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Design and Optimization of Rapimelt Nimodipine Tablets of Anti Hypertensive Management

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Abstract

Rapimelt 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 superdisintegrants to improve the disintegration and dissolution rate of tablets were found in order. The disintegration of NF1, NF2, NF3 with 1.5%, 3%, 6% Crosspovidone formulations to be as 8, 6, 5secs respectively and is almost better than NF4, NF5, F6, NF7, NF8, N F9 formulations, formulation NF3 In-vitro Dissolution studies 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 glycollate.

The drug release profiles of Nimodipine rapimelt tablets were fitted to various kinetic models such as Zero order, First order, Higuchi, Peppas and Hixson-Crowell. The dissolution parameters such as dissolution efficiency (DE) at 10 and 30 minutes were increased proportionately. Half-life of drug *i.e.,* T50 was found to be 1.81, 1.70, 1.53, 2.42,1.94,1.59, 2.81, 1.98 and 1.73min for NF1, NF2, NF3, NF4, NF5, NF6, NF7, NF8 and NF9 formulations respectively. Shelf-life of the drug *i.e.,*T90 was found to be 9.75, 8.75, 8.24, 9.28 and 8.92 minutes for NF1, NF2, NF3, NF5 and NF6 formulations respectively. 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 optimized formulation NF3 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 1st month, 2nd month and 3rd month. The results indicated that there was no significant change in evaluation of the

tablets. *In-vivo* Studies the limit had been sufficient for PK studies of Nimodipine. From the pharmacokinetic analysis, it can be concluded that the in vivo studies mimic the in vitro results. In vitro results demonstrated considerable difference in the percentage drug release between pure drug and Optimized formulation, similarly differences were observed in C_{max}, Tmax and AUC0-t between pure drug and optimized formulations. The average peak plasma concentration obtained for the drug and fast-dissolving tablet, indicated an increase in the extent of absorption (AUC0-t). The decrease in the Tmax values indicated faster absorption from the optimized formulation and increase in the C_{max} values indicated higher attainable plasma drug concentrations with the same dose of the drug. The higher values of PK parameters (AUC_{0-t}, C_{max}, T_{max} and $t_{½}$) showed enhancement in bioavailability of Nimodipine by formulating fast-dissolving tablet. The in vivo studies clearly indicated that Standard Drug approach can be adopted for formulation of Nimodipine tablets in order to achieve a faster onset of action.

Key words: Rapimelt tablets, nimodipine, superdisintegrants, T_{max}, C_{max}, fast-dissolving tablet

INTRODUCTION

Recent advances in technology have presented viable dosage alternative for patients who may have difficulty in swallowing tablets or capsules [1]. Traditional tablets and capsules administered with an 8-oz. glass of water may be inconvenient or impractical for some patients. To overcome these problems, formulators have considerably dedicated their effort to develop novel drug delivery systems (NDDS) which enhance safety and efficacy of drug molecule and to achieve better patient compliance [2]. One such approach is ''Rapimelts Oral Tablets", which disintegrate or dissolve in saliva and are swallowed without water as tablet disintegrate in mouth, this could enhance the clinical effect of drug through pregastric absorption from the mouth, pharynx, esophagus. This leads to an increase in the bioavailability by avoiding first pass liver metabolism. The centre for drug evaluation and research states an orally dissolving tablet to be "A dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon tongue''[3]. This system is recognized with other synonyms like fast dissolving tablets; melt in mouth tablets, porous tablets, rapidly disintegrating tablets, quick dissolving, and rapimelt tablets. Despite various nomenclatures the function and concept of all these Drug Delivery System (DDS) is similar [4].

Advantages of orally disintegrating tablets are being recognized in both industry and academia. Their growing importance was underlined recently when the European Pharmacopoeia adopted the term Oro-dispersible tablet as a "tablet to be placed in the mouth where it disperses rapidly before swallowing" Aim of the work: In the present work an attempt will be made to formulate nimodipine Rapimelt tablets, using different superdisintegrants for treatment of hypertension, the rapimelt tablet provides a rapid onset of action [5]. Nimodipine is a poorly water soluble drug. The oral bioavailability is only 13 % with a half life of just 8-9 hours. Nimodipine is metabolized by the first pass metabolism. The dihydropyridine ring of the Nimodipine is dehydrogenated in the hepatic cells of the liver, a process governed by cytochrome P-450 3A (CYP3A).

Therefore, the present study is designed to formulate the Nimodipine rapimelts and increase the solubility along with the bioavailability by using different polymers and disintegrates for rapid disintegration and dissolution[6].

MATERIAL AND METHOD

Nimodipine and Crosscarmellose Sodium (CCS) was purchased from Cipla Dewas MP. Sodium Starch Glycolate (SSG) and microcrystalline cellulose was obtained as a gift sample from Hi Media Laboratories Maharastra, India, All other ingredients were of analytical grade.

Methodology

Preparation of Standard Graph

Preparation of Stock solution with Distilled water [7]

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 (λ max) of drug sample in water[8]

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 1800 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 of 2, 4, 6, 8, 10 and 12µg/ml respectively [9,10]. 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 [11].

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[12]. 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 (λ max) 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 1800 spectrophotometer[13]. 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[14]. The absorbance was plotted against the concentrations and the graph with the straight line equation and r^2 value were obtained.

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[15]. 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[16].

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 [17, 18].

Bulk Density [19]:

Apparent bulk density was determined by pouring pre-sieved drug excipients 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 [20]. 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.

Carr's index:

It is expressed in percentage and is expressed by

Carr's Index = (ρtapped-ρbulk)/ρtapped*100

With

ρ tapped: the tapped bulk density of the material (kg/m3) ρ bulk: the loose bulk density of the material (kg/m^3)

Hausner's ratio:

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula [21].

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).

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[22]. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

tan (θ) = h / r θ = 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[23].

Method of formulation

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[24].

Representation of Direct Compression Technique for design of Rapimelts 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 [25]. 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 1: Formulations of different batches

Ingredients (mg)	Formulation Code								
	NF1	NF2	NF3	NF4	NF5	NF6	NF7	NF8	NF9
Nimodipine	30	30	30	30	30	30	30	30	30
Crospovidone	3	6	12	-	-	-	-	-	-
Croscarmellose 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

Evaluation of Rapimelts Tablets

Hardness test:

Using a Monsanto hardness tester the rigidity (hardness) of the tablet was determined [26].

Friability:
The friability of a sample of 20 tablets was measured using a Roche friabilator (Electro lab). 20 previously weighed tablets were rotated at 25 rpm for 4 min. The weight loss of the tablets before and after15 Measurement was calculated using the following formula Percentage friability = Initial weight – Final weight x 100 Initial weight

Weight Variation [27]:
It was performed as per the method given in the United States pharmacopoeia. Twenty tablets were selected randomly from each formulation, weighed individually and the average weight and % variation of weight was calculated[28].

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 [29].

In- vitro Disintegration Time:
Disintegration times for Rapimelt tablets were determined using USP tablet disintegration apparatus with saline phosphate buffer of pH 6.8 as medium[30]. Maintained the medium temp at 37±2°C. 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[31]

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[32].

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 ^{0}C. 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 [33].

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 Rapimelt but is used less frequently due to specific physical properties of tablets [34].

Drug release kinetics [35]:

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. Where t is the time, y is the percentage of drug dissolved at time t, and $\int$ is the area under the curve.

Zero order kinetics [36]:

The zero order release has the ability to deliver a drug at a rate independent of time and drug concentration in a dosage form. Zero order ensures a steady amount of drug is released over time. This model represents the drug dissolution from dosage forms that do not disaggregate and release the drug slowly including transdermal systems or matrix tablets with low soluble drugs. The model is represented by the Equation below

$$Q1 = Q0 + K0t$$

Where (Q1) is the amount of drug dissolved;
(t) is the time;
(Q0) is the initial amount of drug in the solution; and
(K0) is the zero order release constant.

First order kinetics:

This first order model is used to describe the absorption and elimination of some drugs. This model releases the drug proportionally to the amount of drug remaining in the interior of the dosage form, allowing for the amount of drug released per unit of time to diminish. The dosage forms which follow this dissolution profile include water soluble drugs in porous matrices. The model is represented by Equation below.

$$logQ1 = logQ0 + K1t2.303$$

Where (Q1) is the amount of drug released; (Q0) is the initial amount of drug in solution; (t) is the time; and (K1) is the first order release constant.

Hixon-crowell cubth root model:

The Higuchi model is used to study the release of water soluble and low soluble drugs incorporated in a semi-solid or solid matrix. This model describes drug release as a diffusion process based on Fick's law. The Higuchi model is used to describe drug dissolution from several types of modified release dosage forms such as transdermal systems or matrix tablets containing water soluble drugs [37]. The model is represented by Equation below.

$Q1 = KH\sqrt{t}$

Where (Q1) is the amount of drug released; (KH) is the Higuchi dissolution constant; and (t) is the time.

Higuchi model:

The Higuchi model is used to study the release of water soluble and low soluble drugs incorporated in a semi-solid or solid matrix. This model describes drug release as a diffusion process based on Fick's law. The Higuchi model is used to describe drug dissolution from several types of modified release dosage forms such as transdermal systems or matrix tablets containing water soluble drugs. The model is represented by Equation below.

$Q1 = KH\sqrt{t}$

Where (Q1) is the amount of drug released

(KH) is the Higuchi dis

Korsmeyer-peppas model:

The Korsmeyer-Peppas model is a simple model relating, exponentially, the drug release to the elapsed time[38]. The different release mechanisms are characterized by using an n-value, which differs depending on a slab or a cylinder. This model is used to analyze polymeric dosage forms that do not have a well-known release mechanism or more than one type of release is occurring simultaneously. The model is represented by Equation below.

$F = Mt/M\infty = K_m t^n$

Where (F) is the fraction of drug release at specific time; (Mt) is the amount of drug release; (M∞) is the total amount of drug in dosage form; (K_m) is the structural and geometric constant; and (n) is the release exponent.

RESULTS AND DISCUSSION

Objective of this study was to formulate directly compressible orally disintegrating tablets of Nimodipine with sufficient mechanical integrity, content uniformity, and acceptable palatability to assist patients of any age group for easy administration for the treatment of Hypertension, nausea and vomiting, and motion sickness for rapid dissolution and absorption of drug which may produce rapid onset of action. It is also helpful for vestibular symptoms of other origins [39].

Calibration curve of Nimodipine

Table 2: 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

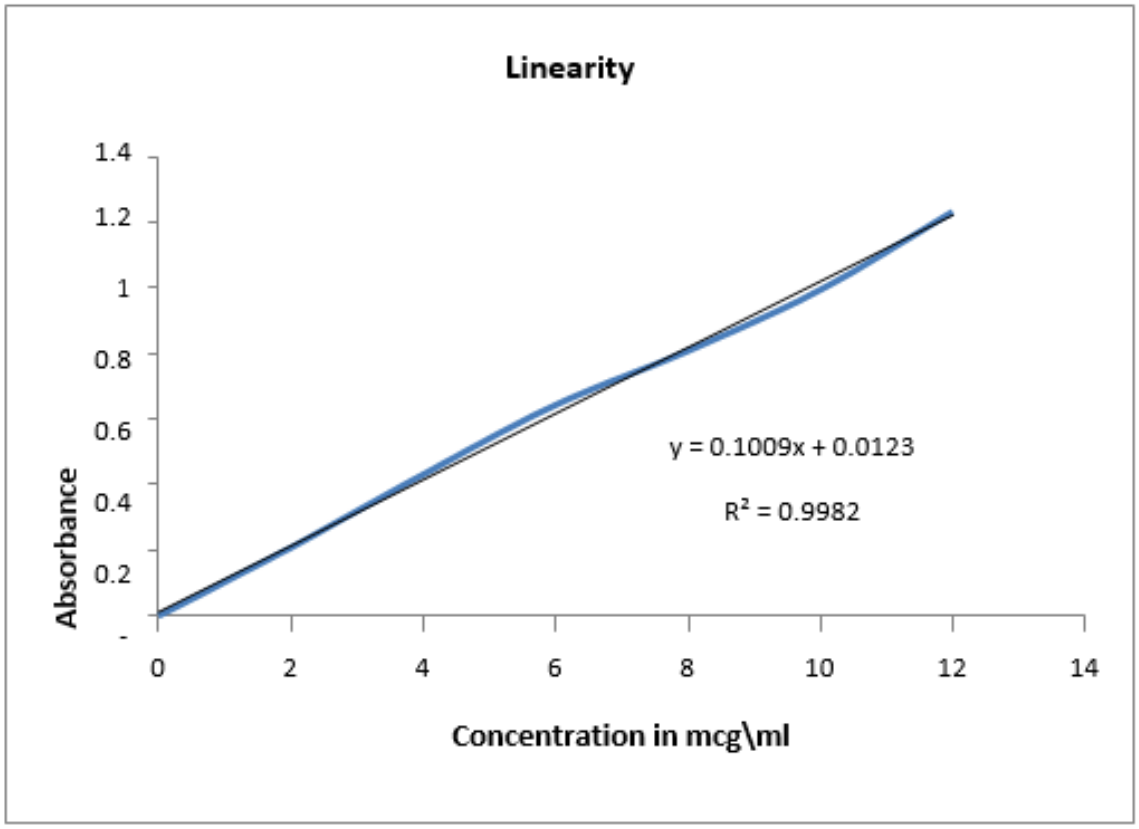

Figure 1: Standard Calibration curve of Nimodipine with Distilled water

In the current investigation, analytical method obeyed beer-lamberts law in the concentration range of 2-12µg/ml and it was suitable for the estimation of Nimodipine using Distilled water [40]. 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 3: Standard Calibration curve of Nimodipine with 6.8 pH phosphatebuffer

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

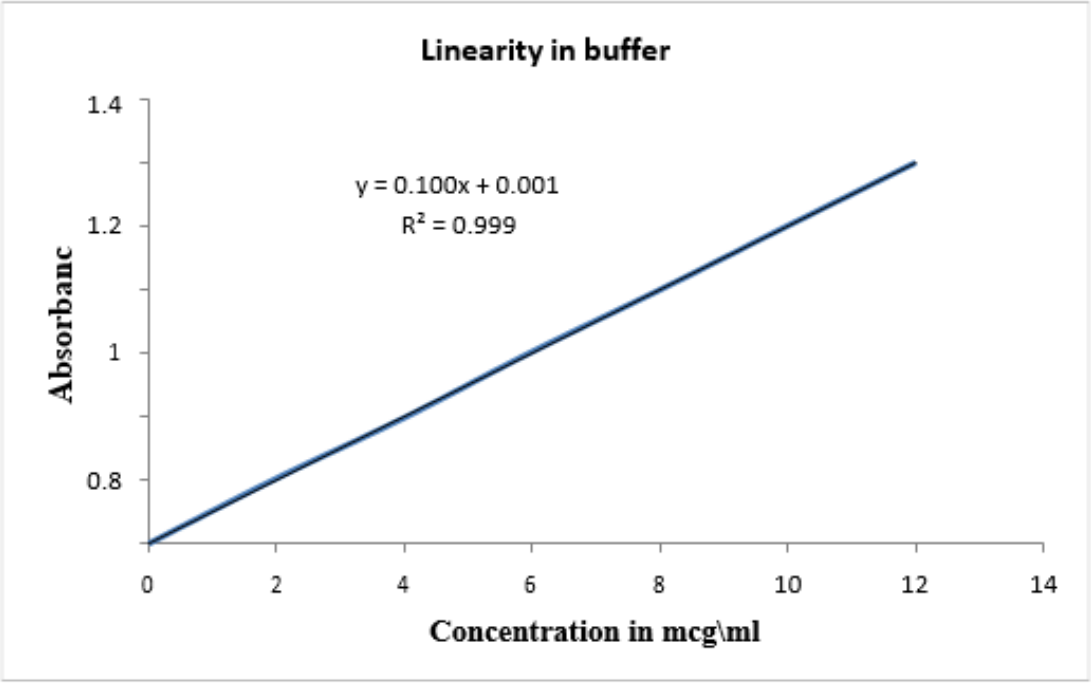

Figure 2: Standard Calibration curve of NMD with 6.8 pH phosphate buffer

FT-IR studies

FT-IR spectra of pure Nimodipine and the physical mixtures of drug and excipients were given in Table 4. Pure Nimodipine showed principal absorption peak sat782.17cm-1(C-H aromatic bending), 1368.54cm-1 (NO_2 stretching), 1464.94 cm-1(C=C aromatic stretching), 1626.06cm-1 (N-H bending), 2972.38 cm^{-1} (C-H stretching) and 3411.22cm-1 (O-H stretching).The identical peaks of C-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 Rapimelt tablets preparation [41].

Table 4: FT-IR interpretations of pure drug and physical mixtures

S.No	Functionalgroup	Characteristic peaks	Observed peaks						
			Nimodipine	Nimodipine:MCC	Nimodipine:SSG	Nimodipine:CCS	Nimodipine :Crospovidone	Nimodipine :Mannitol	Nimodipine: Mg.stearate
1	C-H (Aromatic bending)	680-860cm^{-1}	782.17cm^{-1}	782.17cm^{-1}	781.20 cm^{-1}	781.20cm^{-1}	782.17 cm^{-1}	783.13cm-1	782.12cm^{-1}
2	NO_2 (stretching)	1300-1600 cm^{-1}	1369.52cm^{-1}	1368.55cm^{-1}	1369.52 cm^{-1}	1369.52cm-1	1369.52 cm^{-1}	1369.52cm-1	1369.52cm-1

3	C=C (Aromaticst retching)	1400-1600 cm^{-1}	1465.96$c m^{-1}$	1465.96cm^{-1}	1415.81 cm^{-1}	1415.81cm^{-1}	1465.00 cm^{-1}	1415.81cm-1	1426.42cm^{-1}
4	N-H (bending)	1580-1650 cm^{-1}	1626.06$c m^{-1}$	1627.03cm^{-1}	1638.60 cm^{-1}	1637.64cm^{-1}	1627.99 cm^{-1}	1626.06cm-1	1624.13cm-1
5	C-H (stretching)	2850-3000 cm^{-1}	2973.40$c m^{-1}$	2936.75cm^{-1}	2937.71 cm^{-1}	2936.75cm^{-1}	2938.68 cm^{-1}	2943.50cm-1	2934.82cm-1
6	O-H (stretching)	3200-3500 cm^{-1}	3411.26$c m^{-1}$	3258.81cm^{-1}	3397.26 cm^{-1}	3272.38cm^{-1}	3273.34 cm^{-1}	3261.77cm-1	3271.41cm-1

Pre-compression parameters Nimodipine rapimelts tablets.

The angle of repose less than 31.82, which reveals good flow property it shown in for formulations NF1-NF9 .The loose bulk density and tapped bulk density for all formulation (NF1 – NF9) varied from 0.442 gm/cm^3 to 0.485gm/cm^3 and 0.502 gm/cm^3 to 0.593 gm/cm^3 respectively. The results of carr's consolidate index or % compressibility index for the entire formulation (NF1 – NF9) blend range from 15 to 19 shows fair flow properties [42].

Table 5: Evaluation of tablet blend for formulations (NF1-NF9)

Formulation	Bulk Density (g/cc)	Tapped Density(g/cc)	Hausner'sratio	Compressibility index (%)	Angle of repose
NF1	0.464	0.574	1.23	19.1	29.47
NF2	0.423	0.502	1.16	15.5	27.63
NF3	0.456	0.542	1.22	15.8	25.54
NF4	0.467	0.559	1.25	16.4	26.23
NF5	0.485	0.593	1.10	18.2	27.21
NF6	0.460	0.556	1.21	17.2	30.38
NF7	0.478	0.575	1.24	16.8	28.46
NF8	0.450	0.554	1.28	18.7	25.71
NF9	0.442	0.537	1.27	17.6	31.82

Post compression parameters Nimodipine Rapimelt tablets.

Table 6: Evaluation of Rapimelt tablets for formulations (NF1- NF9)

Formulation	Hardness (kg/cm2)	Friability (%)	Weight (mg)	Thickness (mm)	Drug content(%)
NF1	3.0±0.17	0.25	201±0.59	3.9±0.05	97.2
NF2	2.8±0.20	0.23	198±0.62	4.2±0.02	97.72
NF3	3.1±0.18	0.26	201±0.45	3.7±0.07	98.4
NF4	2.9±0.15	0.24	202±0.88	3.8±0.10	97
NF5	3.2±0.16	0.28	204±0.55	3.9±0.03	98.44
NF6	2.8±0.22	0.32	198±0.74	3.9±0.06	100.8
NF7	3.2±0.25	0.27	201±0.67	3.8±0.15	97.2
NF8	2.9±0.22	0.29	201±0.77	3.9±0.03	98.4
NF9	2.8±0.17	0.24	203±0.86	4.1±0.01	95.34

The hardness values ranged from 2.8 ± 0.17 kg/cm^2 to 3.2 ± 0.25 kg/cm^2 for formulation (NF1-NF9) 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 NF1, NF2, NF3, NF4, NF5, NF6, NF7, NF8, NF9 formulations[43].

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 ± 0.62 mg to 204 ± 0.55 mg. The weight of all the tablets was found to be uniform with less deviation [45]. The maximum concentration among all the formulations was found to be 100.8% and minimum % drug content from all formulation was found to be 95.34%. The results of drug content of all batches are shown in.

Evaluation of Nimodipine Rapimelt tablets.

Table 7: Evaluation of Rapimelt tablets for formulations (NF1-NF9)

Formulation	Disintegration time (sec)	Wetting time (sec)	Water Absorption ratio (%)	*In vitro* dispersion time (sec)
NF1	8	20	19.42	8
NF2	6	15	22.47	5
NF3	5	12	19.78	5
NF4	10	16	16.13	15
NF5	9	14	17.27	11
NF6	8	19	12.17	9
NF7	18	27	15.32	14
NF8	10	20	12.047	12
NF9	9	20	13.92	8

Disintegration test carried out in modified dissolution apparatus[46], it shows the formulations with 1.5%, 3%, 6% Sodium Starch Glycolate showed high value for disintegrating time as 18, 10, 8 secs. The results showed that the disintegration time of NF1, NF2, NF3 with 1.5%, 3%, 6% CP formulations to be as 8, 6,5 secs respectively and is almost better than NF4, NF5, NF6, NF7, NF8, NF9 formulations and comparative profile.

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 up take and subsequent wetting of tablet. This shows the wetting process was very rapid in almost all formulations [47]. 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 NF1, NF2, NF3 (1.5 - 6%) have better wetting time comparing with that of croscarmellose sodium starch glycolate, and comparative profile result was shown in table 7. Water absorption ratio which is important criteria for understanding the capacity of disintegrates 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 capacity result was shown in table 7.
The in-vitro dispersion time is measured by time taken to uniform dispersion, the rapid dispersion[47]. It was found to be in the range of 5secs to 15secs (Graph). The result showed that the in vitro dispersion time of NF1, NF2, and NF3 formulations is almost equal and better than NF4, NF5, NF6, NF7, NF8, NF9 formulations and comparative profile result was shown in Table 7.

***In-vitro* dissolution studies of Nimodipine Rapimelt tablets.**

Table 8: Cumulative % drug release for formulations (NF1-NF9)

Cumulative % drug release									
Time	NF1	F2	NF3	NF4	NF5	NF6	NF7	NF8	NF9
2Min	55.15	58.9	65.5	48.07	51.5	62.7	45.93	50.54	57.9
4Min	68.6	72.1	74.9	57.29	61.5	71.1	55.97	61.7	61.07
6Min	71.12	80	82.64	72.93	76.55	81.16	71.44	73.2	77.2
8Min	81.9	87.08	89.06	79.68	84.61	86.5	76.05	81.8	84.12
10Min	91.17	94.82	96.96	88.40	93.3	94.1	85.2	87.07	89.2

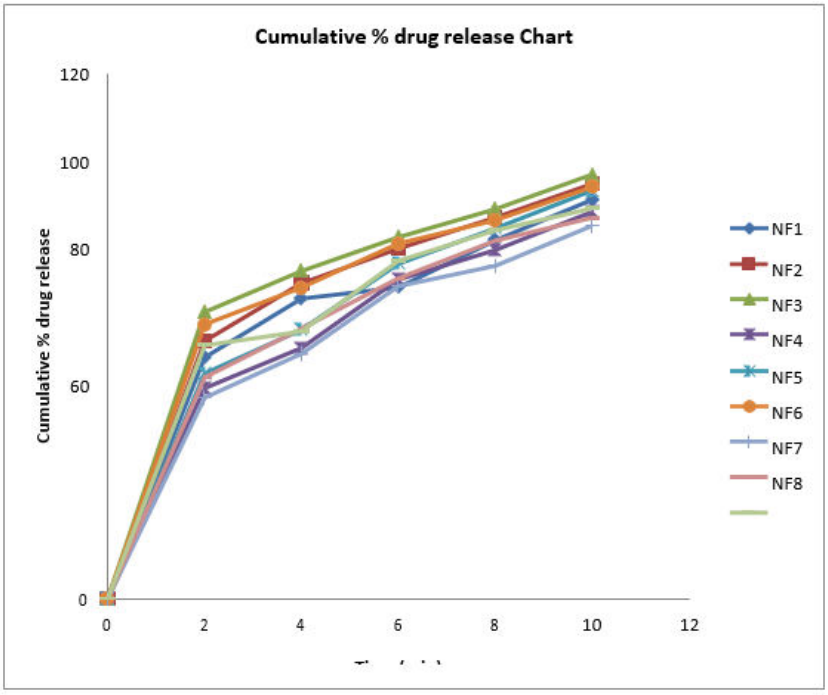

Figure 3: Comparison between cumulative percentage drug releases forformulations (NF1-NF9)

Dissolution is carried out in USP-2 type apparatus at 50rpm in the volume of 500 ml dissolution media (phosphate buffer pH 6.8) for 10 minutes[47, 48]. 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% Crospovidone .

Drug release kinetics of Nimodipine Rapimelt tablets.

Correlation coefficient (r) & constant (k) Values of Nimodipine rapimelt tablets containing Crospovidone, croscarmellose sodium, sodium starchglycolate.

Table 9: Drug release kinetics of Nimodipine Rapimelt tablets

Kinetic model		NF1	NF2	NF3	NF4	NF5	NF6	NF7	NF8	NF9
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
	r	0.9945	0.9913	0.9646	0.9943	0.9737	0.9833	0.9953	0.9927	0.9797
Higuchi	k	35.17	37.09	39.09	29.63	31.80	37.17	28.82	31.76	32.71
	r	0.9963	0.9939	0.9991	0.9981	0.9994	0.9903	0.9989	0.9991	0.9822
First order	k	0.2697	0.3192	0.3456	0.2127	0.2466	0.3104	0.2057	0.241	0.24
	r	0.9796	0.9995	0.9985	0.9892	0.9914	0.9125	0.9914	0.9971	0.9615
Peppas	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
T50		1.81	1.70	1.53	2.42	1.94	1.59	2.81	1.98	1.73
T90		9.75	8.75	8.24	0	9.28	8.92	0	0	0

The drug release profiles of Nimodipine tablets were fitted to various kinetic modelssuch as Zero order, First order, Higuchi, Peppas and 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 be1 81, 1.70, 1.53, 2.42, 1.94, 1.59, 2.81, 1.98 and1.73min for NF1, NF2, NF3, NF4, NF5, NF6, NF7, NF8 and NF9 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 NF1, NF2, NF3, NF5andNF6 formulations respectively. The drug release data of nimodipine Rapimelt tablets have treated with different kinetic models are shown in Table 9. The drug release patterns of nimodipine Rapimelt tablets had followed the first order kinetic model. This release patterns are evident with the correlation coefficient 'r' values which are nearer to 1.

***In-vivo* studies of Nimodipine Rapimelt tablets.**

The linear regression analysis of Nimodipine (NF3) (Table 10) was constructed by plotting the peak-area ratio of drug versus analyte concentration (mcg/ml) in spiked plasma samples. The average regression equation and correlation coefficients were calculated. r^2 = 0.999 for Nimodipine showed good linear relationship between the under peak areas and the concentrations. The lower limit of quantization was 0.05 mcg/ml for determination of Nimodipine

in plasma. The limit had been sufficient for PK studies of Nimodipine[48]. From the pharmacokinetic analysis, it can be concluded that the in vivo studies mimic the in vitro results. In vitro results demonstrated considerable difference in the percentage drug release between pure drug and Optimized formulation, similarly differences were observed in C_{max}, T_{max} and AUC_{0-t} between pure drug and optimized formulations.

The average peak plasma concentration obtained for the drug (Table 10) and rapimelt tablet, indicated an increase in the extent of absorption (AUC_{0-t}). The decrease in the T_{max} values indicated faster absorption from the optimized formulation and increase in the C_{max} values indicated higher attainable plasma drug concentrations with the same dose of the drug. The higher values of PK parameters (AUC_{0-t}, C_{max}, T_{max} and $t_{½}$) showed enhancement in bioavailability of Nimodipine by formulating rapimelt tablet.

Table 10: In vivo cumulative percentage drug release at 40±2°C, 75±5% RHfor Nimodipine

Time inminutes	Cumulative percentage drug release		
	Initial *N* = 3 mean ± SD	After 3 months *N* = 3 mean ± SD	After 6 months *N* = 3 mean ± SD
2	61.6±0.2	61.2±0.20	61.7±0.4
4	70.6±0.43	70.8±0.14	70.0±0.12
6	81.1±0.09	81.6±0.34	81.9±0.13
8	88.48±0.00	88.2±0.10	88.0±0.62
10	93.8±0.64	93.7±0.38	93.2±0.53

Table 11: Pharmacokinetic parameters of rapimelt tablets of Nimodipine

Pharmacokineticparameters	Pure drug	Prepared formulation	Marketed formulation
Peak plasma concentration Cmax (µg/mL)	80.34	200.87	94.66
Time to reach peak plasma concentration Tmax (h)	1.0 h	0.5 h	1 h
Biological half-life t ½ (h)	24.54	24.55	24.58
Elimination rate constantKe (h−1)	0.0282	0.028	0.0281
Area under the curve (0-t)(total) (µg/mL)h*)	251.45	740	321.57

Conclusion

Rapimelt 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 NF1, NF2, N F3 with 1.5%, 3%, 6% Crosspovidone formulations to be as 8, 6, 5secs respectively and is almost better than NF4, NF5, F6, NF7, NF8, NF9. Formulation NF3 In-vitro Dissolution studies 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 glycollate. The drug release profiles of Nimodipine Rapimelt tablets were fitted to various kinetic models such as Zero order, First order, Higuchi, Peppas and 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 be1 81, 1.70, 1.53, 2.42, 1.94, 1.59, 2.81, 1.98 and1.73min for NF1, NF2, NF3, NF4, NF5, NF6, NF7, NF8 and NF9 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 NF1, NF2, NF3, NF5and NF6 formulations respectively. 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 optimized formulation NF3 is kept for stability studies.

In-vivo Studies the limit had been sufficient for PK studies of Nimodipine. From the pharmacokinetic analysis, it can be concluded that the in vivo studies mimic the in vitro results. In vitro results demonstrated considerable difference in the percentage drug release between pure drug and Optimized formulation, similarly differences were observed in C_{max}, T_{max} and AUC_{0-t} between pure drug and optimized formulations.

The average peak plasma concentration obtained for the drug and fast-dissolving tablet, indicated an increase in the extent of absorption (AUC_{0-t}). The decrease in the T_{max} values indicated faster absorption from the optimized formulation and increase in the C_{max} values indicated higher attainable plasma drug concentrations with the same dose of the drug. The higher values of PK parameters (AUC_{0-t}, C_{max}, T_{max} and $t_{½}$) showed enhancement in bioavailability of Nimodipine by formulating fast-dissolving tablet. The in vivo studies clearly indicated that Stander Drug approach can be adopted forformulation of Nimodipine tablets in order to achieve a faster onset of action.

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