth G., and Akila S., Formulation and Evaluation of Salbutamol Sulphate Fast Dissolving Tablet, IJRPBS, 2010,1(2): 105-108.
28. Jeevanadham S., Dhachinamoorthy D., Chandra Shekar K B., Muthukumaran M., Sriram N., Joyasaruby., Formulation and evaluation of Naproxen sodium Orodispersible tablets, A sublimation technique, AJP,2010, 4(1):48-51.

29. Praveen Khirwadkar., Kamlesh Dashora., A Review: Fast Dissolving Drug Delivery System, Current Developments in Novel System Design and Technology, IJBAR, 2012, 03(12):82-98.
30. Gohel M., Patel M., Amin A., Agrawal R., Dave R and Bariya N, Formulation Design and Optimization of Mouth Dissolve Tablets of Nimesulide using Vacuum Drying Technique, AAPS Pharm.Sci.Tech, 2004, 5(3):36.
31. Vijaykumar Ghorwade., Ajaykumar Patil., Satishkumar Patil., Karunasri Srikonda., Raghavender Kotagiri and Priya Patil., Development and Evaluation of Fast-Dissolving Film of Montelukast Sodium, WJMPBS.,2011,1(1):06-12.
32. Raghavendra Rao N G., and Upendra Kulkarni., Formulation and Design of Fast Dissolving Tablets of Felodipine using Novel Co-Processed Superdisintegrants, IJPRD,2010, 2(9),113-121.
33. Bailey W C., Richards J M., Brooks C M., Soong S J., Windsor R A., Manzella B, A Randomized trial to improve self-management practices of adults with asthma. Arch.Intern. Med. Aug 1990,150(8):1664-8.
34. Barnes PJ, Inhaled Glucocorticoids for asthma, N.Eng.J.Med,1995,332(13):868-75.
35. Busse WW., Calhoun WF., Sedgwick JD., Mechanism of airway inflammation in asthma,1993, 147:S20-4.
36. Nayak A., A Review of montelukast in the treatment of asthma and allergic rhinitis. Expert Opin Pharmacother, Mar 2004,5(3):679-86.
37. Majmudar P A., Conjunctivitis, Allergic, Medicine Word Medical Library.
38. ICH guidelines Q1A (R2)., Guidance for industry stability testing of new drug substance and products (Available on: http://http.//www.ich.org.).
39. Agarwal SP., Ragesh Khanna., Physical Pharmacy, New Delhi, CBS Publishers and distributer, 2th Edn, 2000: 247.
40. Suryakant B., Jadhav., Sakarkar., Datta R., Kaudewar, Der. Pharmacia Sinica,2011,26:23-31.
41. Priyanka., gowri., Formulation development and evaluation of Montelukast sodium chewable tablets, Journal of Chemical and Pharmaceutical Sciences, Vol.6,1:35-40.
42. Kaur Harbir et al., Processing technologies for pharmaceutical tablets, International Research Journal of Pharmacy 3(7), 2012:20-23.

43. Swati J., Mahesh G., Dhaval B., Bhanudas K., Aniruddha C., Formulation and Evaluation of chewable tablet of levamisole, Int. J. Res. Pharm.Sci 2010,1(3):282-289.
44. Kanaka D N., Prameela R A., Radha M B., Sai M B., Formulation and evaluation of montelukast sodium chewable tablets, Int. J. Pharm. Sci. Bio, 2010,1(1):20-4.
45. Kathiresan K., Vijin P., Moorthi C., Manavaln R., Formulation and evaluation of loratadine chewable tablets, Res. J. Pharm. Bio .Che. Sci, 2010,1(4):763-74.
46. Hiroyuki S., Hiraku O., Yuri T., Masanori I., Yoshiharu M., Development of oral acetaminophen chewable tablets with inhibited bitter taste, Int. J. Pharma, 2003,251:123-32.
47. Maddi SS., Tandon S., Aithal KS., Clinical evaluation of sodium fluoride chewable tablets in dental caries, Indian J. Dent. Res, 1999, 10(4):146-9.
48. Shajan A and Narayanan N., Formulation and evaluation of bilayer tablets of Doxoflline Hcl and Montelukast sodium, International Journal of Advanced Pharmaceutics,Vol 2,2,2012:119-124.
49. Ganji Amarnath reddy., Balaji., Naveen K J Rajesh B S and Yedla Anil Chowdary, Formulation and evaluation of oral fast disintegrating tablets by using amlodipine besylate solid dispersion by Direct Compression Method, Der Pharmacia lettre, 2012, 4 (2):683-694.
50. Errolla Mahesh., Kiran Kumar G.B., Mohammed G Ahmed., Kiran kumar P., Formulation and Evaluation of Montelukast Sodium Fast Dissolving Tablets, Asian Journal of Biomedical and Pharmaceutical Sciences, 2(14) 2012, 75-82.
51. Mahalami Rathnanand., Manisha Kandi., Sreenivasa Reddy M K., Formulation and evaluation of chewable tablet of metformin Hcl using by different techniques. International Journal of Phrm. Tech. Research,Vol.5,3:1364-1372.
52. Rajesh M., Anusha V., Palanichamy S., Sugumar M., Parasakthi N.,Godwin Raja Das T., Ramasubramaniyan P., And Thanga Thirupathi, Formulation and Characterization of albendazole chewable tablets. Der.Pharmacia Sinica, 2012,3(2):211-216.
53. Mohd abdul hadi., Lokeswara babu v., Narottam pal., and Srinivasa Rao Formulation and evaluation of sustained release matrix tablets of montelukast sodium. Inter. Journal. Pharm, 2012, 2(3), 574-582 :2249-1848.

54. Janugade B U., Patil S S., Patil S V., Lade P., Formulation and evaluation of press-coated montelukast sodium tablets for pulsatile drug delivery system, International Journal of Chem.Tech Research, Vol.1,3:690-691.
55. Halder A., Behera A., Biswal SSI., Dinda A., Preparation of Loperamide Hydrochloride chewable tablet, method validation by HPLC, International Journal of Pharmacy and Pharmaceutical science,Vol 4,2,2012:372-376.
56. Balasubramaniam J., Bindu K., Rao V U., Effect of Superdisintigrants on dissolution of cat ionic drugs dissolution technologies, 2008:18-25.
57. Tatsuya Ishikawa., Baku Mukai., Suzi Shiraishi., Preparation of rapidly disintegrating tablets using new types of Microcrystelline cellulose and low substituted hydroxyl propyl cellulose or spherical sugar granules by direct compression method, Chem.Pharm.Bull.2001, 49(2):134-139.
58. Ganesh Mahadev C., Kundan Suresh Patil., Dhananjay S Ghodke., Effect of some physical parameters and crospovidone on directly compressed frusemide tablets. Asian journal of Pharmaceutics, 2008: 235-240.
59. Amelia Avachat and V J Ahire., Characterization and evaluation of spray dried compressed excipients and their application in solid dosage form, Indian Journal of Pharmaceutical Sciences,2007,69(1) 85-90.
60. Toshifusa shu., Hideshi Suzuki., Studies of rapidly disintegrating tablets in oral cavity using Co-ground mixtures of mannitol and crospovidone, Chem.Pharm.Bull,2002.