Article

Formulation, Development and Optimization of Sublingual Drug Delivery for Antihypertensive Drug

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ABSTRACT

The purpose of this investigation was to formulate, development of optimization of sublingual drug delivery for antihypertensive drug. Sublingual tablets of model drug (nimodipine) was formulated using mannitolAvicel pH102(microcrystalline cellulose) as diluents .Sublingual tablet was prepared by direct compression technique as it's a cost effective methods.As partameas sweetening agent. Magnesiumstearate(3%to4%) as lubricants.Superdisintegrants used are crosspovidone, crosscarmellosesodium , sodium starch glycol late disintegrantsodiumCMC. The sublingual drug showed acceptable results in all studies such as thickness, strength, , disintegration test time, surface pH and drug relese are developed. Sublingual tablets of nimodipine can be successfully prepared by direct. Compression method used 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.

Key Words: sublingual drug delivery, antihypertensive drug, nimodipine, mannitol

INTRODUCTION

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[1].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 system and 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-intestinalinfluences.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[2,3].

Superdisintegrants are used at low concentration have greater disintegrating efficiency. They are more effective intra granularly and exert less effect on compressibility and flow ability. 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[4].

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[5,6].

Nimodipine is chemically 3-(2-methoxyethyl)5-propane-2-yl,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine- 3,5-dicarboxylate. It is white, yellowish crystalline powder or colorless crystals. Nimodipine binds specifically to L-type voltage-gated calcium channels and prevent vasospasm. It selectively relaxes cerebral vasculature, approved for prevention and treatment of neurological deficit[7-11].

The purpose of this investigation was to formulate, development of optimization of sublingual drug delivery for antihypertensive drug.

MATERIALS AND METHODS

Stock solution Preparation

Accurately weighed 100mg of drug was transferred into the 100 ml volumetric flask. Sufficient quantity of methanol was used to dissolve drug and volume was made up to the mark with methanol to get a 1000 µg/ml solution. Prepared Standard stock solution contains 1 mg/ml of model drug (Stock 1).

UV Absorption Maxima (λmax) of drug sample

Stock solution, strength of 10 (µg/ml) was prepared by diluting one ml of the above solution to 100 ml with water. 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 2ml, 4ml, 6ml, 8ml, 10ml and 12 ml were transferred to 10 ml volumetric flasks and were diluted with the water, up to the mark to obtain concentration of 2, 4, 6, 8, 10 and 12µg/ml respectively. Absorbance of each solution was measured at 226 nm under UV. Triplicate of Standard curve preparation was prepared. The absorbance was plotted against the concentrations and the graph with the straight line equation and r2 value were obtained.

Preparation of Stock solution with 6.8 PH Phosphate Buffer

Standard stock solution containing 1 mg/ml of model drug.(Stock 1) was prepared by dissolving Accurately weighed 100mg of drug in100 ml volumetric flask with 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 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 2ml, 4ml, 6ml, 8ml, 10ml 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 r2 value were obtained.

FT-IR 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. 1: Drug excipient compatibility study protocol

Sl. No.	Name of the substance	Drug Excipients 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**

Preformulation Parameters

An investigation of physical and chemical properties of a drug substance alone and when combined with excipients, called pre formulation testing. 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 dosageform.

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, V0Bulk 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[12,13].

Carr’s index:

It is expressed in percentage and is expressed byI = Dt - Db/Dt; Where, Dt is the tapped density of the powder Db is the bulk density of the powder[7,8].

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) [12,13].

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 eachother through the sides of the funnel. Relationship between angle of repose and powder flow property.

Formulation Development

With a total weight of 200mg, Sublingual tablets containing 30 mg of model drug were prepared. 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.

Formulation

Sublingual tablets of model drug (nimodipine) 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. Aspartame as sweetening agent.Magnesium stearate (3% to 4%) as lubricant. Superdisintegrants used are Crosspovidone, Crosscarmellose sodium, Sodium starch glycol late, disintegrant sodium CMC.

Formulation of different batches

The primary 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.

Method of formulation

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

Representation of Direct Compression Technique:

Except lubricants, the drug and the excipients were passed through sieve no: 40. This blend was further lubricated with Magnesium stearate (#:60) and the powdered blend was 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. 2: Formulations of different batches

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nimodipine	30	30	30	30	30	30	30	30	**30**
Crosspovidone	3	6	12	_	_	_	_	_	_
Crosscarmellose	_	_	_				_	_	_
Sod.				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							6		
Stearate	6	6	6	6	6	6		6	**6**
Talc	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**

Evaluation of tablets

Hardness test:

Using a Monsanto hardness tester the rigidity (hardness) of the tablet was determined14.

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-

Percentage friability = Initial weight – Final weight x 100

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 Verniercalipers using micrometer.

Drug ContentUniformity:

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.

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 (Wb). The wetted form of tablet was taken from petridish and reweighed (Wa). The water absorption ratio (R) can be the determined according to the following equation.

R= 100 x (Wa-Wb) / Wb

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. 3: Formulations of different batchesSummary 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	Lemda max	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.

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 T50 and T90 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. 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 DE30 would relate to the dissolution of the drug from a particular formulation after 30 minutes could only be compared with DE30 of other formulations.

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: 250 C ± 20 C / 60% RH ± 5% for 12 Months
- Accelerated Testing: 400 C ± 20 C /75% RH± 5% for 6 Months

Stability studies were carried out at 400C ± 20C /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 400 C ± 20 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 AND DISCUSSION

FT-IR interpretations of pure drug and physical mixtures

The pure drug nimodipine contains 2 carboxylic functions of a ring substitution exhibiting two intense peaks at 3529 cm-1 and 3409 cm-1 supporting the presence of carboxylate moieties. The pyridine N-H which is substituted by ortho methyl group shows a absorption peak at 3313cm-1 hence it is not pyrimidine nucleus, it is a pyridine nucleus. The C-H peaks are seen at 3027 cm-1 due to the presence of aromatic ring system. the aliphatic absorption peak of C-H are seen at 2950 cm-1 to 2915 cm-1, the carboxylate absorption of C=O give a distinct peak at 1751 cm-1 and 1673cm-1 these data's are full agreement with the structure of the drug used is nimodipine during the present research work.

Figure No.1: FT-IR spectra of Nimodipine

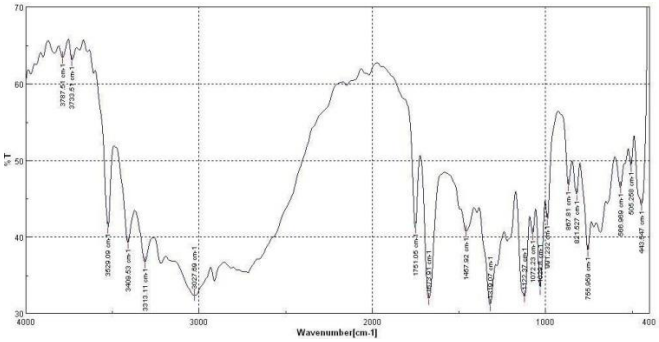


Figure No.2: FT-IR Spectra of Nimodipine with Mannitol

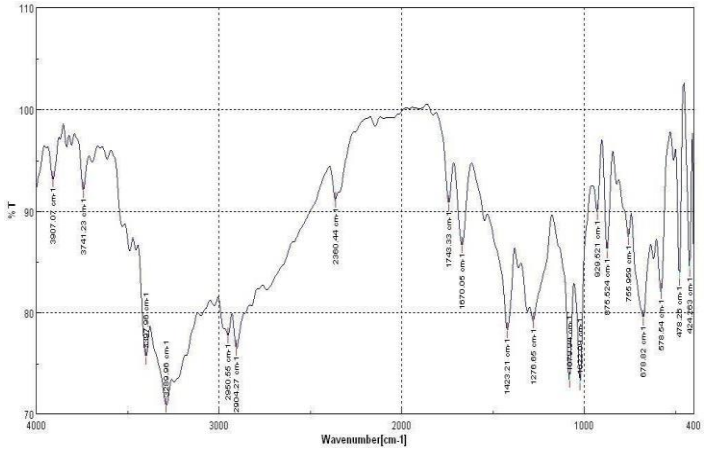


Figure No.3: FT-IR Spectra of Nimodipine with microcrystalline cellulose

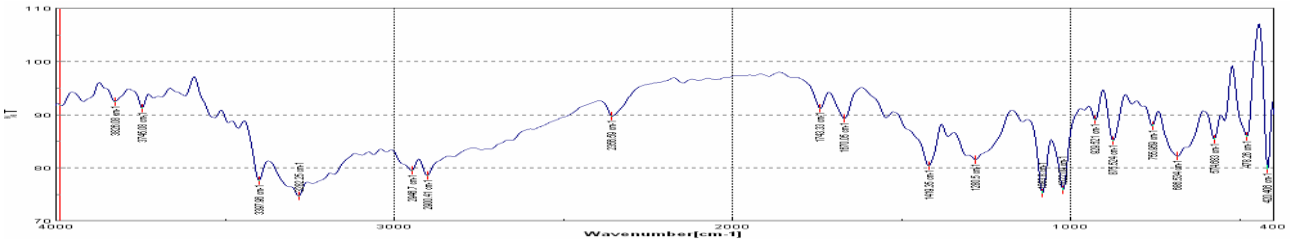


Figure No.4: FT-IR Spectra of Nimodipine with crospovidone

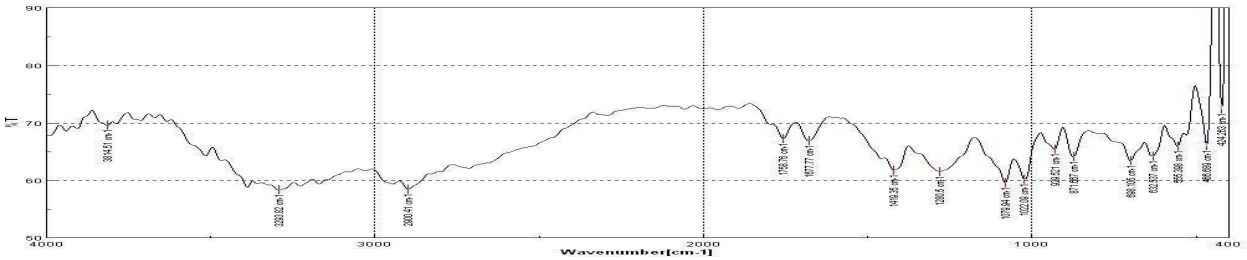


Figure No.5: FT-IR Spectra of nimodipine with cross carmellose sodium

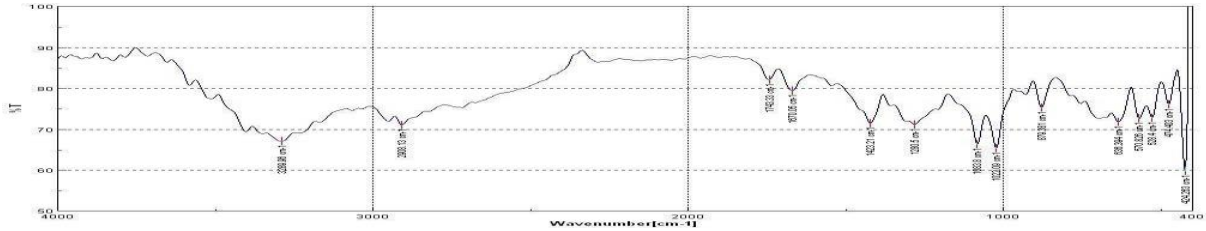


Figure No.6: FT-IR Spectra of Nimodipine with sodium starch glycolate

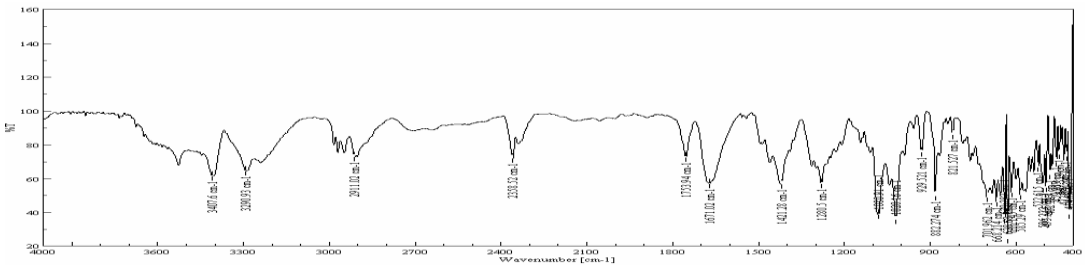


Figure No.7: FT-IR Spectra of Nimodipine with magnesium stearate

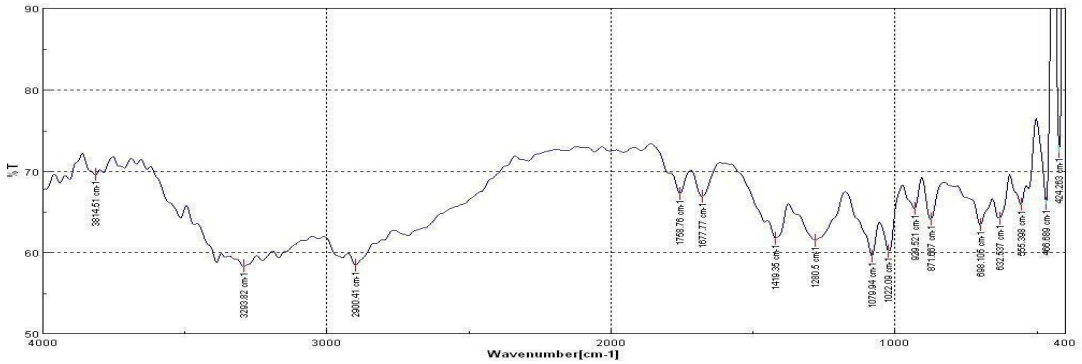


Table No. 4: Evaluation of tablet blend for formulation (F1-F9)

Formulation	Bulk density (g/cc)	Tapped Density(g/cc)	Hausner' s ratio	Compressibility index(%)	Angle of repose
F1	0.426	0.554	1.21	18.1	**28.34**
F2	0.416	0.530	1.12	14.2	**26.45**
F3	0.432	0.534	1.21	15.3	**24.23**
F4	0.439	0.549	1.26	15.9	**25.67**
F5	0.476	0.563	1.11	18.3	**26.21**
F6	0.465	0.559	1.19	16.7	**29.41**
F7	0.468	0.571	1.23	16.9	**27.42**
F8	0.448	0.551	1.25	18.1	**23.69**
F9	**0.439**	**0.532**	**1.26**	**16.9**	**30.83**

Precompression studies

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 0.416 gm/cm3 to 0.468 gm/cm3 and 0.530 gm/cm3 to 0.571gm/cm3respectively. The results of carr's consolidate index or % compressibility index for the entire formulation (F1 – F9) blend range from 14 to 18 shows fair flow properties.

Post compression studies

The hardness values 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%. 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 99.2% and minimum % drug content from all formulation was found to be 92.41%. The results of drug content of all batches are shown in **Table 5.**

Evaluation of tablets

Sublingual tablets are then subjected to various evaluation parameters so to determine and confirmation of their properties **Table 6.**

Disintegration test

Disintegration test carried out in modified dissolution apparatus, it shows the formulations showed high value for disintegrating time as 16 seconds.(F50 The results showed that the disintegration time of F1, F2, F3 formulations 7, 6, 6 seconds respectively and is almost better than F4, F5, F7, F8, F9 formulations and comparative profile.

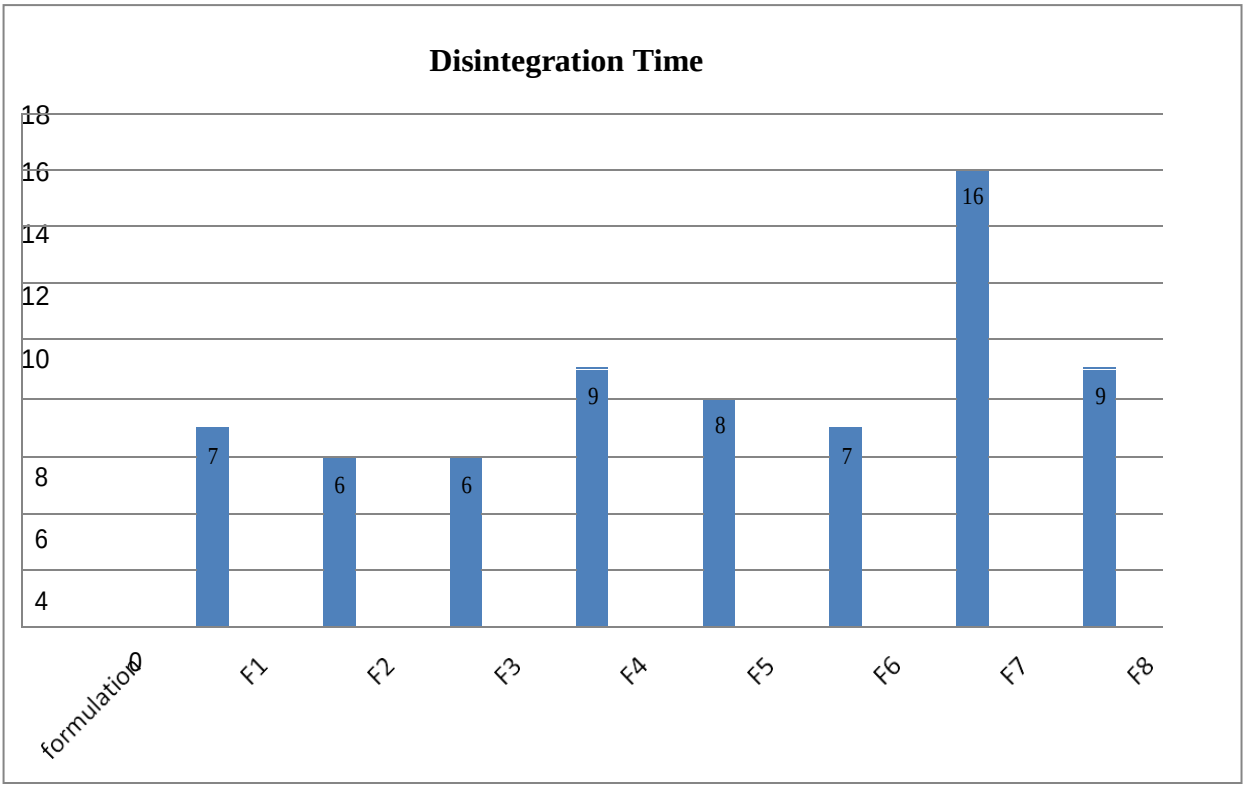
Table No 5 : Evaluation of sublingual tablets for formulations (F1 – F9)

Formulation	Hardness (kg/cm2)	Friability (%)	Weight (mg)	Thickness (mm)	Drug content (%)
F1	2.9 ±0.14	0.23	201±0.51	3.4±0.09	**96.1**
F2	2.9±0.18	0.21	197±0.61	3.9±0.01	**98.27**
F3	3.2±0.14	0.24	201±0.42	3.4±0.09	**93.41**
F4	2.7±0.16	0.25	203±0.76	3.2±0.14	**97.21**
F5	3.1±0.17	0.27	204±0.55	3.7±0.02	**92.41**
F6	2.7±0.21	0.31	198±0.71	3.5±0.18	**99.2**
F7	3.1±0.21	0.24	201±0.66	3.8±0.17	**94.8**
F8	2.7±0.21	0.25	201±0.75	3.2±0.02	**97.9**
F9	**2.6±0.15**	**0.22**	**202±0.82**	**4±0.02**	**94.29**

Table No. 6: Evaluation of Sublingual tablets for formulations (F1 – F9)

formulation	Disintegration time	Wetting time	Water absorption ratio	In vitro dispersion time
F1	7	20	18.24	**7**
F2	6	14	23.41	**5**
F3	6	12	17.54	**6**
F4	9	15	14.23	**14**
F5	8	13	16.32	**10**
F6	7	18	11.19	**9**
F7	16	25	14.24	**13**
F8	9	24	12.32	**11**
F9	**8**	**21**	**13.43**	**16**

Graph No. 1: Bar graph comparison between disintegration times for formulations (F1- F9)



Wetting Time

Wetting time is closely related to the inner structure of tablet. The experiment mimic 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 shows crosspovidone formulations F1, F2, F3 have good wetting time comparing with that of cross carmellose sodium starch glycolate, and comparative profile result was shown in tableno:7.

Water absorption ratio

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 11.19 to 23.41% . This shows that all the formulations have good water absorption capacityresult was shown in table no:7.

In-vitro dispersion time:

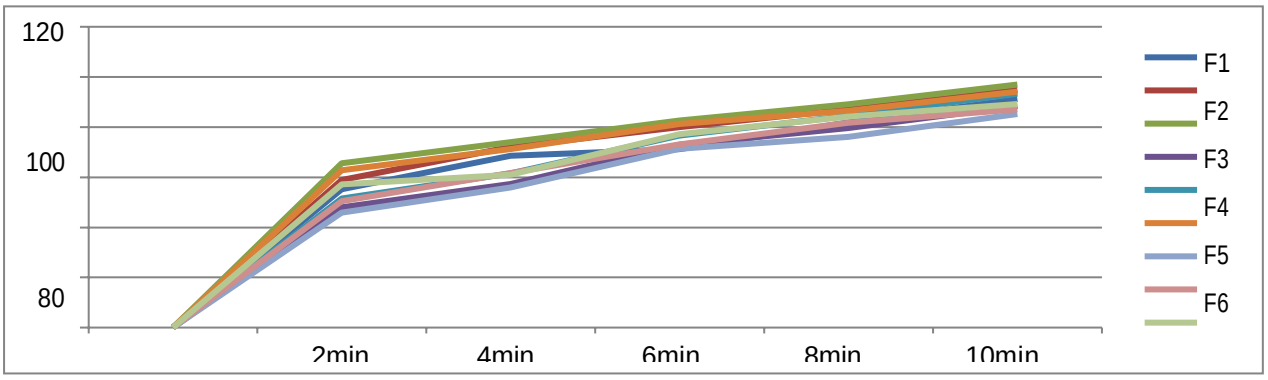
The in vitro dispersion time is measured by time taken to uniform dispersion, the rapid dispersion. It was found to be in the range of 5secs to 15secs (Graph). The result showed that the in vitro dispersion time of F1, F2, and F3 formulations is almost equal and better than F4, F5, F6, F7, F8, F9 formulations and comparative profileresult was shown in **Table No:7.**

In vitro dissolution studies

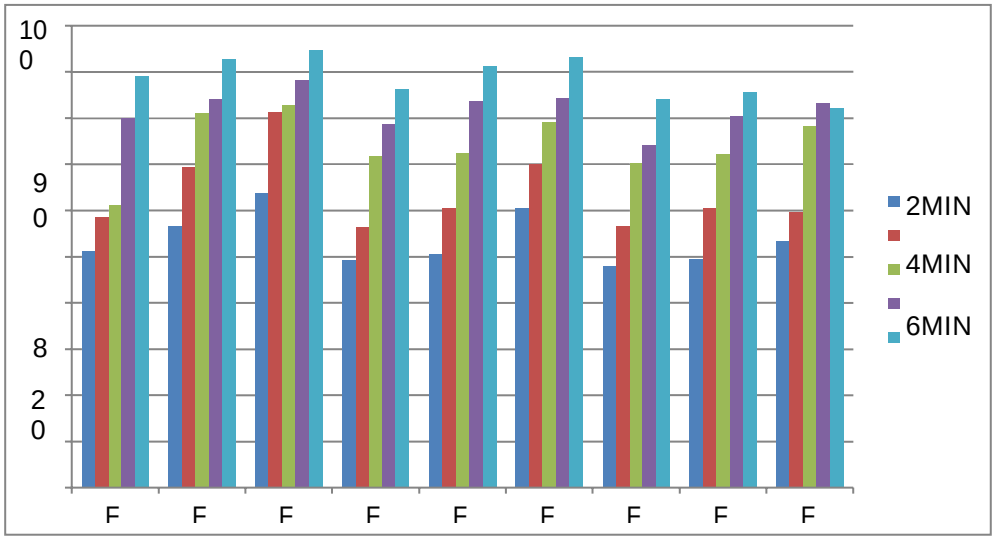
Table No. 7: Cumulative % drug release for formulations (F1 – F9)

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
2 MIN	51.13	56.7	63.80	49.27	50.40	60.35	47.81	49.51	**53.29**
4 MIN	58.6	69.4	81.36	56.39	60.46	70.0	56.66	60.35	**59.60**
6 MIN	61.14	81.0	82.69	71.83	72.49	79.12	70.23	72.10	**78.20**
8 MIN	79.9	84.12	88.25	78.61	83.58	84.25	74.12	80.40	**83.11**
10 MIN	**89.14**	**92.81**	**94.69**	**86.30**	**91.15**	**93.11**	**84.15**	**85.67**	**82.21**

Graph No.2: Comparison between cumulative % drug releases for formulations (F1- F9)



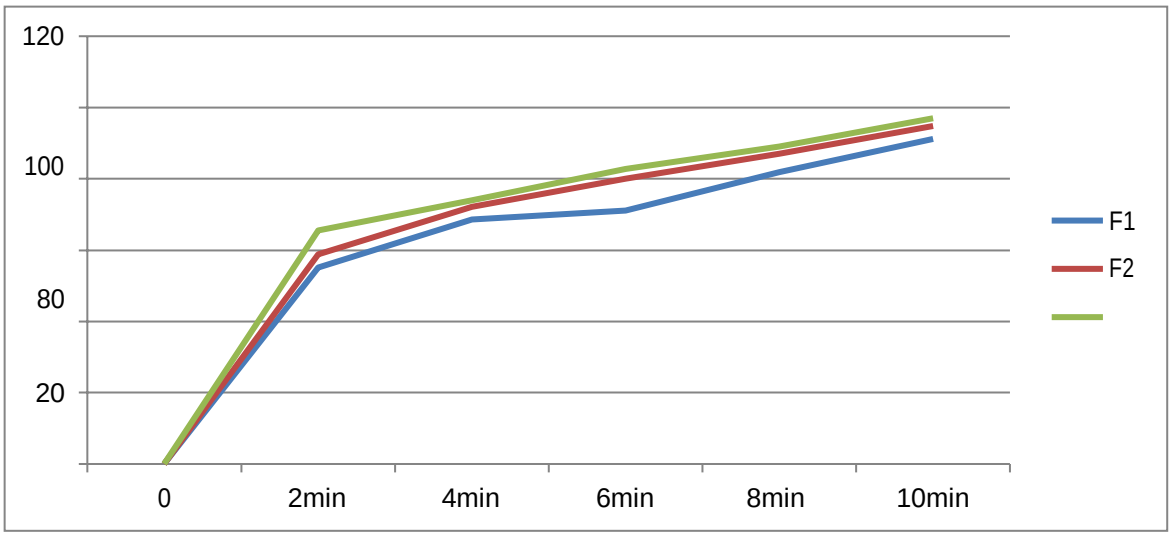
Graph No.3 Comparison between cumulative % drug releases for formulations (F1- F9)



Comparasion among (%) drug release of different formulations:

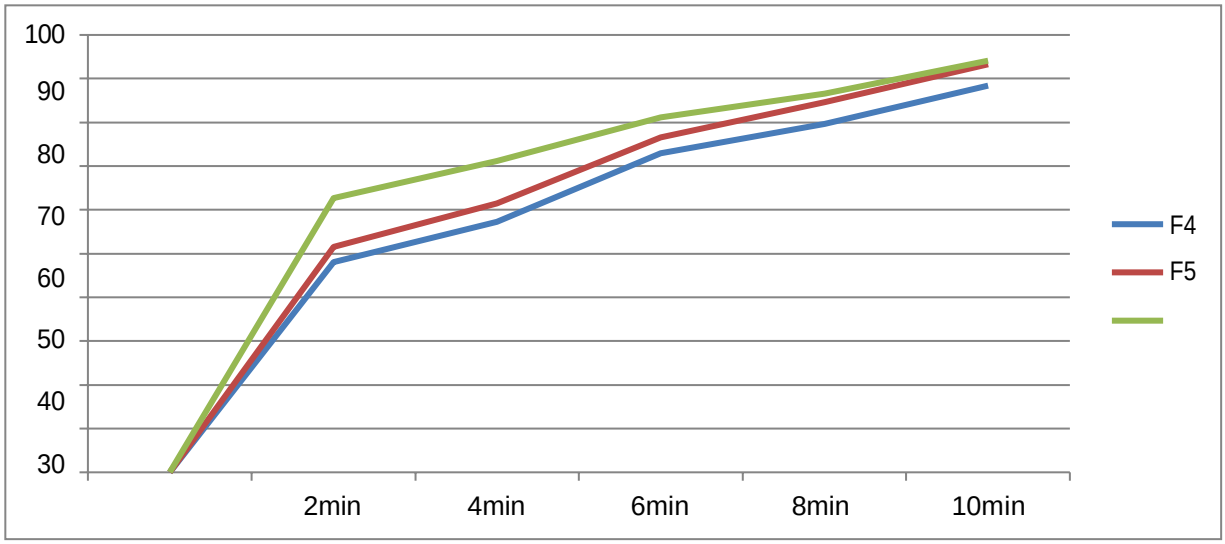
When the formulations F1, F2, F3 were compared, the comparative (%) drug release was found. See Figure

Graph No. 4: Comparison between cumulative % drug releases for formulations (F1- F3)



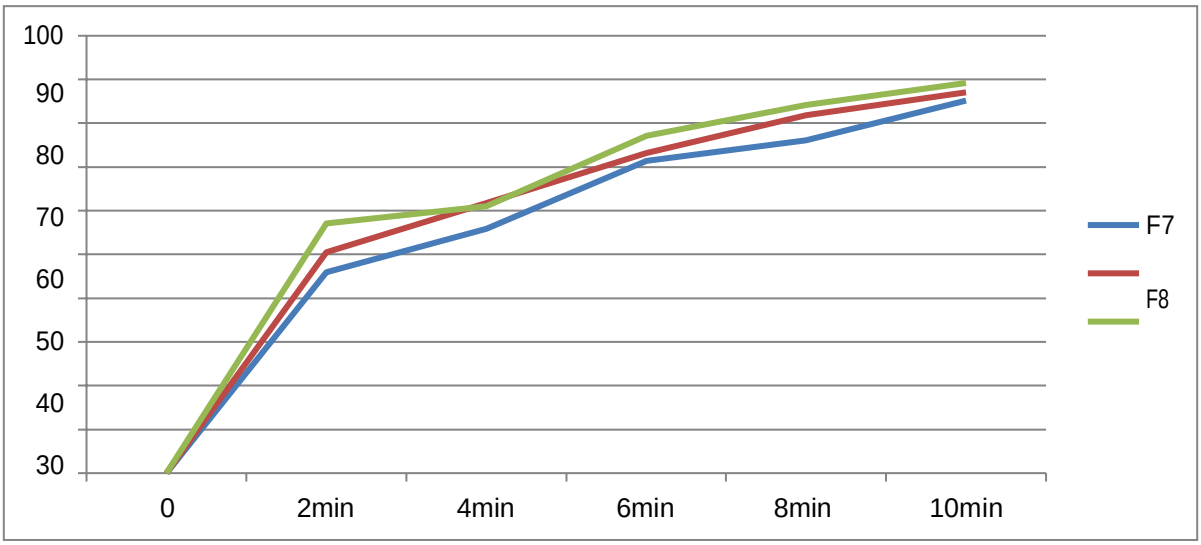
When the formulations F4, F5, F6 were compared, the comparative (%) drug release was found. See Figure

Graph No.5: Comparison between cumulative % drug releases for formulations (F4- F6)



When the formulations F7, F8, F9 were compared, the comparative (%) drug release was found. See Figure

Graph No. 8: Comparison between cumulative % drug releases for formulations (F7- F9)



Dissolution was done in USP-2 type apparatus at 50 rpm 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.

Drug release kinetics:

The drug release profiles of Nimodipine sublingual tablets were subjected to various kinetic models such as Zero order, First order, Higuchi. The dissolution parameters such as dissolution efficiency (DE) at 10 and 30 minutes were increased proportionately. Half-life of drug i.e., T50, and shelf life T90 were obtained as mentined in table.The drug release data of nimodipine fast dissolving tablets have treated with different kinetic models are shown in Table No. 9.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.

Table No. 8: Drug release kinetics for formulations (F1 – F9)

KINETICS		F1	F2	F3	F4	F5	F6	F7	F8	F9
Zero order	**r**	0.9269	0.9292	0.9089	0.9263	0.9419	0.9240	0.9323	0.8281	**0.8171**
	k	16.13	17.23	17.72	13.23	14.31	16.67	12.78	14.40	**14.24**
First order	**r**	0.9936	0.9943	0.9990	0.9980	0.9993	0.9901	0.9983	0.9990	**0.9818**
	k	0.2399	0.3193	0.3552	0.2225	0.2468	0.3103	0.2058	0.2532	**0.2420**
Higuchi	**R**	0.9955	0.9953	0.9646	0.9953	0.9737	0.9853	0.9989	0.8933	**0.9727**
	k	34.19	33.12	34.12	27.68	31.98	37.23	31.75	28.80	**32.72**

DE 10		44.72	47.44	51.44	38.33	41.06	49.12	36.67	40.43	**44.36**
DE 30		58.94	62.64	64.88	53.52	54.95	60.54	81.83	54.59	**52.71**
T50		1.82	1.68	1.53	2.39	1.91	1.53	2.79	1.94	**1.71**
T90		**9.70**	**8.71**	**8.42**	**0**	**9.17**	**8.89**	**0**	**0**	**0**

Stability Study

The optimized formulation F3 is kept for stability studies. Accelerated stability studies were carried out at 400C/75%RH for 3 months. The tablets were then evaluated for hardness, friability, disintegration and drug content at 1st month, 2nd month and 3rd month. The results indicated that there was no significant change in evaluation of the tablets. The results were tabulated in **Table No: 10**

Table No. 9: Comparison of Various Parameters for Stability Study

EVOLUTION PARAMETERS	INITIAL	ONE MONTH	TWO MONTH	THREE MONTH
HARDNESS (kg/cm2)	3.2 ± 0.19	3.1±0.28	3.3±0.03	**3.3±0.89**
(%) FRIABILITY	0.27	0.26	0.25	**0.25**
DISINTEGRATION TIME (SECONDS)	6	7	8	**9**
DRUG CONTENT	**98.5**	**99.8**	**99.1**	**99.6**

The optimized formulation F3 is kept for stability studies. Accelerated stability studies were carried out at 400C/75%RH for 3 months. The tablets were then evaluated for hardness, friability, disintegration and drug content at 1st month, 2nd month and 3rd month. The results indicated that there was no significant change in evaluation of the tablets. The results were tabulated in Table No: 10.

Table No. 10: Comparison of Drug Release Profile of Batch F3

TIME	INITIAL	ONE MONTH	TWO MONTH	THREE MONTH
2 min	63.83	62.91	61.49	**59.48**
4 min	73.91	73.68	72.23	**71.64**
6 min	81.60	81.45	80.00	**79.56**
8 min	87.13	88.90	87.21	**86.18**
10 min	**94.94**	**94.56**	**94.44**	**94.01**

CONCLUSION

The present study was carried out to formulate and optimize oral sublingual tablets of quick onset of action by fast disintegrating in a few seconds without the need of water with better patient compliance.In this cases, bioavailability of drug is significantly greater and adverse event is diminished than those observed from conventional tablet dosage form. 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 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 various parameters such as 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 .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.

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.

Formulation F3 In-vitro Dissolution study 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

CONFLICT OF INTEREST

Authors don't have any conflict of interest

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