"FORMULATION DEVELOPMENT AND EVALUATION OF ORO-DISPERSIBLE TABLETS OF LEVOSALBUTAMOL"

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Submitted

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EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"Formulation Development and Evaluation of Oro-Dispersible Tablets of Levosalbutamol"** is a bonafide work carried out by **Mrs. P. KIRUBHASHINI (261910554)** to the Tamil Nadu Dr. M.G.R Medical University, Chennai, in partial fulfilment for the award of Degree of **Master of Pharmacy** in **Pharmaceutics** was evaluated.

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DECLARATION

I hereby declare that the synopsis of the thesis entitled **"Formulation Development and Evaluation of Oro-Dispersible Tablets of Levosalbutamol"** submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai was carried out by me in the **Department of Pharmaceutics, The Erode College of Pharmacy & Research Institute, Erode,** under the valuable and efficient guidance of **Prof. Dr. V. GANESAN, M Pharm., Ph.D.** HOD cum Principal, **Department of Pharmaceutics The Erode College of Pharmacy & Research Institute, Erode.** I also, declare that the matter embodied is a genuine work and the same was not performed as basis for the award of any degree, diploma, associateship, fellowship of any other university or institution.

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CONTENTS

LIST OF FIGURES

EVALUATION OF STABILITY STUDIES:

SAMPLING TIME:30 DAYS

EVALUATION OF STABILITY STUDIES:

SAMPLING TIME: 90 DAYS

LIST OF TABLES

EVALUATION OF STABILITY STUDIES

SAMPLING TIME- 30 DAYS

EVALUATION OF STABILITY STUDIES

SAMPLING TIME-90 DAYS

LIST OF ABBREVIATIONS

- NDDS-Novel drug delivery system
- DDS-Drug delivery system
- ODT-Oro-dispersible tablets
- MDT-Mouth dissolving tablets
- UV-Ultra violet spectroscopy
- FT-IR Fourier transform infrared spectroscopy
- MCC-Micro-crystalline cellulose
- SSG-Sodium starch glycollate
- USP-United states pharmacopoeia
- BP-British pharmacopoeia
- IP- Indian pharmacopoeia
- WHO-World health organization
- ICH-International conference on harmonization
- FDA-Food and drug authority
- BCS-Biopharmaceutics classification system
- RH-Relative humidity
- DOE-Design of experiment
- ANOVA-Analysis of variance

ORO DISPERSIBLE TABLETS

INTRODUCTION

TABLETS:

Solid medicaments may be administered orally as powders, pills, cachets, capsules or tablets. These dosage forms contain a quantity of drug which is given as a single unit and they are known collectively as solid unit dosage forms, even in the case of sustained action preparations which, technically, contain the equivalent of several normal doses of drug. Tablets and capsules, on the other hand, currently account for well over two third of the total number and cost of medicines produced all over the world [1,2] .

Definition:

Tablet is defined as a compressed solid dosage form, flat or biconvex dishes, containing medicaments with or without excipients. It is the most popular dosage form and 70 % of the total medicines are dispensed in the form of Tablet [1] . Advantages: They are unit dosage form and 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 form. Lighter and compact. Easiest and cheapest to package and strip. Easy to swallowing with least tendency for hang-up. Sustained release product is possible by enteric coating. Objectionable odour and bitter taste can be masked by coating technique. Suitable for large scale production. Greatest chemical and microbial stability over all oral dosage form. Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face [2,3] . Disadvantages: Difficult to swallow in case of children and unconscious patients. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability. Bitter testing drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating. In such cases, capsule may offer the best and lowest cost [2,3] .

Types of tablets: Tablets ingested orally: Compressed tablet (Paracetamol tablet), Multiple compressed tablet , Repeat action tablet, Delayed release tablet (Enteric coated Bisacodyl tablet), Sugar coated tablet (Multivitamin tablet), Film coated tablet (Metronidazole tablet) and Chewable tablet (Antacid tablet); Tablets used in oral cavity: Buccal tablet (Vitamin-c

tablet), Sublingual tablet (Vicks Menthol tablet), Troches or lozenges and Dental cone; Tablets administered by other route: Implantation tablet and Vaginal tablet (Clotrimazole tablet); Tablets used to prepare solution: Effervescent tablet (Dispirin tablet), Dispensing tablet (Digiplex), Hypodermic tablet and Tablet triturates (Enzyme tablet) (3,4).

Oro dispersible Drug Delivery systems:

Fast disintegrating or Oro dispersible tablets (ODTs) is one such novel approach to increase consumer acceptance by virtue of rapid disintegration, self-administration without water or chewing. This novel type of delivery system offers convenience for treatment-resistant population who have difficulty in swallowing unit oral dosage form, namely tablets and capsules.

These formulations are particularly beneficial to paediatric and geriatric patients, also during travelling where excess of water is not there. These fast-disintegrating tablets can also be designed in such a way that the drug is absorbed through the buccal and oesophageal mucosa as the saliva passes into the stomach. Due to this, the bioavailability of the drug is greater than that observed conventional dosage form. Furthermore, the side effects caused by first pass metabolism may be reduced.

These tablets dissolve, disintegrate or disperse in saliva within a few seconds. Super-disintegrants like cross-linked sodium carboxymethylcellulose (Croscarmellose), cross-linked polyvinylpyrrolidone (Crospovidone), sodium carboxymethyl starch (Sodium starch glycolate) etc. are used in this formulation.

Drugs released from ODTs get absorbed from the oral cavity, pharynx and oesophagus as the saliva passes down into the stomach. So as a result, the bioavailability of Oro-dispersible tablets is more than the other conventional oral tablets like film coated tablets, enteric coated tablets, multiple compressed tablets, sugar coated tablets, etc., Dispersion of therapeutic drug in the saliva in oral cavity causes pregastric absorption of drug which avoids first-pass hepatic or intestinal metabolism that increases bioavailability. The European Pharmacopoeia defined the term “Oro disperse” as that the tablet can be placed in the mouth where it disperses rapidly before swallowing.[5,6]

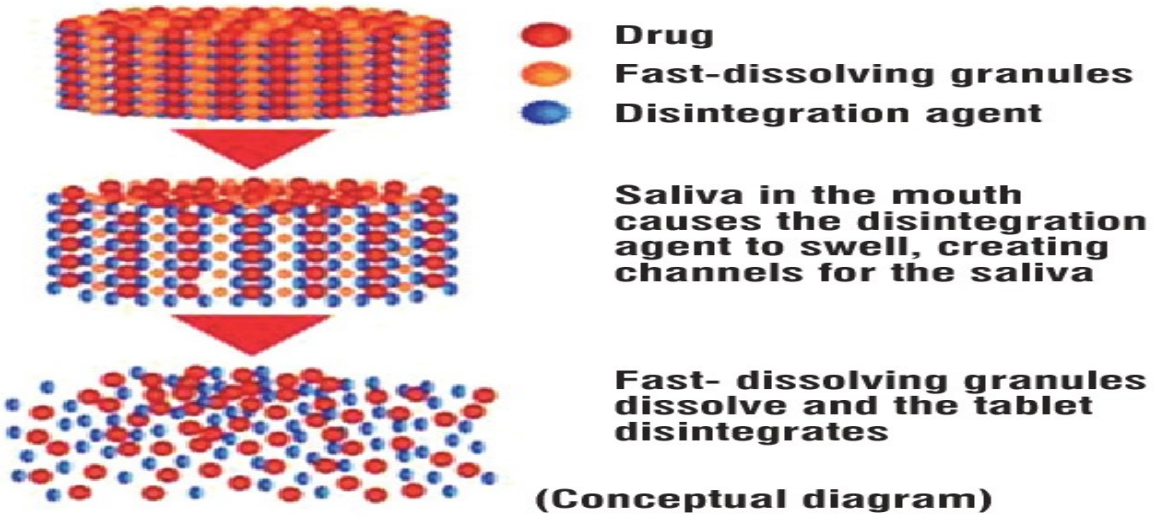

Figure 1: Mechanism of super disintegrants

ANATOMY OF ORAL CAVITY:

The oral cavity lies anterior to the oropharynx and is separated from it by the circumvallate papillae, soft palate and anterior tonsillar pillars, which make up its posterior boundary. The oral cavity is bounded superiorly by the hard palate, laterally by the cheek, and inferiorly by the mylohyoid muscle. In addition to the mucosal area of the oral cavity (the dominant structure of which is the oral tongue), the mylohyoid muscle cleaves the lower oral cavity into the sublingual and submandibular spaces. The sublingual space is frequently invaded by tumors of the floor of the mouth. The submandibular space is most commonly involved by inflammatory processes or metastases to level-I lymph node.

Oral Mucosa: The oral mucosa is the mucous membrane lining the inside of the mouth. It comprises stratified squamous epithelium and an underlying connective tissue termed lamina propria. The oral cavity has sometimes been described as a mirror that reflects the health of the individual. The oral mucosa is an attractive delivery site due to its large surface area for absorption (100 to 200 cm^2), easy accessibility, limited proteolytic activity and high degree of vascularization.[6]

Mechanism of drug permeation in oral cavity: The buccal mucosa and the skin have similar structures with multiple cell layers at different degrees of maturation. The buccal mucosa, however, lacks the intercellular lamellar bilayer structure found in the stratum corneum, and hence is more permeable. An additional factor contributing to the enhanced permeability is the rich blood supply in the oral cavity. The lamina propria, an irregular dense connective tissue, supports the oral epithelium. Though the epithelium is avascular, the

lamina propria is endowed with the presence of small capillaries. These vessels drain absorbed drugs along with the blood into three veins-lingual, facial, and retro-mandibular, which open directly into the internal jugular vein. [7]

Physicochemical properties and routes of permeation:

There are two possible routes of drug absorption through the squamous stratified epithelium of the oral mucosa: Transcellular (intracellular, passing through the cell) Paracellular (intercellular, passing around the cell) Permeation across the buccal mucosa has been reported to be mainly by the paracellular route through the intercellular lipids produced by membrane-coating granules. Although passive diffusion is the main mechanism of drug absorption, specialized transport mechanisms have been reported to exist in other oral mucosa (that of the tongue) for a few drugs and nutrients; glucose and cefadroxil were shown to be absorbed in this way. Shows the two routes of permeation that can be used by drugs to pass through the buccal mucosa. The buccal mucosa is a potential site for the controlled delivery of hydrophilic macromolecular therapeutic agents (biopharmaceuticals) such as peptides, oligonucleotides and polysaccharides. However, these high molecular weight drugs usually have low permeability leading to a low bioavailability, and absorption enhancers may be required to overcome this. The buccal mucosa also contains proteases that may degrade peptide-based drugs. In addition, the salivary enzymes may also reduce stability.

salient Features:

1. Ease of administration.
2. A better mean for unpalatable drugs
3. No requirement of water.
4. Rapid dissolution.
5. Increased bioavailability.
6. Accurate dosing over liquids.
7. More conventional dosage form for uncooperative patients.

Desired Characteristics of ODT:

1. Bioavailability.
2. Rapid drug therapy intervention is possible.
3. Sufficient mechanical strength.
4. Allow high drug loading.
5. Rapid onset of therapeutic action.

6. Good compatibility with development technology.
7. Leaves no residue in mouth after oral administration.
8. Stability.
9. Conventional packaging and processing equipment which allows the tablet manufacturing in low cost.
10. Compatible with taste masking and other excipients.[7]

Advantages of ODT:

1. It can be administered to the patient who cannot swallow conventional dosage form such as bedridden patients, elderly and patient who has renal failure and thus improves patient compliance.

2. It is suitable for bedridden, disabled, traveller and busy persons who does not has water every time.

3. Good mouth feel property helps to mask the bitterness of medicines.

4. Rapid drug therapy intervention.

5. It provides rapid absorption of drugs and increased bioavailability.

6. It allows high drug loading.

7. No chewing is needed.[8]

Disadvantages of ODT's:

1. It requires proper packaging for safety and stabilization of stable drugs.

2. It is hygroscopic in nature, so it must be stored in dry place.

3. It shows the fragile, effervescence granules property.

4. If it is not formulated properly, it may leave unpleasant taste in mouth.

5. Since the tablet has insufficient mechanical strength, it should be handled carefully.

Development need for ODTs:

The necessity for non-invasive delivery systems persists due to patient's poor compliance with existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management. Patient factor ODTs are mainly

appropriate for patients, who for one reason or the other; find it inconvenient to swallow traditional tablets and capsules with water. These include the following:

1.Paediatric and geriatric patients who find it difficult to swallow or chew solid dosage forms,

2.Patients who are unwilling to take solid preparation due to fear of choking.

3.A patient with persistent nausea during journey, who has little or no access to water.

4.A schizophrenic patient in an institutional setting who may try to hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic.

5.An eight-year-old with allergies who desires a more convenient dosage form than antihistamine syrup.

6.A middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2-blocker.[8,9]

Effectiveness factor:

Increased bioavailability and rapid onset of action are a major claim of these formulations. Dispersion in saliva in oral cavity causes pregastric absorption from some formulations in cases were drug dissolves quickly. Buccal, pharyngeal and gastric regions are the areas of absorption for many drugs. Pregastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo a great deal of hepatic metabolism. Furthermore, safety profiles may be improved for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism, for drugs that have a substantial fraction of absorption in the oral cavity and pregastric segments of GIT.

Manufacturing and marketing factor:

Developing novel drug delivery technologies and employing them in product development is vital for pharmaceutical industries to endure, regardless of their size. As a drug nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and superior dosage form. A new dosage form allows a manufacturer to extend market uniqueness, value-added product line extension, and extend patent protection, while offering its patient population a more convenient dosage form.

Marketers build an improved brand and company image when they present a unique easier-to-take form that satisfies the need of an underserved patient population.

Desired characteristics and challenges for developing fast disintegrating drug delivery systems:

1) Time required for disintegration.

2) MDTs should disintegrate/dissolve/disperse or melt in mouth without the need of water in very short duration of time, possibly within 60 seconds.

3) Taste of the active ingredient.

4) As most drugs are unpalatable, fast disintegrating drug delivery systems usually contain the medicament in tastemasked form. Delivery systems dissolve or disintegrate in patient's mouth, thus releasing the active ingredients which come in contact with the taste buds and hence, taste masking of the drugs becomes critical to patient compliance.

5) Tablet strength, Friability and porosity: In order to allow fast disintegrating tablets to disintegrate in the mouth, they are made of either very porous or soft- moulded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle.

6) Hygroscopic nature: Several fast disintegrating drug delivery dosage forms are hygroscopic and cannot maintain physical integrity under normal condition from humidity which calls for specialized product packaging.

7) Mouth feel: Mouth feel is critical, and patients should receive a product that feels pleasant. Any large particles from the disintegrating tablet that are insoluble or slowly soluble in saliva would lead to an unpleasant gritty feeling.

This can be overcome by keeping the majority of the particles below the detectable size limit. In some cases, certain flavors can imbibe an improved mouth feel perception, resulting in a product that is perceived as being less gritty, even if the only change is the flavor. Effervescence can be added to aid disintegration and improve mouth feel by reducing the "dryness" of a product [10]

Selection of ODT Drug Candidates:

Several factors must be considered when selecting drug candidates for delivery of ODT dosage forms.

1. It is assumed that the absorption of a drug molecule from the ODT occurs in the post gastric GIT segments, similar to the conventional oral dosage form.

2. But this scenario may not always be the case. An ODT may have varying degrees of pre-gastric absorption and thus, the pharmacokinetic profiles will vary. Therefore, the ODT will not be bioequivalent to the conventional oral dosage form.

3. For example, ODT formulations of selegiline, apomorphine and buspirone have significantly different pharmacokinetic profiles compared with the same dose administered in

4. It is possible that these differences may, in part, be attributed to the drug molecule, formulation or a combination of both.

5. If significantly higher plasma levels have been observed, pre-gastric absorption leading to the avoidance of first pass metabolism may play an important role.

6. This situation may have implications for drug safety and efficacy, which may need to be addressed and assessed in a marketing application for an ODT.[11]

Direct Compression Method:

In this method, tablets are compressed directly from the mixture of the drug and excipients without any preliminary treatment. The mixture to be compressed must have adequate flow properties and cohere under pressure thus making pre-treatment as wet granulation unnecessary. Few drugs can be directly compressed into tablets of acceptable quality. A type of disintegrant and its proportion are of prime importance. The other factors to be considered are particle size distribution, contact angle, pore size distribution, tablet hardness and water absorption capacity. All these factors determine the disintegration. The disintegrant addition technology is cost effective and easy to implement at industrial level. Cousin et al, using carboxymethyl cellulose as disintegrating agent and one swelling agent consisting of modified starch or microcrystalline cellulose formulated rapidly disintegrable multi particular tablets. The tablets disintegrate in the mouth in less than 60 seconds. Gas evolving disintegrants have been used to formulate fast dissolving tablets. The evolution of carbon dioxide as a disintegration mechanism called OROSOLV and DURASOLV have been

described in two US Patents assigned to CIMA Labs J. Michaelson described the use of intimate mixture of alginic acid and a water-soluble metal carbonic acid to prepare tablets. When the tablet was placed in water, an acid base reaction takes place forming a metal alginic acid salt and carbonic acid. The salt causes the tablet to swell and the carbonic acid produces carbon dioxide within the swelling tablet whereby rapid disintegration of tablet was affected.

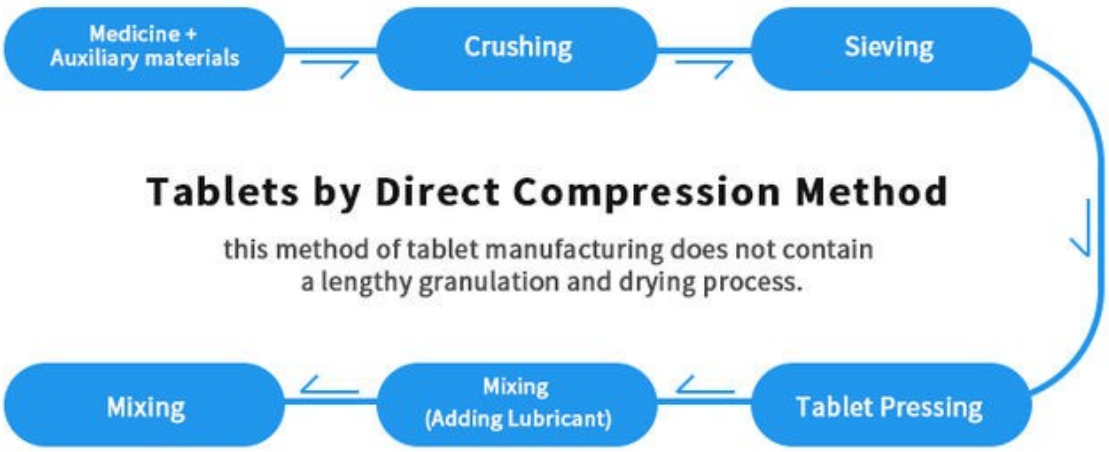

Figure 2: Direct compression technology

Advantages of direct compression technology;

- The prime advantage of direct compression over wet granulation is economic due to fewer unit operations.
- It is more suitable for moisture and heat sensitive APIs because it eliminates wetting and drying steps and increases the stability of active ingredients by reducing detrimental effects.
- Changes in dissolution profiles are less likely to occur in tablets made by direct compression on storage than in those made from granulations.
- 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, whereas disintegration or dissolution is the rate limiting step in absorption in the case of tablets of poorly soluble API prepared by wet granulation.

- The high compaction pressure involved in the production of tablets by slugging or roller compaction could be avoided by using direct compression technique.
- There are minimum chances of wear and tear of punches and dies.
- Materials are "in process" for a shorter period of time, therefore less chance for contamination or cross contamination, and making it easier to meet the requirement of current good manufacturing practices.
- Chance of microbial growth is minimum due to absence of water [12,13]

Figure 3: Direct compression technology – Tablet punching machine

Patented technologies for fast dissolving tablets:

Each technology has a different mechanism, and each fast dissolving/disintegrating dosage forms varies regarding the following.

1. Mechanical strength of final product
2. Drug and dosage form stability
3. Mouth feels
4. Taste
5. Rate of dissolution of drug formulation in saliva
6. Swallowability
7. Rate of absorption from the saliva solution
8. Overall bioavailability

Zydis Technology:

Using concept of Gregory et al, Scherer has patented the Zydis technology. Zydis, the best known for the fast- dissolving/disintegrating tablet preparations and was the first marketed new technology tablet. The tablet dissolves in the mouth within seconds after placement on the tongue. Zydis tablet is produced by lyophilizing or freeze-drying the drug in a matrix usually consisting of gelatine. The product is very lightweight and fragile, and must be dispensed in a special blister pack. Patients should be advised not to push the tablets through the foil film, but instead peel the film back to release the tablet. The Zydis formulation is also self-preserving because the final water concentration in the freeze-dried product is too low to allow for microbial growth. A major claim of the Zydis product is increased bioavailability when compared to traditional tablets. Because of its dispersion and dissolution in saliva in the oral cavity, there can be a substantial amount of pregastric absorption from this formulation.

Buccal, pharyngeal and gastric regions are all the areas of absorption of the Zydis formulation. Any pre-gastric absorption avoids first pass metabolism and can be an advantage in drugs that undergo a great deal of hepatic metabolism. However, if the amount of swallowed drug varies, there is the potential for inconsistent bioavailability.

While the claimed increase in bioavailability is debatable, it is clear that the major advantage of the Zydis formulation is convenience.

The amount of drug that could be incorporated should generally be less than 60 mg for soluble drugs. The particle size of the insoluble drugs should be less than 50mm and not more than 200mm to prevent sedimentation during processing. There are some disadvantages to the Zydis technology. The process of freeze-drying is a relatively expensive manufacturing process.

As mentioned earlier, the Zydis formulation is very lightweight and fragile, and therefore should not be stored in backpacks or the bottom of purses. Finally, the Zydis formulation has poor stability at higher temperatures and humidity. It readily absorbs water, and is very sensitive to degradation at humidity greater than 65%.[15,16,17]

Orasolv technology:

The Orasolv technology, unlike Zydis, disperses in the saliva with the aid of almost imperceptible effervescence. The Orasolv technology is best described as a fast-disintegrating tablet. The tablet matrix dissolves in less than one minute, leaving coated drug powder. The taste masking associated with the Orasolv formulation is two-fold. The unpleasant flavour of a drug is not merely counteracted by sweeteners or flavours; both coating the drug powder and effervescence are means of taste masking in Orasolv. This technology is frequently used to develop over-the-counter formulations.

The major disadvantage of the Orasolv formulations is its mechanical strength.

The Orasolv tablet has the appearance of a traditional compressed tablet.

However, the Orasolv tablets are only lightly compressed, yielding a weaker and more brittle tablet in comparison with conventional tablets. For that reason, Cima developed a special handling and packaging system for Orasolv. An advantage that goes along with the low degree of compaction of Orasolv is that the particle coating used for taste masking is not compromised by fracture during processing. Lyophilisation and high degrees of compression, as utilized in Orasolv primary competitors, may disrupt such a taste masking approach. The Orasolv technology is utilized in six marketed products.

These formulations can accommodate single or multiple active ingredients and tablets containing more than 1.0 gm of drug have been developed. Their disintegration time is less than 30 sec.

DuraSolv technology:

DuraSolv is Cima's second-generation fast-dissolving/disintegrating tablet formulation. It is produced in a fashion similar to Orasolv.

DuraSolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tableting. DuraSolv tablets are prepared by using conventional tableting equipment and have good rigidity (friability less than 2%). The DuraSolv product is thus produced in a faster and more cost- effective manner. DuraSolv is so durable that it can be packaged in traditional blister packaging, pouches or vials.

One disadvantage of DuraSolv is that the technology is not compatible with larger doses of active ingredients, because the formulation is subjected to such high pressures on compaction. Unlike Orasolv, the structural integrity of any taste masking may be compromised with high drug doses.

The drug powder coating in DuraSolv may become fractured during compaction, exposing the bitter-tasting drug to a patient's taste buds. Therefore, the DuraSolv technology is best suited for formulations including relatively small doses of active compound.

Wow tab Technology:

"Wow" means without water. Combinations of two different types of saccharides are used to obtain a tablet. One is low mouldability saccharide and another is high mouldability saccharide, thus produces a formulation having adequate hardness and rapid dissolution. Various low mouldability saccharides are lactose, mannitol, sucrose, glucose and xylitol. Various high mouldability saccharides are maltose, maltitol and sorbitol. A tablet prepared with low mouldability or high mouldability saccharide alone does not achieve adequate hardness and quick disintegration simultaneously. However, if both the saccharides are physically mixed before compression, quick disintegration cannot be obtained. For this reason, the active ingredients are mixed with a low mouldability saccharide and granulated with a high mouldability saccharide and compressed with a tablet. This technology was patented by Flash Yamanouchi pharmaceutical company

Flash dose:

Flash dose tablets consist of self-binding shear form matrix termed as "floss". Shear form matrices are prepared by flash heat processing and are of two types. Single floss or Uni floss, consisting of a carrier, and two or more sugar alcohols, of which one is xylitol. Dual floss consists of a first shear form carrier material (termed "base floss", contains a carrier and

at least one sugar alcohol generally sorbitol), and a second shear form binder matrix ("binder floss", contains a carrier and xylitol). In flash heat process, the feed stock (carbohydrates including sugars and polysaccharides) is simultaneously subjected to centrifugal force and to a temperature gradient, resulting in discrete fibres. The preformed matrices obtained are partially crystallized and have good self-binding and flow properties. The so formed matrices are complex crystalline structures with high specific surface area and result in rapid dissolution rate of the drug. The shear form matrix is blended with drug and other tableting ingredients, and compressed into tablets using conventional tableting equipment. Flash dose tablets are soft, friable and hygroscopic dosage forms, which require specialized packaging.

Flash tab:

This technology involves the preparation of rapidly disintegrating tablet, which consists of an active ingredient in the form of micro crystals. Drug micro granules may be prepared by using the conventional techniques like coacervation, micro encapsulation, extrusion-spherization or simple pan coating method. The micro crystals or micro granules of the active ingredient are added to the granulated mixture of excipient prepared by wet or dry granulation, and compressed into tablets.

Ora quick (kv pharmaceutical company inc.):

The Oraquick mouth dissolving tablet formulation utilized a patent taste masking technology. KV pharmaceutical claims its microsphere technology, known as micro mask, has superior mouth feel over taste masking alternatives. The taste masking process does not utilize solvents of any kind, and therefore leads to faster and more efficient production. Also, lower heat of production than alternative fast dissolving technologies make Oraquick appropriate for heat sensitive drugs. Oraquick claims quick dissolution in a matter of seconds, with good taste masking.

Shear form technology:

The Shear form technology is based on preparation of floss that is also known as shear form matrix, which is produced by subjecting a feedstock containing sugar carrier to flash heat processing. In this process, the sugar is simultaneously subjected to create an internal flow condition, which permits part of it to move with respect of the mass. The flowing mass exists through the spinning head that flings the floss, the floss so produced is amorphous in nature, which is further chopped and re-crystallized by various techniques to

provide uniform flow properties and thus facilitate blending. The crystallized matrix is then blended with other tablet excipients and an active ingredient. Other excipients can be blended with floss before carrying out re-crystallization. The shear form floss, when blended with the coated or uncoated microsphere, is compressed into tablets on slandered tabletting equipment.

Ceform technology:

In Ceform technology, microsphere containing active drug ingredient are prepared. The essence of Ceform microsphere manufacturing process involves placing a drug powder, containing substantially pure drug material or a special blend of drug material plus other pharmaceutical compounds and excipients into precision engineered and rapidly spinning machine. The centrifugal force of the rotating head of Ceform machine throws the drug blend at high speed through small, heated openings. The carefully controlled temperature of the resultant microburst of heat liquefies the blend to form a sphere without adversely affecting the drug stability. The microsphere is then blended and/or compressed into the pre-selected oral delivery dosage form. The ability to simultaneously process both the drug and excipients generates a unique micro environment in which materials can be incorporated into the microsphere that can alter the characteristics of the drug substance, such as enhancing solubility and stability. The microsphere can be incorporated into a wide range of fast dissolving dosage forms such as EZ chew, spoon dose as well as conventional tablets.

Pharma burst technology:

SPI Pharma, New castle, patents this technology. It utilizes the co processed excipients to develop ODT, which dissolves within 30-40 seconds. This technology involves dry blending of drug, flavour, and lubricant followed by compression into tablets. Tablets obtained have sufficient strength so they can be packed in blister packs and bottles.

EFVDAS technology (Elan Corporation):

EFVDAS or Effervescent Drug Absorption System is a drug delivery technology that has been used in the development of a number of both OTC and prescription medications. This is particularly advantageous for conditions such as colds and flu, for which Elan has modified its EFVDAS technology to develop hot drink sachet products that combine medicines and vitamins for OTC use. The granular contents of the sachets can be added to boiling water to produce pleasant-flavoured solutions. In these cases, the effervescence of the

granulate mixture is modified to accommodate the use of heated water. Examples of products that Elan has developed include effervescent ibuprofen, acetaminophen, cimetidine, naproxen, and acetaminophen and codeine combination product.

AdvaTab technology (Eurand):

In this technology, microencapsulation process is used for coating the drug particles with gastro soluble polymer to mask the taste along with restriction of drug dissolution in mouth cavity. AdvaTab tablets disintegrate rapidly in the mouth, typically in less than 30 seconds. These tablets are especially suited to those patients that have trouble in swallowing capsules and tablets. AdvaTab is distinct from other orally disintegrating tablet technologies as it can be combined with Eurand's complimentary particle technologies like its world leading Microcaps® (taste-masking technology) and its Diffucaps® (controlled-release technology).

Frosta technology (Akina):

Akina patents this technology. It utilizes the concept of formulating plastic granules and coprocessing at low pressure to produce strong tablets with high porosity. Plastic granules composed of porous and plastic material, water penetration enhancer, and binder. The process involves mixing the porous plastic material with water penetration enhancer followed by granulating with binder. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30 seconds depending on size of tablet.

Lyoc Technology (Cephalon Corporation):

Lyoc technique was owned by Cephalon Corporation. Lyoc utilizes a freeze-drying process but differ from Zydis in that the product is frozen on the freeze dryer shelves. The liquid solution or suspension preparation involves fillers, thickening agents, surfactant, non-volatile flavouring agents, and sweeteners along with drug. This homogeneous liquid is placed in a blister cavity and subjected to freeze-drying. To prevent inhomogeneity by sedimentation during this process, these formulations require a large proportion of undissolved inert filler (mannitol), to increase the viscosity of a suspension. The high proportion of filler reduces the potential porosity of the dried dosage form and results in denser tablets with disintegration rates are comparable to loosely compressed fast melt formulations.

TASTE MASKING TECHNOLOGIES:

Pharmaceutically active ingredients may leave an unpleasant taste after administration. A new generation of rapidly dissolving and safely swallowable tablets, films etc., that are being developed should have sweet and pleasant taste. Various investigators have patented orally disintegrating/dissolving system containing taste masked drugs.

Chewing Gums:

Chewable tablets containing coated particles of active drugs are well-known dosage form. They are intended to disintegrate in the mouth during chewing. Advantages over dosage forms meant for swallowing include improved bioavailability through the immediate disintegration, patient convenience (elimination of the need for water) and patience acceptance (pleasant taste). Nevertheless, a common problem of chewable tablets is that chewing can cause a breakdown of the membrane that coats the active particles. Furthermore, the extent of mastication, which is associated with the length of time for which a drug remains in the mouth, plays a critical role in determining the amount of taste masking. As a result, the drug's unpleasant taste and throat grittiness are often perceived by the patient. Sozzi et al. (2008) patented a method of producing a chewing gum powder for use in preparing compressed chewing gum. It was prepared by mixing a soft gum base (penetration index >15 ddm) followed by drying (35°C-75° C). The mixture was cooled from 0 to -40°C and then ground to form particles of 10 mesh size. The powder was mixed with additional ingredients and compressed to form chewing gums having chewability and softness characteristics comparable to or better than extruded chewing gum. Nissen (2008) patented chewing gum tablets comprising at least two cohered chewing gum modules. The tableted chewing gum was formed by compression of chewing gum granules. The gum base granules contained an elastomer system (10% w/w of the tablet weight. The compressed chewing gum tablet was found to have extremely impressing abilities of incorporating well-defined amounts of chewing gum ingredients combined with acceptable rheological properties of the compete tablet. A palatable, edible soft chewable medication vehicle was patented by Paulsen et al. (2008). The process for manufacturing did not involve heat or addition of water during mixing. The process resulted in stable concentration of active ingredient. The product had consistent weight and texture.

Nanocrystals:

Nanocrystal technology is aimed at improving compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. This can be accomplished predictably and efficiently using Nanocrystal technology. Nano Crystal particles are small particles of drug substance, typically less than 1000 nanometres (nm) in diameter, which are produced by milling the drug substance using proprietary wet milling technique. Nanocrystal colloidal dispersions of drug substance are combined with water-soluble GRAS ingredients. They are then filled into blisters, and lyophilized. The resultant wafers are remarkably robust, yet dissolve in very small quantities of water within seconds. This approach is especially attractive while working with highly potent or hazardous materials because it avoids manufacturing operations (granulation, blending, and tableting) that generate large quantities of aerosolized powder and present a higher risk of exposure. The freeze-drying approach also enables small quantities of drug to be converted into ODT dosage forms because manufacturing losses are negligible.

Methods employed for taste masking of pharmaceuticals:

The methods commonly employed for achieving effective taste masking include various physical and chemical methods that prevent the drug substance from interaction with the taste buds. So, the various methods are available to mask undesirable taste of the drugs. Some of these are as given below.

Use of flavour enhancers for flavouring and perfuming agents:

These agents can be obtained from either natural or synthetic sources. Natural products include fruit juices, aromatic oils such as peppermint and lemon oils, herbs, spices and distilled fractions of these materials. They are available as concentrated extracts, alcoholic or aqueous solutions, syrups or spirit. Use of flavour enhancers are limited only to unpleasant tasting substances, and is not applicable to oral administration of extremely bitter tasting drugs like various antibiotics. It is important to understand that only soluble portion of the drug can generate the sensation of taste. Addition of flavours & sweeteners is the most & simplest approach for taste masking especially in the case of paediatric formulation. This approach is however not very successful for highly bitter & highly water-soluble drugs. This approach is also used to improve the aesthetic appeal of the product specially to make it more attractive for paediatric patient as well as used for the liquid formulation & the chewable tablets.

Coating of drug particles with inert agents:

Coating is an extremely useful technique for number of applications in the pharmaceutical field. By coordinating the right type of coating material, it is possible to completely mask the taste of a bitter drug, while at the same time, not adversely affecting the intended drug release profile. Any nontoxic polymer that is insoluble at pH 7.4 and soluble at acidic pH would be an acceptable alternative for taste masking. Taste masking of ibuprofen has been successfully achieved by using the air suspension coating technique to form microcapsules, which comprises a pharmaceutical core of a crystalline ibuprofen and methacrylic acid copolymer coating that provides chewable taste masked characteristics. Various inert coating agents like starch, povidone, gelatin, methylcellulose and ethyl cellulose are used for coating drug particles. One of the most efficient methods of drug particle coating is the fluidized bed processor. In this approach, powder is as fine as 50µm, are fluidized in expansion chamber by means of heating. High velocity air and the drug particles are coated with a coating solution and introduced usually from the top as spray through nozzle. The coated granules are dried with warm air. Prepared microcapsules of APIs (Active Pharmaceutical Ingredients) with various cellulose polymers have a pH-dependent solubility with the aim to mask its taste while assuring its release in the intestinal cavity. The drug release studies and the stability assay of the encapsulated moiety demonstrated microspheres represent a useful approach to achieve the proposed objectives. Low melting point substances, like lipophilic waxes, are also used for masking the bitter taste of the drugs. Such substances also have a deteriorating effect on the dissolution kinetics and, therefore are not applicable to fast-disintegrating and fast-dissolving compositions.

Taste masking by formation of inclusion complexes:

In inclusion complex formation, the drug molecule fits into the cavity of a complexing agent i.e., the host molecule forming a stable complex. The complexing agent is capable of masking the bitter taste of the drug by either decreasing its oral solubility on ingestion or decreasing the amount of drug particles exposed to taste buds thereby reducing the perception of bitter taste. Van der Waals forces are mainly involved in inclusion complexes. Beta-cyclodextrin is a most widely used complexing agent for inclusion type complexes. It is sweet, nontoxic, cyclic oligosaccharide obtained from starch. Strong bitter taste of gabapentin citrate syrup was reduced to approximately 50% by preparing a 1:1 complex with

cyclodextrin. The suppression of bitter taste by cyclodextrin was in increasing order of alpha, gamma, and beta cyclodextrin.

Molecular complexes of drug with other chemicals:

The solubility and absorption of drug can be modified by formation of molecular complexes. Consequently, lowering drug solubility through molecular complex formation can decrease the intensity of bitterness of drug. Higuchi and Pitman reported that caffeine forms complexes with organic acids that are less soluble than xanthine and as such can be used to decrease the bitter taste of caffeine.

Microencapsulation:

Microencapsulation process has been defined as a means of applying relatively thin coating to small particles of solid, droplets of liquid and dispersion. This process can be used for masking of bitter tasting drugs by microencapsulating drug particles with various coating agents. Coating agents employed includes gelatin, povidone, hydroxy propyl methylcellulose, ethyl cellulose, bees wax, carnauba wax, acrylics and shellac. Bitter tasting drugs can be first encapsulated to produce free flowing microcapsules, which can then be blended with other excipients and compressed into tablets. Microencapsulation can be accomplished by variety of methods including air suspension, coacervation, phase separation, spray drying and congealing, pan coating, solvent evaporation and multiorifice centrifugation techniques. Diclofenac Sodium microcapsules were successfully prepared using a system of ethyl cellulose - toluene - petroleum ether. Tinidazole was microencapsulated within various cellulose polymers like ethyl cellulose, eudragit–L & cellulose acetate phthalate with the final aim to mask its taste without affecting its bioavailability.

Ion exchange resin:

Another popular approach in the development of taste masking is based on ion exchange resin. Ion exchange resins are solid and suitably insoluble high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium. The resulting ion exchange is reversible and stoichiometric with the displacement of one ionic species by another. Synthetic ion exchange resin has been used in pharmacy and medicine for taste masking or controlled release of drug. Being high molecular weight water insoluble polymers, the resins are not absorbed by the body and are therefore inert. The long-term safety of an ion exchange resins, even while ingesting large doses in the use of

cholestyramine to reduce cholesterol establishes unique advantage of an ion exchange resins fixed positively or negatively charged functional groups attached to water insoluble polymer backbone. The adsorption of bitter drugs onto synthetic ion exchange resins to achieve taste coverage has been well documented. Ion exchange resins like Amberlite CG 50 was used for taste masking of pseudoephedrine in the chewable Rondec decongestant tablet38. Antibacterial belonging to quinolone category like ciprofloxacin was loaded on cation exchanger and administered to animals. The taste was improved when an animal accepted the material more readily binding to a cation exchange resin like Amberlite IRP-69 masked the taste of peripheral vasodilator buflomid. Manek S.P. et al. evaluated resins like Indian CRP 244 and CRP 254 as taste masking agents. Drug release from the resin depends on two factors, the ionic environment (i.e., pH electrolyte concentration) within the GIT and the properties of resin. Drug molecules attached to the resin are released by exchanging with appropriately charged in GIT, followed by diffusion of free drug molecule out of resin. The process can be depicted by the following equation 1 & 2 for anion exchange & cation exchange respectively, where X & Y are ions in the GIT.

Resin + — Drug + X = Resin + —X + Drug ————Equation 1

Resin + — Drug +Y = Resin + —Y + Drug ————Equation 2

Ion exchange resin can be classified into four major groups,

1. Strong acid cation exchange resin, e.g., Amberlite IRP-69.

2.Weak acid cation exchange resin, e.g., Amberlite IRP-65.

3. Strong base anion exchange resin, e.g., Amberlite IRP-276.

4. Weak base anion exchange resin, e.g., Dimethylamine resin Ion exchange resins (IER) have received considerable attention from pharmaceutical scientists because of their versatile properties as drug delivery vehicles. In past few years, IER have been extensively studied in the development of novel drug delivery system and other biomedical applications. Several ion exchange resin products for oral and parenteral administration have been developed for immediate release and sustained release purposes. Research over last few years has revealed that IER are equally suitable for drug delivery technologies including controlled release, transdermal, nasal, topical, and taste masking. Bitter taste is masked by ion exchange resin. Taste Masking Agent-104 is derived from cross-linked polymer of Methacrylic acid. It has carboxylic acid which functionally enables its use as a taste masking agent, while the

cross-linked porous nature makes it suitable as a sustain release agent. Taste masking rosin-134 is derived from cross-linked polymer of acrylic acid and has a K+ ionic form. Taste masking rosin-134 is a very high purity polymer finding use in pharmaceutical formulations for taste masking of certain drugs, particularly B-lactam antibiotic.

Solid dispersions:

They are dispersions of one or more active ingredients in an inert carrier or matrix in solid state, and insoluble or bland matrices may be used to mask the taste of bitter drugs. Carriers used in solid dispersion systems include povidone, polyethylene glycols, hydroxypropyl methylcellulose, urea, mannitol and ethyl cellulose. Various approaches for preparation of solid dispersion are described below.

1. Melting method- In this method, the drug or drug mixture and a carrier are melted together by heating. The melted mixture is cooled and solidified rapidly in an ice bath with vigorous stirring. The final solid mass is crushed and pulverized.

2. Solvent method- In this method, the active drug and carrier are dissolved in a common solvent, followed by solvent evaporation and recovery of the solid dispersion.

3. Melting solvent method- In this method, the drug in solution is incorporated into a molten mass of polyethylene glycol at a temperature below 700^{O}C without removing the solvent.

Multiple emulsions:

A novel technique for taste masking of drugs employing multiple emulsions has been prepared by dissolving drug in the inner aqueous phase of w/o/w emulsion under conditions of good shelf stability. The formulation is designed to release the drug through the oil phase in the presence of gastrointestinal fluid.

Liposome:

Using liposome, another way of masking the unpleasant taste of therapeutic agent is to entrap them into liposome. For example, incorporating into a liposomal formulation prepared with egg phosphatidyl choline masked the bitter taste of chloroquine phosphate in HEPES (N-2- hydroxyetylpiperzine-N'- 2- ethane sulfonic acid) buffer at pH 7.[14,15,16,17]

Excipients used for preparation of ODTs:

1. Super disintegrants: It increases the rate of disintegration and dissolution. For the success of orally disintegrating tablet, the tablet having quick dissolving property is achieved by super disintegrants. Disintegrating agents are substances routinely included in tablet formulations and in some hard-shell capsule formulations to promote moisture penetration and dispersion of the matrix of the dosage form in dissolution fluids. An oral solid dosage form should ideally disperse into the primary particles from which it was prepared. Although various compounds have been proposed and evaluated as disintegrants, relatively few are in common usage today. Traditionally, starch has been the disintegrant of choice in tablet formulations, and it is still widely used. However, starch is far from ideal. For instance, starch generally has to be present at levels greater than 5% to adversely affect compatibility, especially in direct compression. Moreover, intragranular starch in wet granulations is not as effective as dry starch. In more recent years, several newer disintegrants have been developed. Often called "super disintegrants," these newer substances can be used at lower levels than starch. Because they can be a smaller part of the overall formulation than starch, any possible adverse effect on fluidity or compatibility would be minimized. These newer disintegrants may be organized into three classes based on their chemical structure. Examples - Crospovidone, MCC, Sodium starch glycolate, CMC, Carboxy methyl cellulose and modified corn starch.

2. Sweeteners and sugar-based excipients: Sugar based excipient acts as bulking agents. They exhibit high aqueous solubility and sweetness and impart taste masking property. Examples -Aspartame, Sugar derivative, Dextrose, Fructose, Mannitol, Sorbitol, Maltose etc.

3. Flavours: It increases patient compliance and acceptability. Examples -Vanilla, Citrus oil, Fruit essence, Eucalyptus oil, Clove oil, Peppermint oil, etc.,

4. Surface active agents: It reduces interfacial tension and thus enhances solubilization of ODTs. Examples- Sodium lauryl sulphate, Sodium – dodecyl sulphate, Polyoxyethylene sorbitan fatty acid esters, Polyoxyethylene stearates etc.

5. Binders: It maintains integrity of dosage form. Examples- PVP, Polyvinyl alcohol, Hydroxy propyl methylcellulose.

6. Colours: It enhances appearance and organoleptic properties of dosage form. Examples - Sunset yellow, red iron oxide, Amaranth.

7. Lubricants: It helps reducing friction and wear by introducing a lubricating film. Examples -Stearic acid, Magnesium stearate, Zinc stearate, Talc, Polyethylene glycol, Liquid paraffin, Colloidal silicon Di-oxide etc.

8. Fillers: It enhances bulk of dosage form. Examples -Mannitol, Sorbitol, Xylitol, Calcium carbonate, Magnesium carbonate, Calcium sulphate, Magnesium trisilicate etc.[18,19,20]

Mechanism of action of super disintegrants: Tablet breaks into primary particles by one or more of the mechanisms listed below [21,22,23,24]

1. Because of heat of wetting (air expansion)

2. Swelling

3. Porosity and capillary action (Wicking)

4. Due to disintegrating particle/particle repulsive forces

5. Due to deformation

6. Due to release of gases

1. By capillary action: Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipient and on tableting conditions. For these types of disintegrants, maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particle and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

2. By swelling: Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force, on the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration again slows down.

3. Because of heat of wetting (Air expansion): When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents.

4. Due to release of gases: Carbon dioxide is released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablets. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added into two separate fractions of formulation.

5. By enzymatic reaction: Enzymes presents in the body also acts as disintegrants. These enzymes destroy the binding action of binder and helps in disintegration. Actually, due to swelling, pressure exerted in the outer direction or radial direction causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

6. Due to disintegrating particle/particle repulsive forces: Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non swellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that non swelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

7. Due to deformation: Hess had proved that during tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

Three major groups of compounds have been developed which swell to many times their original size when placed in water while producing minimal viscosity effects:

1. **Modified Starches**:[29] Sodium Carboxymethyl Starch (Chemically treated Potato Starch) i.e., Sodium Starch Glycolate (Explotab, Primogel). Mechanism of action: Rapid and extensive swelling with minimal gelling.

Effective concentration: 4-6%. Above 8%, disintegration times may actually increase due to gelling and its subsequent viscosity producing effects.

2. **Cross-linked polyvinylpyrrolidone:** Water insoluble and strongly hydrophilic i.e., crospovidone (Polyplasdone XL, Kollidon CL).
   Mechanism of action: Water wicking, swelling and possibly some deformation recovery.

Effective concentration: 2-4%.

3. **Modified cellulose:** Internally cross-linked form of Sodium carboxymethyl cellulose i.e., AcDi-Sol (Accelerates Dissolution), Nymcel. Mechanism of Action: Wicking due to fibrous structure, swelling with minimal gelling. Effective Concentration: 1-3% (Direct Compression), 2-4% (Wet Granulation).

Microcrystalline Cellulose (Avicel 102):

Microcrystalline cellulose is partially depolymerised cellulose prepared from alpha cellulose. Microcrystalline cellulose for direct compression tabletting comes in a number of grades like PH 101 (original product) & PH 102 (more agglomerated, large particle size with better fluidity). When compressed, the MCC particles are deformed plastically due to the presence of slip planes & dislocation. A strong compact is formed due to the extremely large number of clean surfaces brought in contact during plastic deformation & the strength of hydrogen bonds formed. Here Avicel 102 is used as a diluent cum disintegrant. The mechanism of Avicel 102 is interlocking. The particle size of Avicel 102 is small. The decrease in particle size increases binding strength and decreases disintegration time. So, here we have used Avicel 102.

MCC is found in the concentration of 10-25% as a filler binder disintegrant. MCC can be used as a disintegrant at a level of 5-15%. The MCC is effective as a binder in direct compression. Its binding advantages in granulation decreases with an increase in water addition. MCC is useful as a disintegrant when used in proportion of at least 5-15%. The disintegration time of tablets of cation exchange resin was reduced significantly in the presence of MCC.

L-HPC (Low-substituted hydroxypropyl cellulose):

It is preferable in wet granulation and directly compressed tablets. Larger particle size and higher hydroxypropyl content show higher degree of swelling. It is useful to prevent capping. Now a days, it is widely used as a super-disintegrant in fast dissolving tablets.

Crospovidone (Kollidon):

It is white, free flowing and compressible powder. It is synthetic homopolymer of cross-linked N-vinyl-2-pyrrolidone. It is completely insoluble in water, acids, alkalis, and all organic solvents and swells rapidly in water. Rapidly disperses in water, but does not gel even after prolonged exposure. It is chemically inert and has a high adsorptive capacity, forms reversible physical complexes with many molecules without the formation of covalent chemical bonds. It is used as a super-disintegrant and dissolution agent in granules, hard gelatine capsules and tablets prepared by direct compression method. Greatest rate of swelling is compared to other disintegrants.

Croscarmellose Sodium (Ac-di-sol):

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. 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.

STABILITY STUDIES

Stability studies of pharmaceutical products may be expressed as the time during which the pharmaceutical products retain its physical, chemical, microbiological, pharmacokinetic properties and characteristics throughout the shelf life from the time of manufacture. Shelf life of the product can be defined as the substance reduces to 90% of its original concentration.[31,32]

Importance of stability studies:

- Product instability of active drug may lead to under medication due to the lowering of the drug in dosage form.
- During the decomposition of the drug or product it may lead to toxic products.
- During the marketing from one place to another during the transportation the drug has the compatibility to change its physical properties.
- Instability may be due to changing in physical appearance through the principles of kinetics are used in predicting the stability of drug there different between kinetics and stability study.

Types of stability studies:

Physical stability:

The original physical properties such as appearance, colour, dissolution, palatability, suspend ability are retained. The physical stability may affect the uniformity and release rate, hence it is important for the efficacy and safety of the product.

Chemical stability:

It is the tendency to resist its change or decomposition due to the reactions that occur due to air, atmosphere, temperature, etc.

Microbiological stability:

The microbiological stability of the drugs is the tendency to resistance to the sterility and microbial growth. The antimicrobial agents used in the preparation retain the effectiveness. within specified limits. This microbiological instability could be hazardous to the sterile drug product.

Therapeutic stability:

The therapeutic effect (Drug Action) remains unchanged.[33,34]

Toxicological stability:

Toxicological stability has no significant increase in the toxicity occurs.

Types of Stability Studies	Storage Conditions	Minimum Time Period
Long Term	25±2°C and 60±5% RH	12
Intermediate	30±2°C and 65±5% RH	6
Accelerated	40±2°C and 75±5% RH	6

Table 1: Types of stability studies

Stability Testing Methods:

1.Real-time stability testing

2. Accelerated stability testing

3. Retained sample stability testing

4. Cyclic temperature stress testing.

1. Real-time stability testing:

Real-time stability testing is normally performed for a long duration of time to allow significant degradation of the product under the storage conditions recommended. The period for the test of the product depends on the stability of the product which clearly tells that the product is not degraded or decomposed for a long time from inter-assay variation. While, testing the samples are collected at regular intervals such that the data is collected at the appropriate frequency such that the analyst can distinguish the degradation day-to day. The data can be increased by including the single batch of reference material for which stability characteristics have been established. In this the reagents and the instruments used should be in the consistency throughout the stability testing. The control of drift and discontinuity results in the changes of both reagents and instruments should be monitored.[35,36,37,38]

Climatic Zones	Climate	Countries	MAT*	Long-Term Testing Conditions
I	Temperate	United Kingdom, Russia, USA	<15°C/11hPa	21°C/45%RH
II	Subtropical and Mediterranean	Japan, Southern Europe	>15-22°C />11-18hPa	25°C/60%RH
III	Hot and Dry	Iraq, India	>22°C/<15hPa	30°C/35%RH
IV a	Hot and Humid	Iran, Egypt	>22°C/>15-17hPa	30°C/65%RH
IV b	Hot and very humid	Brazil, Singapore	>22°C/>27hPa	30vC/75%RH

Table 2: Climatic Zones and Long-term stability conditions

Test Schedule for stability testing of new products

Environment	Sampling Time Points (Months)	Method & Climatic zone
25°C/60% RH	3, 6, 9, 12, 18, 24,36	% RH Long term for zones I and IV
30°C/35% RH	3, 6, 9, 12, 18, 24,36	Long term for zones III
30°C/65% RH	3, 6, 9, 12, 18, 24,36	Long term for zone IV a, or intermediate condition for zones I and II
30°C/75% RH	3, 6, 9, 12, 18, 24,36	Long term for zone IV a, or intermediate condition for zones I and II
40°C/75% RH	3, 6, 9, 12, 18, 24,36	Accelerated condition for all zones

Table 3: Test Schedule for stability testing of new products

AIM

- The ***Aim*** of the present work was to Design and Evaluate oral dispersible tablets (ODTs) containing Levosalbutamol using super disintegrants.

OBJECTIVES

- The main ***Objective*** of the study was to improve the disintegration and dissolution rate of Levosalbutamol.
- Selection of a suitable drug Candidate.
- Selection of appropriate excipients including super disintegrants.
- Optimization of the formulation.
- Preformulation Studies
- Formulation, Development of oral dispersible tablet by direct compression method.
- Characterization and evaluation of the formulations.
- Stability Study of Optimized Formulations.

PLAN OF WORK

1. Literature review.

2. Selection of drug and excipients.

3. Pre formulation studies.

- Organoleptic characteristics.
- Solubility of drug.
- Particle size distribution.
- Physio-mechanical characterization.
- Drug-excipient Compatibility study.

4. Optimization of suitable formula.

5. Formulation of tablets by using direct compression method.

6. Evaluation of the formulated tablets.

- Thickness
- Hardness and friability
- Disintegration time
- *In vitro* dissolution
- Drug Content
- Weight variation
- Wetting time
- Water absorption ratio

7. Stability study of optimized formulation.

REVIEW OF LITERATURE

Sneha Mohapatra et al explained an approach for drug delivery in buccal cavity. Oral delivery is the most convenient, economical and safest route for drug delivery. Still, it possesses a demerit of difficulty in swallowing of tablets and capsules. The Oral Dispersible Tablets (ODTs) is a novel approach to overcome the above-mentioned problem. The ODTs is rapidly disintegrated and dissolved in saliva. The oral cavity is highly vascularized and internally lined with epithelial and mucous membrane which favours rapid absorption of drug, thus OTDs provides quick onset of action. The ODTs possess other merits of ease the administration especially in case of paediatrics and geriatrics, low-cost production, less use of water and less drug loss. The patients suffering from dysphasia, motion sickness, repeated emesis and mental disorders preferably use ODTs because they cannot swallow large quantity of water. The ODTs can be designed by employing several techniques such as melt granulation, effervescent method, cotton candy process, direct compression, tablet moulding, sublimation, phase transition, freeze drying and mass extrusion. The several marketed ODTs formulations along with numerous scientific advancements has been focused in this review study.[39]

Takao Mizumoto et al had developed formulation design for a novel fast disintegrating tablet. A novel fast-disintegrating tablet was investigated in this study as a user-friendly dosage form for the aged. Advantages of this formulation have sufficient hardness and can be manufactured by commonly used equipment. Saccharides can be divided into high and low compressibility categories, and an appropriate material for fast-disintegrating tablets which was created by taking advantage of this fact. To improve the compressibility of low-compressibility saccharides, particle modification was conducted by coating and granulating a low-compressibility saccharide with a high one to enable the production of a fast-disintegrating tablet. Another discovery was that the high-compressibility saccharide used as a binder solution was present in an amorphous state after the granulation process. The crystal change from amorphous to crystal state is intentionally by a conditioning process after compression was enabled to increase tablet hardness by strengthening adhesion between particles. The conditioning process made it possible to achieve sufficient hardness while maintaining the fast disintegration time. As a result, this fast-disintegrating tablet that can be manufactured by commonly used equipment, can be used for the dosing of a wide range drugs. [40]

A Gupta et al explained about the recent trends of fast dissolving tablets. In recent decades, a variety of pharmaceutical research has been conducted to develop new dosage forms. Among the dosage forms developed to facilitate ease of medication, the rapid disintegrating tablet (RDT) is one of the most widely employed commercial products. As our society is becoming increasingly aged, the development of fast or mouth dissolving tablets have been formulated for paediatric, geriatric, bedridden patients and for active patients who are busy and traveling and may not have access to water. Such formulations provide an opportunity for product line extension in the many elderly persons who have difficulties in taking conventional oral dosage forms (viz., solutions, suspensions, tablets, and capsules) because of hand tremors and dysphagia. Swallowing problems are also common in young individuals because of their underdeveloped muscular and nervous systems. Other groups that may experience problems using conventional oral dosage forms include the mentally ill, the developmentally disabled and patients who are uncooperative on reduced liquid intake plans, or are nauseated. In some cases, such as motion sickness, sudden episodes of allergic attack or coughing, an unavailability of water and swallowing conventional tablets may be difficult. This paper summarizes the future formulation methods and drug formulations in the market. [41]

G.K. Bolhuis et al explained the efficiency of **SCG Sodium Starch Glycolates** tested had a high swelling capacity, but the rate of water uptake into the disintegrant particles varied from high for **Sodium Potato Starch Glycolate** to low for sodium rice starch glycolate. As an effect of the high swelling capacity, it was found that the origin of the starch plays a minor role for the disintegration time of dicalcium phosphate dihydrate tablets, where swelling and the subsequent development of a disintegration force is the predominant disintegration mechanism. On the other hand, for tablets prepared from alpha-lactose monohydrate, where the rate of water penetration plays a paramount role in the disintegration process, the disintegration time depends on the origin of the starch in the sodium starch glycolate. The disintegration time decreased with an increase of the rate of water penetration into the disintegrant particles. The differences in water penetration rates into the sodium starch glycolate particles were attributed to differences in chemical composition, crystallinity and particle size of the starches from which the sodium starch glycolates were prepared. [42]

P Thulasamma et al developed UV analytical methods for levosalbutamol drug. Two simple, precise and accurate UV methods have been developed for the simultaneous estimation of **Levosalbutamol Sulphate (LS)** and Beclomethasone dipropionate (BD) in bulk and pharmaceutical formulation. Method A applied Area Under Curve (AUC) for the analysis of LS in the wavelength range of 272-282nm and for BD in the wavelength range of 234-244nm.Method B is Q-absorbance method based on the measurement of absorptivity at 269nm (as an iso-absorptive point) and 277 nm.LS and BD shows a maximum absorption at 277nm and 239nm respectively with a linearity range of 10-50 µg/ml and 5-25 µg/ml respectively for both the methods.[43]

H. K. Patil et al were provided a detailed review about mouth dissolving tablets. The demand for MDT (Mouth Disintegrating Tablet) has been increasing from the last decade particularly in geriatric, paediatric and patient with some sort of disabilities in swallowing. MDTs are those tablets which when placed in mouth get dissolved rapidly in saliva without the need of liquid and can be swallowed. European pharmacopoeia adopted the term Oro dispersible tablet for MDTs.This article reviews the potential benefits offered by MDTs as an oral drug delivery system for various kinds of patients suffering from different diseases and disabilities. Desired characteristics and challenges for developing fast disintegrating drug delivery systems, quality control tests, various techniques used in the preparation of fast disintegrating drug delivery systems like lyophilization technologies, tablet moulding method, sublimation techniques, spray drying techniques, mass extrusion technology, direct compression method and uses of super-disintegrates. It also reviews the patented technologies for fast dissolving tablets, advantages and disadvantages of different technologies for preparing fast disintegrating dosage form, future prospective for MDTs.[44]

K.B. Deshpande et al were provided an overview of formulation and evaluation of Oro dispersible tablets. Oro dispersible tablets (ODTs) have gained considerable attention as a preferred alternative to conventional tablets and capsules due to better patient compliance, improved solubility and stability profiles. ODTs are solid dosage forms containing medicinal substances which disintegrate rapidly, usually in a matter of seconds, when placed on the tongue. New ODT technologies addresses many pharmaceutical and patient needs, ranging from enhanced life-cycle management to convenient dosing for paediatric, geriatric, and psychiatric patients with dysphagia. This has encouraged both academia and industry to generate new orally disintegrating formulations and technological approaches in this field. The aim of this article is to review the development of ODTs, challenges in formulation, new

ODT technologies, evaluation methodologies, suitability of drug candidates and future prospects.(45)

Aloke dey has explained about factorial design. In many scientific investigations, interest lies in studying the effects of several input variables simultaneously on an output variable. Factorial experiments are ideally suited for such investigations. The importance of factorial experiments stems from the fact that such experiments allow the estimation of individual effects of the input variables as also their inter-dependence at the same time, thus providing a basis for drawing inference over a wide range of conditions. Some basic ideas of factorial experiments and issues related to the designing of such experiments are discussed with emphasis on symmetric 2- and 3-level experiments.(46)

André I. Khuri et al The purpose of this article is to provide a survey of the various stages in the development of response surface methodology (RSM). The coverage of these stages is organized in three parts that describe the evolution of RSM since its introduction in the early 1950s. Part I covers the period, 1951–1975, during which the so-called classical RSM was developed. This includes a review of basic experimental designs for fitting linear response surface models, in addition to a description of methods for the determination of optimum operating conditions. Part II, which covers the period, 1976–1999, discusses more recent modelling techniques in RSM, in addition to a coverage of Taguchi's robust parameter design and its response surface alternative approach. Part III provides a coverage of further response surface models with random effects, generalized linear models, and graphical techniques for comparing response surface designs.(47

Raymond H. Mayers et al explained the uses and history of response surface methodology. Response surface methodology (RSM) is a collection of tools developed in the 1950s for the purpose of determining optimum operating conditions in applications in the chemical industry. This article reviews the progress of RSM in the general areas of experimental design and analysis and indicates how its role has been affected by advances in other fields of applied statistics.(48)

S.L.C. Ferreira et al had explained about the box Behnken design. It establishes also a comparison between this design and composite central, three-level full factorial and Doehlert designs. A detailed study on factors and responses involved during the optimization of analytical systems is also presented. Functions developed for calculation of multiple responses are discussed, including the desirability function, which was proposed by Derringer

and Suich in 1980. Concept and evaluation of robustness of analytical methods are also discussed. Finally, descriptions of applications of this technique for optimization of analytical methods are presented.[49]

Priyanka Patel et al gives introduction about the **Drug Excipient Compatibility Studies**. drug-excipient compatibility represents an important phase in the pre formulation stage of the development of all dosage forms. The potential physical and chemical interactions between drugs and excipients can affect the chemical, physical, therapeutical properties and stability of the dosage form. The present review contains a basic mode of drug degradation, mechanism of drug- excipient interaction like physical, chemical and biopharmaceutical. Different Thermal and Non-thermal method of analysis, Tools and software for incompatibility is also discussed. Once the type of interaction is determined we can take further steps to improve the stability of drug and dosage form. From review, we conclude that consequent use of thermal and non-thermal method provide data for drug- excipient interaction which can further help in selection of excipient for the development of stable dosage form.[50]

Karin Liltorp et al explained about **Solid State Compatibility Studies with Tablet Excipients** using non thermal methods Compatibility between two new active pharmaceutical ingredients (API) and several pharmaceutical excipients used in solid formulations has been investigated by FT-IR and HPLC following storage under two different conditions. Compatibility was investigated by storage at isothermal stress conditions for (i) 3 days and subsequently analysed by FT-IR and (ii) 12 weeks of storage and analysis by HPLC. For the majority of the examined excipients a large degradation measured by HPLC after 12 weeks storage was also detected by FT-IR following storage at isothermal stress conditions for 3 days, i.e., there was a general agreement between the results obtained by the two protocols. Further, the FT-IR method showed clear incompatibility with three excipients where no degradation products were detected by HPLC, but where a significant decrease in the API quantified by the HPLC assay, was observed. [51]

E. M. Rudnic et al explained about the Effect of molecular structure variation on the **Disintegrant Action Of Sodium Starch Glycolate**. The effect of variation in the degree of cross-linkage and extent of carboxymethylation on the disintegration and dissolution properties of sodium starch glycolate has been examined. Samples of sodium starch glycolate were evaluated for particle size distributions and bulk and tapped densities. The bulk powders

were also tested for sedimentation volumes, water uptake, and bulk swelling. Direct compression formulations containing aspirin and hydrochlorothiazide and varying concentrations of the modified starches were tableted on a rotary tablet press and evaluated for weight variation, hardness, disintegration, and dissolution. The results indicate that relatively small changes in molecular structure can cause substantial modification of disintegrant properties and suggest that the specifications for one commercially available sodium starch glycolate are within optimal specifications for both cross-linkage and degree of substitution.(52)

Goldstein DA et al had developed a method for formulation of levosalbutamol in pure and tablet dosage form. As a treatment, **Levosalbutamol** is used in asthma and Chronic Obstructive Pulmonary Disease (COPD). Patients with conditions such as coughing, wheezing and shortness of breath have been benefited from the use of levosalbutamol. It relaxes the muscles in the airways and increases airflow to the lungs. Levosalbutamol makes breathing easier by widening the airways (53)

Md.Nehal Siddiqui et al had developed a method for preparation and evaluation of Oro dispersible tablets. Oral route is the most preferred route for administration of various drugs because it is regarded as safest, most convenient and economical route. Recently, researchers have developed the fast-dissolving tablet (FDT) with improved patient compliance and convenience. FDTs are solid dosage forms which dissolve rapidly in saliva without chewing and additional water. FDTs overcome the disadvantages of conventional dosage form especially dysphagia (difficulty in swallowing) in paediatric and geriatric patients. This review includes ideal properties, characteristics, challenges in formulation, suitability of drug candidates, various technologies developed for FDT, patented technologies, evaluation methods and various marketed products.(54)

Honey Goel et al were innovated many formulations and technologies in Oro dispersible tablets. Research in developing orally disintegrating systems has been aimed at investigating different excipients as well as techniques to meet these challenges. A variety of dosage forms like tablets, films, wafers, chewing gums, microparticles, nanoparticles etc., have been developed for enhancing the performance attributes in the orally disintegrating systems. Advancements in the technology arena for manufacturing these systems include the use of freeze drying, cotton candy, melt extrusion, sublimation, direct compression besides the classical wet granulation processes. Taste masking of active ingredients have become an essential in these systems because the drug is entirely released in the mouth. Fluid bed

coating, agglomeration, palletisation and infusion methods have proven useful for this purpose. It is important to note that although freeze dried and effervescent disintegrating systems rapidly disintegrate in contact with fluids, they do not generally exhibit the required mechanical strength. Similarly, the candy process cannot be used for thermolabile drugs. In the light of the paradoxical nature of the attributes desired in orally disintegrating systems (high mechanical strength and rapid disintegration), it becomes essential to study the innovations in this field and understand the intricacies of the different processes used for manufacturing these systems. This article attempts at discussing the patents relating to orally disintegrating systems with respect to the use of different formulation ingredients and technologies.[55]

Deepika Jain et al were involved in the formulation and development of Oro dispersible tablets. The oral route of drug administration is the most important method for administering drugs for systemic effects. Except in certain cases, the parenteral route is not routinely used for self-administration. e.g., insulin. The topical route of administration has only recently been employed to deliver drugs to the body for systemic effects. The parenteral route of administration is important in treating medical emergencies in which the subject is comatose or cannot swallow. Nevertheless, it is probable that at least 90% of all drugs used to provide systemic effects are administered by the oral route. A Fast-dissolving tablet, orally disintegrating tablet or Oro dispersible tablet (ODT) is a drug dosage form available for a limited amount of over-the-counter (OTC) and prescription medications. ODTs differ from traditional tablets in that they are designed to be dissolved on the tongue rather than swallowed whole. The ODT serves as an alternative dosage form for patients who experience dysphasia (difficulty in swallowing) or for where compliance is a known issue and therefore an easier dosage form to take ensures that medication is taken.[56]

Sudipta Das et al were developed neoteric technology for the Oro dispersible tablets. Among the different routes, the oral route is more preferable due to convenience of administration, low cost, no need for sterilization, and variety of dosage forms. Oro dispersible tablets (ODTs) differ from traditional tablets which were designed to be dissolved on the tongue rather than swallowed as a whole. The ODT serves as an alternative dosage form for patients who experience dysphagia (difficulty in swallowing) or for faster systemic absorption. The ODTs disintegrate or dissolve rapidly in the saliva within a few seconds without the need of water. The basic approach used in development of oral dispersible tablet is the use of super disintegrants like cross-linked sodium carboxymethylcellulose, cross-linked

polyvinylpyrrolidone, sodium carboxymethyl starch, etc., This review describes the challenges, significance, various methods of preparation, technologies used and evaluation of ODTs.(570

Tanmoy Ghosh et al reviewed on new generation Oro dispersible tablets and its future prospective. A number of companies have marketed products using various nomenclatures including ODT as well as their own trademarked names- a convenient, potentially safer alternative to conventional tablets and capsules. ODTs are solid dosage forms that disintegrate in the mouth in less than 60 seconds and are thus swallowed without the need of water.(58)

Yourong Fu et al were involved in the development and technologies of novel oral disintegrating tablets. Fast disintegrating tablets (FDTs) have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry. Upon introduction into the mouth, these tablets dissolve or disintegrate in the mouth in the absence of additional water for easy administration of active pharmaceutical ingredients. The popularity and usefulness of the formulation was resulted in development of several FDT technologies. This review describes various formulations and technologies developed to achieve fast dissolution/dispersion of tablets in the oral cavity. In particular, this review describes in detail about FDT technologies based on lyophilization, molding, sublimation and compaction, as well as approaches to enhancing the FDT properties such as spray drying, moisture treatment, sintering and use of sugar-based disintegrants. In addition, taste-masking technologies, experimental measurements of disintegration times and clinical studies are also discussed.(59)

Pranjal Kumar Singh et al had explained the advantages of direct compression technique. Direct compression technology has been used for the compression of tablets, in which mainly contains hygroscopic and thermolabile active pharmaceutical ingredients (API). It acts as an alternative method to other tablet compression technologies because of its simplicity and economy. During the direct compression of powders of excipient and API is converted into the powder blend by using the different types of mills and sieves which produced identical size of particles, then it is compressed into the tablets. The present review highlights the latest advancements in excipients used in direct compression technologies.(60)

DRUG PROFILE

Drug: Levosalbutamol

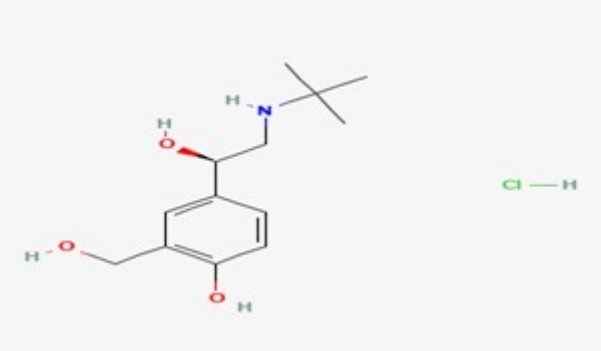

Figure 4: Structure of Levosalbutamol

IUPAC Name:

- 4-[(1*R*)-2-(*tert*-butylamino)-1-hydroxyethyl]-2-(hydroxymethyl) phenol [72]

Chemical formula:

- $C_{13}H_{21}NO_3$

Molecular weight: 239.31 g/mol.

Levosalbutamol, also known as levalbuterol, is a short-acting adrenergic receptor agonist used in the treatment of asthma and chronic obstructive pulmonary disease.

Physical properties;

1. Water solubility: 2.15 mg/ml

2. logP: 0.34

3. logS: -2

Pharmacodynamics:

- Levosalbutamol (Levoalbuterol) is a β_2-adrenoceptor agonist used as a bronchodilator for the treatment of asthma and as a uterine relaxant for the suspension of premature labour. Salbutamol has been marketed as a racemic mixture, although β_2-agonist activity resides almost exclusively in the (*R*)-enantiomer.
- The enantio-selective disposition of salbutamol and the possibility that (*S*)-salbutamol has adverse effects have led to the development of an enantiomerically pure (*R*)-salbutamol formulation known as **Levosalbutamol (Levalbuterol)**.

- Salbutamol is metabolised almost exclusively by sulphotransferase (SULT) 1 A3 to an inactive metabolite.
- (*R*)-Salbutamol is metabolised up to 12 times faster than (*S*)-salbutamol.
- This leads to relatively higher plasma concentrations of (*S*)-salbutamol following all routes of administration, but particularly following oral administration because of extensive metabolism by the intestine.
- Enantiomer concentrations are similar for the first hour following an inhaled dose, reflecting the fact that salbutamol in the lung probably undergoes little metabolism. Subsequently, (*S*)-salbutamol predominates due to absorption and metabolism of the swallowed portion of the inhaled dose.
- Following oral or inhaled administration of enantiomerically pure salbutamol, a small amount (6%) is converted to the other enantiomer, probably by acid-catalysed racemisation in the stomach.
- Tissue binding of salbutamol is not enantioselective and plasma protein binding is relatively low.
- Both enantiomers are actively excreted into the urine. Compared with healthy individuals, patients with asthma do not have substantially different pharmacokinetics of the salbutamol enantiomers, but they do appear to have less drug delivered to the lung following inhaled administration because of their narrowed airways.
- Levosalbutamol elicits an equal or slightly larger response than an equivalent dose of the racemic mixture.
- This is probably due to competitive inhibition between the enantiomers at β-adrenoceptors.
- Pharmacokinetic-pharmacodynamic relationships for levosalbutamol show relatively large interindividual variations.
- Functionally significant genetic polymorphisms have been identified for β_2-adrenoceptors, SULT1 A3 and organic action transporters, all of which affect the disposition or action of levosalbutamol. [63,64]

Mechanism of action

Activation of β_2 adrenergic receptors on airway smooth muscle leads to the activation of adenylate cyclase and to an increase in the intracellular concentration of 3',5'-cyclic adenosine monophosphate (cyclic AMP). The increase in cyclic AMP is associated with the activation of protein kinase A, which in turn, inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in muscle relaxation.

Levosalbutamol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Increased cyclic AMP concentrations are also associated with the inhibition of the release of mediators from mast cells in the airways. Levosalbutamol acts as a functional agonist that relaxes the airway irrespective of the spasmogen involved, thereby protecting against all bronchoconstrictor challenges.

While it is recognized that β_2 adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there are beta receptors in the human heart, 10–50% of which are β_2 adrenergic receptors. The precise function of these receptors has not been established. However, all β adrenergic agonist drugs can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, and restlessness symptoms, and/or electrocardiographic (ECG).[73]

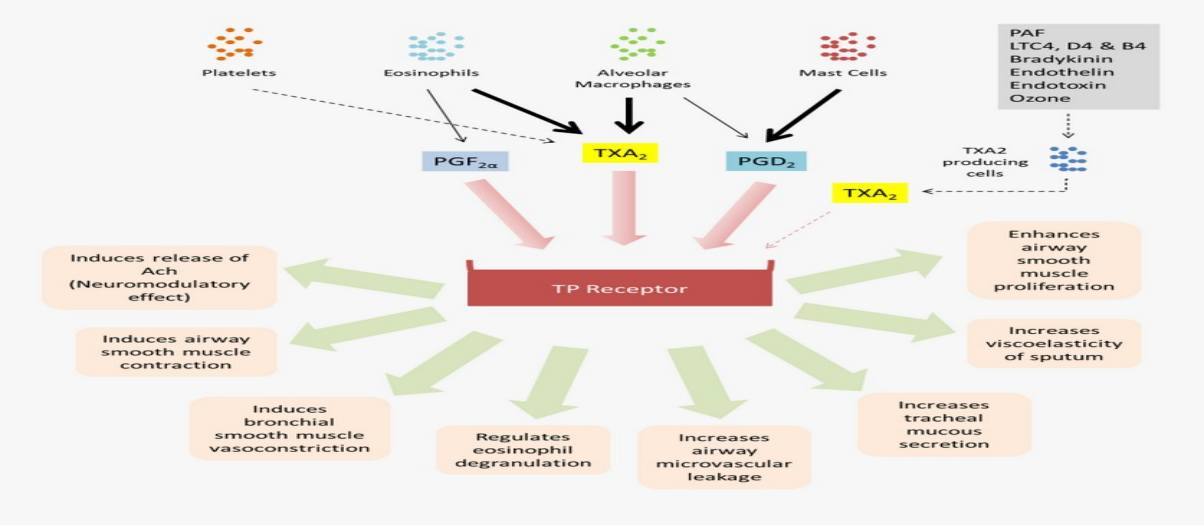

Figure 5: Mechanism of action of Levosalbutamol

Pharmacokinetics:

S.NO	PARAMETER	DATA
1.	Metabolism	By liver
2.	Excretion	By urine
3.	Elimination half life	3.3 – 4 hours
4.	T max	0.6 – 1.8 hours
5.	C max	1.4 – 3.9 mcg/L
6.	AUC	20 mins

Table 4: Pharmacokinetics of Levosalbutamol [74,75]

Drug Interactions

Drug-Drug Interactions: Levosalbutamol may interact with fluid retention drugs (furosemide), heart-related drugs (digoxin), corticosteroids (prednisone, fluticasone, budesonide), bronchodilators (salmeterol, vilanterol, formoterol, albuterol), and medicines treating nausea and vomiting (ondansetron).

Drug-Food Interactions: Limit alcohol intake since it may worsen the side effects like sleepiness and shakiness.

Drug-Disease Interactions: Levosalbutamol is to be cautiously used in heart, liver, kidney diseases, hyperthyroidism (overactive thyroid), stomach ulcer, seizure (fits), high blood pressure and diabetes.

Side Effects of Levosalbutamol

- Nausea,
- Vomiting,
- Restlessness,
- Tremor (Shakiness),

- Headache,
- Muscle Tightness,
- Dryness Or Soreness of The Throat,
- Dizziness,
- Sleepiness,
- Palpitations (Irregular Heartbeat),
- Nasal Congestion (Stuffy Nose),
- Cough And Increased Heart Rate.

Medicinal Uses

- Levosalbutamol Contains 'Levosalbutamol,' Which Is Also Known as Levalbuterol. Levosalbutamol Is A B_2 Adrenergic Receptor Agonist and Belongs to The Class Of 'Bronchodilators.' Levosalbutamol Is Used to Treat Asthma and Chronic Obstructive Pulmonary Disease (COPD).
- Levosalbutamol Helps to Relieve Coughing, Wheezing, And Shortness of Breath. Levosalbutamol Relaxes the Muscles in The Airways and Increases Airflow to The Lung.
- Levosalbutamol Makes Breathing Easier by Widening the Airways.

EXCIPIENTS PROFILE

Sodium Starch Glycollate

Structure:

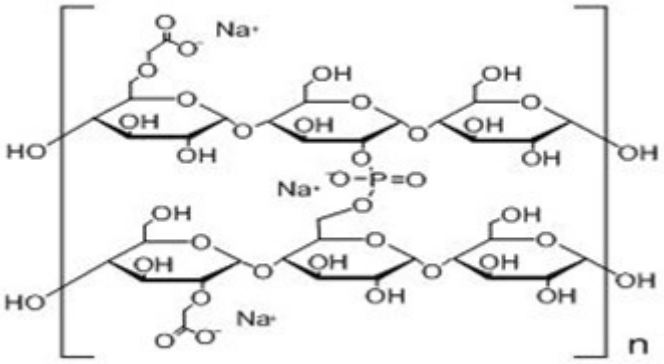

Figure 6: Structure of Sodium Starch Glycolate

Synonyms

Carboxy methyl starch(sodium salt). Explotab, sodium starch glycolate.

Expiosol. Explotab; Glycolys; starch carboxy methyl ether, sodium salt

Chemical names

Sodium carboxy methyl starch

Molecular Weight 429g

Melting point: Does not melt, but chars at approximately 200°C

Particle size distribution

100 % of particle less than 106 mm in size. Average particle size (450) is 38mm and by microscopy and sieving, respectively.

Solubility

Practically insoluble in methyl chloride. It gives a translucent suspension in water.

Application in pharmaceutical formulation technology

SSG widely used pharmaceutical dosage form in capsule and tablet as a disintegrant. SSG used preparation of tablet by both wet granulation method and direct compression, SSG used in concentration range is between 2-8% w/w. it is optimum concentration about 4% w/w. 2% w/w is sufficient show disintegration properties. It disintegration is not effected hardness of tablets.

Stability and storage conditions

Tablets prepared with sodium starch glycolate have good storage properties. Sodium starch glycolate is stable although very hygroscopic, and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause cracking. The physical properties of sodium starch glycolate remain unchanged for up to 3 years if it stored at moderate temperatures and humidity.

Incompatibilities

Sodium incompatible with ascorbic acid.

Safety:

Sodium starch glycolate is widely used in oral pharmaceutical formulation and is generally regarded as non toxic and non irritant material. However oral ingestion o large quantities may be handled.

Regulatory status:

Included in FDA inactive ingredients Guide (Oral capsules and tablets).[66]

CROSS POVIDONE [Poly Vinyl Pyrrolidine]

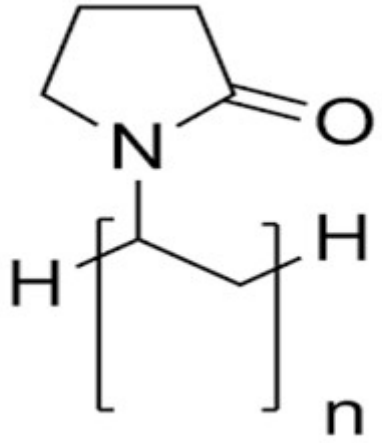

Figure 7: Structure of cross povidone

Synonyms :

Kollidon CL, Kollidon CL–M, Polyplasdone-XL, Polyplasdone XL-10

Chemical Name :

1- ethenyl – 2- pyrrolidinone homopolymer

Non-proprietary Name:

BP – Crospovidone PhEur -Crospovidonum USP NF – Crospovidone.

Description :

Crospovidone is white to creamy white finely divided, free flowing practically tasteless / nearly odourless, hygroscopic powder.

Solubility:

Practically insoluble in water and most organic solvents.

Functional Category:

Tablet disintegrant.

Application in Pharmaceutical Formulation:

Crospovidone is water insoluble tablet disintegrant and used at 2-8% concentration in tablets prepared by direct compression / wet and dry granulation methods. It exhibits high capillary activity and pronounced hydration capacity. Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer with the technique of co-evaporation. It can also used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to crospovidone in the presence of a suitable solvent and solvent is evaporated. This technique results in faster dissolution rate[67]

MANNITOL:

Structure:

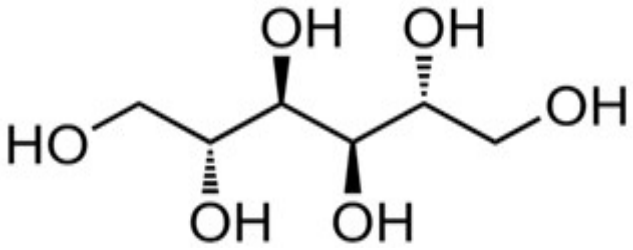

Figure 8: Structure of Mannitol

Properties:

- Mannitol is a polyol (sugar alcohol) and an isomer of sorbitol.
- Mannitol (C6H8(OH)6) is used in pharmaceutical products as a sweeting agent, tablet and capsule diluent, excipient for chewable tablets, a tonicity agent, and as a vehicle (bulking agent) for lyophilized preparations.
- Mannitol is industrially derived from the sugar fructose, and is roughly half as sweet as sucrose. Mannitol has a cooling effect often used to mask bitter tastes, and may be used in gums and candies.
- Mannitol is also found naturally in many species, including plants, bacteria, and fungi.

- Excessive consumption of mannitol may lead to a laxative effect, but the small amount used in pharmaceutical manufacturing processes would not normally pose this risk.
- Mannitol is deemed a safe food ingredient.
- Mannitol does not lead to elevated levels of blood sugar, as glucose may, and may be used in the food industry as a sweetener for patients with diabetes.
- Mannitol contains 1.6 calories per gram.
- On prescription status, mannitol is used as an intravenous osmotic diuretic and works by increasing the amount of fluid excreted by the body.[68]

MAGNESIUM STEARATE:

Structure:

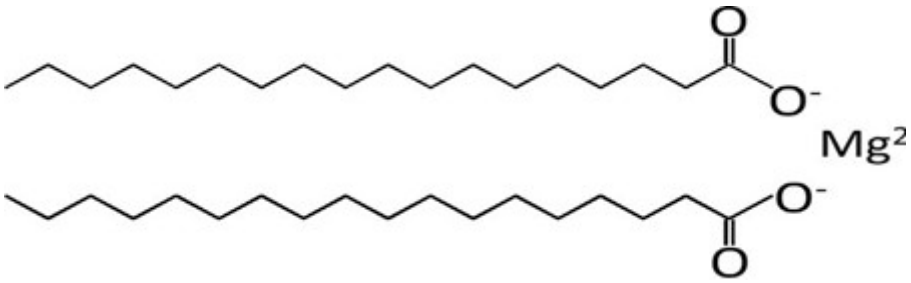

Figure 9: Structure of Magnesium Stearate

Properties:

- Magnesium stearate is produced by the reaction of sodium stearate with magnesium salts or by treating magnesium oxide with stearic acid.
- Some nutritional supplements specify that the sodium stearate used in manufacturing magnesium stearate is produced from vegetable-derived stearic acid.
- Magnesium stearate is often used as an anti-adherent in the manufacture of medical tablets, capsules and powders.
- In this regard, the substance is also useful because it has lubricating properties, preventing ingredients from sticking to manufacturing equipment during the compression of chemical powders into solid tablets; magnesium stearate is the most commonly used lubricant for tablets.
- However, it might cause lower wettability and slower disintegration of the tablets and slower and even lower dissolution of the drug.
- Magnesium stearate can also be used efficiently in dry coating processes.

- In the creation of pressed candies, magnesium stearate acts as a release agent and it is used to bind sugar in hard candies such as mints.
- Magnesium stearate is a common ingredient in baby formulas.[69,70]

TALC:

Structure:

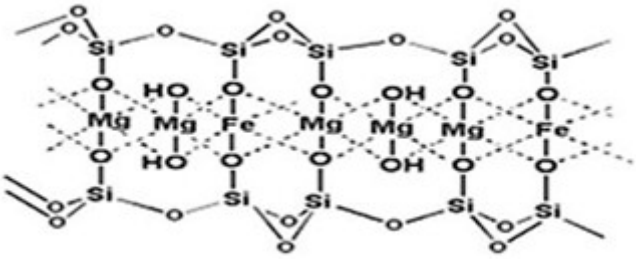

Figure 10: Structure of talc

Properties:

- Talc is a hydrous magnesium silicate having a chemical composition of Mg3Si4O10 (OH)2.
- It has been found in metamorphic belts containing ultramafic rocks.
- The various techniques have been used for talc mining viz straight forward drill, blast and open pit operations which are followed by crushing with the help of jaw crusher, cone crusher or impact crusher.
- Talc can be produced by hydration and carbonation of various minerals.
- Talc demonstrates the high functionality because it has been used as filler, lubricant and glidant in the pharmaceutical formulations as well as in cosmetic formulations as abrasive, absorbent, anticaking agent, opacifying agent and skin protectant.
- Now a day, it has been explored as a dissolution retardant in the controlled release products as well as a novel substrate for pellet design due to its physicochemical, physiological inert and inexpensive nature.
- Due to these attractive features, the wet spherical agglomerates of talc have been used as a substrate for coating and also have been used as a diluent in crystallo-co-agglomeration (CCA).
- Use of such high functionality excipient gives better products with lower costs, shorter time to market, and extended product lifecycle.

- India is a country having huge stores of rocks producing talc, hence, it's a need to systematically explore the talc for various novel pharmaceutical applications, so as to assist development of cost-effective pharmaceutical formulations.

As a tablet glidant and lubricant

- The Glidant activity of the talc is dependent upon particle size compatibility between the talc and the other powders in the formulation.
- As the talc particle size decreases its surface area increases and lubricant efficiency in plastic deforming binders/fillers increases but, even the smallest grade talc is not as effective as magnesium stearate.
- Very large talc aggregates greatly improve powder flow but may create problems in the formation of tablets at all.
- The disintegration behaviour of direct-compression tablet formulation is improved in the presence of talc, which is independent of particle size.
- In combination with magnesium stearate talc restores disintegration and dissolution properties impaired by magnesium stearate.
- Talc around 2.5 microns in size gives the best performance in tableting.
- Talc particles having size range 2 to 3 microns can be used as both lubricant and glidant.[71]

METHODOLOGY

I. DRUG-EXCIPIENT COMPATIBILITY STUDIES:

Compatibility of the drug and formulation is an important pre-requisite for formulation. Therefore, DSC and FTIR spectral analysis of pure drug levosalbutamol and physical mixture of levosalbutamol and super disintegrant were carried out. FTIR spectra of physical mixtures (1:1) of levosalbutamol and various excipients, as well as the formulation were performed to find out any possible drug excipient interaction by ATR method using FTIR spectrophotometer.[72]

FTIR spectrum: The FTIR spectrum was recorded. Infrared Spectrophotometer (Shimadzu). The pellets were prepared on KBr press using mixture of sample and KBr in about1:10 ratio. The spectrum was recorded over the wave no. range of 4000 to 400 cm.[73]

Levosalbutamol and excipients are subjected to FT-IR spectral analysis. The drug was Compatible with excipients since no significant changes were observed in intensity and position of the peaks in the spectra. The results are shown in graph.

II. PRE – COMPRESSION PARAMETERS

Pre compression evaluation:

Angle of Repose:

Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The prepared granules were allowed to flow out of the funnel orifice fixed at a height of 2 cm from the surface on a plane paper kept on the horizontal platform. The gradual addition of the granules from the funnel mouth forms a pile of granules at the surface this is continued until the pile touches the stem tip of the funnel. A rough circle is drawn around the pile base and the radius of the granule cone was measured. Angle of repose was then calculated with the use of the following formula:

$$\tan\theta = h / r$$

where,

θ= angle of repose

h= height of the pile

r = average radius of the powder cone

Bulk Density:

Bulk density of the granules was determined by pouring gently 10g of sample through a glass funnel into a 50ml graduated cylinder. The volume occupied by the sample was recorded. The bulk density will be calculated as follows:

Bulk Density (g/ml) = Weight of sample in grams / Volume occupied by the sample.

Tapped Density:

10 grams of granule sample was be poured gently through a glass funnel into a 50ml graduated cylinder. The cylinder will be tapped from height of 2 inches until a constant volume will be obtained. Volume occupied by the sample after tapping will be recorded and tapped density will be calculated as follows:

Tapped Density (grams/ml) = Weight of sample in grams / Volume occupied by the sample.

Carr's Index:

One of the important measures that can be obtained from bulk and tapped density determinations is the percent compressibility or the Carr's index, I, which is determined by the following equation,

I = Tapped Density – Bulk Density Tapped Density × 100

Haunser's ratio: Hausner's ratio is defined as a ratio of a tapped density to bulk density. It is a measure of relative importance of interparticulate interactions. A Hausner's ratio greater than 1.25 is considered to be an indication of poor flowability.

Method Tapped density and bulk density were measured and the Hausner's ratio was calculated using the formula,

Hausner's ratio = tapped density/ bulk density.

Flow Character	Compressibility index (%)	Hausner's ratio	Angle of repose
Excellent	<10	1.00-1.11	21-30
Good	11-15	1.12-1.18	31-35
Fair	16-20	1.19-1.25	36-40
Passable	21-25	1,26-1.34	41-45
Poor	26-31	1.35-1.45	46-55
Very poor	31-38	1.46-1,59	56-65
Very, very poor	>38	>1.60	>66

Table 5: Flow properties of the powder[74,75,76,77]

III. STANDARD CURVE OF LEVOSALBUTAMOL

Preparation of phosphate buffer pH 6.8:

- 6.805 g of monobasic potassium phosphate was dissolved in water and to that solution, 22.4 ml of 0.2 M sodium hydroxide solution was added and the volume was made 1000 ml with water.

Stock solution:

- Levosalbutamol, 10 mg was accurately weighed and it was dissolved in 10 ml of phosphate buffer at pH 6.8.
- Then the volume was made up to 100 ml with phosphate buffer pH 6.8. The above solution is served as stock solution.

Dilutions:

- From the stock solution 1 ml was taken and it was diluted with phosphate buffer of pH 6.8 to 10 ml to get 10 µg/ml.
- Similarly, 2 ml, 3 ml, 4 ml, 5 ml and 6 ml was taken from stock solution and diluted with phosphate buffer of 10 ml of pH 6.8 to get 20, 30, 40, 50, 60 µg/ml respectively.
- The absorbance of the resulting solutions is determined at nm using UV-visible spectrophotometer.

VI. DIRECT COMPRESSION

It is the simplest and most cost-effective tablet manufacturing technique for ODTs as they can be fabricated using conventional tablet manufacturing and packaging machinery and also due to availability of tableting excipients with improved flow, compressibility and disintegration properties, especially tablet disintegrants, effervescent agents and sugar-based excipients.

The manufacture of tablets by direct compression involves comparatively few steps and they include

1. Premilling of formulation ingredients (active drug substance and excipients)
2. Mixing of active drug substance with the powdered excipients (including the lubricant)
3. Compression of the mixed powders into tablets.[79]

Excipients used in the manufacture of tablets by direct compression method

The production of tablets by direct compression necessitates the inclusion of certain grades of excipients to achieve the correct powder flow and compression properties. These grades have typically been prepared by specific methods (such as spray-drying, wet granulation, slugging, crystallization) to achieve the correct physicochemical properties (e.g., particle size/distribution and flow properties).

Direct compression excipients used in the manufacture of tablets include

a. Diluents/fillers

Examples of diluents used in direct compression technology include

- Spray-dried lactose (Lactopress Spray-Dried, Lactopress Spray-Dried 250, Pharmatose DCL 11, Pharmatose DCL 14).
- Dicalcium phosphate (e.g., Encompress grades)
- Mannitol (granular or spray-dried grades, e.g., Pearlitol)
- Sorbitol
- Microcrystalline cellulose (e.g., Avicel pH-102)

b. Compression aid

Examples of commonly used compression aids include

- Microcrystalline cellulose (e.g., Avicel pH-102).

c. super Disintegrants:

- Pregelatinized starch (e.g., Starch 1500)
- Sodium starch glycolate (e.g., Explotab, Primogel)
- Croscarmellose sodium (e.g., Ac-Di-Sol)
- Crospovidone (e.g., Polyplasdone XL, Polyplasdone XL-10, Kollidon CL, Kollidon CL-M).

d. Lubricants and glidants

The types of lubricants and glidants used in the manufacture of tablets by direct compression method are similar to those used in other tablet manufacture methods and include:

- Lubricants (e.g., magnesium stearate, stearic acid, sodium stearyl fumarate)
- Glidants (e.g., talc, colloidal silicon dioxide).

Advantages of Direct Compression Technology:

1. Direct compression method requires fewer processing steps (unit operations) and less equipment. Therefore, the method is potentially less expensive than other methods used in tablet manufacture.
2. Tablet manufacture can be carried out without the involvement of moisture and heat. Hence, product stability is almost guaranteed.
3. Some direct compressible excipients possess inherent disintegration properties e.g., microcrystalline cellulose.
4. Tablets produced by direct compression method generally show faster dissolution times than those prepared by wet granulation.
5. This is because tablets manufactured by direct compression method disintegrate into primary particle state unlike those manufactured by wet granulation method which breaks down into granules and finally into primary particle state.

6. Changes in dissolution profile are less likely to occur in tablets manufactured by direct compression (if stored for a long time) than in those prepared by wet granulation.
7. Because direct compression excipients have a relatively high binding capacity, the pressure required to manufacture the desired hardness is, in general, less with direct compression vehicles than with conventional granulations, resulting in both higher production rates and longer machine life.
8. Lubrication is performed in the same vessel as powder mixing, thereby reducing both transfer losses and contamination of equipment.

Limitations of direct compression technology:

1. High-dose drugs may present problems with direct compression if it is not easily compressible by itself. The choice of excipients used in the manufacture of tablets by direct compression technology is highly restricted since most materials do not have inherent binding properties. Low-dose drugs may not be uniformly blended.
2. Direct compression excipients are often more expensive than other tablet excipients used in wet granulation or slugging. A vast majority of drug substances are rarely so easy to tablet by direct compression. Thus, in choosing a vehicle, it is necessary to consider the dilution potential of the major filler-binder (i.e., the proportion of the drug substance that can be satisfactorily compressed into tablets with a direct compressible excipient).
3. Direct compression blends are subject to unblending/ segregation in post-blending handling steps. This arises from lack of moisture in the blends (which may give rise to static charges leading to unblending) or variations in particle size or density of formulation ingredients. This problem can be solved by applying the concept of ordered blending and/or use of excipients of narrow particle size ranges.
4. In some instances, direct compression excipients may interact with the drug substance. A good example of such reaction is that which occurs between amine compounds and spray-dried lactose and this results in a yellow discolouration of the tablets.
5. Tablet defects such as sticking, capping and lamination are usually pronounced in tablets manufactured by direct compression method.

VII. EVALUATION OF FAST DISSOLVING TABLETS

1. Weight variation:

The test for uniformity of weight is performed by weighing individually 20 tablets randomly selected from a tablet batch and determining their individual weights. The individual weights are compared with the average weight.

The sample complies with USP standard if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Coated tablets are exempted from these requirements but must conform to the test for content uniformity.

2. Friability: Friability Attempts for decreasing the disintegration time increase the friability of ODTs than the conventional tablets. Dosage forms like Zydis are very fragile. Friability is a measure of mechanical strength of the tablet. If a tablet has more friability, it may not remain intact during packaging, transport or handling. Roche Friabilator is used to determine the friability by following procedure. Pre weighed tablets are placed in the Friabilator. Friabilator consist of a plastic chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets are rotated in the Friabilator for at least 4 minutes. At the end of test tablets are dusted and reweighed; the loss in the weight of tablet is the measure of friability and is expressed in percentage as:

% Friability = 1- (loss in weight / Initial weight) X 100

Figure 11: Friabilator

3. Hardness (Crushing strength): Tablet hardness is measured with hardness testers like Monsanto. A tablet is placed in the hardness tester and load required to crush the tablet is measured. The hardness of ODTs is generally kept lower than conventional tablets as increased hardness delays the disintegration of the tablet. A good compromise between

mechanical strength and disintegration time is achieved for a satisfactory mouth dissolving formulation.

Figure 12: Hardness tester

4. Wetting time: Determination of wetting time is also important. It also helps in studying the effect of various excipients in the disintegration of the tablet. A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small Petri dish (ID = 6.5 cm) containing 6 ml of phosphate buffer pH 6.8. A tablet as put on the paper, and the time for complete wetting was measured.

5. Water absorption ratio:

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of distilled water. A tablet was put on the paper and time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R, was determined using equation:

$$R = Wa - Wb / Wb \times 10$$

Where, Wb = weight of the tablet before water absorption

Wa = weight of the tablet after water absorption

6. Disintegration time: According to the European pharmacopoeia the fast disintegrating or Oro dispersible tablets should disintegrate within 10-30 seconds without leaving any residue on the screen. However, it is difficult to assess the disintegration rate even in small amounts of water. Further the conventional test employs a volume of 900 ml of distilled water compared to the volume of saliva in humans, which is limited to a few ml. Thus, the disintegration rate obtained from conventional test does not appear to reflect the actual disintegration rate in human mouth. In another method, a modified DT apparatus is used.

Here a wire basket of 3cm height and 2 cm diameter and mesh size of #10 is placed above a beaker containing 900 ml of simulated saliva. The basket is so positioned in the liquid that it contains only 6 ml of the liquid. The assembly is supported with a heater to maintain temperature at 37°C and a magnetic stirrer. DT is noted at 25 rpm. One of the simplest methods is to take 6ml of simulated saliva in a measuring cylinder and place the tablet in it. The liquid is neither shaken nor stirred and DT is noted.

Figure 13: Disintegration Apparatus

7. Drug Content

Apparatus:

A shimadzu model 1800 double beam UV- Visible spectrophotometer with spectral width of 1 nm, wavelength accuracy of ± 0.1 nm and a pair of 10 mm matched quartz cell was used to measure absorbance of all the solutions. Spectra were automatically obtained by UV-Probe system software.

Selection of detection:

Wavelength Solution of drug was scanned over the range of 200-400 nm. It was observed that the drug showed considerable absorbance at 277 nm for Levosalbutamol was selected as the wavelength for detection.

Preparation of standard stock solutions:

Levosalbutamol was weighed (100mg) and transferred to 100ml volumetric flasks and make up the volume up to the mark with distilled water and the final concentration of solution containing 1000 µg/ml of LSS.

Preparation of working solutions Aliquot from the stock solution of Levosalbutamol was appropriately diluted with distilled water to obtain working standard of Levosalbutamol

8. In vitro dissolution test: In vitro dissolution study has to be performed by using USP type II Apparatus (paddle type at 50 rpm. Phosphate buffer pH 6.8, 900 ml is mainly used as dissolution medium which is required to maintain at 37±0.5°C. Aliquot of (10ml) dissolution medium is required to withdraw out at specific time interval (2min) and then it is required to subject for process of filtration. The amount of drug dissolved was determined by UV Spectrophotometer by measuring the absorbance of the sample. Three trials of each batch were performed and average % drug release with standard deviation was calculated and recorded.

Apparatus-II - Paddle Apparatus

- Method of First Choice.
- The dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started.
- A small, loose piece of no reactive material such as not more than a few turns of wire helix may be attached to dosage units that would otherwise float.
- Other validated sinker devices may be used.
- Useful for Tablets, Capsules, Beads, Delayed release, enteric coated dosage forms.
- Standard volume: 900/1000 ml.[82,83]

Advantages:

- Easy to use.
- Robust.
- Can be easily adapted to apparatus.
- long experience.
- pH changes possible.
- Can be easily automated which is important for routine investigations.

Acceptance criteria:

- **L1-6** No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time.
- **L2-6** The average value of the **12** dosage units **(L1 + L2)** lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more

than 10% of the labelled content outside each of the stated ranges; and none is more than 10% of labelled content below the stated amount at the final test time.

- **L3-12** The average value of the **24** dosage units **(L1 + L2 + L3)** lies within the stated ranges and is not less than the stated amount at the final test time; not more than 2 of the 24 dosage units are more than 10% of labelled content outside each of the stated ranges; not more than 2 of the 24 dosage units are more than 10% of labelled content below the stated amount at the final test time; and none of the 24 dosage units is more than 20% of labelled content below the stated content at the final test time; none of the units are more than 20% of labelled content outside each of the stated ranges or more than 20% of labelled content below the stated amount at the final test time

VIII. Stability Study Protocol:

The stability testing is one of the processes for drug development. Stability data for the stability studies are used to determine the storage conditions and packaging materials for a bulk of the prepared formulated products. The stability studies are used to determine the expiry date of the substance. These stability protocols are pre-requisite for the stability studies and necessary a written document that has a key of instructions for the regulation and well-controlled stability studies. Each formulation has different types of containers to be packed hence the protocol can also depend on the type of the drug substance. The protocols can also depend on the drugs already in the market and the newly prepared drugs. The protocols should reflect the regions that are proposed by the ICH. A well-designed stability study protocol should include the following information:

1. Number of batches.

2. Containers and Closures.

3. Orientation of storage of containers.

4. Sampling time points.

5. Test storage conditions.

6. Test parameter

1. Number of batches:

Stability testing is carried out in batches as performing the stability studies in a single step is difficult hence, they are divided into batches. For a product that is stable without any reactions the stability studies are performed on a single batch. When the substances are unstable or not when the drug is newly registered the stability studies are performed on three batches. When any one of the batches shows unstable activity then the stability is performed for six respective batches if the unstable repeats, then the whole product formulated must be discarded as they cannot be administered. The initial data is not a full-scale production batch, the first three batches should be post approval which are long term studies using the same protocol as in approved drug applications. The data collected from the laboratory are not accepted for the primary stability data. The selections of batches contribute to the random sample from the population of pilot or production batches.

2. Containers and Closures:

The selection of containers and closures is very important and stability studies on containers and closures as when the products are to be packed in the suitable medium. The packaging materials include the aluminium strip packs, blister packs, Alu-Alu packs, HDFE bottles etc. this may also include the secondary packaging but not the shippers. The products packed in all closures are to be tested for the stability studies as the unsuitable container can degrade the drug physically. For, the bulk containers the prototype containers are allowed. While packaging is done the prepared drug is placed in the suitable containers as the containers can contaminate the product and shelf life of the drug can be reduced than the actual time.

3. Orientation of storage of containers:

The samples of solutions, semi-solid drug products for stability studies must be placed upright in such a way that the drug encounters the containers. This helps to know that when the drug encounters the containers is undergoing any chemical changing which leads to the degradation of the drug. This degradation may be due to the absorption or loss of water.

4. Sampling time points

The testing is important at time intervals to establish the stability profile of the new drug substance. The products with a shelf life of months in the first year, then 6 months for the second year and then yearly thereafter throughout the prediction of shelf-life. In the case of accelerated stability studies, a minimum of three time points like 0, 3, and 6 months. In case, when the same product of different strength, size etc to be tested. Retained stability testing can be used which involves a smaller number of points. The reduced testing plans are based on the bracketing and matrixing statistical designs. Bracketing is the design only when the samples on the certain design factors such as strength and package size are tested at all the three time points as in full design. The factors that can be matrixes can include the strength, batches, container sizes, and intermediate time points.

5. Test storage conditions

The storage conditions to be selected based on the climatic zones in which the product must be marketed. General recommendation on the storage conditions has been given by ICH, CPMP, and WHO.

Intended Storage Condition	Type of Stability Studies	Storage Conditions for					
		ICH			WHO		
		Temperature (°C)	RH* (%)	Time (Months)	Temperature (°C)	RH (%)	Time (Months)
Room Temperature	Long term	25 ± 2°C	60 ± 5%	12	25 ± 2°C	60 ± 5%	12
		30 ± 2°C	65 ± 5%				
	Intermediate	30 ± 2°C	65 ± 5%	6	--	--	--
	Accelerated	40 ± 2°C	75 ± 5%	6	--	--	--
Refrigerator	Long term	5 ±3°C	--	12	5 ±3°C	--	
	Accelerated	25 ± 2°C	60 ± 5%	6			
Freezer	Long term	-20 ± 5°C	--	12	-20 ± 5°C		

*Relative Humidity (RH)

Table 6: Types of stability studies

6. Test parameters:

The test parameters used in the stability studies must be evaluated of the stability samples. The test of sample mainly includes the quality, purity, efficacy, and identity which can be depending upon the climatic conditions. Therefore appearance, assay, degradation products, microbiological tests include sterility, preservative measures etc. The stability testing batches should also reach the testing parameters including the heavy metals, residue of ignition, residual solvents, etc. These tests have also been discussed in the ICH guidelines (QA6). (80,81,82)

RESULTS AND DISCUSSION

DRUG EXCEPIENT COMPATABILITY STUDY

FTIR spectrum of levosalbutamol:

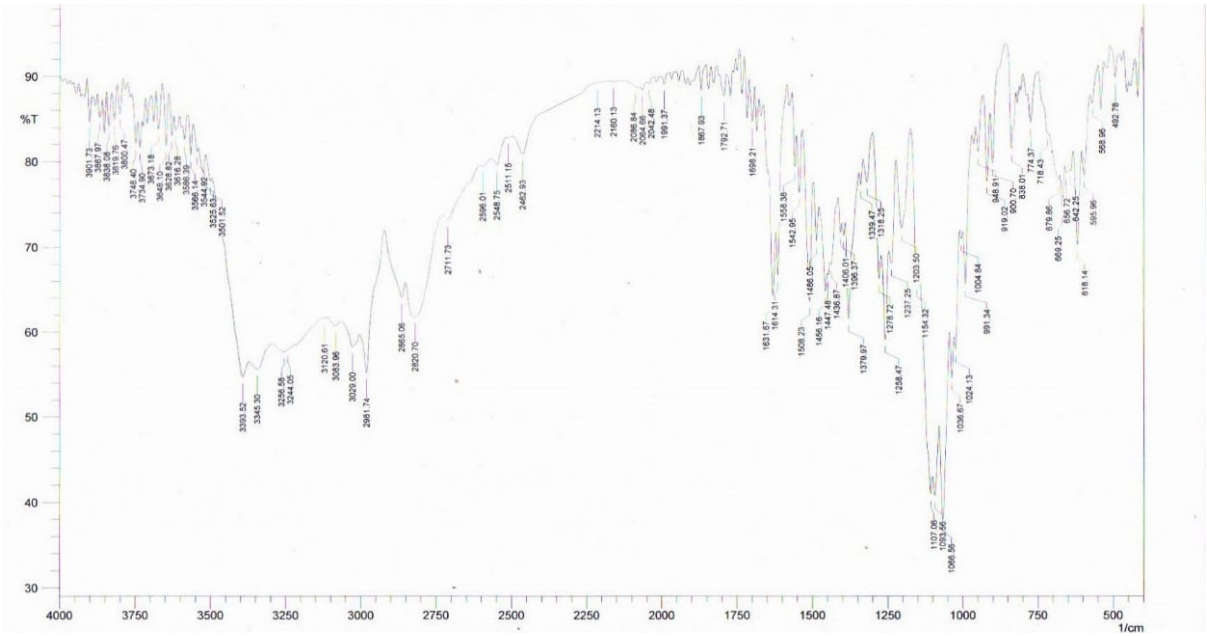

Figure 14: FTIR spectrum of Levosalbutamol

FTIR Spectrum of Sodium Starch Glycolate:

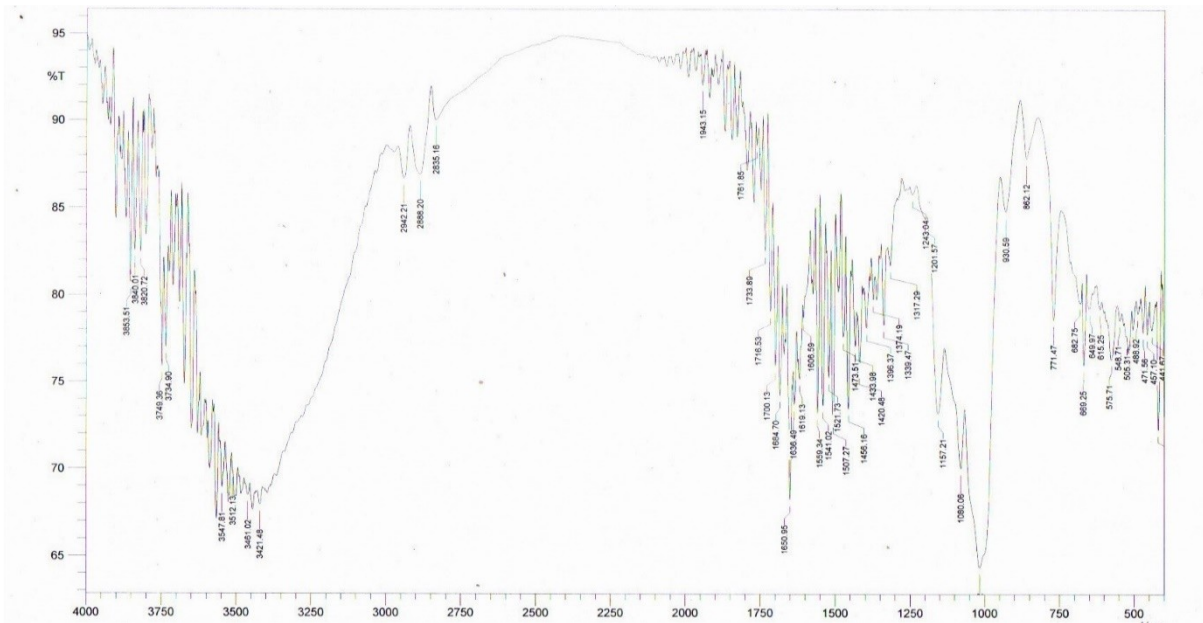

Figure 15: FTIR spectrum of Sodium Starch Glycolate

FTIR Spectrum of Poly vinyl pyrrolidone:

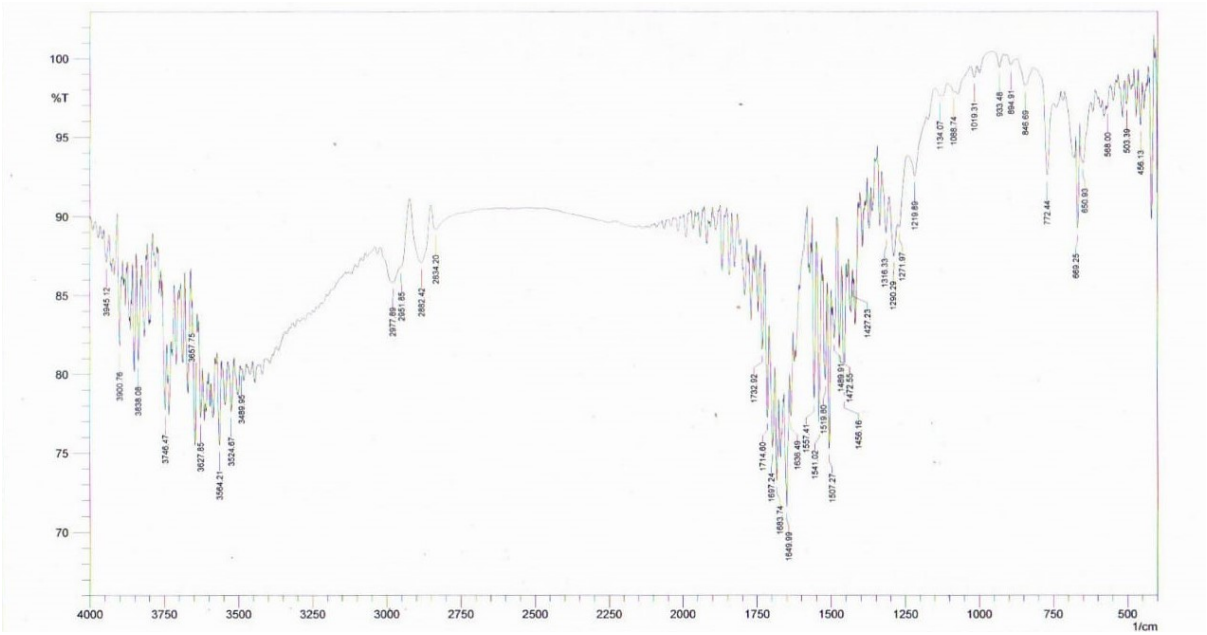

Figure 16: FTIR spectrum Poly vinyl pyrrolidone

FTIR Spectrum of Mannitol:

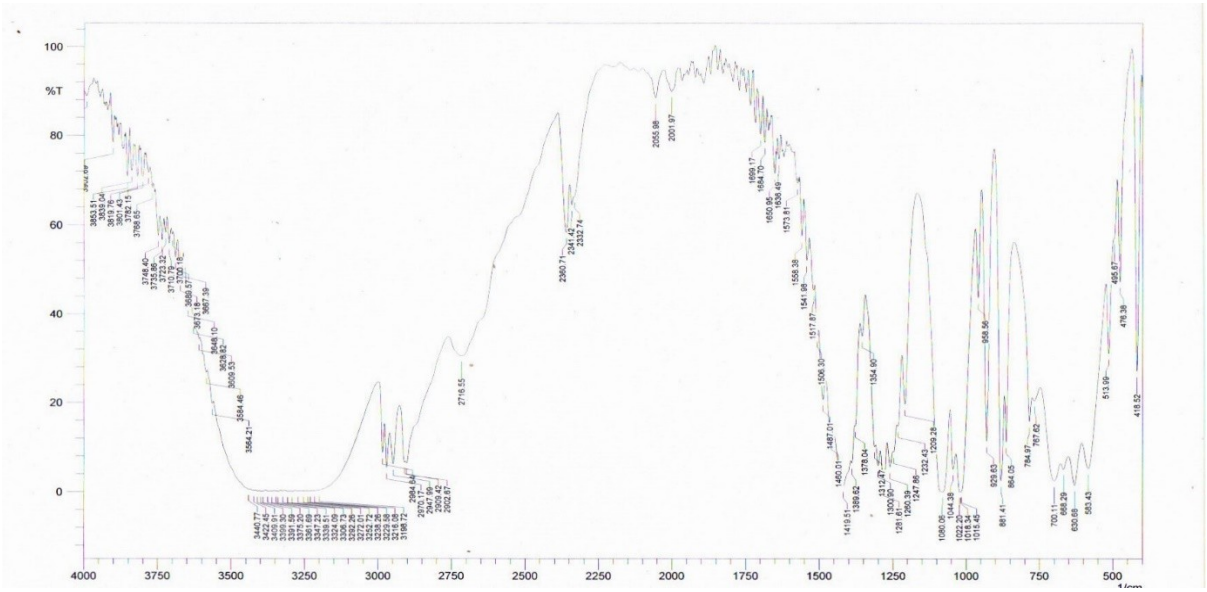

Figure 17: FTIR spectrum mannitol

FTIR Spectrum of Physical Mixture of levosalbutamol:

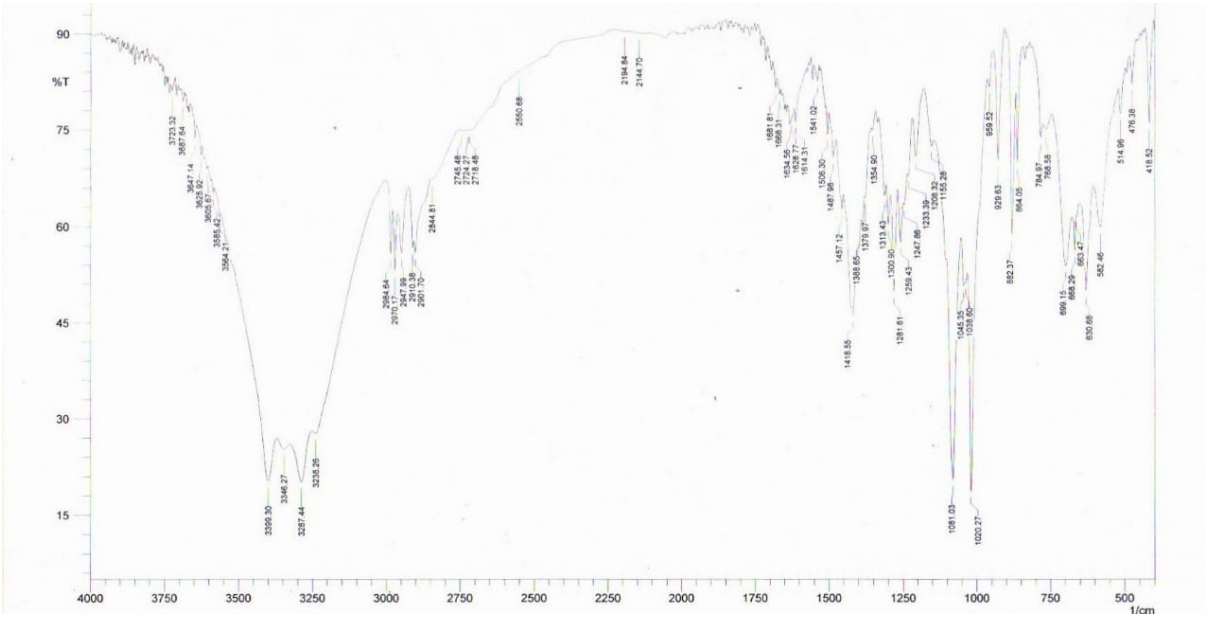

Figure 18: FTIR spectrum of Physical Mixture of Levosalbutamol

STANDARD CURVE OF LEVOSALBUTAMOL:

S NO	Concentration (µg/ml)	Absorbance (nm)
1	10	0.090
2	20	0.095
3	30	0.150
4	40	0.207
5	50	0.257
6	60	0.307
7	70	0.357

Table 7: Calibration curve of Levosalbutamol

PREFORMULATION STUDIES

Flow properties of the drug:

Bulk density	0.283	-
Tapped density	0.342	-
Angle of repose	45	passable
Compressibility index (%)	23%	passable
Hausner's ratio	1.33	passable

Table 8: Flow properties of the drug

Flow properties of the formulation:

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (θ)	Compressibility index (%)	Hausner's ratio	Flow ability
F 1	0.283	0.363	38.50	19.9%	1.25	Fair
F 2	0.289	0.357	39.59	19.7%	1.25	Fair
F 3	0.284	0.360	41.10	19.9%	1.25	Passable
F 4	0.286	0.356	39.88	20%	1.246	Fair
F 5	0.288	0.254	38.45	21%	1.26	Fair

Table 9: Flow properties of the formulation I

EVALUATION OF ORO DISPERSIBLE TABLETS:

Post compression parameters:

Hardness and Friability:

Formulation	Hardness (kg/Cm^2)	Friability (%)
F 1	3.83	0.63
F 2	3.99	0.75
F 3	3.91	0.88
F 4	3.90	0.69
F 5	3.96	0.81

Table 10: Hardness of the formulation

Weight variation test:

As per USP Standards	Max % deviation allowed	As per IP/BP standards
130 mg or less	10 %	80 mg or less
130 to 324 mg	7.5 %	80 to 250 mg
More than 325 mg	05 %	More than 250 mg

Table 11: Weight variation test – Standard Value

Tablet no	F 1	F 2	F3	F 4	F 5
1	0.107	0.1029	0.1043	0.1025	0.1089
2	0.1039	0.1025	0.1033	0.0997	0.1088
3	0.1083	0.0993	0.105	0.098	0.112
4	0.1046	0.1045	0.1056	0.1001	0.1025
5	0.109	0.0989	0.0996	0.1043	0.108
6	0.101	0.1112	0.1043	0.096	0.1073
7	0.103	0.1029	0.1113	0.1115	0.098
8	0.108	0.1027	0.1115	0.1109	0.1058
9	0.097	0.1055	0.1036	0.1078	0.1049
10	0.1075	0.1002	0.1099	0.1088	0.1949
11	0.1033	0.1036	0.1056	0.1008	0.1059
12	0.1045	0.1047	0.1023	0.1043	0.1994
13	0.0989	0.1089	0.1028	0.1056	0.0978
14	0.1085	0.0993	0.1112	0.1130	0.1025
15	0.1053	0.0996	0.1048	0.0986	0.1028
16	0.0999	0.1025	0.1013	0.1003	0.1078
17	0.1053	0.1089	0.1075	0.1027	0.0014
18	0.1044	0.1113	0.1081	0.1054	0.0019
19	0.1058	0.1029	0.0996	0.1027	0.1089
20	0.1003	0.0990	0.1088	0.1079	0.0973
Result	**Pass**	**Pass**	**Pass**	**Pass**	**Pass**

Table 12: Weight variation test of the formulation

Formulation	Wetting time (secs)	Water absorption ratio (%)	Disintegration time (secs)	% Drug content
F 1	0.47	50	16	99.1
F 2	0.52	47	22	95.4
F 3	0.55	51	19	96.8
F 4	0.57	45	26	95.9
F 5	0.51	53	21	96.7

Wetting time, Water absorption ratio, Disintegration time, Assay of the formulation:

Table 13: Wetting time, Water absorption ratio, Disintegration time, Assay of the formulation

Dissolution profile of F 1:

Sampling time	% Amount of drug Release (%)			
	Trial 1	Trial 2	Trial 3	Mean dissolution rate
0	0	0	0	0
2	16.1	19.6	18.2	18
4	28	27.1	26.4	27.2
6	43.2	39.6	37	40
8	51.2	53.4	49	51.2
10	62.4	63	61.4	62.26
15	86.6	87.1	86.7	86.8
30	91.3	90.3	91.6	91
45	94.1	93.5	94	93.8
60	96	95.2	95.3	95.5

n = 3

Table 14: Dissolution profile of F1

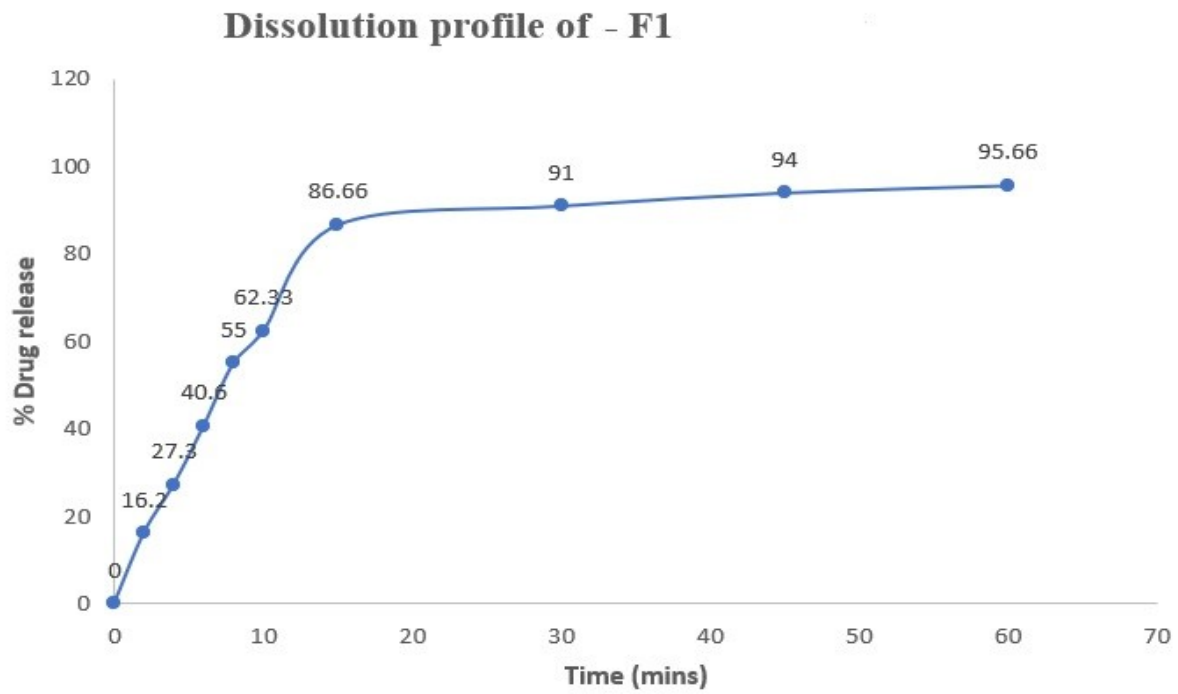

Figure 19: Dissolution profile of F1

Dissolution profile of F 2:

Sampling time	Percentage of drug Release (%)			
	Trial 1	Trial 2	Trial 3	Mean
0	0	0	0	0
2	12	14.3	14.2	13.5
4	25.2	21.8	23.6	24
6	40.1	41.4	38.2	39.9
8	52.1	54.3	50.4	52.3
10	64.4	61.1	62.5	62.6
15	79.5	76.7	75.3	77.2
30	85.3	86.6	84.1	85.33
45	90.2	90.1	92.8	91
60	91.5	90.6	94.2	92.1

n =3

Table 15: Dissolution profile of F2

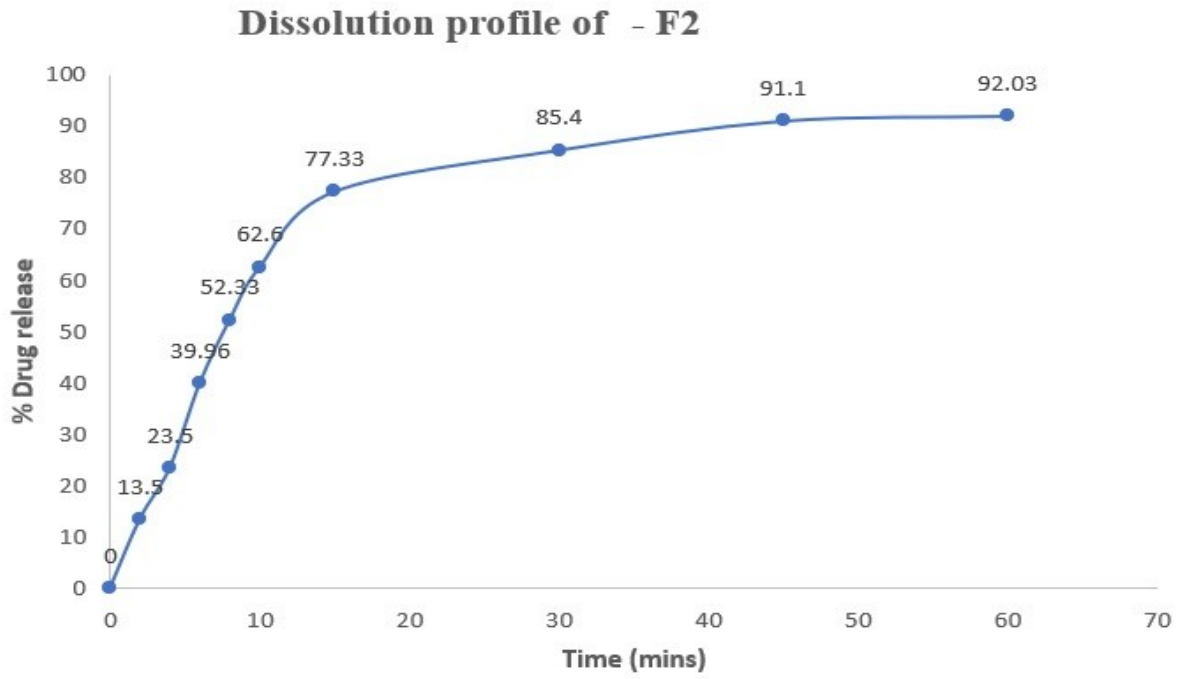

Figure 20: Dissolution profile of F2

Dissolution profile of F 3:

Sampling time	Percentage of drug Release (%)			
	Trial 1	Trial 2	Trial 3	Mean
0	0	0	0	0
2	13.1	12.7	12.5	12.8
4	27.5	28.2	28.8	28.2
6	43.3	44.8	44.6	44.2
8	52.3	55.6	56.7	54.9
10	57.1	58.7	59.8	58.53
15	81.2	81.6	80.8	81.2
30	86.3	85.5	86.7	86.16
45	90.4	91.3	91.7	91.13
60	94.3	95.7	95.2	95

n = 3

Table 16: Dissolution profile of F3

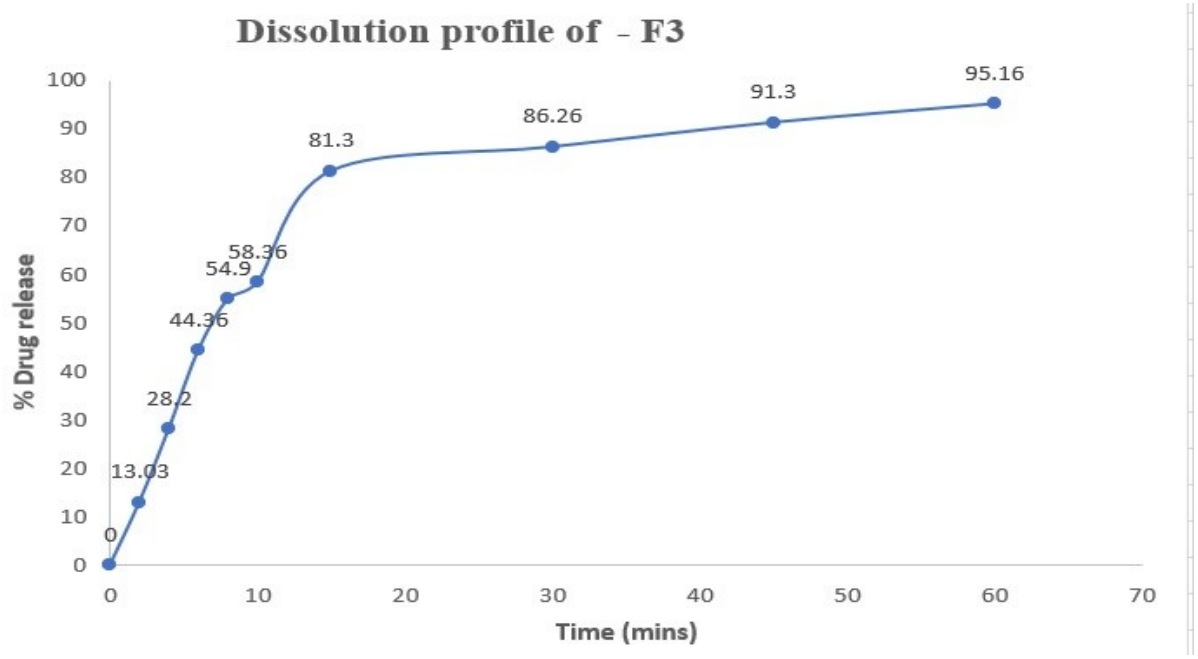

Figure 21: Dissolution profile of F3

Dissolution profile of F 4:

Sampling time	Percentage of drug Release (%)			
	Trial 1	Trial 2	Trial 3	Mean
	0	0	0	0
2	13.2	14.5	14.7	14.1
4	25.3	26.6	27.5	26.46
6	39.5	40.3	41.6	40.5
8	47.2	46.8	47.9	47.3
10	53.7	55.3	55	54.3
15	78.8	75.7	76.6	77
30	83.7	84.8	84.9	84.5
45	87.7	88.4	89.1	88.4
60	91.7	90.4	94.4	92.2

n = 3

Table 17: Dissolution profile of F4

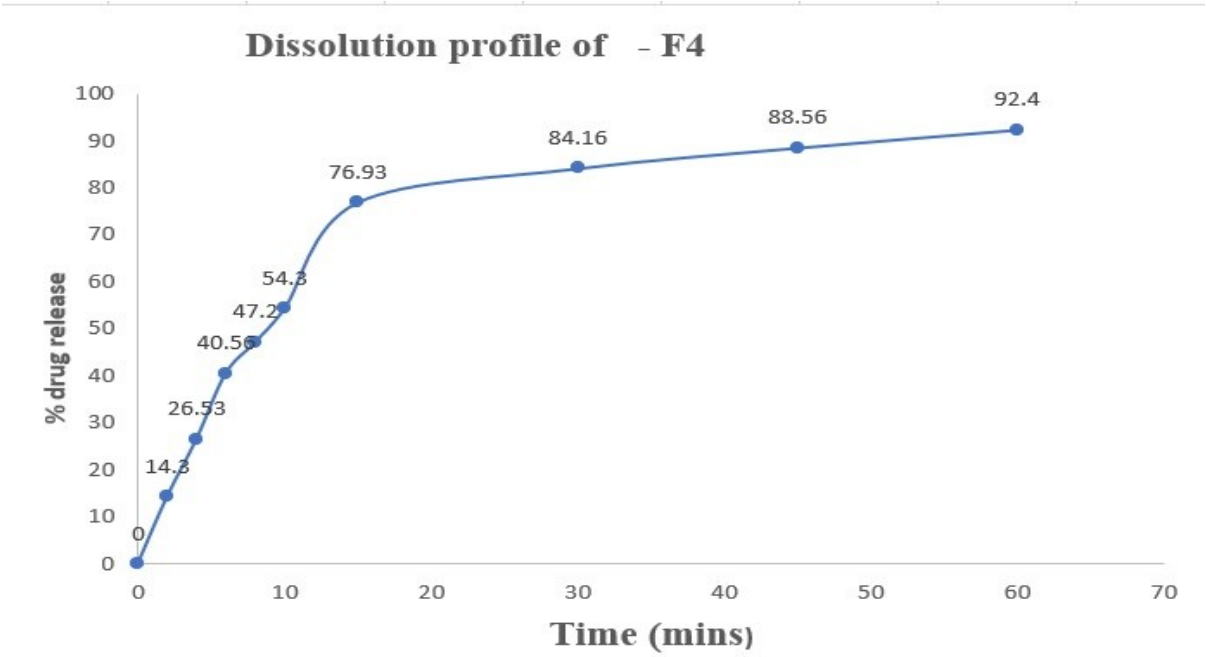

Figure 22: Dissolution profile of F4

Dissolution profile of F 5:

Sampling time	Percentage of drug Release (%)			
	Trial 1	Trial 2	Trial 3	Mean
	0	0	0	0
2	11.7	12.5	13.3	12.5
4	25.7	26.6	27.6	26.6
6	36.6	37.8	38.5	37.6
8	45.9	46.3	47.5	46.5
10	50.6	51.8	50.8	51.06
15	73.9	74.7	75.8	74.8
30	78.2	79.6	78.9	78.9
45	81.9	80.7	80.5	81.03
60	86.5	87.3	88.7	87.5

n = 3

Table 18: Dissolution profile of F5

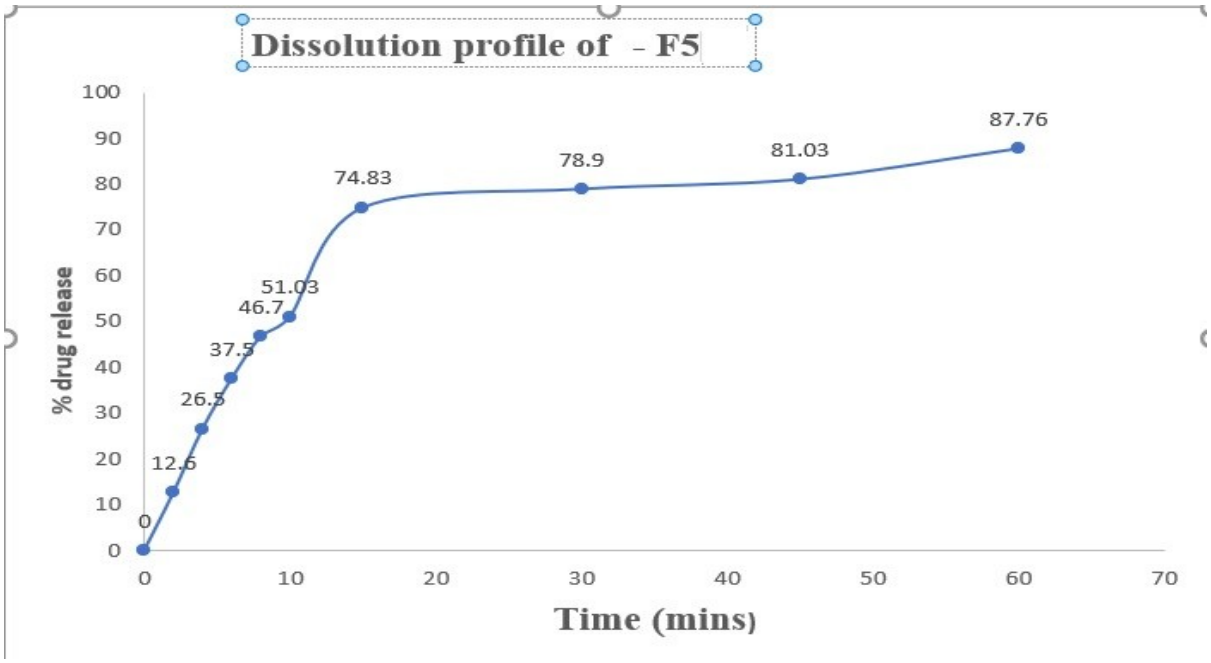

Figure 23: Dissolution profile of F5

Comparative Dissolution profile of F1 to F5:

Sampling time	Percentage of drug Release (%)				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
2	16.4	13.2	13.05	14.5	12.4
4	27.1	23.6	28.4	26.55	26.4
6	40.4	39.95	44.56	40.76	37.8
8	56	52.36	54.7	47.4	46.5
10	62.43	62.8	58.26	54.2	51.23
15	86.46	77.53	81.6	76.73	74.53
30	90	85.7	86.46	84.36	78.7
45	93	91.3	91.7	88.46	81.67
60	95.46	92.05	95.36	92.7	87.56

Table 19: Comparative Dissolution profile of F1 to F5

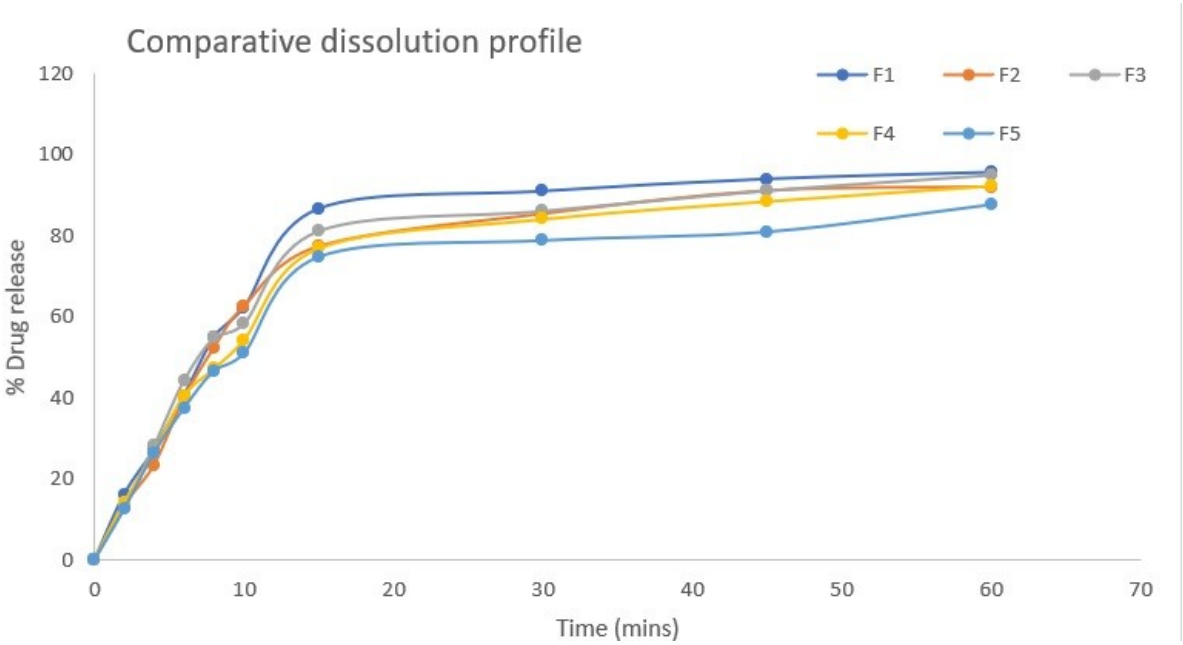

Figure 24: Comparative Dissolution profile of F1 to F5

EVALUATION OF STABILITY STUDIES:

Batch 1: 30°c and 60% RH

Batch 2: 35°c and 65% RH

Batch 3: 45°c and 75% RH

Sampling time: 15 days

Physical appearance:

Colour: White

Odour: Odourless

Hardness and Friability of the Formulation:

Formulation	Hardness (kg/Cm^2)	Friability (%)
Batch 1	3.81	0.69
Batch 2	3.84	0.91
Batch 3	3.77	0.83

Table 20: Hardness and Friability of the Formulation

Weight variation test :

As per USP Standards	Max % deviation allowed	As per IP/BP standards
130 mg or less	10 %	80 mg or less
130 to 324 mg	7.5 %	80 to 250 mg
More than 325 mg	05 %	More than 250 mg

Table 21: Weight variation test – Standard Value

Tablet no	Batch 1	Batch 2	Batch 3
1	0.1024	0.107	0.1092
2	0.0932	0.1012	0.1082
3	0.0997	0.0998	0.1071
4	0.1021	0.0997	0.1091
5	0.1010	0.1031	0.1034
6	0.0996	0.1022	0.1000
7	0.1031	0.1073	0.112
8	0.1048	0.0999	0.1023
9	0.1081	0.0998	0.1023
10	0.0998	0.1022	0.1056
11	0.1032	0.0997	0.1026
12	0.1023	0.1031	0.1058
13	0.1050	0.1026	0.1025
14	0.0999	0.1036	0.1002
15	0.0983	0.1059	0.1003
16	0.0997	0.1057	0.1087
17	0.1058	0.1022	0.1056
18	0.107	0.1032	0.1029
19	0.1058	0.1023	0.110
20	0.1009	0.1056	0.1098

Result	**Pass**	**Pass**	**Pass**

Table 22: Weight variation test of the formulation

Wetting time, Water absorption ratio, Disintegration time, Assay of the formulation

Formulation	Wetting time (secs)	Water absorption ratio (%)	Disintegration time (secs)	% Drug content
Batch 1	0.52	48	18	93.6
Batch 2	0.56	45	23	91.6
Batch 3	0.58	42	25	89.5

Table 23: Wetting time, Water absorption ratio, Disintegration time, Assay of the formulation

Dissolution profile of Batch 1 to Batch 3:

Sampling time	Percentage of drug Release (%)		
	Batch 1	Batch 2	Batch 3
0	0	0	0
2	13.4	13.8	13.6
4	25.9	23.5	23.4
6	39.6	38.4	30.8
8	53.4	51.2	46.1
10	59.4	59.9	55.6
15	75.7	72.4	68.9
30	83.9	83.7	81.3
45	88.4	86.8	85.4
60	92.8	89.9	86.4

Table 24: Dissolution profile of Batch 1 to Batch 3

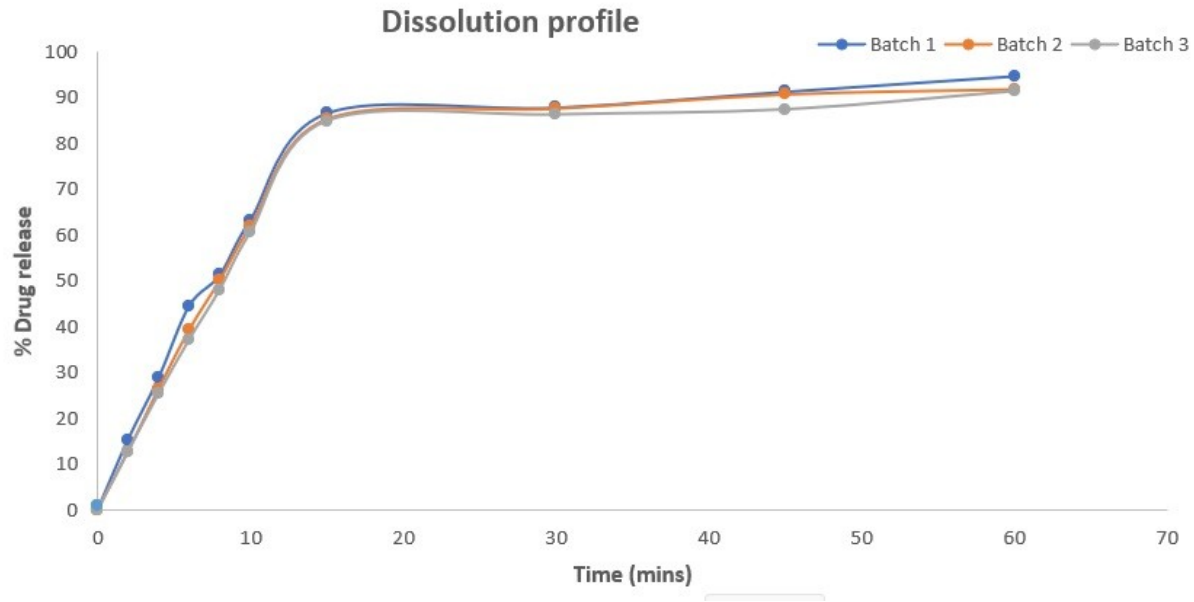

Figure 25: Dissolution profile of Batch 1 to Batch 3

Batch 1: 30°c and 60 % RH

Batch 2: 35°c and 65 % RH

Batch 3: 45°c and 75 % RH

Sampling time: 30 days

Physical appearance:

Colour: White

Odour: Odourless

Hardness and Friability of the Formulation:

Formulation	Hardness (kg/Cm^2)	Friability (%)
Batch 1	3.76	0.68
Batch 2	3.85	0.94
Batch 3	3.71	0.89

Table 25: Hardness and Friability of the formulation

Weight variation test

As per USP Standards	Max % deviation allowed	As per IP/BP standards
130 mg or less	10 %	80 mg or less
130 to 324 mg	7.5 %	80 to 250 mg
More than 325 mg	05 %	More than 250 mg

Table 26: Weight variation test – Standard Value

Tablet no	Batch 1	Batch 2	Batch 3
1	0.1015	0.1023	0.112
2	0.1056	0.1073	0.1080
3	0.1078	0.1042	0.1074
4	0.1046	0.1049	0.1015
5	0.0997	0.1089	0.1075
6	0.1011	0.1034	0.1045
7	0.1052	0.1055	0.108
8	0.1006	0.1087	0.1086
9	0.1088	0.1035	0.1096
10	0.0999	0.0997	0.1071
11	0.1005	0.0997	0.1071
12	0.1050	0.1036	0.1077
13	0.1012	0.1028	0.1006
14	0.1005	0.1025	0.1038
15	0.1001	0.1046	0.1079

16	0.1058	0.1078	0.1077
17	0.1079	0.1040	0.114
18	0.1063	0.1077	0.111
19	0.1045	0.1036	0.1035
20	0.1085	0.1079	0.1006
Result	**Pass**	**Pass**	**Pass**

Table 27: Weight variation test of the formulation

Wetting time, Water absorption ratio, Disintegration time, Assay of the formulation:

Formulation	Wetting time (secs)	Water absorption ratio (%)	Disintegration time (secs)	% Drug content
Batch 1	0.52	49	21	9.1.6.
Batch 2	0.51	44	24	90.3
Batch 3	0.5	42	28	86.4

Table 28: Wetting time, Water absorption ratio, Disintegration time, Assay of the formulation

Dissolution profile of Batch 1 to Batch 3:

Sampling time	Percentage of drug Release (%)		
	Batch 1	Batch 2	Batch 3
2	12.8	12.3	11.4
4	24.9	24.1	23.9
6	34.3	37.1	33.7
8	43.4	52.8	45.7
10	52.1	57.9	55.0
15	68.6	74.6	72.4
30	81.7	81.4	80.6
45	84.9	83.7	83.3
60	90.3	86.3	85.8

Table 29: Dissolution profile of Batch 1 to Batch 3

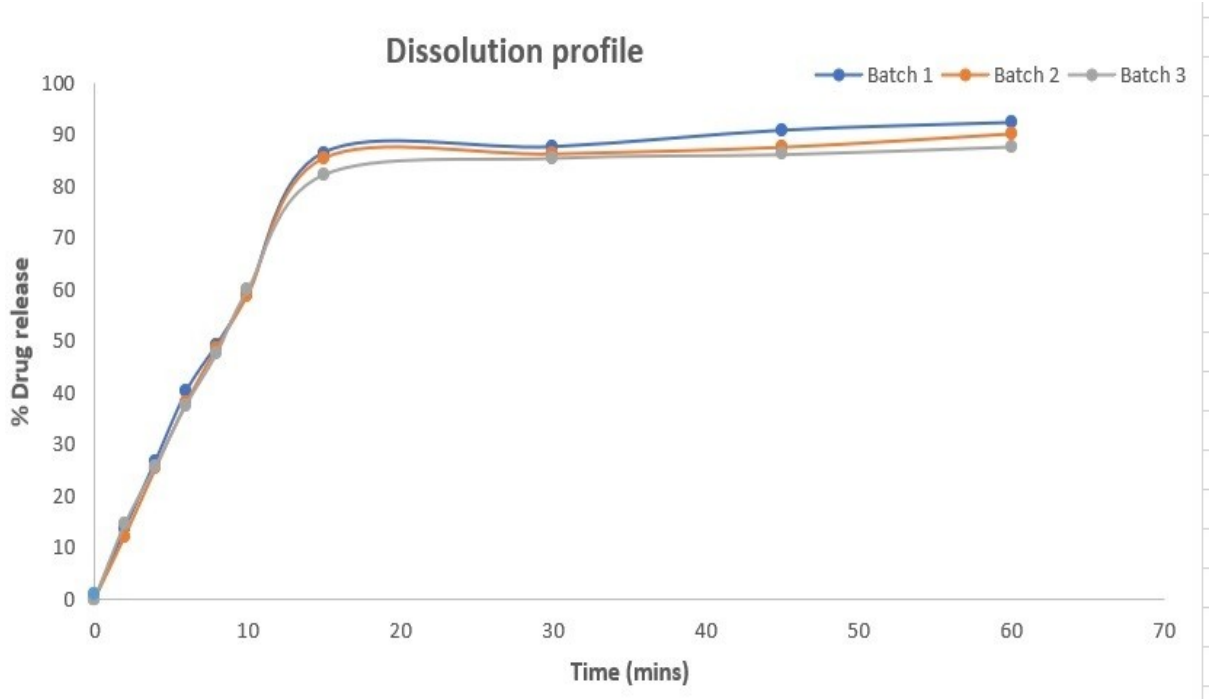

Figure 26: Dissolution profile of Batch 1 to Batch 3

SUMMARY

Levosalbutamol (albuterol) is a β_2-adrenoceptor agonist used as a bronchodilator for the treatment of asthma and as a uterine relaxant for the suspension of premature labour. Salbutamol has been marketed as a racemic mixture, although β_2-agonist activity resides almost exclusively in the (*R*)-enantiomer.

The enantio-selective disposition of salbutamol and the possibility that (*S*)-salbutamol has adverse effects have led to the development of an enantiomerically pure (*R*)-salbutamol formulation known as levosalbutamol (levalbuterol).

The present study is an attempt to develop and formulate fast dissolving tablets of Levosalbutamol with super disintegrants which disintegrates in matter of seconds in the oral cavity, thereby reducing the time of onset of pharmacological action and to prevent the first pass metabolism of Levosalbutamol .

In this system direct compression was used, sodium starch glycollate (SSG), were used as super disintegrants, talc is used as flow promoter, magnesium stearate was used as lubricant, mannitol as sweetener and diluent.

The drug- polymer compatibility was confirmed by FTIR studies. The results obtained by FTIR studies revealed that there was no chemical interaction between the pure drug and excipients.

Direct compression method was employed to formulate the tablets, because of its cost effectiveness and due to reduced number of manufacturing steps.

The post-compression parameters like the thickness, hardness, friability and in vitro disintegration time, wetting time, water absorption ratio and in vitro drug release were carried out and the values were found to be within limits.

The Formulation F1 shows the maximum dissolution rate and % of drug release was found to be 95.5%. The other Formulations shows F2 - 92.1% F3 – 95% F4 – 90.9% and F5 shows the lesser release 87.5%

Based on the % of drug release at 15 minutes shows F1 maximum of 86.8 % and 60 minutes the maximum release of 95.5 %.

The formulation of Levosalbutamol tablets containing 7.50% Sodium starch glycollate (F1) revealed that formulated rapid dissolving tablets of Levosalbutamol were effective and better to meet patient compliance.

The Real time stability studies for formulation (F1) shows acceptable limit within 3 months period.

CONCLUSION

The present work was concluded that to develop a stable, safe, fast release and convenient Oro dispersible tablets of Levosalbutamol for rapid therapeutic action. The formulations were optimized by using design expert software all the Five formulations (F1 to F5) of Oro dispersible tablets of Levosalbutamol were successfully prepared using Sodium Starch Glycollate as a super disintegrants and crospovidone by direct compression method. The Formulations were evaluated for parameters like thickness, hardness, friability, in- vitro disintegration time, wetting time, water absorption ratio, and in- vitro drug release studies. Based on the % of drug release at 15 minutes shows F1 maximum of 86.8 % and 60 minutes the maximum release of 95.5 %. The formulation (F1) was subject to stability studies for 3 months by storing them at 30°C/65%RH, 35°C/70%RH and 40°C/75%RH. The Results of physical appearance, hardness, friability, disintegration test, and % drug release have shown that there was no significant change at different storage conditions.

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