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FORMULATION AND EVALUATION OF ORAL DISINTEGRATING NIMODEPINE TABLETS

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ABSTRACT

More than 50% of pharmaceutical products are orally administered for several reasons. This route of administration is considered as the most widely used route as it offers advantages like ease of administration, versatility, patient compliance and accurate dosing. Undesirable taste is one of the important formulation problems that are encountered with such oral products. Difficulty in swallowing is also a common problem of all groups, especially the elderly and pediatrics, because of physiological changes associated with these groups. Taste of a pharmaceutical product is an important parameter governing compliance. Hence taste masking of oral pharmaceutical has become important tool to improve patient compliance and the quality of treatment especially in pediatrics. Hence formulation of taste masked products is a challenge to the pharmacist.

KEY WORDS: Nimodepine, Oral disintegrating Tablets, Direct compression.

INTRODUCTION

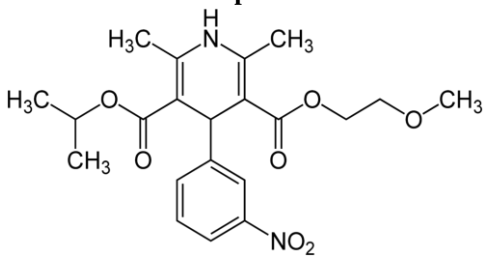
The basic approach in development of ODTs is use of disintegrant [1]. Disintegrant plays an important role in the disintegration and dissolution of ODT [2]. It is essential to choose a suitable disintegrant, in an optimum concentration so as to ensure quick disintegration and high dissolution rates [3].

Super disintegrant provide quick disintegration due to combined effect of swelling and water absorption by the formulation [4]. Due to swelling of super disintegrant, the wetted surface of the carrier increases; this promotes the wetability and dispersibility of the system, thus enhancing the disintegration and dissolution [5]. Care should be taken to taken while selecting concentration of the superdisintegrant. Superdisintegrants are selected according to critical concentration of disintegrant. Below this concentration, the tablet disintegration time is inversely proportional to the concentration of the super disintegrant, whereas if concentration of super disintegrant is above critical concentration, the disintegration time remains almost constant or even increases [6].

MATERIALS AND METHODS

Nimodepine

Fig: 1. Structure of Nimodepine



Formula: $C_{21}H_{26}N_2O_7$

Mechanism of action: Although the precise mechanism of action is not known, nimodipine blocks intracellular influx of calcium through voltage-dependent and receptor-operated slow calcium channels across the membranes of myocardial, vascular smooth muscle, and neuronal cells. Nimodipine binds specifically to L-type voltage-gated calcium channels.

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The inhibition of calcium ion transfer results in the inhibition of vascular smooth muscle contraction. Evidence suggests that the dilation of small cerebral resistance vessels, with a resultant increase in collateral circulation, and/or a direct effect involving the prevention of calcium overload in neurons may be responsible for nimodipine's clinical effect in patients with subarachnoid hemorrhage [7].
Absorption: In humans, nimodipine is rapidly absorbed after oral administration, and peak concentrations are generally attained within one hour. Bioavailability is 100% following intravenous administration and 3-30% following oral administration due to extensive first-pass metabolism.
Protein binding: 95% bound to plasma protein
Metabolism: Hepatic metabolism via CYP 3A4.
Route of elimination: Nimodipine is eliminated almost exclusively in the form of metabolites and less than 1% is recovered in the urine as unchanged drug. Numerous metabolites, all of which are either inactive or considerably less active than the parent compound, have been identified.
Half life: 1.7-9 hours

Crospovidone

Crospovidone is a white to creamy-white, finely divided, free flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder. It is practically insoluble in water and most common organic solvents. It should be stored in a cool, dry place. It rapidly exhibits capillary activity and pronounced hydration capacity, with little tendency to form gels. It is generally as tablet disintegrant, dissolution agent and can also be used as solubility enhancer [8]. Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place. Commercial grades: Kollidon CL, Kollidon CL-M, Polyplasdone XL, Polyplasdone XL-10. It is official: IP, BP and USP.

Sodium Starch Glycolate

Sodium starch glycolate is a white to off-white, odorless, tasteless, free-flowing powder. It consists of oval or spherical granules, 30-100µm in diameter, with some less-spherical granules ranging from 10-35µm in diameter. Sparingly soluble in ethanol (95%); practically insoluble in water. At a concentration of 2% w/v sodium starch glycolate dispersed in cold water and settles in the form of a highly hydrated layer. It is generally used as tablet and capsule disintegrant. Sodium starch glycolate is stable and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature. The physical properties of sodium starch glycolate remain unchanged for up to 4 years if it is stored at moderate temperatures and humidity. Commercial grades: Explotab, Primojel, Viva-star P. It is official: IP, BP, USP and PhEur.

Croscarmollose Sodium

Croscarmellose sodium occurs as an odorless, white or grayish- white powder. Insoluble in water, croscarmellose sodium rapidly swells to 4-8 times its original volume on contact with water. It is generally used in oral pharmaceutical formulations as a disintegrant for capsules, tablets, and granules. It is stable, but hygroscopic, should be stored in a well-closed container in a cool, dry place. Commercial grades: Ac-Di-Sol, Explocel, Nymcel, ZSX, Pharmacel XL. It is official in IP, BP, USP and PhEur.

Pregelatinized Starch

Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has a slight characteristic taste. It is a starch that has been chemically and/or mechanically processed to rupture all or part of the starch granules and so render the starch flowable and directly compressible. Pregelatinized starch contains 5% of free amylose, 15% of free amylopectin, and 80% unmodified starch. It is practically insoluble in organic solvents and slightly soluble to soluble in cold water, depending upon the degree of pregelatinization. It is used as tablet disintegrant in 5-10 % w/w concentration. It is a stable but hygroscopic material, which should be stored in a well-closed container in a cool, dry place. It is official in BP, and USP.

Microcrystalline Cellulose Phosphate: (Avicel pH 102)

Microcrystalline cellulose phosphate is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline product composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications. Slightly soluble in 5%w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents. It is generally used as absorbent, suspending agent, tablets, and capsules diluent; tablet disintegrant. Microcrystalline cellulose is stable though hygroscopic material. The bulk material should be in a well-closed container in a cool, dry place. Commercial grades: celphere, ceolus KG, Emcocel, Fibrocel. It is official in IP, BP and USP.

PEARLITOL SD 200

Pearlitol is D-mannitol, a hexahydric alcohol related to mannose. It is a white, odourless, crystalline powder or free-flowing granules. It has sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth. It is freely soluble in *water;* slightly soluble in *pyridine;* very slightly soluble in *ethanol (95%);* insoluble in *chloroform*and in *ether*. It is used as a diluent in 10-90 % concentration in tablet formulation. It is stable in the dry state and in aqueous solution state. It should be stored in a well-closed container in a cool, dry place [9]. It is official in IP, BP, and USP.

Sucralose

Sucralose is a white to off-white colored, free-flowing, crystalline powder. It is used as a sweetening agent in beverages, foods, and pharmaceutical applications. It has a sweetening power approximately 300–1000 times that of sucrose and has no aftertaste. It is freely soluble in water, methanol, and ethanol (95%); slightly soluble in ethyl acetate. It is a relatively stable material. It is most stable at pH 5–6. It should be stored in a well-closed container in a cool, dry place, at a temperature not exceeding 21°C. It is generally regarded as a nontoxic and nonirritant material. The FDA, in April 1998, approved Sucralose for use as a tabletop sweetener and as an additive in a variety of food products. It is official in USP.

Sodium Stearyl Fumarate

Sodium stearylfumarate is a fine, white powder with agglomerates of flat, circular-shaped particles. Sodium stearylfumarate is used as a lubricant in capsule and tabletformulations at 0.5–2.0% w/w concentration. It is practically insoluble in acetone, chloroform and ethanol, and slightly soluble in methanol. It is stored in amber glass bottles with polyethylene screw caps. The bulk material should be stored in a well-closed container in acool and dry place. It is official in PhEur, BP, USP.

Colloidal Silicon Dioxide

Colloidal Silicon Dioxide synonym is Aerosol. Colloidal silicon dioxide is a submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, amorphous powder. Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting and capsule filling. It is used as Adsorbent, anticaking agent, emulsion stabilizer, glidant (0.1 – 1.0), suspending agent, tablet disintegrant, thermal stabilizer, viscosity-increasing agent. Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water. For Aerosil, solubility in water is 150 mg/L at 258C (pH 7).Colloidal silicon dioxide powder should be stored in a well-closed container. It is official in IP, BP, and USP.

Preparation of Standard Graph

A standard graph of pure drug in suitable medium was prepared by plotting the concentrations on X – axis and absorbance on Y – axis.

Procedure for preparation of standard graph of Nimodepine

Accurately weighed amount of 100mg of Nimodepine is taken in a 100ml volumetric flask. The volume was made up to 100ml with distilled water, which constitutes the stock solution of 1mg/ml. by further diluting the stock solution suitably with distilled water solutions of 5, 10, 15, 20, 25 and 30µg/ml concentrations were prepared. These solutions were checked for their absorbance using UV – Visible spectrophotometer at λ_{max}238 nm against distilled water as blank and a standard graph was potted.

Calibration curve for the estimation of Nimodepine

The present analytical method obeyed Beer's law in the concentration range of 5 – 30 µg/ml and is suitable for the estimation of Nimodepine form different solutions. The correlation coefficient (r) value for the linear regression equation was found to be 0.998, indicating a positive correlation between the concentration of Nimodepine and its corresponding absorbance values.

Formulation design

Nimodepine ODTs were prepared using direct compressiontechnique. Direct compression technique is a convenient method but the excipients used in this method are costlier when compared to the excipients used in the wet granulation technique. Different formulations of Nimodepine ODTs were designed to be prepared by direct compression technique using three super disintegrants, (Crosspovidone, Croscarmellose sodium and Sodium starch glycolate). Super disintegrant is varied with 4 different concentrations, (i.e., 3, 6, 9, 12% respectively) keeping all other ingredients constant, there are assigned with formulation codes.

General formulation

A formula is set using following ingredients:

Drug: Nimodepine
Disintegrants: Cross povidone / Croscarmellose sodium / Sodium starch glycolate
Bulking agent: Pearlitol SD 200, Avicel pH 102
Sweetening agent: Sucralose
Flavouring agent: Orange
Lubricant: Sodium stearyl fumerate
Glidant: Colloidal silica
Total table weight was set to be 80 mg; Punch size is set to be 5 mm s/c.

Procedure

All the required ingredients were passed through 40 mesh to get uniform size particles and weighed accurately. Whole amount of drug, pearlitol SD 200, Avicel pH 102, sodium saccharine and flavour except lubricant were mixed in the increasing order of their weights in a mortar. To this mixture colloidal silica and sodium stearyl fumarate were added. The final mixture was shaken manually for 5-10 minutes in a plastic bag. This powder was passed through the hopper of 16 station rotary tabletting machine and punched into tablets using 5 mm s/c. The process is similar for all the formulations, which are prepared by direct compression technique.

Evaluation of orally disintegration tablet formulations

Different quality control tests were performed for all the ODT formulations to check whether these have met the specifications given in USP along with other In *vitro* tests like wetting time and water absorption ratio.

Various *In vitro* tests performed are

- Weight variation test
- Thickness measurement
- Hardness and Friability
- Assay
- Wetting time and Water absorption ratio
- Disintegration Time
- Dissolution test

Weight variation test

20 tablets were randomly selected from each formulation and their average weight was calculated using digital balance. Individual weight of each tablet was also calculated using the same and compared with the average weight. Thee Mean ± S.D. were noted. The tablets meet USP specifications if no more than 2 tablets outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Thickness measurement

Randomly 10 tablets were taken from each formulation and their thickness was measured using a digital screw gauge. The individual tablet was placed between two anvils of the screw guage and sliding knob was rotated until the tablet was tightly fitted. The digital reading displayed was noted. The Mean ± S.D. were noted. The tablet thickness should be controlled within a ± 5% variation of standard value.

Hardness

The tablet hardness of different formulations was measured using the Monsanto hardness tester. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger was placed in contact with the tablet, and a zero was taken. The upper plunger was then forced against the spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture is recorded, and the zero force reading is deducted from it. Generally, a minimum hardness of 4 kg is considered acceptable for uncoated tablets. The hardness for ODTs should be preferably 1-3 kg.

Friability

This test is performed using a laboratory friability tester known as Roche Friabilator. 10 tablets were weighed and placed in a plastic chambered friabilator attached to a motor, which revolves at a speed of 25 rpm, dropping the tablets from a distance of 6 inches with each revolution. The tablets were subjected to 100 revolutions for 4 minutes. After the process, these tablets were dedusted and reweighed. Percentage loss of tablet weight was calculated.

$$\% \text{ Friability} = (W_1 - W_2) \times 100/W_1$$

Where,

W1 = Initial weight of the 20 tablets before testing.

W2 = Final weight of the 20 tablets after testing.

Friability values below 1% are generally acceptable.

Assay

20 tablets were randomly selected, weighed and finely powdered; powder equivalent to one tablet was added to 100ml of pH 6.8 phosphate buffer in a conical flask. Conical flasks were placed on a rotary shaker overnight. An aliquote of solution was centrifuged and supernatant was filtered through a 0.22µ filter. Absorbance of the resulted supernatant solution was measured using U.V Visible spectrophotometer at a wavelength of 238nm against pH 6.8 phosphate buffer as blank. Concentrations were calculated with the help of standard graph and total amount present in the formulation was calculated [11].

Wetting time and Water absorption ratio (R)

Five circular tissue papers were placed in a petri dish with a 10-cm diameter. Ten milliliters of water containing eosin, a water-soluble dye, was added to the petri dish. The dye solution is used to identify the complete wetting of the tablet surface. A tablet was carefully placed on the surface of tissue paper in the petri dish at room temperature. The time required for water to reach the upper surface of the tablets and completely wet them was noted as the wetting time. To check for reproducibility, the measurements were carried out in replicates (n=6). The wetting time was recorded using a stopwatch [12].

The weight of the tablet before keeping in the petri dish was noted (W_b) using Shimadzu digital balance. The wetted tablet from the petri dish was taken and reweighed (W_a) using the same. The Water absorption ratio, R, was determined according to the following equation:

$$R = 100 (Wa - W_b) / W_b$$

Where $W_b$and$W_a$are the weight before and after water absorption respectively.

Disintegration Time

Disintegration time is considered to be one of the important criteria in selecting the best formulation. To achieve correlation between disintegration time *In vitro* and *In vivo* (in oral cavity) several methods were proposed, developed and followed at their convenience. One of the simple methods followed is described below. Disintegration time was also measured using a modified disintegration

method (n=6). For this purpose, a Petri dish (10 cm diameter) was filled with 10 ml of water. The tablet was carefully put in the center of the Petri dish and the time for the tablet to completely disintegrate into fine particles was noted using a stop watch [13].

Dissolution test

Dissolution test was carried out using USP rotating paddle method (apparatus 2). The stirring rate was 50 rpm. 6.8 pH phosphate buffer was used as dissolution medium (900ml) and was maintained at 37 ± 1^0C. Samples of 5ml were withdrawn at pre –determined intervals (2, 4, 6, 8, 10, 15, 20, 25, 30 min), filtered and replaced with 5ml of fresh dissolution medium. The collected samples were suitably dilutedwith dissolution fluid, where ever necessary and were analyzed for the Nimodepine at 238 nm by using UV spectrophotometer. Each dissolution study was performed for three times and mean values were taken.

Stability Studies

FDA and ICH specifies the guidelines for stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human life.The ICH tripartite guidelines have established long term stability testing to be done at 25^0C/60%RH for 12 months. Accelerated stability testing should be done at 40^0 C/75%RH for 6 months and stability testing at intermediate storage conditions should be done at 30^0C/65%RH. The following table shows different storage conditions and period of stability testing.

Table 1. Calibration curve for the estimation of Nimodepine

S.No.	Concentration(µg/ml)	UV Absorbance (n=5)
1	**5**	**0.132**
2	**10**	**0.242**
3	**15**	**0.395**
4	**20**	**0.528**
5	**25**	**0.656**
6	**30**	**0.813**

Table 2. Solubility Studies

Solvent	Approx. pH	Solubility mg/mL
0.1N HCl	1.2	71.43
Acetate Buffer pH 4.5	4.5	68.40
Purified Water	6.5	108.6
Phosphate Buffer pH 6.8	6.8	120.5
Phosphate Buffer pH 7.2	7.2	104.23

Table 3. ICH Guidelines for stability study

Study	Storage Condition	Duration
Long term	25±2°C, RH 60±5%	12 months
Intermediate	30±2°C, RH 65±5%	6 months
Accelerated temperature	40±2°C, RH 75±5%	6 months

RESULTS AND DISCUSSION

Table 4. Formulae of Nimodepine ODTs prepared by direct compression method with various superdisintegrants

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18	F19	F20
Nimodepine	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Crosspovidone	2.4	4.8	7.2	9.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Croscarmellose Sodium	0	0	0	0	2.4	4.8	7.2	9.6	0	0	0	0	0	0	0	0	0	0	0	0
Sodium Starch Glycolate	0	0	0	0	0	0	0	0	2.4	4.8	7.2	9.6	0	0	0	0	0	0	0	0
Crosspovidone+ Croscarmellose Sodium	0	0	0	0	0	0	0	0	0	0	0	0	4.8	6.4	8	9.6	0	0	0	0
Crosspovidone+ Sodium Starch Glycolate	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4.8	6.4	8	9.6
Avicel PH 102	55.6	53	50.8	48.4	55.6	53.2	50.8	48.4	55.6	53.2	50.8	48.4	53	51.6	50	48.4	53.2	51.6	50	48.4
Pearlitol	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Sucralose	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Orange flavor	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Sodium stearyl fumerate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Colloidal silica	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total weight (mg)	80	80	80	80	80	80	80	80	80	80	80	80	80	80	80	80	80	80	80	80

Table 5. Preformulation characteristics of Nimodepine ODTs

Formulation	Bulk density (g/cc)	Tapped density (g/cc)	Hausner ratio	Compressibilty index (%)	Angle of repose (ɵ)
F1	0.435	0.522	1.2	16.66	32.67
F2	0.429	0.518	1.2	17.18	29.08
F3	0.43	0.524	1.21	17.93	31.78
F4	0.432	0.528	1.22	18.18	30.64
F5	0.428	0.518	1.21	17.37	30.36
F6	0.42	0.51	1.21	17.64	31.05
F7	0.416	0.509	1.22	18.27	32.54
F8	0.417	0.515	1.23	19.02	29.67
F9	0.425	0.515	1.21	17.47	31.85
F10	0.421	0.509	1.2	17.28	29.56
F11	0.419	0.515	1.22	18.64	30.17
F12	0.415	0.512	1.23	18.94	32.08
F13	0.42	0.52	1.23	19.23	29.67
F14	0.423	0.512	1.21	17.38	29.54
F15	0.435	0.52	1.2	16.34	31.76
F16	0.422	0.512	1.21	17.57	32.04
F17	0.425	0.523	1.23	18.73	30.56
F18	0.434	0.526	1.21	17.49	31.23
F19	0.426	0.512	1.2	16.79	29.52
F20	0.42	0.519	1.23	19.07	29.32

Table 6. Tabletting characteristics of Nimodepine ODTs

Formulation	Weight (mg)	Drug content (%)	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)
F1	79.9±0.70	98.96±0.47	3.05±0.13	0.48	3.84±0.032
F2	79.52±0.85	99±0.65	3.10±0.15	0.53	3.85±0.028
F3	78.9±0.52	99.11±0.52	2.95±0.08	0.44	3.86±0.024
F4	80.2±1.17	99.15±0.60	2.95±0.10	0.57	3.86±0.051
F5	79.0±0.49	99.2±0.4	3.08±0.12	0.43	3.88±0.048
F6	78.8±0.58	98.85±0.58	3.11±0.14	0.56	3.90±0.052
F7	79.3±0.54	99.31±0.24	2.92±0.08	0.53	3.92±0.038
F8	80.4±1.0	98.96±0.28	3.0±0.09	0.45	3.91±0.042
F9	79.6±0.95	99.3±0.38	2.9±0.07	0.6	3.90±0.040
F10	79.2±0.97	99.36±0.29	3.05±0.08	0.49	3.89±0.042
F11	79.4±0.86	98.75±0.40	3.05±0.09	0.53	3.89±0.034
F12	78.5±0.42	99.21±0.38	2.93±0.08	0.58	3.87±0.031
F13	80.3±1.18	98.56±0.49	3.19±0.05	0.47	3.86±0.034
F14	79.3±0.53	98.61±0.60	3.16±0.04	0.52	3.86±0.023
F15	80.1±0.75	98.98±0.56	3.10±0.10	0.63	3.87±0.044
F16	80.3±0.86	99.03±0.58	3.05±0.09	0.58	3.89±0.051
F17	79.1±0.84	97.75±0.69	3.15±0.04	0.58	3.85±0.029
F18	78.8±0.56	98.76±0.56	2.92±0.08	0.53	3.88±0.046
F19	79.6±0.60	99.08±0.29	3.00±0.09	0.51	3.86±0.025
F20	80.0±0.75	98.86±0.39	3.12±0.12	0.55	3.84±0.034

Table 7. Wetting characteristics of Nimodepine ODTs

Formulation	Wetting time (sec)	*In vitro* dispersion time (sec)	Disintegration time (sec)	Water absorption ratio (%)
F1	24.83±0.98	221.33±1.03	116.5±1.37	58.45
F2	21.16±0.75	180.5±1.04	95.16±0.75	59.25
F3	14.66±0.51	75±0.89	56.50±1.64	58.9

F4	11.66±0.51	54±0.63	27.83±1.16	60.65
F5	57.33±0.81	244.5±1.04	168.83±1.94	59.88
F6	22.33±1.36	215.5±0.54	98±0.63	61.48
F7	28±1.09	177.83±1.16	73.16±1.47	59.55
F8	19.66±0.81	126.66±0.81	36.66±1.21	60.01
F9	37.33±0.81	259.83±1.47	171.83±1.16	64.37
F10	28.33±0.81	225.33±0.81	153±0.89	67.54
F11	26.66±0.81	186.83±0.75	81.5±1.04	65.5
F12	36.83±1.16	154.5±0.83	42.66±1.75	65.89
F13	19.33±0.51	91.66±1.21	82.5±1.04	59.49
F14	14.33±0.51	49.33±1.03	46±0.89	56.59
F15	11.16±0.75	30.66±0.81	17.66±0.51	57.08
F16	12.5±0.54	35.16±0.75	20.33±0.81	58.72
F17	19.1±0.75	96.83±0.40	86.16±0.75	57.95
F18	14.83±0.75	54.16±1.72	47.5±1.04	60
F19	11.5±0.54	46.66±0.81	23.66±0.51	61.5
F20	13±0.89	43.83±0.75	20.83±1.16	58.24

Table 8. Cumulative percent Nimodepine released from ODTs containing varying concentrations of different superdisintegrants

Cumulative percent (±S.D.) drug released						
Time (min)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
2	27.35±0.28	22.35±0.52	20.46±0.25	28.31±0.23	18.35±0.34	15.43±0.30
4	40.33±0.28	34.36±0.28	29.28±0.19	41.33±0.24	25.5±0.28	23.43±0.32
6	55.46±0.31	45.31±0.27	42.35±0.25	59.33±0.26	37.36±0.25	37.36±0.26
8	69.46±0.27	62.35±0.25	61.31±0.23	73.48±0.34	57.41±0.23	54.38±0.26
10	74.38±0.27	75.48±0.30	76.4±0.36	85.38±0.34	64.55±0.28	67.38±0.37
15	83.35±0.20	87.4±0.31	82.53±0.30	98.6±0.29	72.48±0.35	75.46±0.26
20	94.45±0.30	96.31±0.29	97.31±0.20	98.89±0.32	80.45±0.28	82.31±0.23
25	94.89±0.24	96.57±0.28	97.76±0.28	98.95±0.24	86.5±0.26	87.48±0.24
30	95.78±0.27	96.85±0.32	97.96±0.25	98.99±0.23	89.53±0.19	92.36±0.25
Cumulative percent (±S.D.) drug released						
Time (min)	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
2	22.33±0.25	14.38±0.31	19.33±0.20	23.43±0.16	18.48±0.33	19.4±0.32
4	33.36±0.31	22.1±0.59	28.36±0.32	35.31±0.27	27.18±0.18	27.41±0.26
6	45.46±0.26	36.43±0.30	36.45±0.25	47.36±0.29	34.43±0.23	35.28±0.29
8	62.43±0.23	55.46±0.30	49.43±0.26	53.5±0.34	45.61±0.17	52.43±0.26
10	70.28±0.20	62.46±0.25	55.48±0.26	64.45±0.30	52.41±0.36	65.41±0.33
15	78.41±0.26	75.58±0.27	68.46±0.32	72.6±0.27	61.25±0.55	78.45±0.35
20	86.28±0.24	80.4±0.26	74.58±0.27	78.41±0.14	70.46±0.21	84.51±0.24
25	90.28±0.17	83.48±0.30	78.43±0.27	83.45±0.28	75.41±0.24	88.36±0.18
30	94.46±0.25	95.43±0.19	85.4±0.22	88.45±0.18	90.4±0.33	92.38±0.19

Table 9. Formulae of Nimodepine ODTs prepared with combination of superdisintegrants

Ingredients	**CP + CCS**				**CP + SSG**			
	6%	8%	10%	12%	6%	8%	10%	12%
Nimodepine	4	4	4	4	4	4	4	4
Superdisintegrants	4.8	6.4	8	9.6	4.8	6.4	8	9.6
Avicel PH 102	53.2	51.6	50	48.4	53.2	51.6	50	48.4
Pearlitol SD200	10	10	10	10	10	10	10	10
Sucralose	5	5	5	5	5	5	5	5

Orange flavor	2	2	2	2	2	2	2	2
Sodiumstearyl fumerate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Colloidal silica	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total weight (mg)	80	80	80	80	80	80	80	80

Note: CP – Crosspovidone, CCS – Croscarmellose Sodium, SSG – Sodium Starch Glycolate

Table 10. Preformulation characteristics of Nimodepine ODTs prepared with combination of superdisintegrants

Formulation	Bulk density (g/cc)	Tapped density (g/cc)	Hausner ratio	Compressibilty index (%)	Angle of repose (ɵ)
F13	0.420	0.520	1.23	19.23	29.67
F14	0.423	0.512	1.21	17.38	29.54
F15	0.435	0.520	1.20	16.34	31.76
F16	0.422	0.512	1.21	17.57	32.04
F17	0.425	0.523	1.23	18.73	30.56
F18	0.434	0.526	1.21	17.49	31.23
F19	0.426	0.512	1.20	16.79	29.52
F20	0.420	0.519	1.23	19.07	29.32

Table 11. Tabletting characteristics of Nimodepine ODTs prepared with combination of superdisintegrants

Formulation	Weight (mg)	Drug content (%)	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)
F13	80.3±1.18	98.56±0.49	3.19±0.05	0.47	3.86±0.034
F14	79.3±0.53	98.61±0.60	3.16±0.04	0.52	3.86±0.023
F15	80.1±0.75	98.98±0.56	3.10±0.10	0.63	3.87±0.044
F16	80.3±0.86	99.03±0.58	3.05±0.09	0.58	3.89±0.051
F17	79.1±0.84	97.75±0.69	3.15±0.04	0.58	3.85±0.029
F18	78.8±0.56	98.76±0.56	2.92±0.08	0.53	3.88±0.046
F19	79.6±0.60	99.08±0.29	3.00±0.09	0.51	3.86±0.025
F20	80.0±0.75	98.86±0.39	3.12±0.12	0.55	3.84±0.034

Formulation	Wetting time (sec)	*In vitro* dispersion time (sec)	Disintegration time (sec)	Water absorption ratio (%)
F13	19.33±0.51	91.66±1.21	82.5±1.04	59.49
F14	14.33±0.51	49.33±1.03	46±0.89	56.59
F15	**11.16±0.75**	**30.66±0.81**	**17.66±0.51**	**57.08**
F16	12.5±0.54	35.16±0.75	20.33±0.81	58.72
F17	19.1±0.75	96.83±0.40	86.16±0.75	57.95
F18	14.83±0.75	54.16±1.72	47.5±1.04	60
F19	11.5±0.54	46.66±0.81	23.66±0.51	61.50
F20	13±0.89	43.83±0.75	20.83±1.16	58.24

Table 12. Cumulative percent Nimodepine released from ODTs prepared by varying concentrations of combination of superdisintegrants

Cumulative percent (±S.D.) drug released				
Time (min)	**F13**	**F14**	**F15**	**F16**
2	17.41±0.26	26.21±0.17	25.43±0.29	21.4±0.24
4	25.43±0.25	32.38±0.21	37.41±0.31	31.43±0.33
6	37.43±0.33	45.31±0.27	51.36±0.28	40.25±0.18
8	53.45±0.26	60.25±0.15	68.35±0.31	64.45±0.28
10	66.43±0.24	75.31±0.29	77.35±0.28	71.53±0.26
15	78.45±0.24	87.48±0.24	89.4±0.2	79.46±0.22
20	83.45±0.24	89.31±0.17	93.38±0.24	84.53±0.25
25	85.35±0.25	96.52±0.19	99.87±0.18	89.55±0.16
30	94.5±0.21	------	------	96.38±0.24
Cumulative percent (±S.D.) drug released				

Time (min)	F17	F18	F19	F20
2	13.48±0.27	24.55±0.32	24.35±0.30	26.3±0.28
4	25.35±0.30	35.3±0.28	31.41±0.25	38.3±0.28
6	33.4±0.20	42.4±0.31	43.53±0.21	50.36±0.24
8	50.38±0.18	53.38±0.27	57.43±0.33	61.48±0.21
10	61.4±0.30	65.43±0.35	69.53±0.24	69.35±0.28
15	75.55±0.32	76.5±0.28	77.48±0.34	76.51±0.17
20	77.43±0.29	82.45±0.30	85.38±0.23	81.48±0.24
25	82.45±0.18	86.5±0.26	91.45±0.18	84.45±0.27
30	88.56±0.21	92.5±0.14	95.48±0.18	94.51±0.19

Table 13.Results of stability studies of optimized formulation F15

S.No.	Parameters	Initial	1 month	2 month	3 month	Limits as per specification
1	40^0C/75% RH % Release	98	98.52	97.79	96.56	Not less than 85 %
2	40^0C/75% RH Assay Value	98	97.96	96.22	96.00	Not less than 90 % Not more than 110 %

Fig: 2. Calibration curve for the estimation of Nimodepine

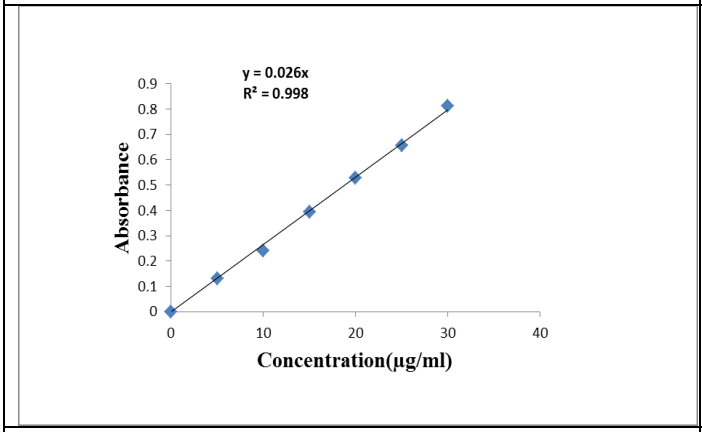


Fig: 3. Graphical representation of wetting time of Nimodepine ODTs prepared by varying concentrations of superdisintegrants

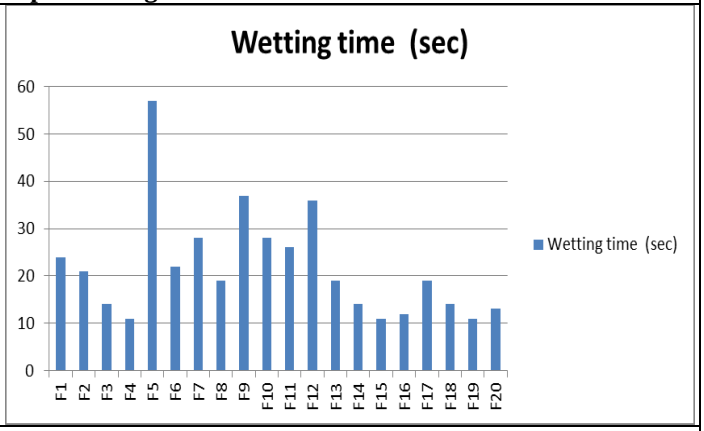


Fig: 4. Graphical representation of disintegration times of Nimodepine ODTs prepared by varying concentrations of superdisintegrants

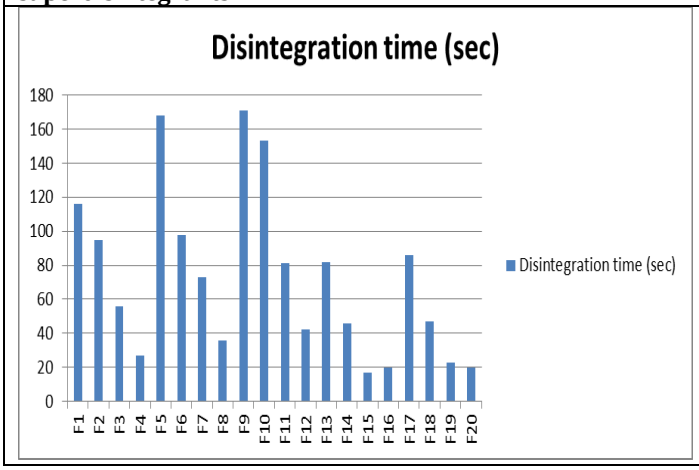


Fig: 5. Graphical Representation of Weight variation

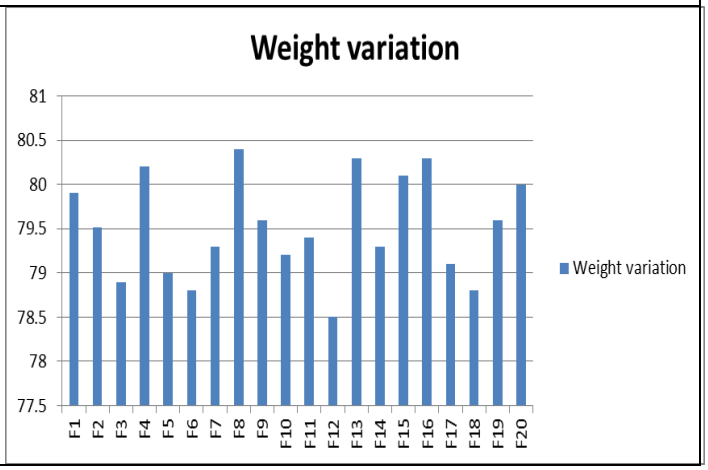


Fig: 6. Graphical Representation of Drug content

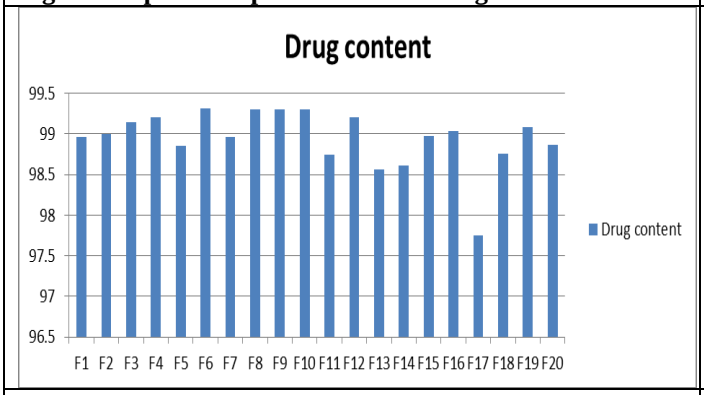


Fig: 7. Graphical Representation of Hardness

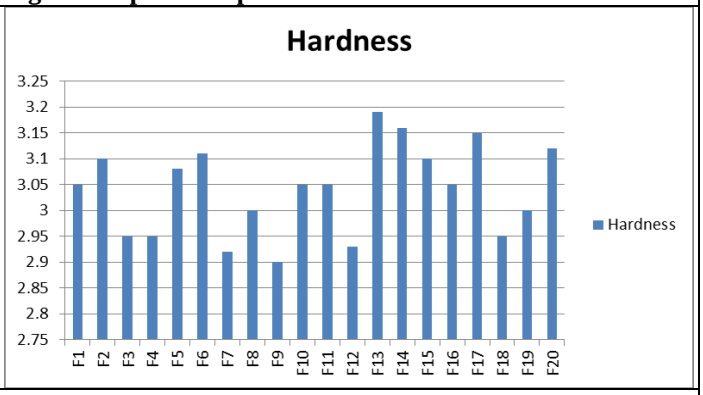


Fig: 8. Graphical Representation of friability

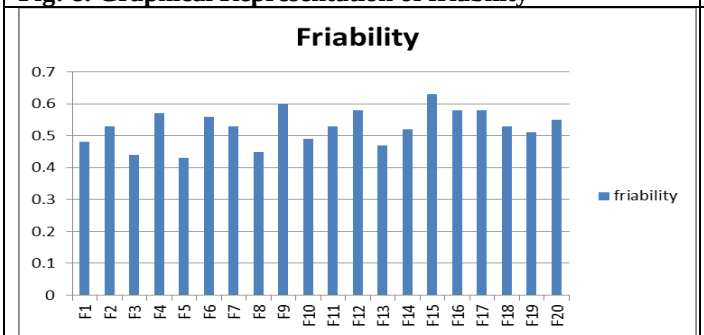


Fig: 9. Graphical Representation of Thickness

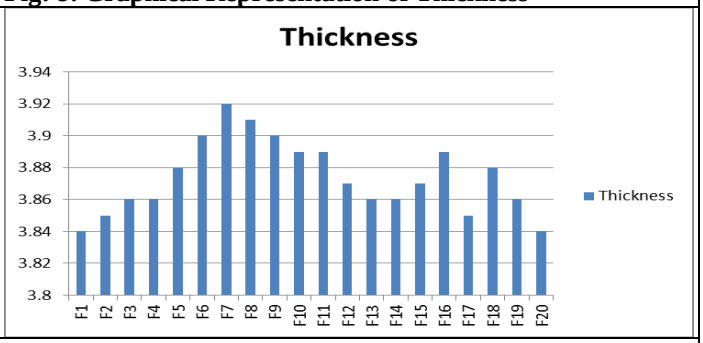


Fig: 10. Graphical representation of Cumulative percent Nimodepine released from ODTs containing varying concentrations of crosspovidone

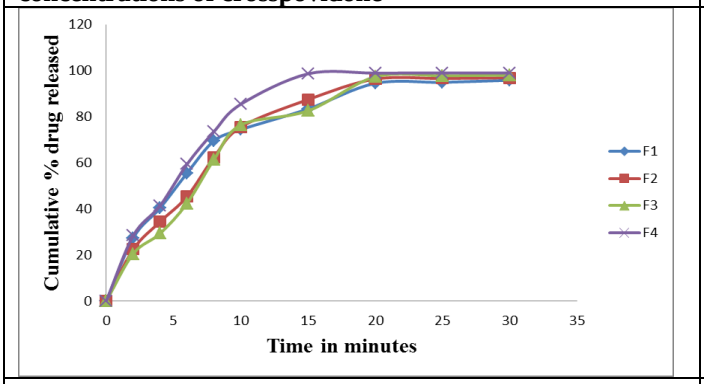


Fig: 11. Graphical representation of Cumulative percent Nimodepine released from ODTs containing varying concentrations of croscarmellose sodium

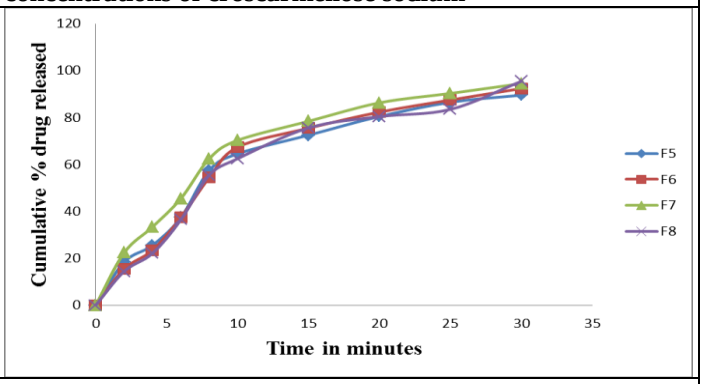


Fig: 12. Graphical representation of Cumulative percent Nimodepine released from ODTs containing varying concentrations of sodium starch glycolate

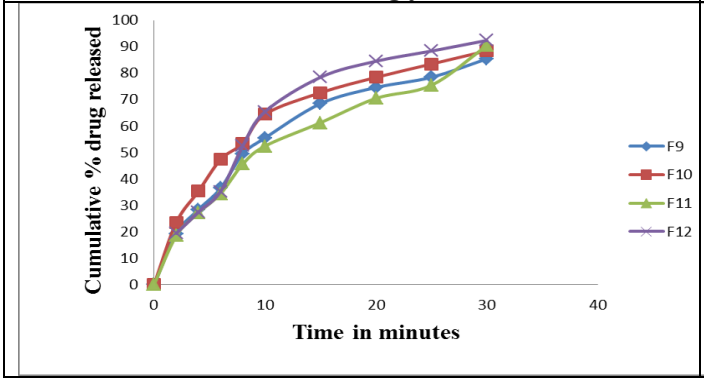


Fig: 13. Graphical representation of witting time of Nimodepine ODTs prepared by varying concentrations of combination of superdisintegrants

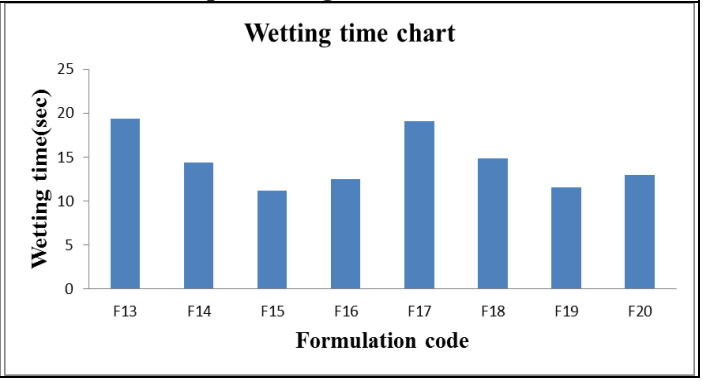


Fig: 14. Graphical representation of disintegration times of Nimodepine ODTs prepared by varying concentrations of combination of superdisintegrants

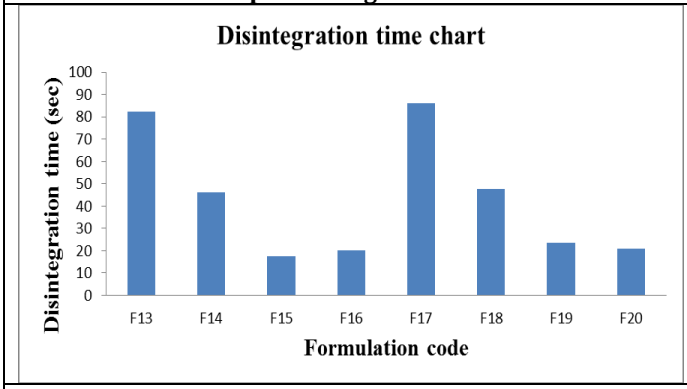


Fig: 15. Graphical representation of Cumulative percent Nimodepine released from ODTs containing varying concentrations of CP + CCS

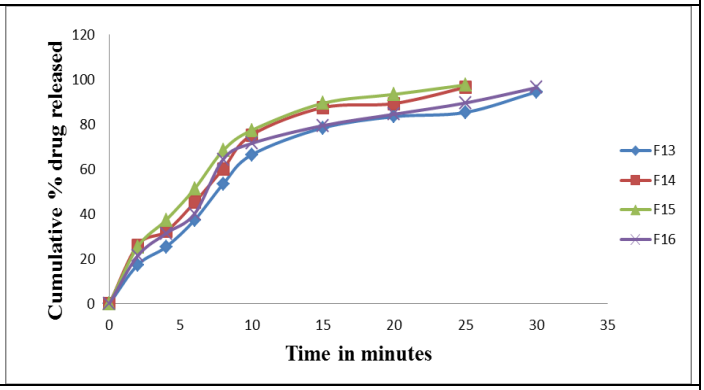


Fig: 16. FTIR spectra of Nimodepine

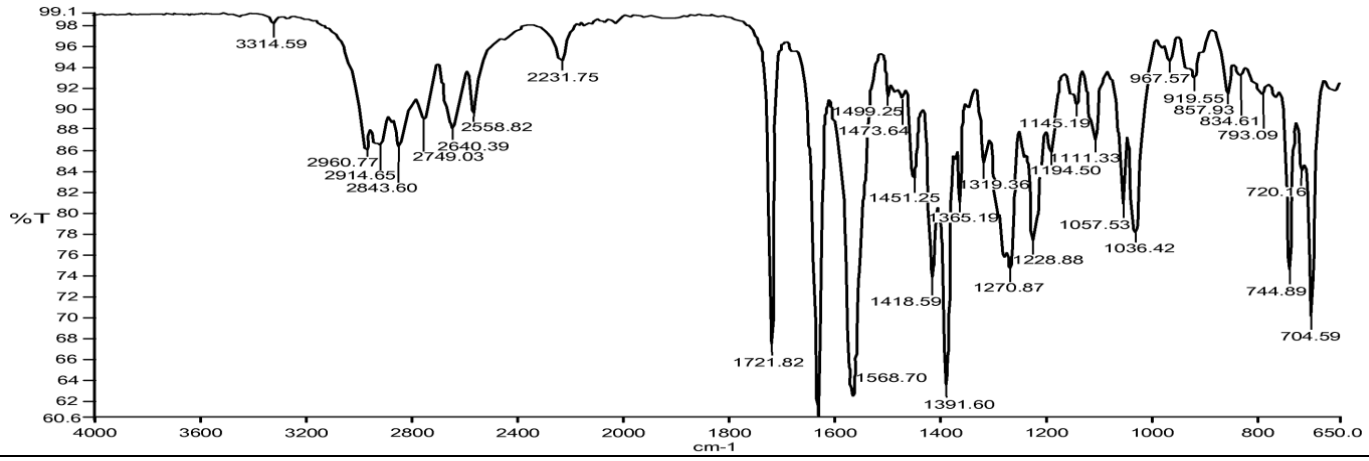
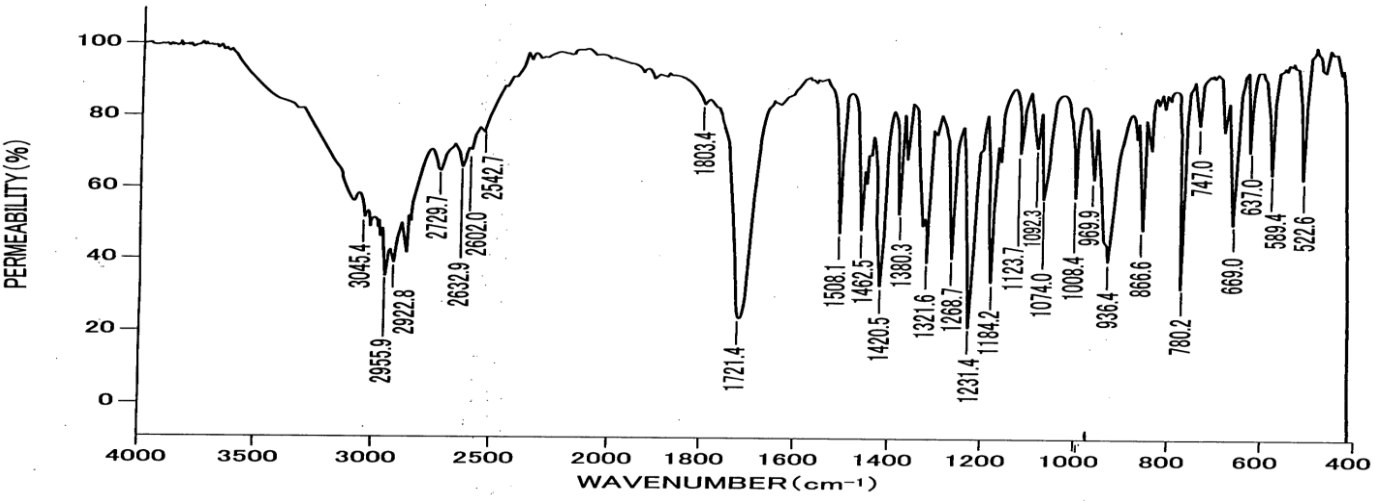


Fig: 17. FTIR for optimized formulation F15



FTIR studies

FTIR spectra of IR spectrum of pure Nimodepine, croscarmellose sodium, crosspovidone, sodium starch glycolate and combination thereof were recorded on Perkin Elmer spectrophotometer. The scans were evaluated for presence of principal peaks of drug, shifting and masking of drug peaks due to presence of polymer. The FT – IR spectra of pure Nimodepine. The Fourier transform infrared spectroscopy studies were carried out for pure drug along with excipients. The above peaks are considered as

characteristic peaks of Nimodepine. These peaks were not affected and prominently observed in IR spectra of drug and excipients. This indicates there is no interaction between drug and excipients.

Stability Studies

There was no significant change in physical and chemical properties of the tablets of formulation F15 after 3 Months. Parameters quantified at various time intervals were shown.

DISCUSSION

The overall objective of this study was to design oral disintegrating Nimodepine tablets and films that disintegrate or disperse in the saliva within a matter of seconds.

Oral Disintegrating Tablets

Using various disintegrants like Crosspovidone, Croscarmellose sodium, Sodium starch glycolate tablets were prepared along with other additives. Direct compression method was used for the preparation of tablets. A total number of 20 formulations were prepared and evaluated.

To achieve such a formulation, most of the excipients selected must be water soluble by nature. Pearlitol SD 200 is a directly compressible grade of mannitol with good flow properties and gives a refreshing or cooling effect in the mouth due to its negative heat of solution. This excipient was used a bulking agent to achieve the desired tablet weight. Avicel 102 was included in the formulation mainly as a disintegrant at the concentrations used and to some extent as diluents. This grade of microcrystalline cellulose is granular in nature and thus displays excellent flow. To impart pleasant taste and mouth feel sodium saccharin and orange were included as sweetening and flavoring agents respectively. Sodium stearyl fumerate was employed as a lubricant instead of magnesium stearate to overcome the metallic taste of the latter and also due to its water soluble nature.

Crosspovidone polymers are densely crosslinked homopolymers of N – vinyl 2 – pyrrolidones. Their porous particle morphology helps to rapidly wick liquids into the tablet by capillary action to generate the rapid volume expansion and hydrostatic pressures that cause tablet disintegration. In addition to its unique particle size and morphology, crosspovidone is non ionic and its disintegration performance will neither be influenced by pH changes in the gastrointestinal tract nor will they complex with ionic drug actives. They can also be used as solubility enhancers resulting in a faster dissolution rate without forming gels.

Croscarmellose sodium is crosslinked carboxymethyl cellulose sodium which can be used at concentrations of upto 5% as a disintegrant. Its unique fibrous nature gives excellent water wicking capabilities and crosslinking makes it hydrophilic and highly absorbent material, resulting in its swelling properties. It rapidly swells upto 4 – 8 times its original volume on contact with water. Like crosspovidone, it is also used as a dissolution aid, hence the name Ac-Di-Sol (accelerates dissolution).

Sodium starch glycolate is a sodium salt of carboxymethyl ether of starch,usually employed at concentrations between 2 – 8% although an optimum concentration of 4% may sufficient in many cases. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling, which is its primary mechanism of action. It (explotab) swells upto 300 times its original volume in water.

In all formulations, tablet weight and thickness were within mean ±7.5% and mean ±5% respectively. The weight variation in all the twenty formulations was found to be 78.5 mg to 80.4 mg, which was in pharmacopoeial limits. The thickness varies between 3.84 to 3.92 mm. Friability values were less than 1% in all cases. Hardness of all the tablets was maintained at 2.9 to 3.19 kg for all the formulations as mentioned before. Assay was performed and percent drug content of all the tablets were found to be between 97.75% and 99.36% of Nimodepine, which was within the acceptable limits.

Wetting time was determined for all the formulations. The values lie between 11.16±0.75 to 57.33±0.81. The variability in wetting time for different formulations may be due to the changes in the compaction which cannot be controlled during tablet preparation and the type of the disintegrant affected the wetting of the tablets. On comparing the superdisintegrants the formulations containing crosspovidone + croscarmellose sodium and crosspovidone + sodium starch glycolate take less wetting time than the other formulatios containing single superdisintegrants.

Water absorption ratio ranged from 56.59 % – 67.54 %. Crosspovidone and croscarmellose sodium perform their disintegrating action by wicking through capillary action and fibrous structure, respectively with minimum gelling. The relative ability of the various disintegrants to wick water into the tablets was studied. After contact with water the tablets containing sodium starch glycolate swelled, the outer edge appeared gel like. Tablets containing crosspovidone quickly wicks water and were hydrated, but were soft as compared with tablets prepared with crosscarmellose sodium and sodium starch glycolate. The center of the tablets with sodium starch glycolate and croscarmellose sodium remained dry and hard.

Disintegration time is considered to be important criteria in selecting the best ODT formulation. The *in vitro* disintegration time for all the twenty formulations varied from 17.66±0.51 to 171.83±1.16 seconds. The rapid disintegration was seen in the formulations containing crosspovidone and formulations containing combination of superdisintegrants (CP + CCS, CP + SSG). This is due to rapid uptake of the water from the medium, swelling and

burst effect. It is also noticed that as the disintegrant concentration was increased from 9 to 12% the time taken for disintegration was reduced. The disintegration time of formulation (F15) containing 5% CP + 5% CCS was found to be lower (17.66±0.51) and was selected as the best ODT formulation among all the 20 formulations.

In vitro dispersion is a special parameter in which the time taken by the tablet for complete dispersion is measured. The time for all the twenty formulations varied between 30.66±0.81 and 259.83±1.47 sec.

The development of dissolution method for ODTs is almost similar to the approach taken for conventional tablets until they utilize the taste masking. The taste masking aspect greatly influences dissolution method development, specifications, and testing. Several factors like varied thickness and pH dependent solubility of drug particle coating influence dissolution profiles of ODTs containing taste masked actives. Since Nimodepine is not bitter in taste, the metallic taste of drug was masked by using sweeteners and flavors. It has been reported that USP type II apparatus with a paddle speed of 50 rpm is commonly used for ODT formulations. Slower paddle speeds are utilized to obtain good profiles as these formulations disintegrate rapidly.

In *vitro* dissolution studies of the prepared ODTs was performed in pH 6.8 phosphate buffer using USP dissolution apparatus type 2. The dissolution rate was found to increase linearly with increasing concentration of superdisintegrant. Formulations F1, F2, F3 and F4 which contained increasing concentrations of crosspovidone have recorded drug release 95.78%, 96.85%, 97.96 and 98.99% respectively within 20 to 30 min. Formulations F5, F6, F7 and F8 which contained increasing concentrations of croscarmellose sodium have recorded drug release 89.53%, 92.36%, 94.46% and 95.43% respectively, at the end of 30 min. Formulations F9, F10, F11 and F12 which contained increasing concentrations of sodium starch glycolate have recorded drug release 85.4%, 88.45%, 90.4% and 92.38% respectively, at the end of 30 min.

Formulations F13, F14, 15 and F16 which contained increasing concentrations of combination of CP + CCS have recorded drug release 94.5%, 96.52%, 99.87% and 96.38% respectively, at the end of 25 to 30 min. Formulations F17, F18, F19 and F20 which contained increasing concentrations of combination of CP + SSG have recorded drug release 88.56%, 92.5%, 95.48% and 94.51respectivel, at the end of 30 min.

CONCLUSION

Oral DisintegratingTabl of Nimodepine were formulated with an aim to improve the versatility, patient compliance and accurate dosing. The formulations ere developed with an objective to use by the pediatric and geriatric patients. Nimodepine Oral Disintegrating Tablets were prepared by direct compression method using crosspovidone, croscarmellose sodium, sodium starch glycolate and combinations of CP+CCS, and CP + SSG as superdisintegrants exhibited good preformulation and tabletting properties. Of three superdisintegrants, the formulation contained combination of CP + CCS showed better performance in terms of disintegration time when compared to other formulations. Order of the superdisintegrant activity is as follows (CP + CCS) > (CP + SSG) > CP > CCS > SSG. The formulation F15 was found to be the best among the all twenty Nimodepine ODT formulations because it has exhibited faster disintegration time (17.66 sec) when compared to the other formualaions and it showed 99.87±0.18%drug release at the end of 25 min. Nimodepine Oral Disintegrating Films were prepared by solvent casting method using different grades of Hydroxy Propyl Methyl Cellulose like HPMC – E15, HPMC – 5cps, HPMC – 50cps. Based on disintegration and dissolution results it was concluded that the formulation F15 contained CP 5% + CCS 5% was the best formulation among the all other formulations. FTIR study showed no drug excipient interaction. The metallic taste of the drug was masked by Sodium saccharin, and Orange flavor.

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