# FORMULATION AND EVALUATION OF NIMODIPINE SUBLINGUAL TABLETS

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**THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY, CHENNAI**

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**MASTER OF PHARMACY**
**IN**
**PHARMACEUTICS**


**Submitted By**

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## CERTIFICATE

This is to certify that the dissertation entitled "**FORMULATION AND EVALUATION OF NIMODIPINE SUBLINGUAL TABLETS**" submitted by **SHAIK BAJID BASHA(Reg No.261311056)** in partial fulfillment of the Degree of Master of Pharmacy in Pharmaceutics of The Tamil Nadu Dr.M.G.R Medical University, Chennai at Annai Veilankanni's Pharmacy College, Chennai- 600 015 is the Bonafide work carried out by her under my guidance and supervision during the academic year 2014-2015. The dissertation or any part of this has not been submitted elsewhere for any other Degree.

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## TO WHOMSOEVER IT MAY CONCERN

This is to certify that **SHAIK BAJID BASHA**, (Reg.No.261311056) who is the Student of Annai Veilankanni's Pharmacy College, Chennai undergone Project Training on **"FORMULATION AND EVALUATION OF NIMODIPINE SUBLINGUAL TABLET"** for the period from 21.11.2014 to 20.03.2015.

Duing this period, we found him sincere, honest and diligent. We wish all success in his future endeavours.

With regards,

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# DECLARATION

I hereby declare that the dissertation work entitled **"FORMULATION AND EVALUATION OF NIMODIPINE SUBLINGUAL TABLETS"** is based on the original work carried out by me in Annai Veilankanni's Pharmacy College, Chennai and formulation R&D MEDOPHARM, CHENNAI under the guidance of Mrs.S.Valarmathi, M.Pharm, Associate Professor, Department of Pharmaceutics, Annai Veilankanni's Pharmacy College for submission to The Tamil Nadu Dr.MGR Medical University in the partial fulfillment of the requirement for the award of Degree of Master of Pharmacy in Pharmaceutics. The work is original and has not been submitted in part or full for any other diploma or degree of this or any other university. The information furnished in this dissertation is genuine to the best of my knowledge and belief.

Chennai

Date : 07.8.2015 Reg.No. 261311056

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# *Dedication*

*Every challenging work needs self efforts as well as guidance of elders especially those who were very close to our heart.*

*My humble effort I dedicate to my sweet and loving*

*Father& Mother*

*Whose affection, love, encouragement and prays of day and night make me able to get such success and honor,*

*Along with all hard working and respected*

*Teachers*

# *Introduction*

# 1 INTRODUCTION

Development of a formulation involves a great deal of study and experimental work to get optimum results. While doing so we have to keep in mind various factors are considered like choice of excipients, drug bioavailability, drug stability in required dosage form, cost effectiveness, manufacturing aspects.

Now a day's formulation research is breaking barriers of conventional methods. Present day's drugs can be delivered with a convenience manner, performance and bioavailability[1].

Drugs have been applied to the mucosa for topical application for many years. However, recently there has been interest in exploiting the oral cavity as a portal for delivering drugs to the systemiccirculation[2].

The Drug delivery through sublingual route have desire to provide quick onset of pharmacological effect. Dysphasia (difficulty in swallowing) is a common problem of all age groups, especially elderly, children, and patients who are mentally retarted, un cooperative, nauseated or on reduced liquid- intake/diets have difficulties in swallowing these dosage forms. Sublingual administration of the drug means placement of the drug under the tongue and drug reaches directly in to the blood stream through the ventral surface of the tongue and bottom of the mouth[3].

The sublingual route usually produces a faster onset of action than the orally ingested tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes[4.]

## 1.1.Oral Mucosa

The oral cavity comprises the lips, cheek, tongue, hard palate, soft palate and floor of the mouth. The lining of the oral cavity is referred to as the oral mucosa, and includes the buckle, sublingual, gingival, palatal and labial mucosa. The oral mucosa top quarter to one-third is made up of closely compacted epithelial cells. The main role of the oral epithelium is to protect fluid loss and underlying tissue against potential harmful agents in the oral environment. Beneath the epithelium is the basement membrane, lamina propia and submucosa. The oral mucosa also having many taste receptors of the tongue and sensory receptors.

The lining mucosa is found in the outer oral vestibule (the buckle mucosa) and the sublingual region (floor of the mouth) The specialized mucosa is found on the dorsal surface of tongue, while the masticatory mucosa is found on the hard palate (the upper surface of the mouth) and the gingiva (gums). The lining mucosa comprises approximately 60%, the masticatory mucosa approximately 25%, and the specialized mucosa approximately 15% of the total surface area of the oral mucosal lining in an adult human. The masticatory mucosa is located in the regions particularly susceptible to the stress and strains resulting from masticatory activity. The superficial cells of the masticatory mucosa are keratinized, and a thick lamina propia tightly binds the mucosa to underlying periosteum. The mucosa of the dorsum of the tongue is specialized gustatory mucosa's, which has a well papillae surface; which are both keratinized and some non-keratinized[5].

Whereas keratinized regions contain predominantly neutral lipids (creaminess). Non-keratinized areas are composed of glycosylceramides that appears to be derived from membrane coating granules that differ morphologically from the lamellate membrane coating granules of keratinized tissue.

The amount of a certain drug absorbed through the oral mucosa is determined by many factors, including the pKa of the base, the rate of partition of the unionized form of the drug, the lipid – water partition coefficient of that particular drug, and lastly, on the pH of the solution[6].

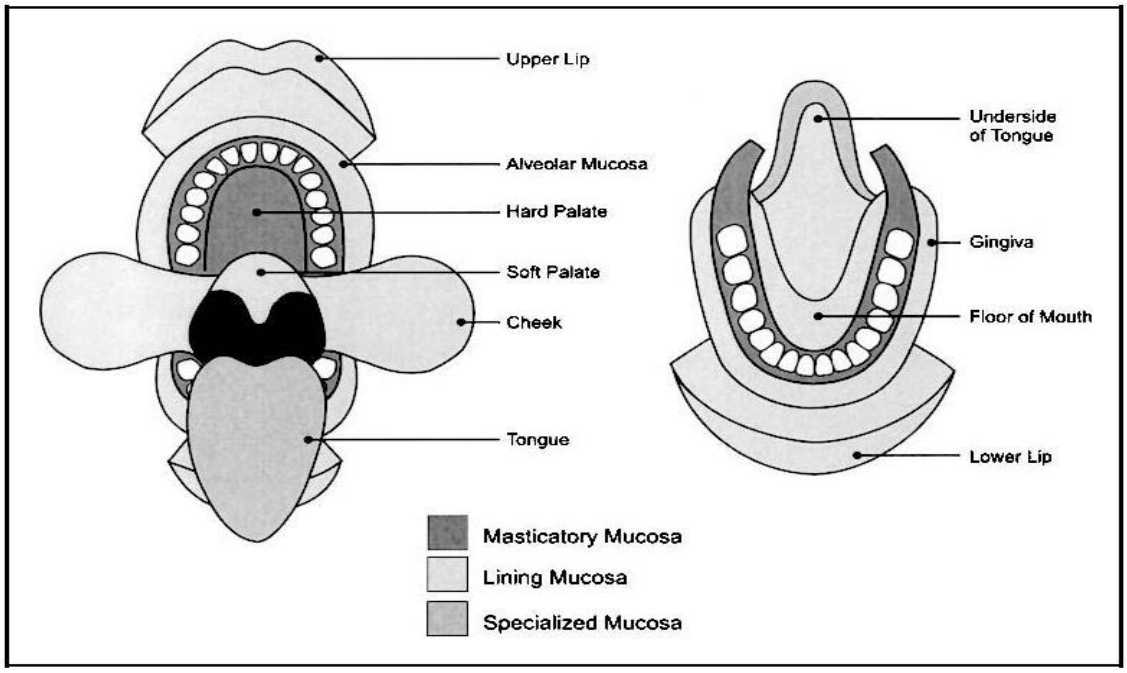



**Figure No. 1: Schematic representation of the different linings of mucosa in mouth**

**1.2.The oral mucosal cavity, delivery of drugs is classified into three categories:**

- **Sublingual delivery:** which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth.
- **Buccal delivery**: which is drug administration through the mucosal membranes lining the cheeks (buckle mucosa), and
- **Local delivery:** which is drug delivery into the oral cavity[7]

**1.3.Advantages:**

- Rapid onset of effect - particularly for pain, emesis, insomnia or allergy relief.
- Easy, painless and convenient self-administration.
- To get pharmacological effect with less drugs, less side effect.
- Inexpensive to manufacture per dose.
- Flexible formulation options.
- The blood supply is rich with a capillary network close to mucosa[6]
- To easy administration such as geriatric, pediatric and psychiatric patients.
- A relatively rapid onset of action can be achieved compared to the oral route, and the formulation can be removed if therapy is required to be discontinued.

- Due to more contact surface area of oral cavity it provide good absorption.
- Liver is bypassed and also drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.
- They also present the advantage of providing fast dissolution or disintegration in the oral cavity, without the need for water or chewing[8].

**1.4.Disadvantages:**

- It is difficult to convert a high dose poorly compressible API into a tablet of suitable size for human use.
- Difficult to formulate a drug with poor wettability, slow dissolution into a tablet.
- To show Slow onset of action as compared to parenterals, liquid oral form and capsules.
- Patients cannot undergoing radiotherapy swallow tablet.

**1.5.Sublingual Absorption**

Sublingual, meaning literally 'under the tongue' refers to a method of administering substances via the mouth in such a way that the substances are rapidly absorbed via the blood vessels under the tongue rather than via the digestive tract However, not all substances are permeable and accessible to oral mucosa[3].

Sublingual drug administration is applied in the field of cardiovascular drugs, steroids, some barbiturates and enzymes. It has been a developing field in the administration of many vitamins and minerals which are found to be readily and thoroughly absorbed by this method. Sublingually absorbed nutrition, which avoids exposure to the gastric systemand liver, means direct nutritional benefits, particularly important for sufferers of gastro-intestinal difficulties such as ulcers, hyperactive gut, coeliac disease, and digestion, the elderly and invalids the nutritional advantage is independent of gastro-intestinal influences. Examples of drugs administered by this route include antianginal like nitrites and nitrates, anti hypertensive like nifedipine, analgesics like morphine and bronchodilators like fenoterol. Certain steroids like estradiol and peptides like oxytocin can also be administered e.g. fentanyl citrate, apomorphine, prochlorperazinedimaleate (PRO), and hydrazine HCl[8,6] .

Glyceryltrinitrate one of the best used regularly it is rapid symptomatic relief of angina and potent coronary vasodilator. It has been found impressively effective when administered sublingually; pharmacologically active after only 1 – 2 minutes. The rapid relief of symptoms an aerosol spray was found due to first pass metabolism. The extent of first pass metabolism when compare to sublingual spray decreased to 48% with sublingual tablets and 28% with oral dose. Following sublingual administration, nitrates après in plasma concentrations can be maintained 24 hours. Sublingual varapamil was effective in controlling the ventricular rate following sublingual administration[3].

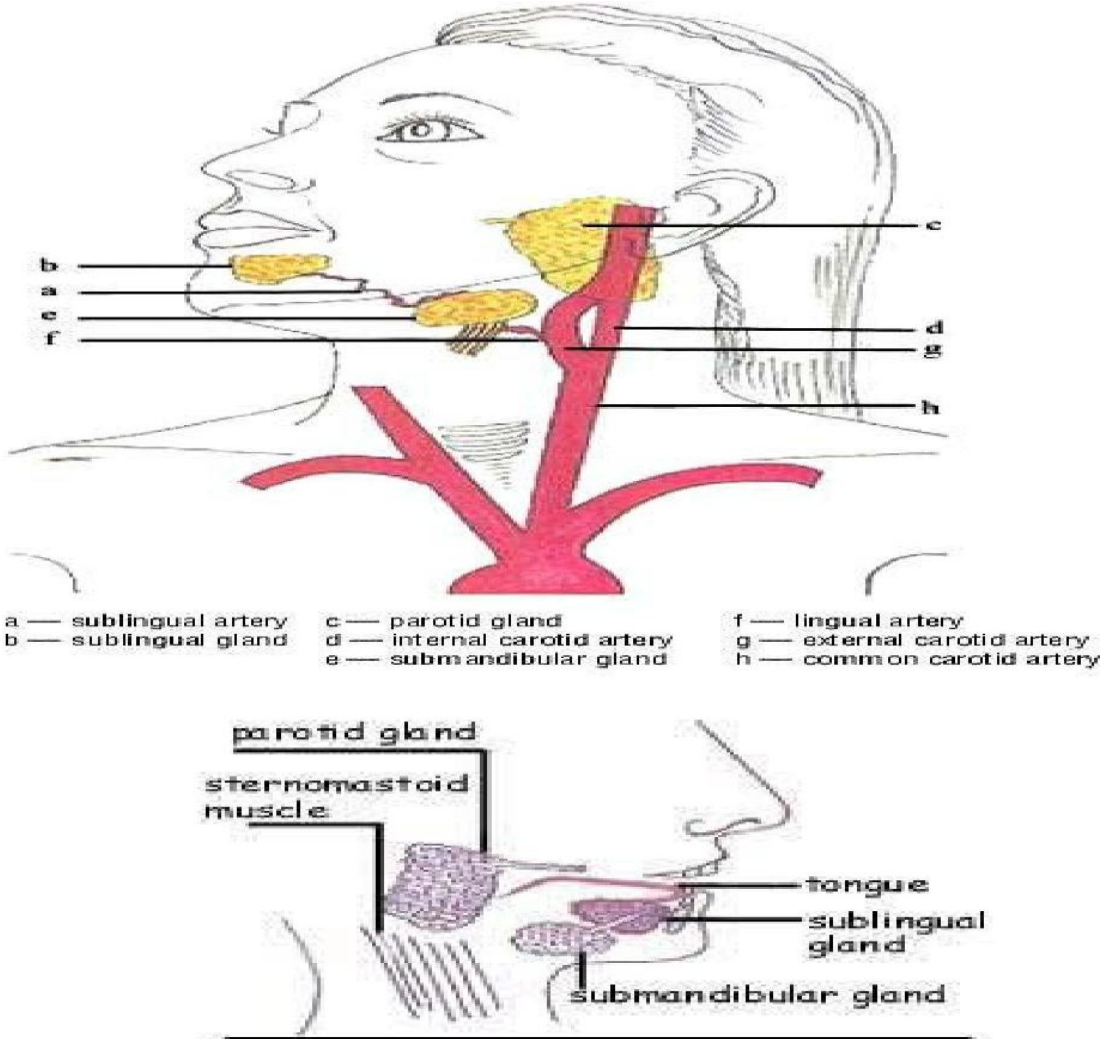



**Figure No. 2: Diagram of Sublingual Gland and Sublingual Artery**

**1.6.The mechanism of sublingual absorption**

The cells of the oral epithelium and epidermis are also capable of absorbing by endocytosis (the uptake of particles by cells. These engulfed particles are usually too large to diffuse through its wall). However, it is believed that acidic stimulation of the salivary glands, with the additional vasodilatation, facilitates absorption and uptake into the circulatory system. The salivary glands consist of lobules of cells which produce saliva through the salivary ducts into the mouth. The three pairs of salivary glands are present i.e. the parotid, the submandibular and the sublingual which lies on the floor of the mouth. The more acidic the taste, the greater the stimulation of salivary output; serving to avoid potential harm to acid-sensitive tooth enamel by bathing the mouth in copious neutralizing fluid The mouth is lined with a mucous membrane which is covered with squamous epithelium and contains mucous glands. The sublingual mucosal tissue is similar to that of buckle mucosa. In order for a drug to be effectively absorbed sublingually, it needs to be able to travel across the buckle mucous membranes; by a process of diffusion known as osmosis governing both intestinal and sublingual absorption.

**1.6.1. Osmosis:**

The present of water across cell walls mainly depends on the osmotic difference in the blood between the extracellular and intracellular fluid. Small particles that readily dissolve in water, rarely present a difficulty in permeation and diffusion, and so are able to move easily between the tissues of the body. Active transportation into cells leads to rapid metabolism of the substances. Molecules such as glucose (fructose) and amino acids are essential for cell metabolism and special mechanisms have evolved to facilitate their rapid diffusion and permeation across cellmembranes7.The main mechanism for the absorption of the drug in to oral mucosa is via passive diffusion into the lipoidal membrane .The absorption of the drug through the sublingual route is 3 to10 times greater than oral route and is only surpassed by hypodermic injection[9, 10].

**1.7.Superdisintegrants**

There has been a considerable demand for faster disintegrating formulations and faster dissolution, hence the need to formulate modified disintegrates with still higher efficacies has lead to the new generation of Superdisintegrants at low concentration have greater disintegrating efficiency. They are more effective intra granularly and exert less effect on compressibility and flow ability. But superdisintegrants have some drawbacks - they are hygroscopic therefore not used with moisture sensitive drugs, functionality is not as desired at higher concentrations and some are anionic and may cause some cationic drugs slight *in-vitro* binding.

These superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration[10].

**Table No. 1: List of super disintegrants**

| Superdisintegrants | Example | Mechanism Of Action | Special comment |
|---|---|---|---|
| Crosscarmellose<br>Ac-Di-Sol<br>Nymce ZSX<br>PrimelloseSolutab<br>VivasolL-HPC | Crosslinked Cellulose | Swells 4-8 folds in< 10 seconds. Swelling and wicking both. | Swells in two dimensions.<br>Direct compression or granulation<br>Starch free |
| Crosspovidone<br>Crosspovidon M<br>Kollidon<br>Polyplasdone | Crosslinked PVP | Swells very little and returns to original size after compression but act by capillary action | Water insoluble and spongy in nature so get porous tablet |
| Sodium starch glycol ate<br>Exploitable<br>Primo gel | Crosslinked Starch | Swells 7-12 folds in < 30 seconds | Swells in three dimensions and high level serve as sustain release matrix |
| Algonac acid NF<br>Satialgine | Crosslinked alginic acid | Rapid swelling in aqueous medium or wicking action | Promote disintegration in both dry or wet granulation |
| Soy polysaccharides<br>Emcosoy | Natural super Disintegrant | | Does not contain any starch or sugar. Used in nutritional products. |
| Calcium silicate | | Wicking Action | Highlyporous,Optimum concentration is between 20-40% |

**1.8.Sublingual Dosage Forms:**

Drugs administered by this route rapid produce systemic/ local effects. In general, absorption form this route is observed because of the thin mucous membrane and rich blood supply.

The sublingual dosage forms can be classified into the following:

• Sublingual Tablets

• Sublingual Spray

• Sublingual Capsules

• Sublingual Films

**Sublingual Tablets:**

Sublingual tablets are intended to be placed beneath the tongue and held until Absorption has taken place. They must dissolve or disintegrate quickly, allowing the medicament to be rapidly absorbed.

**Sublingual Spray:**

Sublingual sprays are the dosage forms in which the drug is dissolved or dispersed in a vehicle and filled in vial with metered value. On actuation a desired dose of the drug will deliver through the valve.

**Sublingual Capsules:**

These are the solid dosage forms in which the powder was filled into capsule, it should be cut open and the contents are poured below the tongue. e. g. Nifedipine sublingual capsule.

**Sublingual Films:**

These are the thin, transparent films, which are kept under the tongue form which drug will reach and absorbed into blood stream. e. g. diazepam [11]

**1.9.Formulation of sublingual tablets**

The formulation of sublingual tablets involves the selection of suitable excipients of bland taste that shall ultimately resulting in a rapid disintegrating tablet their by enhancing the dissolution of active ingredient. There are two different types of sublingual Tablets[13,14].

A. Molded Sublingual Tablets

B. Compressed Sublingual Tablet

**1. Molded Sublingual Tablets**

The sublingual tablets are usually prepared from soluble ingredients so that the tablets are completely and rapidly soluble. They contain, in addition of drug, excipients or base namely lactose, dextrose, sucrose, Mannitol. This tablet shows the same bioavailability as conventional tablets but has the advantage of markedly improved stability.

**2. Compressed Sublingual Tablets**

The compressed sublingual tablets are speed of absorption and a correspondingly rapid physiological response, which are normally best achieved with a rapidly soluble. Compressed sublingual tablets can be prepared by two different methods:

a) Wet Granulation Method

b) Direct Compression Method.

**Wet Granulation Method:**

The excipients and drugs to get uniform mixture to passed through particular sieve. Suitable granulating agents like water, starch paste, providence can be added to the powder mixture in the appropriate proportion to produce a coherent mass. This mass is passed through a suitable sieve and dried at optimum temperature and sieved to get uniform granules. Then the granules are lubricated and compressed into a tablet.

**Direct Compression Method:**

The term direct compression is used to define a process by which tablets are compressed directly from the powder blends of active ingredients and suitable excipients, which will flow uniformly into the die cavity and compact. The great advantage of direct compression is the manufacturing cost. It uses conventional equipment, commonly available excipients, and a limited number of process steps. Direct compression is the easiest way to manufacture tablets and also fast melting tablets.

**3. Freeze drying / lyophilization:**

Lyophilization is used to prepare tablets that have porous open matrix network into which saliva rapidly disperses when placed in mouth. The drug is incorporate in a matrix water soluble which is freeze dried to make a unit which rapidly disperses when take in mouth. Apart from the matrix and active constituents, the final formulation may contain other excipients, which improve the process characteristics or enhance the quality of the final product. These include suspending agents, wetting agents, preservatives, antioxidants, colours and flavours. The preferred drug characteristics for freeze drying formulations are water in solubility, low dose, chemically stable, small particle size. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability[12]

**4. Sublimation:**

Sublimation technique is addition of a volatile salt to the tabletting component, mixing the components to obtain a substantially homogenous mixture and volatizing salt. The removal of volatizing salt creates pores in the tablet, which help in achieving rapid disintegration when the tablet comes in contact with saliva. The tablets were then subjected to vacuum at 80º C for 30 minutes to eliminate volatile components and thus create pores in the tablet. Volatile salts such as camphor, ammonium bicarbonate, naphthalene, urea, etc., were also used as sublimable components to prepare porous.

**5. Spray drying:**

Spray drying produces highly porous and fine powder as the processing solvent is evaporated during process. Spray dryers are widely used in pharmaceuticals and biochemical process. Spray drying can be used to prepare rapidly disintegrating

tablets by using support matrix such as hydrolyzed an non hydrolyzed gelatin and other components like Mannitol as bulking agent, sodium starch glycolate, Crosscarmellose sodium as disintegrants, acidic material like citric acid and alkali like sodium bicarbonate to enhance disintegration and dissolution[13].

**6. Mass Extrusion**

This technology involves softening of the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into segments using heated blade to form tablets. The dried cylinder can also be use to coating granules of bitter tasting drugs and there by masking bitter taste[12].

**1.10. Mechanism of superdisintegrants**

There are four main mechanisms for tablets disintegration as follows

***1. Swelling:***

The most accepted general mechanism of action for tablet disintegration is swelling. The tablets with high porosity nature show poor disintegration due to have lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. Note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down[14].

***2. Porosity and capillary action (Wicking):***

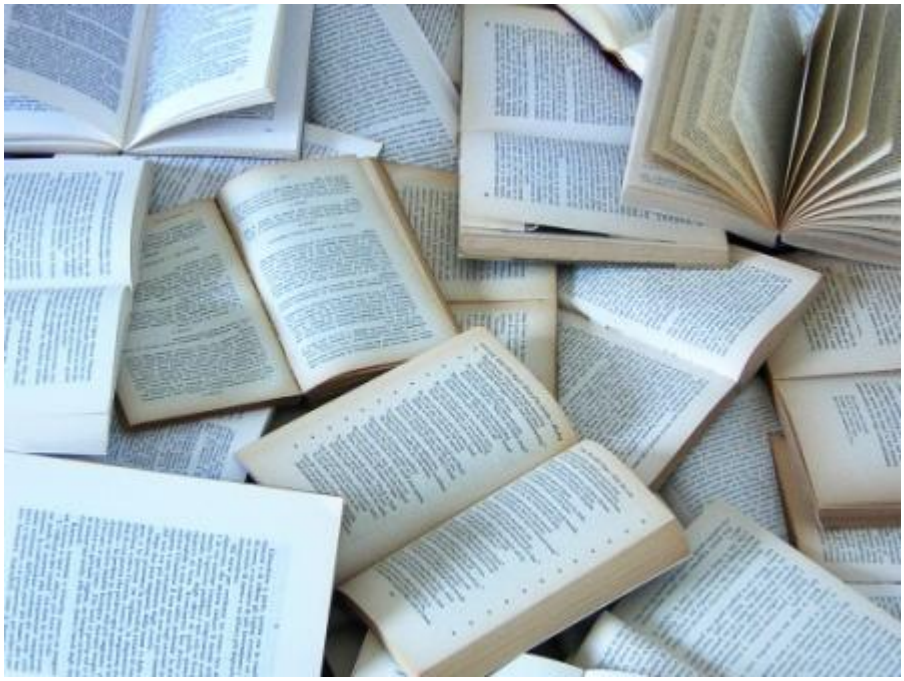
Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. The water up take by tablet mainly depends upon hydrophilicity of the drug/excipients and tableting conditions.

***3. Disintegrating particle/particle due to repulsive forces:***

The another mechanism of tablet disintegration attempts to explain the swelling of tablet made with ‘non-swellable’ disintegrants. Particle repulsion theory based on the observation that non swelling particle also cause disintegration of tablets. Water is required for The electric repulsive forces between particles are the mechanism of disintegration. Wicking is secondary.

***4. Due to deformation:***

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. The swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a break up of the tablet[10].



# *Literature Review*

## 2. LITERATURE REVIEW

**J.Nikunj *et al.* (2012)** Now a day's formulation research is breaking barriers of conventional methods. First pass metabolism can be overcome by sublingual drug delivery, and quick drug delivery into the systemic circulation can be obtained. Sublingual administration can offer an attractive alternative route of administration. The advantage of the sublingual drug delivery is that the drug can be directly absorbed into systemic circulation bypassing enzyme degradation in the gut and liver. These formulations are particularly beneficial to pediatric and geriatric patients. the sublingual region allow excellent drug penetration to achieve high plasma drug concentration In addition sublingual mucosa and abundance of blood supply and show rapid onset of an action[1].

**K.patel Nibha *et al.* (2012)** Oral mucosal drug delivery is an alternative and promising method of systemic drug delivery which offers several advantages. Sublingual literally meaning is "under the tongue", administrating substance via mouth in such a way that the substance is rapidly absorbed via blood vessels under tongue. Sublingual route offers advantages such as bypasses hepatic first pass metabolic route which gives better bioavailability, quick onset of action, patient fulfillment, self-medicated. Dysphasia (difficulty in swallowing) is common between in all ages of people and more in pediatric, geriatric, psychiatric patients. Sublingual area of oral cavity is more permeable compare to buccal and palatal area[2].

**Nehanarang *et al.* (2010)** Drug delivery system are becoming more complex as pharmaceutical scientist acquire better understanding of the physiochemical and biochemical parameters pertinent to their performance. Over the last decade, the demand of fast disintegrating tablet has been growing mainly for geriatric and pediatric patients, because of swallowing difficulties, the characteristics of fast disintegrating tablet for potential emergency treatment. The superdisintegrants used in this study was Crosspovidone. The tablets were evaluated for weight variation, hardness, friability, wetting time, water absorption ratio, and disintegration time and dissolution study. The tablets were prepared by wet granulation procedure. The systematic formulation approach helped in understanding the effect of formulation processing variables[3].

**Amitkumar *et al.* (2013)** Sublingual tablets offer fast release of drug from the formulation and it reaches systemic circulation directly, which bypasses the metabolism of drug in liver. The demand of fast disintegrating sublingual tablets has been growing, during the last decade especially for geriatric and pediatric patients because of swallowing difficulties. Drug delivery system are becoming more complex as pharmaceutical scientist acquire better understanding of the physiochemical and biochemical parameters pertinent to their performance. Various techniques can be used to formulate sublingual tablets i.e. direct compression, freeze drying etc. The sublingual tablets require faster disintegration. So, we need to formulate disintegrates i.e. superdisintegrants which are effective at low concentration and have greater disintegrating efficiency[4].

**F.Viralkumar *et al.* (2010)** Oral transmucosal delivery, especially buccal and sublingual delivery, has progressed far beyond the use of traditional dosage forms with novel approaches emerging continuously. the advances and opportunities for buccal/sublingual drug delivery. The advances and opportunities for buccal/sublingual drug delivery This review highlights the challenges as well as Particular attention is given to new approaches which can extend dosage form retention time or can be engineered to deliver complex molecules such as proteins and peptides. The review will also provide a link between the physiology and local environment of the oral cavity *in vivo* and how this relates the performance of transmucosal delivery systems[5].

**Agheranikunj Jamnadas *et al.* (2012)** Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enteral methods. Because the oral mucosa is highly vascularised, drugs that are absorbed through the oral mucosa directly enter the systemic circulation, bypassing the gastrointestinal tract and first-pass metabolism in the liver. For some drugs, this outcome in rapid onset of action via a more easy and convenient delivery route than the intravenous site. How ever, can be administered through the oral mucosa because of the characteristics of the oral mucosa and the physicochemical properties of the drug[6].

**N.Nishan *et al.* (2013)** Bioadhesion can be defined as a phenomenon of interfacial molecular attractive forces in the midst of the surfaces of biological substrate and the natural or synthetic polymers, which allows the polymer to adhere to biological surface for an extended period of time. The buccal region is an offers adorable route of administration drugs for systemic delivery. Among the various transmucosal sites available, mucosa of the buccal cavity was found to be the most convenient and easily approachable site for the delivery of therapeutic agents for both local and systemic delivery retentive dosage form. Because buccal drug delivery system prolong the residence time of dosage form at the site[7].

**Amit Kumar Bind *et al.* (2013)** Drug delivery via the oral mucous membrane is considered to be a promising alternative to the oral route. Sublingual route is a rapid onset of action and better patient compliance than orally ingested tablets. Sublingual literally meaning is "under the tongue", administrating substance via mouth in such a way that the substance is rapidly absorbed via blood vessels under tongue. The portion of drug absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes giving acceptable bioavailability. Different techniques are used to formulate the sublingual dosage forms[8].

**Kamal Saroha *et al.* (2008)** Mucoadhesive drug delivery system prolong the residence time of the dosage form at the site of application or absorption and facilitate an intimate contact of the dosage form with the underline absorption surface and thus contribute to improved and better therapeutic performance of the drug. The bioadhesive polymers that adhere to the mucin/epithelial surface are effective and lead to overcome the relatively short gastrointestinal (GI) time and improve localization for oral controlled or sustained release drug delivery systems improvement in oral drug delivery. Improvements are also expected for other mucus-covered sites of drug administration. Bioadhesive polymers find application in the eye, nose, and vaginal cavity as well as in the GI tract, including the buccal cavity and rectum[9].

**Debjit Bhowmik *et al.* (2009)** Fast- or mouth dissolving tablets have been formulated for pediatric, geriatric, and bedridden patients and for active patients who are busy and traveling and may not have access to water. The formulations gives an opportunity for product line extension in the Many difficulties in taking conventional

oral dosage forms (solutions, suspensions, tablets, and capsules) because of hand tremors and dysphagia. Oral route problems also are common in young persons because of their underdeveloped muscular and nervous systems[10].

**K.patel Nibha *et al.* (2012)** Oral mucosal drug delivery is an alternative and promising method of systemic drug delivery which offers several advantages. Sublingual literally meaning is "under the tongue", administrating substance via mouth in such a way that the substance is rapidly absorbed via blood vessels under tongue. Sublingual route offers advantages such as bypasses hepatic first pass metabolic process which gives improved bioavailability, rapid onset of action, patient fulfillment, self-medicated. Dysphasia (difficulty in swallowing) is common amid in all ages of people and more in pediatric, geriatric, psychiatric patients. In terms of permeability, sublingual area of oral cavity is more permeable than buccal area which is in turn is more permeable than palatal area[11].

**PriyankPatel *et al.* (2010)** Drug delivery via sublingual mucous membrane is considered to be a promising alternative to the oral route. This route is useful when rapid onset of action is desired as in the case of anti emetics such as ondansetron. In terms of permeability, the sublingual area of the oral cavity is more permeable than cheek and palatal areas of mouth. The drug absorbed via sublingual blood vessels bypasses the hepatic first-pass metabolic processes giving acceptable bioavailability with low doses and hence decreases the side effects. Sublingual drug delivery system is convenient for pediatric, geriatric, and psychiatric patients with dysphagia[12].

**F R sheeba *et al.* (2009)** The aim of this study was to evaluate the effect of increasing nifedipine load on the characteristics of fast-disintegrating sublingual tablets for the potential emergency treatment of anginal pain and hypertension. Nifedipine undergoes first pass metabolism in liver and gut wall which has oral bioavailability of 43-77%. Fast relieve anginal pain and hypertension, An attempt has been made to prepare fast dissolving tablets of nifedipine Sublingual dosage form bypasses the metabolism of the nifedipine in liver. Using super disintegrates like cros carmellose sodium, sodium starch glycolate, Crosspovidone. Three different groups of formulations (A, R, and V) with variation in tablet excipients were prepared by direct compression method[13].

**Sindhu Abraham *et al.* (2010)** The objective of this research was to develop and optimize sublingual tablets of Rabeprazole Sodium, a class of Proton pump inhibitors which is effective in the treatment of acid peptic disorders. The tablets were prepared by wet granulation method based on a central composite design. The formulation variables included quantity of Crospovidone, (X1), and quantity of Croscarmellose Sodium (CCS), (X2), while the response variables determined were wetting time and *In vitro* dispersion time. A quadratic model was used to quantitatively evaluate the main effects and interaction. Surface response plots are presented, to graphically represent the effect of the independent variables on the wetting time and disintegration time. The hardness of all the formulations was in the range 3.0 – 4.0 kg/cm2[14].

**A.Naimish *et al.* (2013**) Schizophrenia and schizoaffective disorder are severe and chronic psychiatric illnesses for which treatment compliance is important in the prevention of relapse. Atypical antipsychotic drugs, such as risperidone, have been found to be effective in the treatment of a range of psychiatric disorders. Sublingual tablet of oral formulations of these drugs have been developed to improve their acceptability to patients and thus improve compliance. Improve solubility, bioavailability and to achieved rapid onset action was focus of present investigation[15].

**Gupta *et al.* (2010)** 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 pediatric, geriatric, and bedridden patients and for active patients who are busy and traveling and may not have access to water. Such formulations provide an chance for product line addition in the many elderly persons will have difficulties in taking predictable oral dosage forms (viz., solutions, suspensions, tablets, and capsules) because of hand tremors and dysphagia. Swallowing problems also are common in young individuals because of their underdeveloped muscular and nervous systems[16].

**H.Zhang *et al.* (2002)** Oral mucosal delivery of sedatives such as midazolam, triazolam and etomidate has shown favorable results with clinical advantages over other routes of administration. Oral mucosal delivery of the anti nausea drugs

scopolamine and prochlorperazine has received some attention, as has oral mucosal delivery of drugs for erectile dysfunction. Oral transmucosal formulations of testosterone and estrogen have been developed. In clinical studies, sublingual testosterone has been shown to result in increases in lean muscle mass and muscle strength, improvement in positive mood parameters, and Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enteral methods. Because the oral mucosa is highly vascularised, drugs that are absorbed through the oral mucosa directly enter the systemic circulation, bypassing the gastrointestinal tract and first-pass metabolism in the liver[17].

**David harries *et al.* (1992)** The delivery of drugs via the mucous membranes lining the oral cavity. with consideration of both systemic delivery and local therapy ,the structure and composition of mucousa at different site in the oral cavity, factor affecting mucosal permeability, penetration enhancement, selection of appropriate experimental systems for studying mucosal permeability ,and formulation factor relevant to the design of systems for oral mucosal delivery are discussed. The sublingual delivery gives raped absorption and good permeability this system is not suitable for sustained delivery systems. For this reason buccal mucosa is good for number of peptide drugs. It mainly low molecular weight, high potency. it is safe route for penetration enhancement and to delivery in systemic[18].

**P.V Divya *et al.* (2006)** Recently a new approach using local delivery systems containing antimicrobial has been introduced. This produces more constant and prolonged concentration profiles. Both topical delivery system and controlled release system have been termed as local delivery. The term local delivery and site-specific delivery are sometimes used synonymously. The potential therapeutic advantage of local delivery approach has been claimed to be several fold. Local delivery devices are systems designed to deliver agents locally into periodontal pocket but without any mechanism to retain therapeutic levels for a prolonged period of time[19].

**Mitchell *et al.* (2009)** This study examined cardiac patients knowledge and use of sublingual glycerylnitrate. A non-experimental, retrospective descriptive design with a convenience sampling strategy was used setting and .participate were cardiac in patients who were prescribed sublingual glecerylnitrate at the study hospital .main

outcome measure :participant knowledge and use was assessed using the sublingual nitroglycerine interview schedule Which is a valid and reliable tool. Findings indicates that patients have limited knowledge of and do not always appropriately used slats, particularly in terms of the way men transport the medication. There for there is needed to develop and improvement educational strategies to feciliy Tate greater self management of angina[20].

**H. Kazerani *et al.* (2009)** This study aimed to evaluate the response rate, clinical efficacy and onset of action of sublingual captopril in patients diagnosed with hypertensive urgency. In this cross-sectional study (67 female and 34 male) patients with a diagnosis of hypertensive urgency (systolic pressure greater than or equal to 180 mmHg and/or diastolic pressure greater than or equal to 110 mmHg, and no findings of target organ damage) was included. and blood pressure was measured during a follow-up period of 120 minutes. The Sublingual captopril (25 mg) was administered and blood pressure was measured during a follow-up period of 120 minutes, Sublingual captopril can be used as an successful, simply applicable and safe treatment and management of hypertensive need for 120 minutes for those who do not get multidrug antihypertensive regimens[22].

**DN John *et al.* (1992)** The pharmacokinetics and pharmacodynamics of verapamil administered via the oral and sublingual routes were compared in a randomized, two-way cross-over study involving six healthy male volunteers. Administered sublingually, a verapamil 40 mg crushed tablet produced a significantly higher peak plasma concentration, a greater rate of absorption, and greater bioavailability when compared with orally administered verapamil. In comparison with oral dosing, PR intervals were significantly (P less than 0.05) prolonged between 30 and 90 min after sublingual verapamil dosing. Correlations between log plasma verapamil concentration and percentage increase in PR interval were greater after sublingual compared with oral dosing in all volunteers[23].

**Tine W. Hansen *et al.* (2010)** Circadian profile of systolic BP. We analyzed studies in hypertensive patients (n_23 856) separately from those in individuals randomly recruited from populations (n_9641). We pooled summary statistics and individual subject data, respectively. In both patients and populations, in analyses in which night time BP was additionally adjusted for day time BP. With adjustment for the 24-hour

BP, both the night-to-day BP ratio and dipping status remained significant predictors of outcome but added little prognostic value over and beyond the 24-hour BP level. In the absence of conclusive evidence proving that non dipping is a reversible risk factor, the option whether or not to restore the diurnal blood pressure profile to a normal pattern should be Current guidelines on the interpretation of ambulatory BP recording need to be updated[23].

**A.V Chobanian *et al.* (2003)** The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" provides a new guideline for hypertension prevention and management. The following are the key messages: (1) In persons older than 50 years, systolic blood pressure (BP) of more than 140 mm Hg is a much more important cardiovascular disease (CVD) risk factor than diastolic BP; (2) The risk of CVD, beginning at 115/75 mm Hg, doubles with each increment of 20/10 mm Hg; individuals who are at 55 years of age have a 90% lifetime risk for developing hypertension; (3) Individuals with a systolic BP of 120 to 139 mm Hg or a diastolic BP of 80 to 89 mm Hg[24].

**Mulrow *et al.* (1995)** Trends in prevalence, awareness, treatment, and control of hypertension in the adult US population are reported. The data are from the National Health and Nutrition Examination Surveys (NHANES) carried out in four separate surveys, the last being NHANES III 1988-1991. Age adjusted prevalence of hypertension at (160/95) mm Hg declined from 20% to 14%, and at ( 140/90 mm Hg declined from 36.3% to 20.4% in NHANES III. Hypertension awareness increased significantly to as high as 89% for those with blood pressures (160/95). For all people with blood pressure ( 160/95 nearly 64% have it controlled below that level, but only 29% have their blood pressure controlled below 140/90. Although the data from these surveys are encouraging, there are still too many people in the USA with uncontrolled hypertension[25].

# *Aim and Objective*

## 3. AIM AND OBJECTIVE

Difficulty in swallowing (dysphagia) is a common problem of all age groups, especially the elderly and pediatrics, because of physiological changes associated with these groups. Other categories that experience problems using conventional oral dosage forms include are the mentally ill, uncooperative and nauseated patients, those with condition of motion sickness, sudden episodes of allergic attack or coughing.

Sometimes it may be difficult to swallow conventional products due to unavailability of water. These problems led to the development of a novel type of solid dosage form called sublingual tablets, which disintegrate and dissolve rapidly in saliva without the need of drinking water. They are also known as fast dissolving tablets, melt-in-mouth tablets, rapimelts, porous tablets, orodispersible tablets, quick dissolving tablets or rapidly disintegrating tablets. Upon ingestion, the saliva serves to rapidly dissolve the dosage form.

The saliva containing the dissolved or dispersed medicament is then swallowed and the drug is absorbed in the normal way. Some drugs are absorbed from the mouth, pharynx, and oesophagus as the saliva passes down into the stomach. In these cases, the bioavailability of drugs is significantly greater than those observed from conventional dosage forms.

**Aim of the work:**

In the present work an attempt will be made to formulate nimodipine sublingual tablets, using different superdisintegrants for treatment of hypertension, the fast dissolving tablet provides a rapid onset of action.

**The objectives of the work:**

1. To design the formula for sublingual tablet.
2. To selected model drug and develop formula and prepare tablets.
3. To evaluate the formulated tablets.
4. To study the *in-vitro* dissolution profile of prepared tablets.
5. To carry out stability studies of the selected formulations.

# *Plan of work*

## 4. PLAN OF WORK

- Literature survey
- Preformulation studies with physicochemical parameters:

**API characterization**

- Solubility
- Bulk density
- Tapped density
- Angle of repose
- Compressibility index
- Hausner's ratio
- Drug excipient compatibility study

**Physical Evaluation of blend**

- Bulk density
- Tapped density
- Angle of repose
- Compressibility index
- Hausner's ratio

**Evaluation of tablets**

- Hardness
- Uniformity of thickness
- Friability
- Weight variation
- Content uniformity
- Disintegration
- Wetting time
- *In vitro* dissolution studies
- Drug release kinetics.

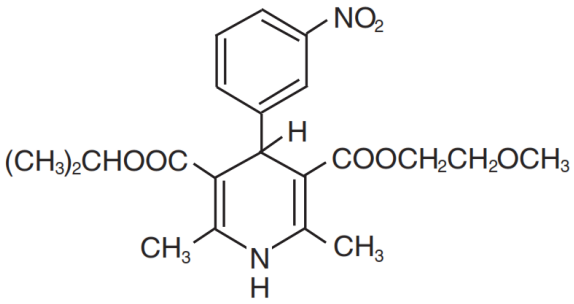
# *Drug and excipients profile*

## 5. DRUG PROFILE

### 5.1. Drug profile

**Nimodipine** belongs to the class of pharmacological agents known as calcium channel blockers.

**Structure:**




**CHEMISTRY**

**IUPAC Name** **:** Isopropyl 2 – methoxyethyl 1, 4 - dihydro - 2, 6 - dimethyl - 4 - (m-nitrophenyl) - 3, 5 - pyridinedicarboxylate

**Empirical Formula** **:** $C_{21}H_{26}N_2O_7$**.**

**Molecular Weight** **:** 418.5

**Melting Point** **:** 118°C to 122°C

**Solubility** **:** Practically insoluble in water.

**PHYSICAL PROPERTIES**

**Nature** **:** Nimodipine is a yellow crystalline nature.

**Storage** **:** Store in a well-closed container, protected from light. Store at 25°C (77°F).

**CLINICAL PHARMACOLOGY:**

**Mechanism of Action:**

Nimodipine is a calcium channel blocker. The contractions of smooth muscle are dependent upon calcium ions. Nimodipine inhibits calcium ion transfer into these cells and thus inhibits contractions of vascular smooth muscle. In animal experiments, Nimodipine had a greater effect on cerebral arteries than on arteries elsewhere in the

body perhaps because it is highly lipophilic, allowing it to cross the blood-brain barrier; concentrations of nimodipine as high as12.5 ng/mL have been detected in the cerebrospinal fluid of nimodipine-treated subarachnoid hemorrhage (SAH) patients.

The precise mechanism of action of nimodipine in humans is unknown. Although the clinical studies described below demonstrate a favorable effect of nimodipine on the severity of neurological deficits caused by cerebral vasospasm following SAH, there is no arteriographic evidence that the drug either prevents or relieves the spasm of these arteries.

**Pharmacokinetics and Metabolism:**

In man, nimodipine is rapidly absorbed after oral administration, and peak concentrations are generally attained within one hour. There were no signs of accumulation when Nimodipine was given three times a day for seven days. Nimodipine is over 95% bound to plasma proteins. The binding was concentration independent over the range of 10 mg/mL to 10 µg/mL. Nimodipine is eliminated almost exclusively in the form of metabolites and less than 1% is recovered in the urine as unchanged drug. Because of a high first-pass metabolism, the bioavailability of nimodipine averages 13% after oral administration. The bioavailability is significantly increased in patients with hepatic cirrhosis, with Cmax approximately double that in normal's which necessitates lowering the dose in this group of patients . In a study of 24 healthy male volunteers, administration of Nimodipine capsules following a standard breakfast resulted in a 68% lower peak plasma concentration and 38% lower bioavailability relative to dose under fast conditions.

In a single parallel-group study involving 24 aged subjects (aged 59–79) and 24 younger subjects (aged 22–40), the experimental AUC and $C_{max}$ of nimodipine was approximately 2-fold higher in the old peoples compared to the younger study subjects following oral administration (given as a single dose of 30 mg and dosed to steady state with 30 mg t.i.d. for 6 days).

**EXCIPIENT PROFILE**

## 5.2. CROSSCARMELLOSE SODIUM

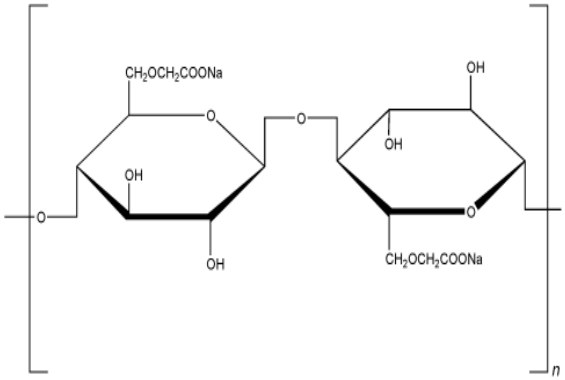
**Synonyms:**

Ac-Di-Sol; crosslinked carboxymethylcellulose sodium*; Explocel*; modified cellulose gum; Nymcel ZSX; *Pharmacel XL*; Primellose; *Solutab*; Vivasol.

**Chemical Name:**

Cellulose, carboxymethyl ether, sodium salt, crosslinked

**Structural Formula:**




**Empirical Formula:**

Croscarmellose sodium is a crosslinked polymer of carboxymethylcellulose sodium.

**Functional Category:**

Tablet and capsule disintegrant.

**Applications in Pharmaceutical Formulation or Technology:**

In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. The crosscarmellose sodium when used in wet granulation added in both the dry and wet stages of process so that the penetrability and swelling capability of the disintegrant is best utilized. Croscarmellose sodium at concentrations up to 5% w/w 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.

**Uses of croscarmellose sodium.**

| Use | Concentration (%) |
|---|---|
| Disintegrant in capsules | 10–25 |
| Disintegrant in tablets | 0.5–5.0 |

**Description:**

Cross carmellose sodium occurs as an odorless, white or grayish-white powder.

**Stability and Storage Conditions:**

Cross carmellose sodium is a stable though hygroscopic material.A model tablet formulation prepared by direct compression, with cross carmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 30°C for 14 months. Cross carmellose sodium should be stored in a well-closed container in a cool, dry place.

**Incompatibilities:**

The efficacy of disintegrants, such as cross carmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct-compression process that contain hygroscopic excipients such as sorbitol.

Cross carmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.

**Safety :**

Cross carmellose sodium is mainly used as a disintegrant in oral pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material. However, oral consumption of large amounts of cross carmellose sodium may have a laxative effect, although the quantities used in solid dosage formulations are unlikely to cause such problems.

**5.3. Crospovidone**

**Synonyms:**

Crosslinked povidone, E1202, *Colliding CL*, *Colliding CL-M*, *Polyplasdone XL*, *Polyplasdone XL-10*, polyvinylpolypyrrolidone, PVPP, and 1-vinyl-2-pyrrolidinone homopolymer.

**Chemical Name:**

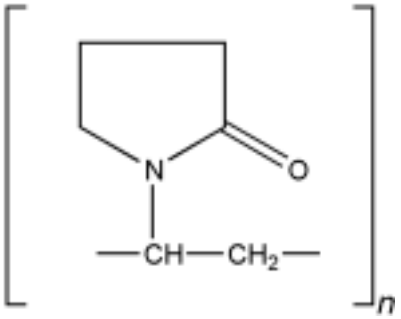
1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

**Empirical Formula and Molecular Weight:**

$(C_6H_9NO)_n > 1\ 000\ 000$

An exact determination of the molecular weight has not been established because of the insolubility of the material.

**Structural Formula:**




**Functional Category:**

Tablet disintegrant

**Applications in Pharmaceutical Formulation or Technology:**

Cross povidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of cross povidone strongly influences disintegration of analgesic tablets. Larger particles provide a faster disintegration than smaller particles. It also used in solubility improving. With the technique of co-evaporation, cross povidone can be used to

enhance the solubility of poorly soluble drugs. The drug is adsorbed on to cross povidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

**Description:**

Cross povidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless, and hygroscopic powder.

**Stability and Storage Conditions:**

Crosspovidone is hygroscopic; it should be stored in a cold, dry, airtight container.

**5.4. Sodium starch glycollate**

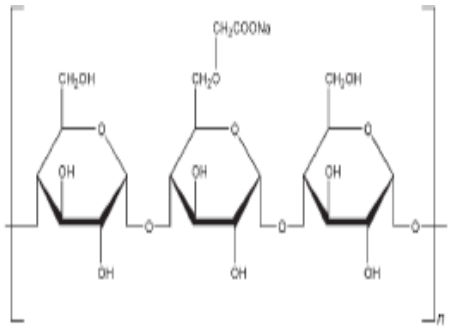
**Synonym:**

Carboxymethyl starch, sodium salt; carboxymethylamylum natricum; Explosol; Explotab; Glycolys; Primojel; starch carboxymethylether, sodium salt; Tablo; Vivastar

**Chemical name:**

Sodium carboxymethyl starch

**Structural formula:**




**Empirical formula:**

Sodium salt of carboxymethyl ether of starch

**Molecular weight:** 500000-1000000 g/mol

**Functional category:**

Tablet and capsule disintegrant.

**Application in pharmaceutical technology:**

Sodium starch glycolate is widely used in oral pharmaceuticals as disintegrant in capsule (1–6) and tablet formulations. It is commonly used in tablets prepared by either direct compression or wet-granulation processes. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. rapid uptake of water followed by rapid enlargement and disintegration. Although the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients such as lubricants, the disintegrant efficiency of sodium starch glycolate is unimpaired. Increasing the tablet compression pressure also appears to have no effect on disintegration time. Sodium starch glycolate has also been investigated for use as a suspending vehicle.

**5.5. Microcrystalline cellulose**

**Synonyms:**

Avicel PH, Celex, Cellulose gel, Celphere, Ceolus KG, crystalline cellulose.

**Functional Category:**

Adsorbent, suspending agent, tablet and capsule diluent, tablet disintegrant.

**Applications:**

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

## 5.6. Magnesium stearate

**Nonproprietary Names:**

BP: Magnesium Stearate

JP: Magnesium Stearate

PhEur: Magnesium Stearate

USP-NF: Magnesium Stearate

**Synonyms:**

Dibasic magnesium stearate; magnesium distearate; magnesia stearas; magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt; Synpro 90.

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

**Molecular Weight:** 591.24

The USP32–NF27 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and

magnesium palmitate (C32H62MgO4). The PhEur 6.5 describes magnesium stearate as a mixture of solid organic acids consisting mainly of variable proportions of magnesium stearate and magnesium palmitate obtained from sources of vegetable or animal origin.

**Structural Formula:** [CH3(CH2)16COO]2Mg

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

**Uses in Pharmaceutical Formulation Technology:**

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is mainly used as a lubricant in capsule and tablet produce at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

## 5.7. Mannitol

**Nonproprietary Names:**

BP: Mannitol

JP: D-Mannitol

PhEur: Mannitol

USP: Mannitol

**Synonyms:**

Cordycepic acid; C*PharmMannidex; E421; Emprove; manna sugar; D-mannite; mannite; mannitolum; Mannogem; Pearlitol.

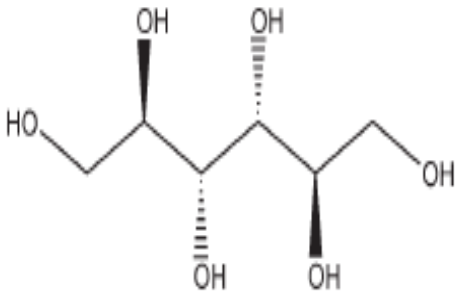
**Chemical Names and CAS Registry Number:**

D-Mannitol [69-65-8]

**Molecular Formula :** $C_6H_{14}O_6$

**Molecular Weight:** 182.17

**Structural Formula:**




**Functional Category:**

Diluent; plasticizer; sweetening agent; tablet and capsule diluent; therapeutic agent; tonicity agent.

**Applications in Formulation Pharmaceutical Technology:**

- Mannitol is widely used in pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet formulations, where it is of due to not hygroscopic it use in moisture

sensitive active ingredients. Mannitol may be used in direct-compression tablet applications, for which the granular and spray-dried forms are available, or in wet granulations.

- Granulations containing mannitol have the advantage of being dried easily. Specific tablet applications include antacid preparations, glyceryl trinitrate tablets, and vitamin preparations.
- Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and 'mouth feel'. In lyophilized preparations, mannitol (20–90% w/w) has been included as a carrier to produce a stiff, homogeneous cake that improves the appearance of the lyophilized plug in a vial.
- A pyrogen-free form is available specifically for this use. Mannitol has also been used to prevent thickening in aqueous antacid suspensions of aluminum hydroxide (<7% w/v). It has been suggested as a plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulations, and as a carrier in dry powder inhalers.
- It is also used as a diluent in rapidly 424 Mannitol dispersing oral dosage forms. Used as a bulking agent and application in food.
- Therapeutically, mannitol administered parenterally is used as an osmotic diuretic, as a diagnostic agent for kidney function, as an adjunct in the treatment of acute renal failure, and as an agent to reduce intracranial pressure, treat cerebral edema, and reduce intraocular pressure.
- Given orally, mannitol is not absorbed significantly from the gastrointestinal tract, but in large doses it can cause osmotic diarrhea.

### 5.8. TALC

**Nonproprietary Names:**

BP: Purified Talc

JP: Talc

PhEur: Talc

USP: Talc

**Synonyms:**

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Imperial; Luzenac Pharma; magnesium hydrogen metasilicate; MagsilOsmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore; talcum.

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

**Molecular Formula :** $Mg_6(Si_2O_5)_4(OH)_4$.

It may having small, variable amounts of iron and aluminum silicate

**Functional Category:**

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

**Applications in Pharmaceutical Formulation or Technology:**

- Talc was once widely used in oral solid dosage formulations as a lubricant and diluent, although today it is less commonly used.
- However, it is widely used as a dissolution retardant in the development of controlled-release products.
- Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets; and as an adsorbant.
- In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves.
- Talc is a natural it may therefore normally have microorganisms and should be sterilized when used as a dusting powder.
- Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

## 5.9. ASPARTAME

**Nonproprietary Names:**

BP: Aspartame

PhEur: Aspartame

USP-NF: Aspartame

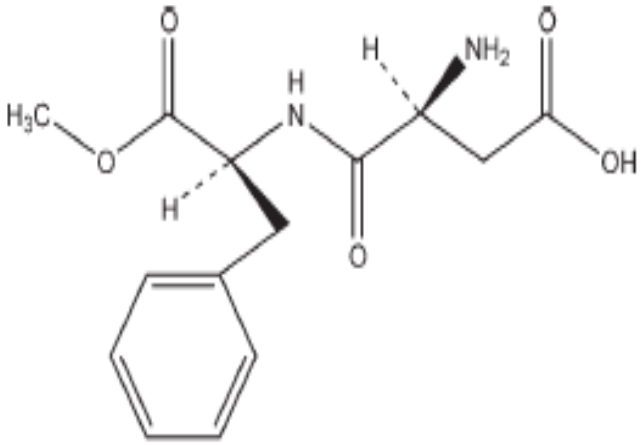
**Synonyms:**

(3S)-3-Amino-4-[[(1S)-1-benzyl-2-methoxy-2-oxoethyl]amino]-4-oxobutanoic acid; 3-amino-N-(a carboxyphenethyl)succinamic acid N-methyl ester; 3-amino-N-(a-methoxycarbonylphenethyl)-succinamic acid; APM; aspartamum; aspartylphenylamine methyl ester; Canderel; E951; Equal; methyl N-L-a-aspartyl-L-phenylalaninate; NatraTaste; NutraSweet; Pal Sweet; Pal Sweet Diet; Sanecta; SC-18862; Tri-Sweet.

**Empirical Formula :** $C_{14}H_{18}N_2O_5$

**Molecular Weight:** 294.30

**Structural Formula:**




**Functional Category:** Sweetening agent.

**Applications in Pharmaceutical Formulation Technology:**

- Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets, powder mixes, and vitamin preparations.
- It enhances flavor systems and can be used to mask some unpleasant taste characteristics; the approximate sweetening power is 180–200 times that of sucrose.
- Unlike some other intense sweeteners, aspartame is metabolized in the body and consequently has some nutritive value: 1 g provides 17 kj (4 kcal)

# *Materials & Equipments*

## 6. MATERIALS AND EQUIPMENTS

**Table No. 2: List of materials used with suppliers**

| S. No. | Materials | Supplier |
|---|---|---|
| **1.** | Model Drug | Natco pharmaceuticals, Hyderabad |
| **2.** | Mannitol | Drug India Pvt.Ltd, Guwahati |
| **3.** | MCC 101 | Drug India Pvt.Ltd, Guwahati |
| **4.** | Crosscarmellose sodium | Drug India Pvt.Ltd, Guwahati |
| **5.** | Crospovidone | Drug India Pvt.Ltd, Guwahati |
| **6.** | SSG | Drug India Pvt.Ltd, Guwahati |
| **7.** | Talc | Drug India Pvt.Ltd, Guwahati |
| **8.** | Aspartame | Drug India Pvt.Ltd, Guwahati |
| **9.** | Magnesium stearate | Drug India Pvt.Ltd, Guwahati |

**Table No. 3: List of equipments used**

| S. No. | Equipments | Manufacturer |
|---|---|---|
| **1.** | Electronic Weighing Balance | Sartorius BSA 224S – CW. |
| **2.** | Hardness Tester | CINTEX Monsanto tester, Mumbai. |
| **3.** | UV- Spectrophotometer | Shimadzu, Model No. UV-2450. |
| **4.** | Friability Test Apparatus | Electro lab EF-2. |
| **5.** | Hot air oven | Bio-tech India. |
| **6.** | Bulk Density Apparatus | Electro lab EF-2. |
| **7.** | Tablet Compression Machine | CADMACH, Ahmadabad. |
| **8.** | Tablet Dissolution Tester | TDT-08L (USP), Electro lab. |
| **9.** | Ultra solicitor bath | Bio-tech India. |
| **10.** | Digital pH meter | Microprocessor pH stat/Analyzer. |
| **11.** | FTIR Spectrophotometer | IR Affinity-1, Shimadzu. |

# *Methodology*

# 7. METHODOLOGY

## PREPARATION OF STANDARD GRAPH

### 7.1. Preparation of Stock solution with Distilled water

100mg of the drug was accurately weighed and transferred into the 100 ml volumetric flask. It was dissolved in sufficient quantity of methanol and volume was made up to the mark with methanol to get a 1000 µg/ml solution. This was the standard stock solution containing 1 mg/ml of model drug (Stock 1).

- **UV Absorption Maxima ($\lambda_{max}$) of drug sample in water**

One ml of the above solution was then further diluted to 100 ml with water to get a stock solution of 10 (µg/ml). UV scanning was done for 10 µg/ml drug solution from 200-400 nm using methanol as a blank in schimadzu, UV 1700 spectrophotometer. The wavelength maximum was found to be at 250 nm.

- **Preparation of the calibration curve**

From the stock solution 2, 4, 6, 8, 10 and 12 ml were transferred to 10 ml volumetric flasks and were diluted with the water, up to the mark to obtain concentration of2, 4, 6, 8, 10 and 12µg/ml respectively. Absorbance of each solution was measured at 226 nm. The Standard curve preparation was performed in triplicate. The absorbance was plotted against the concentrations and the graph with the straight line equation and $r^2$ value were obtained.

### 7.1.1. Preparation of Stock solution with 6.8 PH Phosphate Buffer

100mg of the drug was accurately weighed and transferred into the 100 ml volumetric flask. It was dissolved in sufficient quantity of phosphate buffer and volume was made up to the mark with methanol to get a 1000 µg/ml solution. This was the standard stock solution containing 1 mg/ml of model drug.(Stock 1).

- **UV Absorption Maxima (λmax) of drug sample in 6.8 PH Phosphate Buffer**

One ml of the above solution was then further diluted to 100 ml with phosphate buffer to get a stock solution of 10 (µg/ml). UV scanning was done for 10 µg/ml drug solution from 200-400 nm using methanol as a blank in schimadzu, UV 1700 spectrophotometer. The wavelength maximum was found to be at 250 nm.

- **Preparation of the calibration curve**

From the stock solution 2, 4, 6, 8, 10 and 12 ml were transferred to 10 ml volumetric flasks and were diluted with the phosphate buffer, up to the mark to obtain concentration of 2, 4, 6, 8, 10 and 12µg/ml respectively. Absorbance of each solution was measured at 250 nm. The Standard curve preparation was performed in triplicate. The absorbance was plotted against the concentrations and the graph with the straight line equation and $r^2$ value were obtained.

**7.2. FT-1R Studies**

The IR absorption spectra of the NMD drug and with different superdisintegrants, were taken in the range of 4000-450 cm-1 using KBr disc method, 1-2 mg of the substance to be examined was triturated with 300-400 mg, specified quantity, of finely powered and dried potassium bromide .These quantities are usually sufficient to give a disc of 10-15mm diameter and pellet of suitable intensity by a hydraulic press. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks due presence superdisintegrants.

**Table No. 4: Drug excipient compatibility study protocol**

| Sl. No. | Name of the substance | D:E ratio |
|---|---|---|
| 1 | Model Drug (API) | 1:0 |
| 2 | API + Mannitol | 1:2 |
| 3 | API + MCC | 1:2 |
| 4 | API + crosscarmellose sodium | 1:2 |
| 5 | API + crosspovidone | 1:2 |
| 6. | API + Sodium starch glycollate | 1:2 |
| 7. | API +Magnesium stearate | 1:2 |

Note: D: E – Drug : Excipient

### 7.3. Preformulation parameters

Pre formulation testing is defined as investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It gives information needed to define the nature of the drug substance and provide frame work for the drug combination with pharmaceutical excipients in the dosage form.

**Bulk Density:**

Apparent bulk density was determined by pouring presieved drug excipient blend into a graduated cylinder and measuring the volume and weight "as it is". It is represent in gm/mL and is given by

$$D\ b = M/V0$$

Where, M mass of powder,

V**0** Bulk volume of the powder

**Tapped Density:**

It was determined by placing a graduated cylinder, containing a known mass of drug- excipient blend, on mechanical tapping apparatus. Take the powder to constant volume The tapped volume was measured by tapping. It expressed in gm/mL and is given by

$$Dt = M / Vt$$

Where, M is the mass of powder,

Vt is the tapped volume of the powder[18,19].

**Carr's index:**

It is expressed in percentage and is expressed by

$$I = Dt - Db/Dt$$

Where, Dt is the tapped density of the powder

Db is the bulk density of the powder[20, 21].

**Table No. 5: Relationship between % Compressibility and Flow-ability**

| % Compressibility | Flow-ability |
|---|---|
| 5-15 | Excellent |
| 1-16 | Good |
| 18-21 | Fairly Acceptable |
| 23-35 | Poor |
| 33-38 | Very poor |
| <40 | Very very poor |

**Hausner's ratio:**

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$H = Dt / Db$$

Where, Dt is the tapped density of the powder

Db is the bulk density of the powder.

Lower hausner ratio (< 1.25) indicate better flow properties than higher ones (>1.25)[18,19].

**Angle of Repose:**

The frictional forces of a loose powder can be measured by using angle of repose. It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

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

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

Where,

θ is the angle of repose.

h is the height in cms

r is the radius in cms.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). Angle of repose was calculated by measuring the tallness and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel. Relationship between angle of repose and powder flow property[22,23].

**Table No. 6: Angle of repose as an indication of powder flow properties**

| Angle of repose | Flow |
|---|---|
| <25 | Excellent |
| 25 – 30 | Good |
| 30 – 40 | Passable |
| >40 | Very poor |

### 7.4. Formulation development

Sublingual tablets containing 30 mg of model drug were prepared with a total tablet weight of 200mg. Considering the preformulation studies and the literature survey conducted the excipients were selected and an attempt to produce sublingual tablets with ideal mouth feel maintaining the basic tablet properties was made.

- **Selection of superdisintegrants**:

Short disintegration time with good dispersability is the most important characteristics of a sublingual or mouth dispersible tablets. The necessity of a Sublingual tablet is to disintegrate within seconds, in limited amount of the water available in the form of saliva. Different superdisintegrants croscarmellose sodium, crosspovidone, Sodium starch glycol late in the concentration range of 1.5% to 6% were used which act as disintegrates used at various concentrations and a comparative study was carried out.

- **Selection of diluents**

Since direct compression method was followed the choice of directly compressible diluents was important. Microcrystalline cellulose was selected as the filler or diluents owing to its multiple functionality as binder, disintegrant, compressibility and flowability. Of the various grades available the granular form Avicel PH102 was selected as it had been already reported to provide lower crushing strengths and shorter disintegration times.

Mannitol was selected to produce a cooling and pleasant mouth feel, it was reported* that mannitol above the concentration of 33% gives good mouth feel, thus mannitol in all the batches was fixed at a concentration of 40-47%. Besides mannitol also possesses sweetening properties and reduces the gritty mouth feel effect due to microcrystalline cellulose. It also has good compressibility properties and solubility in water.

- **Selection of additional ingredients**

The flow property of the pure drug was found to be moderate (Hauser's ratio ~ 1.4) thus to still improve the flow of the blend magnesium stearate (2.5% to 4%) as lubricant were incorporated also magnesium stearate decreases the hardness of tablets without affecting the disintegration time. Aspartame was used in the concentration of 2.5% to 6% as the sweetener.

### 7.4.1. Formula

Sublingual tablets of model drug was formulated using mannitol, Avicel pH102 (microcrystalline cellulose) as diluents. Sublingual tablet was prepared by direct compression technique as it's a cost effective method. Superdisintegrants used are Crosspovidone, Crosscarmellose sodium, Sodium starch glycol late, disintegrant sodium CMC. Aspartame as sweetening agent. Magnesium stearate (3% to 4%) as lubricant.

### 7.4.2. Formulation of different batches

The main aim of the present study was to formulate different batches using three various superdisintegrants and other ingredients in varying concentrations. So different batches of formulations was planned accordingly. According to that F1, F2, F3(with Crosspovidone 1.5%, 3%, 6%), F4, F5, F6(with Crosscarmellose 1.5%, 3%,

6%)and F7, F8, F9(with Sodium starch glycol late 1.5%, 3%, 6%).The slight bitter taste of the drug was masked using aspartame (2.5% to 6%) as the sweetening agent.

### 7.4.3. Method of formulation

**1. Direct compression method.**

The model drug (NMD) is thoroughly mixed with the superdisintegrants, and then other excipients are added to the mixer and passed through the sieve (#:40). Collect the powder mixer, blend with magnesium stearate (pre sieved), and subject the blend for tablet compression.

**Representation of Direct Compression Technique for design of Sublingual Tablets**

The drug and the excipients were passed through sieve no: 40 except lubricant. The blend was further lubricated with Magnesium stearate (#:60) and the powder blend is subjected to drying for removal of moisture content and was compressed by direct compression method by using flat faced punches in CADMACH 16 punches tablet punching machine. Round punches measuring 8.7mm diameter were used for compression. Tablet of 200mg was prepared by adjusting hardness and volume screw of compression machine properly

**Table No. 7: Formulations of different batches**

| | **Formulation Code** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Ingredients (mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| Nimodipine | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| Crosspovidone | 3 | 6 | 12 | - | - | - | - | - | - |
| Crosscarmellose sodium | - | - | - | 3 | 6 | 12 | - | - | - |
| SSG | - | - | - | - | - | - | 3 | 6 | 12 |
| MCC 102 | 66 | 64 | 58 | 66 | 64 | 58 | 66 | 64 | 58 |
| Aspartame | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Mannitol | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 |
| Magnesium stearate | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Talc | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

**7.5. Evaluation of tablets**

**Hardness test:**

Using a Monsanto hardness tester the rigidity (hardness) of the tablet was determined[14].

**Friability:**

The friability of a sample of 20 tablets was measured using a Roche friabilator (Electrolab). 20 previously weighed tablets were rotated at 25 rpm for 4 min. The weight loss of the tablets before and after[15]

Measurement was calculated using the following formula

$$\text{Percentage friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

**Weight Variation:**

It was performed as per the method given in the united state pharmacopoeia. Twenty tablets were selected randomly from each formulation, weighed individually and the average weight and % variation of weight was calculated.

**Tablet thickness:**

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the identical thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded Vernier calipers using micrometer.

**Drug Content Uniformity:**

Selected twenty tablets randomly and powdered. A quantity of this powder corresponding to 200mg of model drug was dissolved in 100 ml of 6.8pH phosphate buffer, stirred for 15 min and filtered. The 1ml of filtrate was diluted with 100 ml with 6.8pH phosphate buffer. Absorbance of this solution was measured at 250nm using 6.8pH phosphate buffer as blank and content of drug was estimated[16].

**In- vitro Disintegration Time:**

Disintegration times for sublingual tablets were determined using USP tablet disintegration apparatus with saline phosphate buffer of pH 6.8 as medium. Maintained the medium temp at 37±2°. The time in minute taken for complete disintegration of the tablets with no palatable mass remaining in the apparatus was measured.

**Wetting Time:**

A piece of tissue paper folded twice was placed in a small Petri dish (ID = 6.5 cm) containing 6 mL of simulated saliva pH, a tablet was put on the amaranth powder containing paper the time required for upper surface of the tablet for formation of pink color was measured.

**Water absorption ratio:**

For measuring water absorption ratio, the weight of the tablet before keeping in the petri dish is noted ($W_b$). The wetted form of tablet was taken from petridish and reweighed ($W_a$). The water absorption ratio (R) can be the determined according to the following equation.

$$\mathbf{R = 100 \times (W_a - W_b) / W_b}$$

**In vitro dispersion time:**

In vitro dispersion time was measured by dropping a tablet in a measuring cylinder containing 6ml of pH 6.8 (simulated saliva fluid) .Tablets from each formulation were randomly selected and *in vitro* dispersion time is expressed in seconds.

**In vitro Dissolution studies:**

Dissolution of the tablet of each batch was carried out using USP XXIII dissolution type II apparatus (ELECTRO LAB) using paddles at 50 rpm. As per the official recommendation of IP 900ml of 6.8 pH of phosphate buffer used as dissolution medium and the temperature of the medium was set at 37 ± 0.5 0C. 5 ml of sample was withdrawn at predetermined time interval of 2 .,4., 6., 8 and 10 min. And same volume of fresh medium was replaced. The withdrawn samples were analyzed by an UV spectrophotometer at 250 nm using buffer solution as blank solution.

**Table No. 8: Summary of general dissolution conditions**

| Sl. No. | Parameter | Specifications |
|---|---|---|
| 1. | Dissolution medium | pH 6.8 phosphate buffer +0.5% |
| 2. | Temperature | 37°±0.5°c |
| 3. | Rotation speed | 50 rpm |
| 4. | USP Type II | Paddle |
| 5. | Volume withdrawn | 5 ml every 2 minutes |
| 6. | λmax | 250 nm |

Large tablets approaching or exceeding one gram and containing relatively dense particles may produce a mound in the dissolution vessel, which can be prevented by using higher paddle speeds. These two situations expand the suitable range of stirring to 25-75 rpm.

The USP 1 (basket) apparatus may have certain applications for sublingual but is used less frequently due to specific physical properties of tablets[17].

**7.6. Drug release kinetics:**

As a model independent approach, comparison of time taken for the given proportion of the active drug to be dissolved in the dissolution medium and figures such as $T_{50}$ and $T_{90}$ were calculated by taking the time points of 50% and 90% of the drug dissolved and another parameter dissolution efficiency (DE) suggested by Khan were employed. DE is defined as the area under the dissolution curve up to the time t expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time.

$$\text{Dissolution Efficiency (DE)} = \left( \frac{\int_0^t y.dt}{y_{100}.t} \right) 100$$

Dissolution efficiency can have a range of values depending on the time interval chosen. In any case, constant time intervals should be chosen for comparison. For example, the index $DE_{30}$ would relate to the dissolution of the drug from a particular formulation after 30 minutes could only be compared with $DE_{30}$ of other formulations. As a model dependent approach, for describing the mechanism and also the release kinetics, dissolution data were fitted to popular release models, which have been described as follows:

**Zero order kinetics:**

Dissolution of drug from a dosage form that do not disaggregate and release the drug slowly that is where the drug release rate is independent of its concentration can be represented as follows.

$$1 - \left(\frac{A_t}{A_0}\right) = k_0 t / A_0$$

Where, $A_0$ is initial amount of drug in the dosage form,

$A_t$ is the amount of drug in the dosage form at time't',

$k_0$is the zero order release constant,

1-($A_t$/$A_0$) represents the fraction of drug dissolved at time't'

Graphical representation of fraction of drug dissolved verses time will be linear. This relation can be used to determine the drug dissolution of various types of modified release dosage forms e.g. matrix tablets with low soluble drugs, coated forms etc. The dosage forms following this profile release the same amount of drug by unit time and it is the ideal method of drug release in order to achieve a prolonged pharmacological action.

**First order kinetics:**

The first order kinetics was first applied for drug dissolution studies by Gibaldi and Feldman in 1967 and later by Wagner in 1969. In this case, the drug release rate is concentration dependent and this can be depicted in decimal logarithm as follows.

$$\log A = \log A_0 - \frac{k_1 t}{2.303}$$

Where, $A_t$is the amount of drug released at time't',

$A_0$ is the initial amount of drug in the solution,

$K_1$ is the first order release constant

Graphical representation of the decimal logarithm of percent drug remaining verses time will be linear. Example for the dosage form follows this profile such as those containing water soluble drug in a porous matrices release the drug that is proportional to the amount of drug released by unit time.

**Hixon-crowell cubth root model:**

To evaluate the drug release with changes in the surface area and diameter of the particles, Hixon-Crowell in 1931 recognized that the particle regular area is proportional to the cubic root of its volume and designed an equation as follows.

$$\sqrt[3]{A_0} - \sqrt[3]{A_t} = k_s t$$

Where, $A_0$ is the initial amount of drug in the dosage form,

$A_t$ is the remaining amount of drug in the dosage form at time't',

$K_s$ is a constant incorporating the surface volume relation.

Graphical representation of cubic root of the unreleased fraction of the drug verses time will be linear if the equilibrium conditions are not reached and if the geometrical shape of the dosage form diminishes proportionally over time. This model is used by assuming that release rate is limited by the drug particles dissolution rate and not by the diffusion.

**Higuchi model:**

Higuchi in 1961 developed a model to study the release of water soluble and low soluble drugs incorporated in semisolid and solid matrices. To study the dissolution from a planar system having a homogeneous matrix, the relation obtained as follows.

$$A = \sqrt[2]{[D(2C - C_s t)]}$$

Where, A is the amount of drug released at time't' per unit area,

C is the initial drug concentration,

$C_s$ is the drug solubility in the matrix media,

D is the diffusivity of drug molecules in the matrix substance.

In general, Higuchi model can be simplified as,

$$A = K_H \sqrt[2]{t}$$

Where, $K_H$ is the Higuchi dissolution constant.

**Korsmeyer-peppas model:**

In 1983, Korsmeyer developed a simple and semi-empiric model, when diffusion is the main drug release mechanism, relating the drug release to the elapsed time (t).

$$A_t/A_\infty = at^n$$

Where, n is the diffusion exponent for the drug release,

t is the release time,

a is a constant incorporating geometrical characteristic of the dosage form,

$A_t/A_\infty$ is the fraction of drug release

**Table No. 9: Effect of 'n' value on drug transport mechanism**

| Release exponent (n) | Drug transport mechanism |
|---|---|
| n=0.5 | Fickian diffusion |
| 0.5<n<1 | Non- fickian diffusion |
| n=1 | Case II transport |
| n>1 | Super case II transport |

**7.7. Stability Studies:**

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted.

ICH specifies the length of study and storage conditions.

**Long-Term Testing:** $25^0$ C ± $2^0$ C / 60% RH ± 5% for 12 Months

**Accelerated Testing:** $40^0$ C ± $2^0$ C /75% RH± 5% for 6 Months

Stability studies were carried out at $40^0$C ± $2^0$C /75% RH ± 5% for all the formulations for a period of 3 months.

The selected formulations were closely packed in aluminium foils and then stored at $40^0$ C ± $2^0$ C /75% RH ± 5% in stability chamber for 3 months and evaluated for their physical appearance, drug content and *in-vitro* drug release studies at intervals of 1month. The shelf life period of the prepared buccal tablets is determined by using similarity factor.

# *Results & Discussion*

## 8.RESULTS AND DISCUSSION

### 8.1. Calibration curve of Nimodipine

**Table No. 10:Standard Calibration curve of Nimodipine with Distilled water**

| S.No | Concentration(mcg/ml) | Absorbance |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 2 | 0.209 |
| 3 | 4 | 0.432 |
| 4 | 6 | 0.644 |
| 5 | 8 | 0.809 |
| 6 | 10 | 0.995 |
| 7 | 12 | 1.233 |

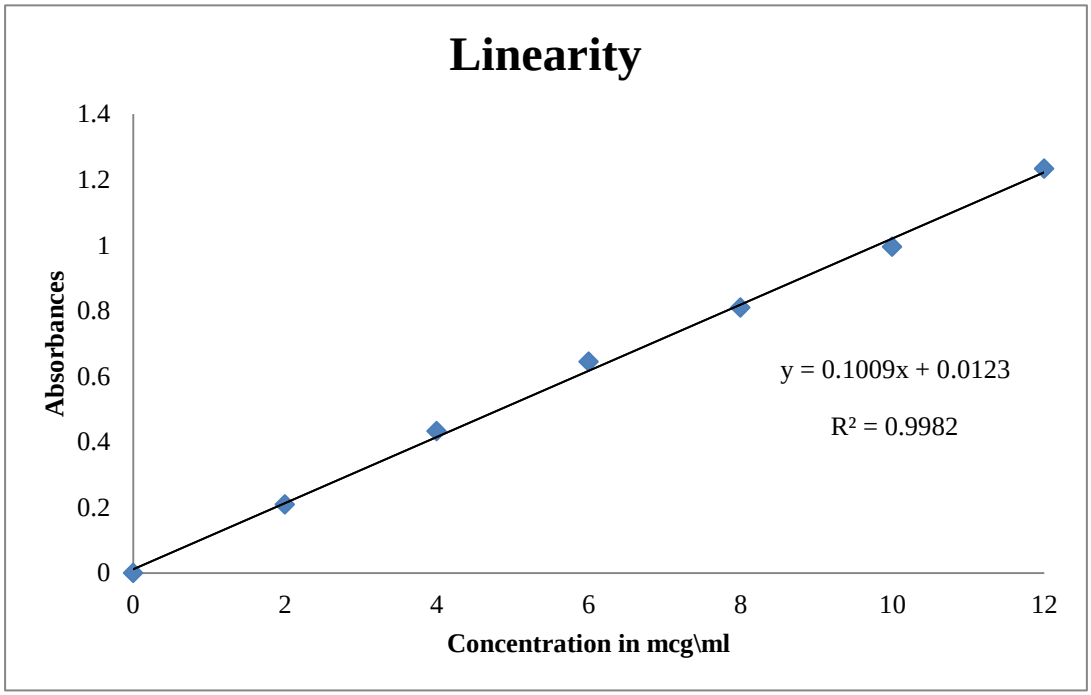



**Figure No.3:Standard Calibration curve of NMD with Distilled water**

In the current investigation, analytical method obeyed beer-lamberts law in the concentration range of 2-12 µg/ml and it was suitable for the estimation of Nimodipine using Distilled water. The value of correlation coefficient (r) for the linear regression equation was found to be more than 0.99 which indicates a positive correlation between the concentration of drug and corresponding absorbance values.

**Table No. 11:Standard Calibration curve of NMD with 6.8pH phosphate buffer**

| S.No. | Concentration (mcg/ml) | Absorbance |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 2 | 0.206 |
| 3 | 4 | 0.398 |
| 4 | 6 | 0.656 |
| 5 | 8 | 0.842 |
| 6 | 10 | 1.044 |
| 7 | 12 | 1.235 |

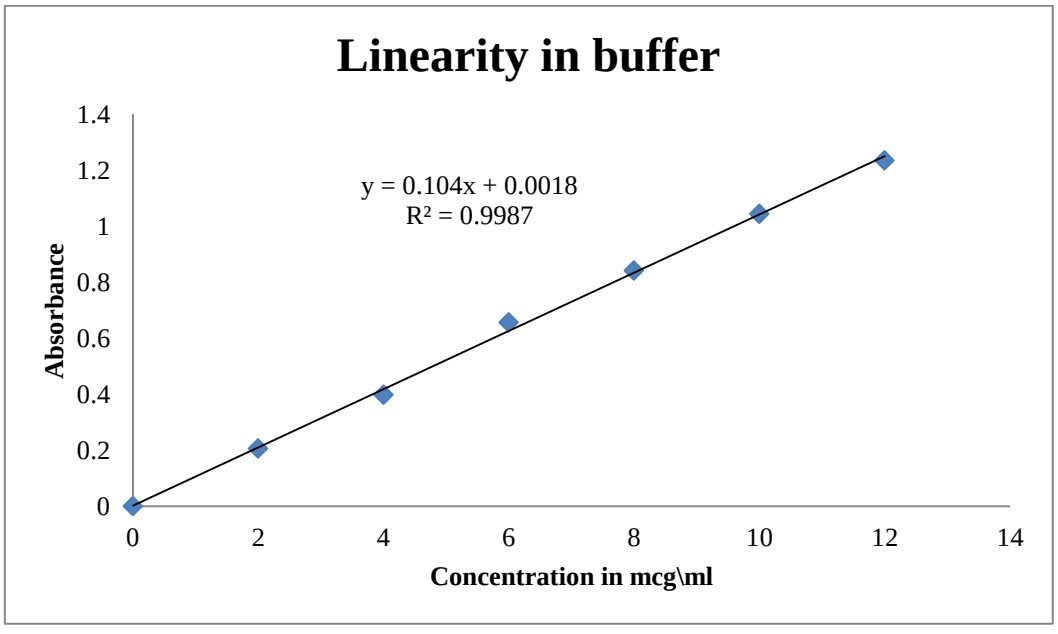



**Figure No.4:Standard Calibration curve of NMD with 6.8pH phosphate buffer**

In the current investigation, analytical method obeyed beer-lamberts law in the concentration range of 2-12 µg/ml and it was suitable for the estimation of nimodipine using phosphate buffer of pH 6.8. The value of correlation coefficient (r) for the linear regression equation was found to be more than 0.99 which indicates a positive correlation between the concentration of drug and corresponding absorbance values.

**8.2. FTIR studies**

**Table No. 12:FT-IR interpretations of pure drug and physical mixtures**

| S.No | Functional group | Characteristic peaks | Observed peaks | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | **Nimodipine** | **Nimodipine : MCC** | **Nimodipine : SSG** | **Nimodipine : CCS** | **Nimodipine : Crospovidone** | **Nimodipine : Mannitol** | **Nimodipine : Mg. stearate** |
| 1 | C-H (Aromatic bending) | 680-860 $cm^{-1}$ | 782.17 $cm^{-1}$ | 782.17 $cm^{-1}$ | 781.20 $cm^{-1}$ | 781.20 $cm^{-1}$ | 782.17 $cm^{-1}$ | 783.13 $cm^{-1}$ | 782.12 $cm^{-1}$ |
| 2 | $NO_2$ (stretching) | 1300-1600 $cm^{-1}$ | 1369.52 $cm^{-1}$ | 1368.55 $cm^{-1}$ | 1369.52 $cm^{-1}$ | 1369.52 $cm^{-1}$ | 1369.52 $cm^{-1}$ | 1369.52 $cm^{-1}$ | 1369.52 $cm^{-1}$ |
| 3 | C=C (Aromatic stretching) | 1400-1600 $cm^{-1}$ | 1465.96 $cm^{-1}$ | 1465.96 $cm^{-1}$ | 1415.81 $cm^{-1}$ | 1415.81 $cm^{-1}$ | 1465.00 $cm^{-1}$ | 1415.81 $cm^{-1}$ | 1426.42 $cm^{-1}$ |
| 4 | N-H (bending) | 1580-1650 $cm^{-1}$ | 1626.06 $cm^{-1}$ | 1627.03 $cm^{-1}$ | 1638.60 $cm^{-1}$ | 1637.64 $cm^{-1}$ | 1627.99 $cm^{-1}$ | 1626.06 $cm^{-1}$ | 1624.13 $cm^{-1}$ |
| 5 | C-H (stretching) | 2850-3000 $cm^{-1}$ | 2973.40 $cm^{-1}$ | 2936.75 $cm^{-1}$ | 2937.71 $cm^{-1}$ | 2936.75 $cm^{-1}$ | 2938.68 $cm^{-1}$ | 2943.50 $cm^{-1}$ | 2934.82 $cm^{-1}$ |
| 6 | O-H (stretching) | 3200-3500 $cm^{-1}$ | 3411.26 $cm^{-1}$ | 3258.81 $cm^{-1}$ | 3397.26 $cm^{-1}$ | 3272.38 $cm^{-1}$ | 3273.34 $cm^{-1}$ | 3261.77 $cm^{-1}$ | 3271.41 $cm^{-1}$ |


**Figure No.5:FT-IR spectra of Nimodipine**


**Figure No.6:FT-IR Spectra of Nimodipine withmannitol**


**Figure No.7:FT-IR Spectra of Nimodipine withmagnesium stearate**


**Figure No.8:FT-IR Spectra of Nimodipine with microcrystalline cellulose**


**Figure No.9:FT-IR Spectra of Nimodipine with crospovidone**

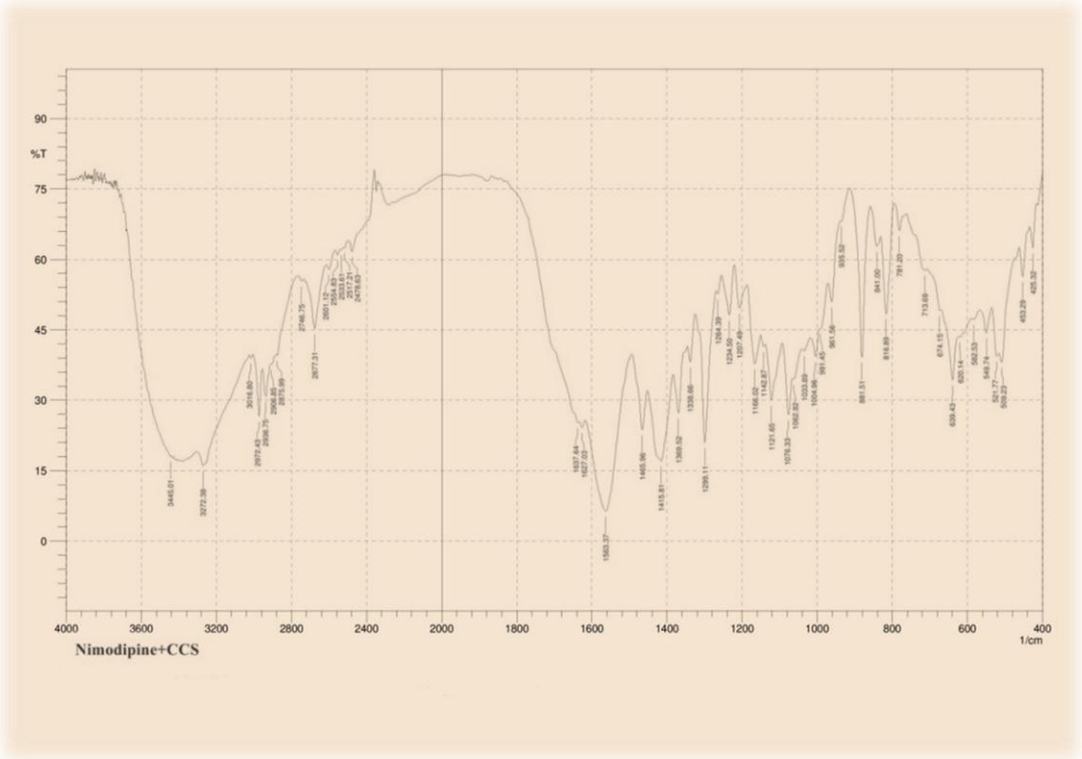



**Figure No.10:FT-IR Spectra of nimodipine with cross carmellose sodium**


**Figure No. 11:FT-IR Spectra of Nimodipine with sodium starch glycolate**

FT-IR spectra of pure Nimodipine and the physical mixtures of drug and excipients were given in Table No. 12 and Figure No. 5, 6, 7, 8, 9, 10 and 11. Pure Nimodipine showed principal absorption peaks at 782.17 $cm^{-1}$ (C-H aromatic bending), 1369.52$cm^{-1}$ ($NO_2$stretching), 1465.96 $cm^{-1}$(C=C aromatic stretching), 1626.06 $cm^{-1}$ (N-H bending), 2973.40 $cm^{-1}$ (C-H stretching) and 3411.26$cm^{-1}$ (O-H stretching). The identical peaks ofC-H aromatic bending, $NO_2$ stretching, C=C aromatic stretching, N-H bending, C-H stretching and O-H stretching, vibrations were also noticed in the spectra of physical mixtures which contains drug and excipients. FT-IR spectra revealed that there was no interaction between the drug and the excipients used for fast dissolving tablets preparation.

### 8.3. Precompression studies

**Table No. 13:Evaluation of tablet blend for formulations(F1-F9)**

| Formulation | Bulk Density (g/cc) | Tapped Density(g/cc) | Hausner's ratio | Compressibility index(%) | Angle of repose |
|---|---|---|---|---|---|
| **F1** | 0.464 | 0.574 | 1.23 | 19.1 | 29.47 |
| **F2** | 0.423 | 0.501 | 1.16 | 15.5 | 27.63 |
| **F3** | 0.456 | 0.542 | 1.22 | 15.8 | 25.54 |
| **F4** | 0.467 | 0.559 | 1.25 | 16.4 | 26.23 |
| **F5** | 0.485 | 0.593 | 1.10 | 18.2 | 27.21 |
| **F6** | 0.460 | 0.556 | 1.21 | 17.2 | 30.38 |
| **F7** | 0.478 | 0.575 | 1.24 | 16.8 | 28.46 |
| **F8** | 0.450 | 0.554 | 1.28 | 18.7 | 25.71 |
| **F9** | 0.442 | 0.537 | 1.27 | 17.6 | 31.82 |

The angle of repose less than 32, which reveals good flow property it shown in for formulations F1 – F9.The loose bulk density and tapped bulk density for all formulation (F1 – F9) varied from 0.442 gm/cm$^3$ to 0.467 gm/cm$^3$ and 0.501 gm/cm$^3$ to 0.574 gm/cm$^3$respectively.The results of carr's consolidate index or % compressibility index for the entire formulation (F1 – F9) blend range from 15 to 19 shows fair flow properties.

**8.4. Post compression studies**

**Table No. 14:Evaluation of sublingual tablets for formulations (F1 – F9)**

| Formulation | Hardness (kg/cm2) | Friability (%) | Weight (mg) | Thickness (mm) | Drug content (%) |
|---|---|---|---|---|---|
| **F1** | 3.0±0.17 | 0.25 | 201±0.59 | 3.9±0.05 | 97.2 |
| **F2** | 2.8±0.20 | 0.23 | 198±0.63 | 4±0.02 | 97.72 |
| **F3** | 3.1±0.18 | 0.26 | 201±0.45 | 3.7±0.07 | 98.4 |
| **F4** | 2.9±0.15 | 0.24 | 202±0.88 | 3.8±0.10 | 97 |
| **F5** | 3.2±0.16 | 0.28 | 204±0.56 | 3.9±0.03 | 98.44 |
| **F6** | 2.8±0.22 | 0.32 | 198±0.74 | 3.9±0.06 | 100.8 |
| **F7** | 3.2±0.24 | 0.27 | 201±0.67 | 3.8±0.15 | 97.2 |
| **F8** | 2.9±0.22 | 0.29 | 201±0.77 | 3.9±0.03 | 98.4 |
| **F9** | 2.8±0.16 | 0.24 | 203±0.86 | 4±0.01 | 95.32 |

The hardness values ranged from 2.8±0.16kg/cm$^2$to 3.2±0.24 kg/cm$^2$ for formulation (F1-F9) and were almost same.

The friability values were found to be within the limit (0.5 - 1%). The above evaluation parameter showed no significant difference between F1, F2, F3, F4, F5, F6, F7, F8, F9 formulations.

The entire tablet passes weight variation test as the average % weight variation was within the Pharmacopeia limit of 7.5%. It was found to be 198±0.63 mg to 204±0.56 mg. The weight of all the tablets was found to be uniform with less deviation.

The maximum concentration among all the formulations was found to be 100.8% and minimum % drug content from all formulation was found to be 95.32%. The results of drug content of all batches are shown in.

**8.5. Evaluation of tablets**

**Table No. 15:Evaluation of Sublingual tablets for formulations (F1 – F9)**

| Formulation | Disintegration time (sec) | Wetting time (sec) | Water absorption ratio (%) | *In vitro* dispersion time (sec) |
|---|---|---|---|---|
| **F1** | 8 | 20 | 19.42 | 8 |
| **F2** | 6 | 15 | 22.47 | 5 |
| **F3** | 5 | 12 | 19.78 | 5 |
| **F4** | 10 | 16 | 16.13 | 15 |
| **F5** | 9 | 14 | 17.27 | 11 |
| **F6** | 8 | 19 | 12.17 | 9 |
| **F7** | 18 | 27 | 15.32 | 14 |
| **F8** | 10 | 20 | 12.047 | 12 |
| **F9** | 9 | 20 | 13.92 | 8 |

Disintegration test carried out in modified dissolution apparatus, it shows the formulations with1.5%, 3%, 6% SSG showed high value for disintegrating time as 18, 10, 8 secs. The results showed that the disintegration time of F1, F2, F3 with 1.5%, 3%, 6% CP formulations to be as 8, 6, 5 secs respectively and is almost better than F4, F5, F6, F7, F8, F9 formulationsandcomparative profile.

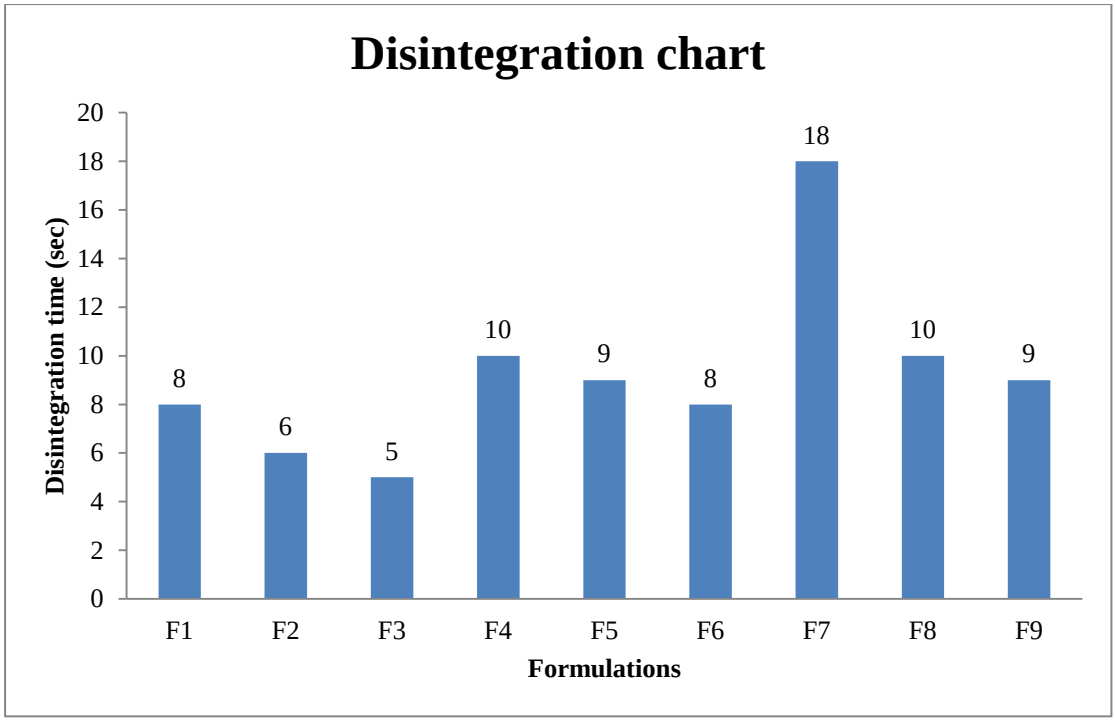



**Figure No. 12:Bar graph comparison between disintegration times for formulations (F1- F9)**

Wetting time is closely related to the inner structure of tablet. The experiment mimics the action of saliva in contact with the tablet to illustrate the water uptake and subsequent wetting of tablet. This shows the wetting process was very rapid in almost all formulations. This may be due to the ability of swelling followed by breaking and also capacity of water absorption and causes swelling. It was found to be in the range of 14 secs to 27secs.It shows crosspovidone formulations F1, F2, F3 (1.5 – 6%) have better wetting time comparing with that of cross carmellose sodium starch glycolate, and comparative profile result was shown in table no:15.

Water absorption ratio which is important criteria for understanding the capacity of disintegrants to swell in the presence of little amount of water, was calculated. It was found to be in the range of 12.17 to 22.47% . This shows that all the formulations have good water absorption capacityresult was shown in table no:15.

The in vitro dispersion time is measured by time taken to uniform dispersion, the rapid dispersion. It was found to be in the range of 5secs to 15secs (Graph). The result showed that the in vitro dispersion time of F1, F2, and F3 formulations is almost equal and better than F4, F5, F6, F7, F8, F9 formulations and comparative profileresult was shown in Table No:15.

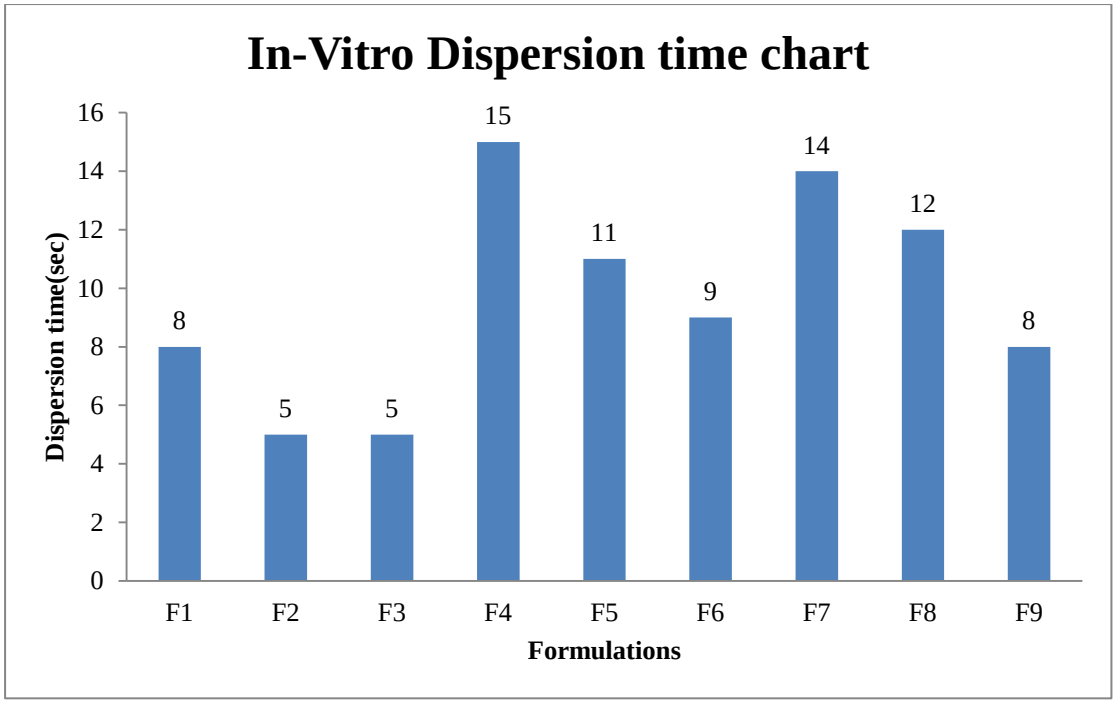



**Figure No. 13:Bar graph comparison between In-vitro dispersion times for formulations (F1- F9)**

### 8.5.1. *In vitro* dissolution studies

**Table No. 16:Cumulative % drug release for formulations (F1 – F9)**

| Cumulative % drug release | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Time** | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** |
| **2 Min** | 55.15 | 58.9 | 65.5 | 48.07 | 51.5 | 62.7 | 45.93 | 50.54 | 57.9 |
| **4 Min** | 68.6 | 72.1 | 74.9 | 57.29 | 61.5 | 71.1 | 55.97 | 61.7 | 61.07 |
| **6 Min** | 71.12 | 80 | 82.64 | 72.93 | 76.55 | 81.16 | 71.44 | 73.2 | 77.2 |
| **8 Min** | 81.9 | 87.08 | 89.06 | 79.68 | 84.61 | 86.5 | 76.05 | 81.8 | 84.12 |
| **10 Min** | 91.17 | 94.82 | 96.96 | 88.4 | 93.3 | 94.1 | 85.2 | 87.07 | 89.2 |

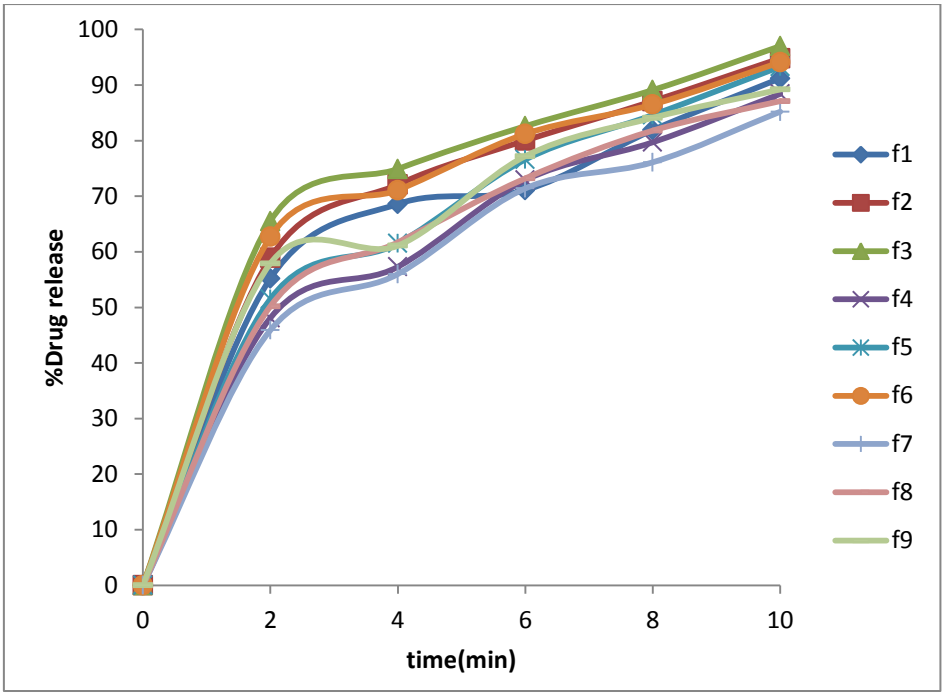



**Figure No. 14:Comparison between cumulative % drug releases for formulations (F1- F9)**

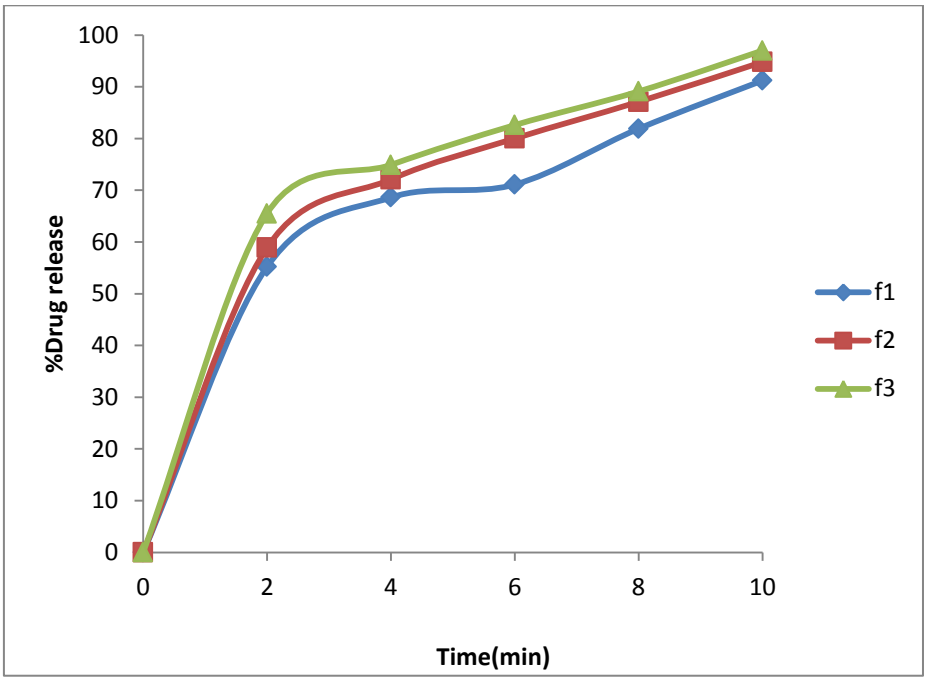



**Figure No. 15:Comparison between cumulative % drug releases for formulations (F1- F3)**

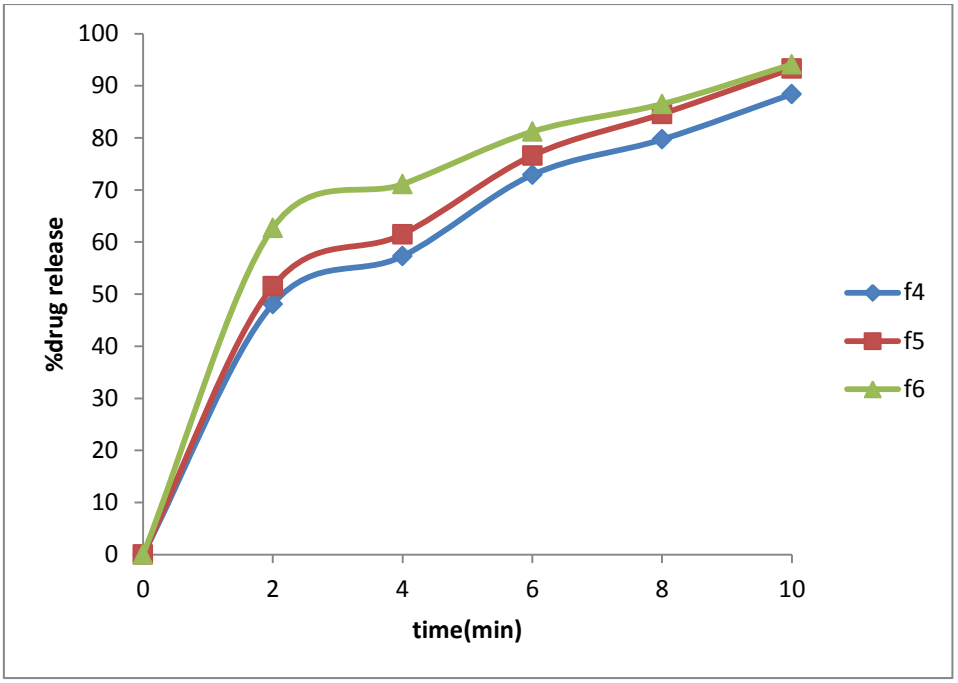



**Figure No. 16:Comparison between cumulative % drug releases for formulations (F4 - F6)**

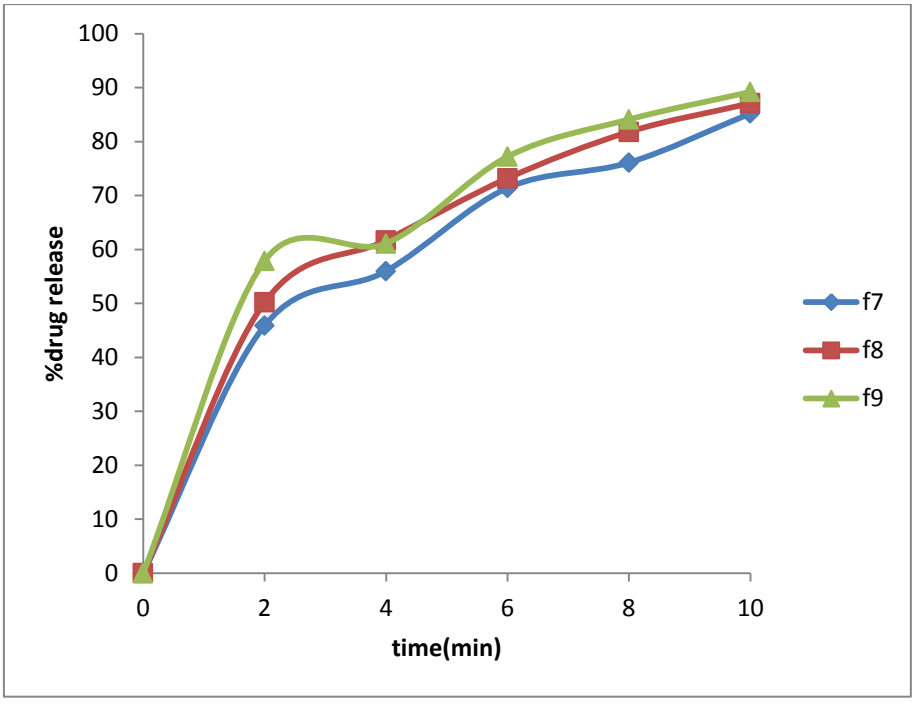



**Figure No. 17:Comparison between cumulative % drug release for formulations (F7- F9)**

Dissolution is carried out in USP-2 type apparatus at 50rpm in the volume of 500ml dissolution media (phosphate buffer pH 6.8) for 10 minutes. At the end of 10 minutes almost total amount of the drug is released (i.e. 96.96%), from the formulation prepared by the direct compression method with 6% crosspovidoneresult was shown in table no:16.

**8.6. Drug release kinetics:**

Correlation coefficient (r) & rate constant (k) Values of Nimodipine sublingual tablets containing Crospovidone, cross carmellose sodium, sodium starch glycolate.

**Table No.17:Drug release kinetics**

| Kinetic model | | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|---|
| Zero order | r | 0.9436 | 0.9391 | 0.9179 | 0.9364 | 0.9318 | 0.9151 | 0.9424 | 0.8383 | 0.8979 |
| | k | 17.15 | 18.25 | 18.72 | 14.32 | 15.37 | 17.77 | 13.99 | 15.42 | 15.42 |
| Higuchi | r | 0.9945 | 0.9913 | 0.9646 | 0.9943 | 0.9737 | 0.9833 | 0.9953 | 0.9927 | 0.9797 |
| | k | 35.17 | 37.09 | 39.09 | 29.63 | 31.80 | 37.17 | 28.82 | 31.76 | 32.71 |
| First order | r | 0.9963 | 0.9939 | 0.9991 | 0.9981 | 0.9994 | 0.9903 | 0.9989 | 0.9991 | 0.9822 |
| | k | 0.2697 | 0.3192 | 0.3456 | 0.2127 | 0.2466 | 0.3104 | 0.2057 | 0.241 | 0.24 |
| Peppas | r | 0.9796 | 0.9995 | 0.9985 | 0.9892 | 0.9914 | 0.9125 | 0.9914 | 0.9971 | 0.9615 |
| | k | 0.294 | 0.2894 | 0.2387 | 0.3878 | 0.3758 | 0.2511 | 0.3894 | 0.3489 | 0.2882 |
| Hixson-crowell | r | 0.9659 | 0.9704 | 0.9626 | 0.9816 | 0.9855 | 0.859 | 0.9761 | 0.9741 | 0.9602 |
| | k | 0.3717 | 0.4022 | 0.4284 | 0.2865 | 0.3162 | 0.3932 | 0.2776 | 0.3177 | 0.3177 |
| DE10 | | 44.73 | 47.48 | 51.48 | 38.36 | 41.13 | 49.13 | 36.96 | 40.47 | 44.38 |
| DE30 | | 58.96 | 63.64 | 66.89 | 54.53 | 57.96 | 64.55 | 52.84 | 56.59 | 59.72 |
| T 50 | | 1.81 | 1.70 | 1.53 | 2.42 | 1.94 | 1.59 | 2.81 | 1.98 | 1.73 |
| T 90 | | 9.75 | 8.75 | 8.24 | 0 | 9.28 | 8.92 | 0 | 0 | 0 |

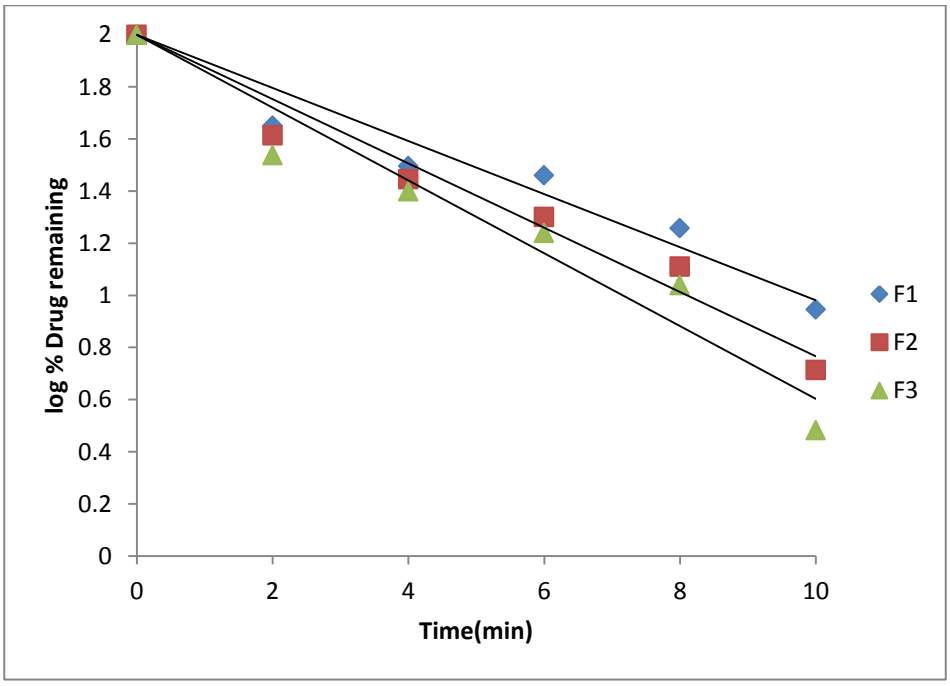



**Figure No. 18:First order plots of Nimodipine sublingual tabletscontaining crospovidone**

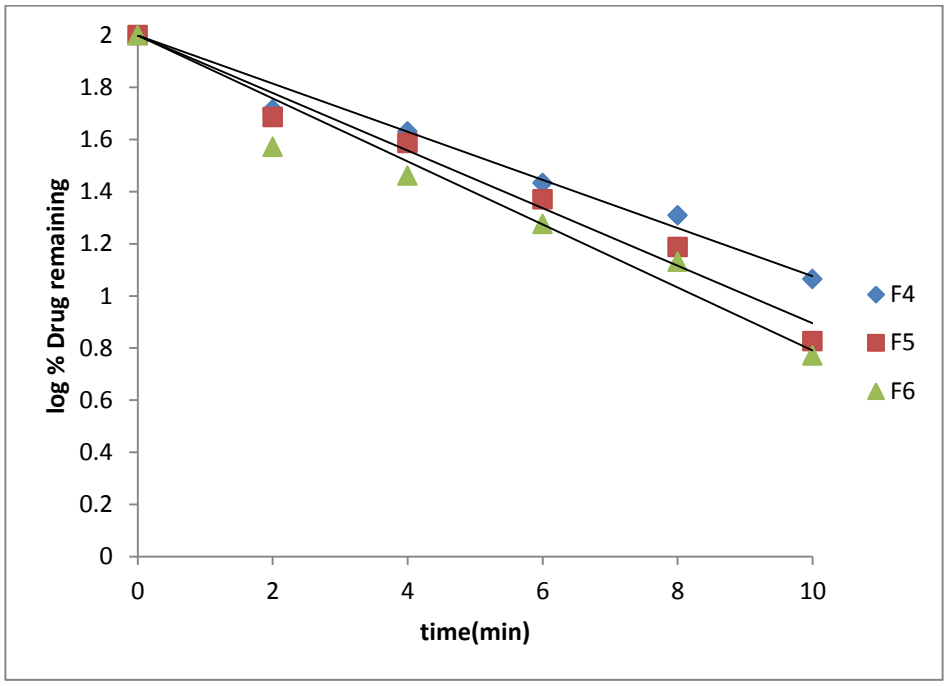



**Figure No. 19: First order plots of Nimodipine sublingual tablets containing Croscarmellosesodium**

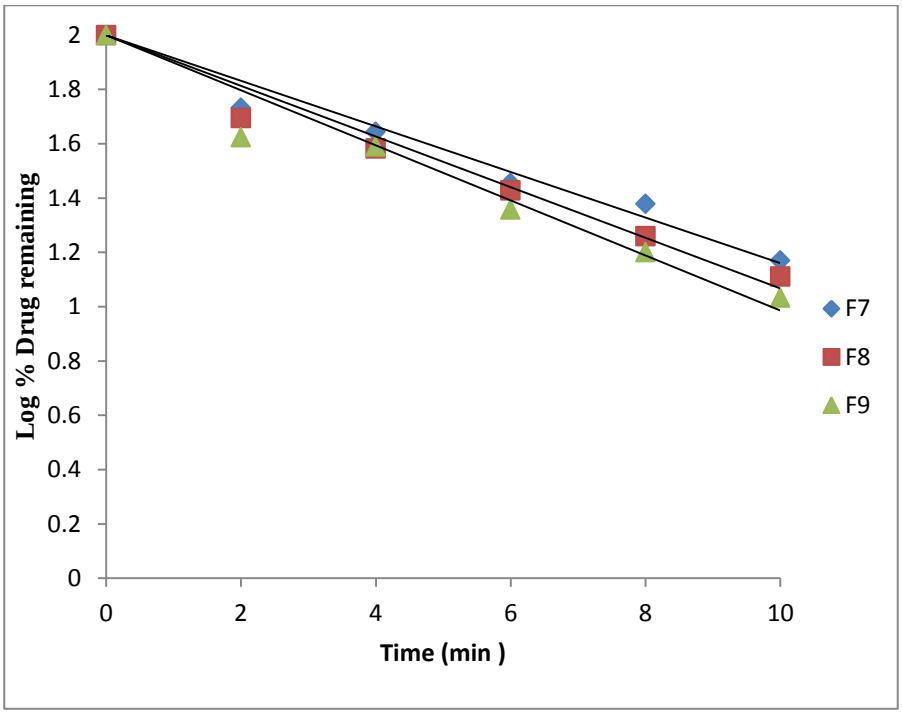



**Figure No.20: First order plots of Nimodipine sublingual tablets containing sodium starch glycolate**

The drug release profiles of Nimodipine sublingual tablets were fitted to various kinetic models such as Zero order, First order, Higuchi, Peppasand Hixson-Crowell. The dissolution parameters such as dissolution efficiency (DE) at 10 and 30 minutes were increased proportionately. Half-life of drug *i.e.*, $T_{50}$ was found to be 1.81, 1.70, 1.53, 2.42, 1.94, 1.59, 2.81, 1.98 and 1.73 min for F1, F2, F3, F4, F5, F6, F7, F8 and F9 formulations respectively. Shelf-life of the drug *i.e.*, $T_{90}$ was found to be 9.75, 8.75, 8.24, 9.28 and 8.92 minutes for F1, F2, F3, F5and F6 formulations respectively. The drug release data of nimodipine fast dissolving tablets have treated with different kinetic models are shown in Table No. 17.The drug release patterns of nimodipine fast dissolving tablets had followed the first order kinetic model. This release patterns are evident with the correlation coefficient 'r' values which are nearer to 1. The first order plots for all nimodipine fast dissolving tablets were shown in Figure No.18, 19 and 20.

## 8.7. Stability Study

**Table No. 18:Comparison of Various Parameters for Stability Study**

| Evaluation Parameter | Initial | 1 month | 2 month | 3 month |
|---|---|---|---|---|
| **Hardness( kg/cm$^2$)** | 3.1 ± 0.18 | 3.2 ± 0.36 | 3.3 ± 0.05 | 3.3 ± 0.90 |
| **% Friability** | 0.26 | 0.25 | 0.24 | 0.24 |
| **Disintegration Time (sec)** | 5 | 7 sec | 8 sec | 9 sec |
| **Drug Content** | 98.4 | 99.6 | 99.2 | 99.80 |

The optimized formulation F3 is kept for stability studies. Accelerated stability studies were carried out at $40^0$C/75%RH for 3 months. The tablets were then evaluated for hardness, friability, disintegration and drug content at 1$^{st}$ month, 2$^{nd}$ month and 3$^{rd}$ month. The results indicated that there was no significant change in evaluation of the tablets. The results were tabulated in Table No: 18.

**Table No. 19:Comparison of Drug Release Profile of Batch F3**

| Time (min) | Initial | 1 month | 2 month | 3 month |
|---|---|---|---|---|
| **2** | 65.5 | 64.90 | 63.50 | 62.42 |
| **4** | 74.9 | 73.71 | 72.25 | 71.64 |
| **6** | 82.64 | 81.09 | 80.04 | 79.64 |
| **9** | 89.06 | 88.90 | 87.25 | 86.09 |
| **10** | 96.96 | 95.99 | 94.84 | 94.01 |

The optimized formulation F3 is evaluated for *in-vitro* drug release studies after keeping the tablets at accelerated stability conditions ($40^0$C/75%RH) for 3 months. It is evaluated initially, $1^{st}$ month, $2^{nd}$ month and $3^{rd}$ month. *In-vitro* drug release studies were performed in phosphate buffer pH 6.8 by using USP dissolution test apparatus-Type II, Rotating Paddle method. The results indicated that there was no significant change in i*n-vitro* drug release studies. The data for *in-vitro* release profilewas shown in Table No: 19.


# *Summary & Conclusion*

# 9. SUMMARY AND CONCLUSION

## 9.1. Summary

The aim of the present study was to develop and optimize oral sublingual tablets of model drug (NMD) to give quick onset of action by rapidly disintegrating in a few seconds without the need of water with better patient compliance. In such cases, bioavailability of drug is significantly greater and adverse event is reduced than those observed from conventional tablet dosage form

**The work done is summarized as follows**:

By performing compatibility studies by IR spectrophotometry, no interaction was confirmed. Oral disintegrating tablets were formulated by direct compression method and suitable analytical method based on UV-Visible spectrophotometer was developed for the model drug

Standard calibration curve prepared to determine the drug content in the prepared tablets and UV analysis was performed to determine the drug during *in vitro* release studies.

Prior to compression, the blend of drug and excipients were evaluated for flow properties such as Angle of repose, loose bulk density, Tapped density, % Compressibility, and Hausner's ratio. All the formulations showed good flow properties.

Sublingual tablets were prepared by direct compression technique using CADMACH 16 station tablet punching machine, equipped with flat round punch of 8.7 mm diameter.

Post compression evaluation of prepared sublingual tablets were carried out with the help of different pharmacopoeial and non pharmacopoeial (industry specified) tests. The shape and colour of all the formulations were found to be circular and white in colour. The thickness was found to be uniform in specific formulations. The hardness and friability are also within the permitted limits.

## 9.2. Conclusion

Sublingual tablets of nimodipine can be successfully prepared by direct compression method using selected superdisintegrants with Crosspovidone 1.5%, 3%, 6%, Crosscarmellose 1.5%, 3%, 6% and Sodium starch glycolate 1.5%, 3%, 6%, for the better patient compliance and effective therapy the relative efficiency of these superdisintegrant to improve the disintegration and dissolution rate of tablets were found in order

The disintegration of F1, F2, F3 with 1.5%, 3%, 6% Crosspovidone formulations to be as 8, 6, 5secs respectively and is almost better than F4, F5, F6, F7, F8, F9 formulations

Formulation F3 In-vitro Dissolution studie 10 minutes almost total amount of the drug is released 6% crosspovidone (i.e. 96.96%).

Crosspovidone shows good result as compare to other superdisintegrants.

Crosspovidone > crosscarmellose sodium > sodium starch glycolate

# Bibliography

## 10. BIBLIOGRAPHY

1. Nikunj J. Aghera, Suresh D. Shah, Kantilal R. Vadalia Formulation and evaluation of sublingual tablets of losartan potassium Asian Pacific Journal of Tropical Disease (2012)S130-S135.
2. K.patel nibha1 and ss. pancholi an overview on: sublingual route for systemic drug delivery international journal of research in pharmaceutical and biomedical sciences vol. 3 (2) apr -jun2012
3. Neha narang1, jyotisharma sublingual mucosa as a route for systemic drug delivery international journal of pharmacy and pharmaceutical sciences issn- 0975-1491 vol 3, suppl 2, 2011.
4. Amitkumar, kamalsaroha, ruchikamohan, chetna, karambira review on sublingual tablets a j ournal of pharmacy research volume 8, issue1. page 98-111,2013.
5. Viralkumar f. patel1, fang liu1, marc b. brown1, advances in oral transmucosal drug delivery 1school of pharmacy, university of hertfordshire, hatfield, uk al10 9ab medpharm limited.
6. Shree H. N. Shukla Institute of Pharmaceutical Education and Research,B/H-Marketing Yard, Nr. Lalpari Lake, Amargadh (Bhichari), Rajkot-360002.
7. Nishan n. bobade , sandeep c. atram, vikrant p. wankhade, dr. s.d.pande, dr. k.k.tapar a review on buccal drug delivery system international journal of pharmacy and pharmaceutical science research 2013; 3(1): 35-40.
8. Amitkumar bind, g. gnanarajan and preetikothiyala review on sublingual route for systemic drug delivery international journal of drug research and technology 2013, vol. 3 (2), 31-36.
9. Kamalsaroha, ruchikamohan, chetna, karambira review on sublingual tablets the pharma research, volume 8, issue1. page 98-111.
10. Debjit Bhowmik, Chiranjib.B, Krishnakanth, Pankaj, R.Margret Chandira overview on Fast Dissolving TabletJournal of Chemical and Pharmaceutical Research, 2009, 1(1): 163-177
11. K.Patel Nibha1 and SS. Pancholi An Overview on: Sublingual Route for Systemic Drug Delivery International Journal of Research in Pharmaceutical and Biomedical Sciences ISSN: 2229-3701,2012.
12. Priyank patel1,sandip makwana1,urvish jobanputra1,mihir ravat1,ankit ajmera1,mandev patel.sublingual route for the systemic delivery of

ondansetroninternational journal of drug development & research october-december 2011 | vol. 3 | issue 4 | issn 0975-9344

13. Sheeba f r, mallige college of pharmacy chikkabanavara post, bangalore-90,india research article formulation and evaluation of nifedipine sublingual tablets vol.2 issue 3, july-september 2009.
14. Sindhuabraham, basavarajb.v, bharath s, deveswaran r, sharonfurtado and madhavan v formulation and optimization of sublingual tablets of rabeprazole sodium volume 5, issue 2, november – december 2010; article-010
15. Naimish A. Sarkhejiya, Krupraj K. Khachar, Vipul P. Patel Formulation Development and Evaluation of Sublingual Tablet ofRisperidone ISSN 0974-3618 Research J. Pharm. and Tech. 6(4): April 2013.
16. Gupta A., Mishra A.K., Gupta V., Bansal P., Singh R and Singh A.K., "Recent Trends of Fast Dissolving Tablet - An Overview of Formulation Technology", International Journal of Pharmaceutical & Biological Archives, 2010, pp. 1-10.
17. Zhang H, Zhang J, Streisand J.B, "Oral Mucosal Drug Delivery: Clinical Pharmacokinetics and Therapeutic Applications", 2002, pp. 661-680.
18. Harris D, Robinson J.R, "Drug Delivery via the Mucous Membrane of the Oral cavity", Journal of Pharmaceutical Science", January 1992.
19. Divya, Nandakumar, "Local Drug Delivery-Periocol, In Periodontics", Trends biomaterartif organ, 2006, pp. 74-80.
20. Fan M, Mitchell M and Cooke M, "Cardiac patients' knowledge and use of sublingual glyceryl trinitrate", Australian Journal of Advanced Nursing, pp. 32-38.
21. John D.N, Fort S, Lewis M.J and Luscombe D.K, "Pharmacokinetics and pharmacodynamics of verapamil following sublingual and oral administration to healthy volunteers", Br. J. clin. Pharmac, 1992, pp. 623-627.
22. Kazerani H, Hajimoradi B, Amini A, Naseri M.H and Moharamzad Y, " Clinical efficacy of sublingual captopril in the treatment of hypertensive urgency", Singapore Med J, 2009, pp. 400-402.
23. Hansen T.W, Yan Li, Boggia J, Thijs L, Richart T, and Staessen J.A, "Predictive Role of the Nighttime Blood Pressure", Journal of American Heart Association, 2011.
24. Chobanian A.V, Bakris G.L, Black H.R, Cushman W.C, lee a. green, "Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure", 2003, pp. 1206-1252.

25. Mulrow P.J and Toledo, "Detection and control of hypertension in the population usa experience", Data from the health examination surveys, 1960-1991, pp. 60-69.
26. Aghera nikunj jamnadas mr. suresh d. shah formulation and evaluation of sublingual
tablets of losartan potassium,may 2012
27. http://www.drugbank.ca/drugs/DB00796.
28. Raymond C Rowe, Paul J Sheskey, Marian E Quinn Handbook of Pharmaceutical Excipients 6th edition, Pharmaceutical Press, pp. 663-666.
29. Raymond C Rowe, Paul J Sheskey, Marian E Quinn Handbook of Pharmaceutical Excipients 6th edition, Pharm
30. aceutical Press, pp. 685-691.
31. Raymond C Rowe, Paul J Sheskey, Marian E Quinn Handbook of Pharmaceutical Excipients 6th edition, Pharmaceutical Press, pp. 185-188.
32. Raymond C Rowe, Paul J Sheskey, Marian E Quinn Handbook of Pharmaceutical Excipients 6th edition, Pharmaceutical Press, pp. 208-210.
33. Raymond C Rowe, Paul J Sheskey, Marian E Quinn Handbook of Pharmaceutical Excipients 6th edition, Pharmaceutical Press, pp. 206-208.
34. Raymond C Rowe, Paul J Sheskey, Marian E Quinn Handbook of Pharmaceutical Excipients 6th edition, Pharmaceutical Press, pp. 424-428.
35. Raymond C Rowe, Paul J Sheskey, Marian E Quinn Handbook of Pharmaceutical Excipients 6th edition, Pharmaceutical Press, pp. 129-133.
36. Raymond C Rowe, Paul J Sheskey, Marian E Quinn Handbook of Pharmaceutical Excipients 6th edition, Pharmaceutical Press, pp. 181-183.
37. Raymond C Rowe, Paul J Sheskey, Marian E Quinn Handbook of Pharmaceutical Excipients 6th edition, Pharmaceutical Press, pp. 404-407.
38. Raymond C Rowe, Paul J Sheskey, Marian E Quinn Handbook of Pharmaceutical Excipients 6th edition, Pharmaceutical Press, pp. 728-731.
39. Suvakanta dash, P. Narasimha murthy, Lilakanta nath, Prasanta chowdhury. Kinetic modeling on drug release from controlled drug delivery systems. Acta Poloniae Pharmaceutica – Drug Research, 2010; 67 (3):217-223.
40. A. Chime Salome, C. Onunkwo and I. Onyishi. Kinetics and mechanisms of drug release from swellable and non swellable matrices: A review. Research journal of pharmaceutical, biological and chemical sciences, 2013; 4(2):97-103.

41. D.M. Brahmankar, Sunil B. Jaiswal. "Biopharmaceutics and pharmacokinetics –A treatise".2nd edition. Vallabh Prakashan, New delhi, 2009; pp no.433

42. Koland M. Sandeep and Charyulu N.R, "Fast dissolving sublingual films of ondansetron hydrochloride: Effect of additives on in vitro drug release and mucosal permeation", J Young Pharmacists , 2010, pp. 216-222.
43. Fusari S.A, "Nitroglycerin sublingual tablets II: Preparation and stability of a new, stabilized, sublingual, molded nitroglycerin tablet", Journal of Pharmaceutical Sciences, December 1973, pp. 2012–2021.
44. Tousey M.D, "The granulation process 101, basic technologies for tablet making", Pharmaceutical technology tableting & granulation, 2002, pp. 8-13.
45. Kaur T, Gill B, Sandeep kumar and Gupta G.D, "Mouth dissolving tablets: a novel approach to drug delivery", International journal of current pharmaceutical research, 2011, pp. 1-7.
46. Agrawal V.A, Rajurkar R.M, Thonte S.S, Ingale R.G, " fast disintegrating tablet as a new drug delivary system: a review", Pharmacophore, an international research journal, 2011, pp. 1-8.
47. Debjit B, Chiranjib, Krishnakanth, Pankaj and Chandira R.M, "Fast Dissolving Tablet: An Overview", Journal of Chemical and Pharmaceutical Research, 2009, pp.163-177.
48. Rameshwari S Sheeba F.R, Acharya G.D, Anandhi J, "Formulation and evaluation of nifedipine sublingual tablets", Asian Journal of Pharmaceutical and Clinical Research, July-September 2009.
49. Abraham S, Basavaraj , Bharath S, Deveswaran R, Furtado S and Madhavan V, "Formulation and optimization of sublingual tablets of rabeprazole sodium", International journal of pharmaceutical sciences review and research, November – December 2010, pp. 50-54.
50. Bolourchian N, Hadidi N, Foroutan S.M, Shafaghi B, "Development and optimization of a sublingual tablet formulation for physostigmine salicylate", Acta Pharm, 2009, pp. 301–312.
51. Bolourtchian N, Hadidi N, Foroutan S.M, and Shafaghi B, "Formulation and Optimization of Captopril Sublingual Tablet Using D-Optimal Design", Iranian Journal of Pharmaceutical Research, 2008, pp. 259-267.

52. Sharma R, Yasir M and Gupta A, "Formulation and Evaluation of Fast Disintegrating Sublingual Tablets of Glipizide: An Attempt to Treat Diabetic Coma" , International Journal of ChemTech Research, Oct-Dec 2010, pp 2026-2033.
53. Shirsand S.B, Para M.S, Ramani R.G, Swamy P.V, Nagendra kumar, and Rampure M.V, "Novel co-processed superdisintegrants in the design of fast dissolving tablets", International journal of pharmtech research, Jan-Mar 2010, pp. 222-227.
54. Bhanja S.B, Ellaiah P, Roy H,K, Samal B.K, Tiwari S and Murthy K.V.R, "Formulation and Evaluation of Perindopril Sublingual Tablets", International Journal of Research in Pharmaceutical and Biomedical Sciences, Jul – Sep 2011, pp.1193-1198.
55. Avulapati S, Roy A, Shashidhar , Reddy T and Reddy U, "Formulation And Evaluation Of Taste Masked And Fast Disintegrating Losartan Potassium Tablets", International Journal of Drug Development & Research, Jan-March 2011, pp. 45-51.
56. Rout P.K, Nayak B.S, Nayak U.K, "Statistical evaluation of losartan microspheres prepared by w/o emulsion method using factorial design and response surface methodology", Asian journal of pharmaceutical and clinical research, October-december 2009.
57. Bhardwaj V, Shukla V, Goyal N, Salim, Sharma P.K, "formulation and evaluation of fast disintegrating sublingual tablets of amlodipine besylate using different superdisintegrants", International journal of pharmacy and pharmaceutical sciences, 2010, pp.89-92.
58. Nagendrakumar, Raju, Shirsand S.B and Para M.S, "Design of fast dissolving granisetron hcl tablets using novel co –processed suprdisintegrants", International journal of pharmaceutical sciences review and research, march – april 2010, pp. 58-62.
59. Jangam V, Javvaji H, Tadikonda R and Gollapudi R, "Formulation and invitro evaluation of orodispersible tablets of carvidilol", An international journal of advances in pharmaceutical sciences, january - february 2011, pp.50-54.
60. Gokel Y, Paydas S, Kuvandik G and Alparslan N, "Sublingual valsartan in hypertensýve urgency", Turk j med sci, 2001, pp. 565-567.

61. Bhowmik D, Jayakar, Sampath kumar, "Design and characterisation of fast dissolving tablet of telmisartan", International journal of pharma recent research, 2009, pp. 31-40.
62. Madan J, Sharma A.K and Ramnik Singh, "Fast Dissolving Tablets of Aloe Vera Gel", Tropical Journal of Pharmaceutical Research, February 2009, pp. 63-70.