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Formulation, Development, and Optimization of Anti-Hypertensive Nisoldipine Extended-Release Tablet Formulation

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ABSTRACT

A drug molecule has to be water-soluble to be readily delivered to the cellular membrane. Many drugs are water-insoluble, which creates numerous problems in the development of dosage forms. Controlled drug delivery formulation releases the drug with controlled kinetics for days and months, reducing the frequency of dosing, minimizing side effects, and improving patient compliance. Nisoldipine is a calcium channel antagonist that is indicated for the treatment of hypertension with very poor aqueous solubility. Thus, there is a need to improve the rate of drug release. Hence, the study was carried out to design, formulate and evaluate sustained-release tablet formulation of nisoldipine. Nisoldipine controlled release matrix tablets were prepared by roll compaction method. Preformulation studies have confirmed the purity and compatibility of drug with excipients used in the formulation. Pre-compression studies have confirmed the stability of formulation blends for compression. All the prepared formulations were evaluated for various physical and compression parameters such as bulk and tapped density, hardness, friability, and *in vitro* drug release studies. The results of drug release from prepared compressed nisoldipine extended-release tablets were found to be within the desired range.

Keywords: Nisoldipine; Extended-release tablet; Roll compaction; Dissolution; Stability study.

1. INTRODUCTION

A drug molecule has to be water-soluble to be readily delivered to the cellular membrane but needs to be hydrophobic to cross the membrane.[1] Numerous problem have recently been experienced in the early development of pharmaceutical dosage forms of drugs.[2] Many drugs require multiple daily dosing, which is inconvenient for the patient and result in missed doses, patient noncompliance, and toxic side effects. Through years of diligent research, many techniques dealing with the formulation issues of water-insoluble drugs have been developed.[3,4]

Controlled drug delivery formulation developed in the year 1952 for a controlled release delivery system by which drug release kinetics can be achieved for days and months. Pharmaceutical dosage forms that release the drug slower than normal at a predetermined rate & reduce the dosage frequency by two folds are termed as extended-release dosage forms. This formulation technology is mainly based on modifying the drug dissolution and diffusion rates. This type of delivery system is used to reduce the frequency of dosing, increase the effectiveness of the drug, uniform drug delivery, minimizing or eliminating side effects and improves patient compliance.[5,6]

1.1. Drug Profile and Rationale for Experimental Design

Nisoldipine is a member of the dihydropyridine class of calcium channel antagonists that inhibit the influx of calcium into vascular smooth muscle and cardiac muscle

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employed for the treatment of hypertension. Inhibition of the calcium channel results in the dilation of the arterioles. Nisoldipine is practically insoluble in water and has an absolute bioavailability of 5%, this low bioavailability is due to pre-systemic metabolism in the gut wall. Food with a high fat content has a pronounced effect on the release of nisoldipine from the coat-core formulation and results in a significant increase in peak concentration (C_{max}) by up to 300%.[7]

The very poor aqueous solubility of nisoldipine gives rise to difficulties in designing pharmaceutical formulations and led to variable oral bioavailability. Thus, there is a need to improve the rate of drug release. Hence, the study was carried out to design, formulate, and evaluate the sustained-release tablet formulation of nisoldipine.[8]

2. MATERIALS AND METHODS

2.1. Drugs and Chemicals

Various chemicals used in the present study are represented in Table 1.

2.2. Instruments

Various instruments used in present study are presented in Table 2.

2.3. Preformulation Studies

2.3.1. *Saturation Solubility Profile of Nisoldipine API*

Solubility studies were performed for nisoldipine API conducted at 37 ± 0.5 ^{0}C and 25 ± 0.2 °C. Nisoldipine was added to different solvents such as 50 ml of purified water with 0.5% SLS at 25°C and 37°C, 0.1 N HCL with 0.5% SLS at 25°C and 37°C and phosphate buffer (pH-6.8) with 0.5% tween 80 at 25°C and 37°C into separate 250 ml stoppered conical flasks. Solubility studies were carried till the saturation point is reached.

Table 1: Chemicals Used

S. No.	Material Name	Manufacturer
1	Nisoldipine API	Orchid Chemicals and Pharmaceuticals Ltd.
2	Sodiumlauryl Sulphate (SLS)	Aged' ore Pvt. Ltd.
3	Eudragit-s-100	Degussa
4	DCL 11	DMV InternationalLtd.
5	Avicel-Ph 102	Dow Ltd.
6	Starch1500	Colorcon
7	Methocel K4M	Stepan Company
8	Magnesium Stearate	Mallinckrodt
9	Aerosil 200	Evonik

2.3.2. *Drug Excipients Compatibility Studies*

To detect any interactions of drug with other excipients, different excipients were mixed in different ratio with drugs according to the functional category (Table 3). These mixtures were kept in 40°C / 75 % RH in a 2 ml glass vial in exposed condition for 1 month. At the interval of 4 weeks, the samples were withdrawn and given to analytical development to analyze various parameters such as physical observation, moisture content and related substances.[9,10,11] The combination of drugs and polymers showed no significant chemical interactions (Table 3).

2.4. Formulation of Nisoldipine Extended-release Tablets

This formulation development's main objective is to design a matrix tablet dosage form a controlled drug

Table 2: Instruments Used

S.No.	Instrument Name	Company
1	Digital Weighing Balance	Sartorius, Hyderabad
2	Mechanical Stirrer	Remi Motors
3	Hot Plate	Pathak electrical works
4	Presscoat500-Compression Machine	Cadmach
5	Tap Density Tester	Electrolab
6	Mechanical Sieve Shaker	Retsch
7	Particle Size Analyzer	Malvern
8	Hardness Tester	Erweka
9	Friability Tester	Electrolab ET-2
10	Dissolution Apparatus (USP II)	Electrolab
11	Sonicater	Bandelin sonorex
12	pH Meter	Thermo Orion
13	Oscillating Granulator	Sams techno mech
14	Octagonal Blender	Sams techno mech
15	HPLC (Photodiode Array Detector)	Waters 996
16	UVSpectrophotometer (Doublebeam)	Perkin Elmer
17	Vernier Caliper	Mitutoyo
18	Coating pan	STM sams techno mech

Table 3: Excipients for Compatibility Studies

S.No.	Excipients	Functional Category
1	Sodium Lauryl Sulphate (SLS)	Anionic Surfactant
2	Eudragit-s-100	Polymer
3	Avicel-ph-102	Diluent
4	Lactose Monohydrate	Diluents
5	Starch 1500	Binder
6	Aerosil	Glidant
7	Magnesium Stearate	Lubricant
8	Methocel K4 M	Polymer

Table 4: Different Formulations of Nisoldipine Extended-release Tablets

S. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
1.	Nisoldipine	40	40	40	40	40	40	40	40
2.	DCL 11 (Lactose)	362	332	140					
3.	Avicel PH 102				302	240	362	382	332
4.	Methocel K4 MCR	60	90	100	120	182	60	40	90
5.	Starch 1500	120		80	120	120	120	120	
6.	Eudragit-S-100		120	28	6				120
7.	Sodium lauryl sulphate	6	6	4	6	6	6	6	6
8.	Aerosil-200	6	6	4	6	6	6	6	6
9.	Magnesium stearate	6	6	4	6	6	6	6	6
Total (mg)		600	600	400	600	600	600	600	600

delivery system. The drug should be released for a prolonged period to achieve zero-order release. Different batches are planned to blend with different controlled release polymers in different ratios, and also trails were carried out with different methods using controlled release polymers (Table 4).

2.5. Evaluation of Pre-compression Parameters

The micrometric properties of prepared powder blend were studied by determining various parameters like the bulk density, tapped density, angle of repose, Hausner's ratio, and Carr's index (compressibility index) according to the standard methods described by Parameshwara *et al.*, 2019. API was also analyzed for particle size distribution through a mechanical sieve shaker machine.[9,10,11]

2.6. Tablet Compression and Coating

The matrix tablets were prepared by direct compression method and roll compaction method and film-coated with opadry white.[10,11]

2.6.1. Preparation of Nisoldipine Extended Release Tablet by Direct Compression Method

The matrix tablets were prepared by direct compression method by using different excipients. In this method, accurately weighed all the ingredients were passed through #40 mesh and mixed well for 15 minutes. The lubricant was added and mixed well for 2 minutes, followed by compression using 10.32 mm punches with flat face beveled edge (FFBE) break-lined or plain punch. The batch 1 and 2 extended-release tablets were formulated by the direct compression method.

2.6.2. Preparation of Nisoldipine Extended Release Tablet by Roll Compaction Method

The matrix tablets were prepared by roll compaction method by using different excipients. This method accurately weighed all the ingredients except extra granular and was passed through #30 sieve and blended for 10 minutes. The blend was subjected to roll compaction at 5 rpm as roller speed and 1.5 tonn pressure. The obtained flakes were passed through the #30 mesh, collect #60 mesh retains and compact the #60 passed blend until the granules not less than 80% of the blend is obtained. Finally, the blend was compressed using 10.32 mm round punches. The batches from 3 to 10 extended-release tablets were formulated by the roll compaction method.

Table 5: Coating of Prepared Nisoldipine Tablet

Ingredients	Quantity (mg)
Opadry White Y 1-7000	30
Purified Water	q.s.

2.6.3. Coating of Tablets

The compressed tablets were film coated with opadry white by using a conventional pan coating machine. The coating solution was prepared by mixing accurately weighed quantities of purified water and opadry white y-1-7000. The solution was stirred continuously until a clear dispersion was produced. Then accurately weighed quantity of tablets were taken and coated until 5% w/w was obtained. The pan's rotation was 25 rpm, rate of spray was 2 rpm, and the inlet temperature was maintained at 55°C (Table 5).

2.7. Evaluation of Post-Compression Parameters

The post-compression parameters of prepared tablets were studied by determining various factors like the average weight, hardness, thickness and friability according to the standard methods described by Parameshwara *et al.*, 2019.[9] The results are reported in Table 9.

2.8. *In Vitro* Dissolution Studies

The prepared tablets formulations of nisoldipine with different ratio of excipients were studied for their dissolution property. The *in vitro* release behaviors of coated tablets were tested. Drug release from the matrix tablets was determined by using the USP apparatus 2-paddle method. The dissolution media of 0.1N HCl with 0.5% SLS was used (900 ml at 37 ± 0.5°C). To ensure that the

Table 6: Saturation Solubility Profile of Nisoldipine API

S. No	Dissolution Media	Quantity (mg/mL)
1	0.1N HCL with 0.5% SLS at 25°C	0.091
2	0.1N HCL with 0.5% SLS - 37°C	0.115
3	Purified water with 0.5% SLS - 25°C	0.069
4	Purified water with 0.5% SLS - 37°C	0.079
5	pH 6.8 Phosphate buffer with 0.5% Tween 80 - 25°C	0.074
6	pH 6.8 Phosphate buffer with 0.5% Tween 80 - 37°C	0.082

Table 7: Drug Excipients Compatibility Studies of Nisoldipine API

S. No	Drug + Excipients	Ratio of Drug and Excipient	Parameter	Initial Value	Condition
					40°C + 75% RH (4Weeks)
1	Nisoldipine	1	Moisture content	0.37	0.55
			Impurities	0.672	0.633
			Assay	100	95.2
			Physical Observation	Dark yellow	No change
2	Nisoldipine + Tartaric Acid	1:1	Moisture content	0.19	0.11
			Impurities	0.608	0.733
			Assay	100	95.1
			Physical Observation	Yellow	No change
3	Nisoldipine + Methocel K4 MCR	1:1	Moisture content	1.18	0.58
			Impurities	0.222	0
			Assay	98.6	89.6
			Physical Observation	Yellow	No change
4	Nisoldipine + Carbopol 971 P	1:5	Moisture content	6.46	6.39
			Impurities	0.349	0.417
			Assay	97.7	92.7
			Physical Observation	Yellow	No change
5	Nisoldipine + Polyethylene Glycol	1:1	Moisture content	0.37	0.36
			Impurities	0.698	0.706
			Assay	101.1	100.5
			Physical Observation	Yellow	No change
6	Nisoldipine + Sodium Lauryl Sulphate (SLS)	1:1	Moisture content	0.52	0.29
			Impurities	0.579	0.644
			Assay	94.6	94
			Physical Observation	Yellow	No change
7	Nisoldipine + Hydroxy Ethyl Cellulose	1:5	Moisture content	5.21	6.49
			Impurities	0.16	0.375
			Assay	97.3	88.9
			Physical Observation	Yellow	No change
8	Nisoldipine + DCL 11	1:5	Moisture content	4.48	2.21
			Impurities	0.167	0
			Assay	101.1	100.5
			Physical Observation	Yellow	No change
9	Nisoldipine + Lactose Monohydrate	1:10	Moisture content	4.9	4.7
			Impurities	0.625	0.67
			Assay	100	95.9
			Physical Observation	Yellow	No change
10	Nisoldipine + Magnesium Stearate	1:5	Moisture content	1.89	1.71
			Impurities	0.635	0.694
			Assay	104.6	101.9
			Physical Observation	Off-white to yellow	No change

pharmaceutical system effectively controlled the release of the drug, the formulations tested in this study were submitted to *in vitro* release tests that would be able to confirm that the low release rate was dependent on the characteristics of any of the dosage form and not the dissolution assay. Dissolution was studied at a rotation speed of 50 rpm per min. The dissolution of the drug was monitored for 12 to 24 hours.

2.9. Accelerated Stability Studies

The lab-scale batch (Batch No: 8) was selected for stability studies. Based on the finalized batch and manufacturing process, formulations were packed in HDPE bottles and loaded in stability chamber for accelerated stability studies at 40°C/75% RH. The required quantity of tablets in 40°C /75% RH were analyzed at the end of first, second, and third month for their physical appearance, assay, water content, and dissolution.[9,10,11]

3. RESULTS

3.1. Saturation Solubility Profile of Nisoldipine API

According to the results obtained, it has been confirmed that nisoldipine has maximum solubility in 0.1 N HCl with 0.5% SLS at 37°C. Hence, there will be no discrimination possible for dissolution in this media. Nisoldipine shows minimum solubility in purified water with 0.5% SLS at 25°C. Hence, there will be discrimination possible for dissolution in this medium in controlled release formulations (Table 6).

3.2. Drug Excipients Compatibility Studies

According to the results of drug excipient compatibility study, the selected excipients have shown related substances within the limit, and physical observation of the samples did not show any abnormal changes. Thus, it can be concluded that the excipients selected for formulation were compatible with API (Table 7).

3.3. Evaluation of the Nisoldipine API

The angle of repose was found to be 39.23º, which shows possible to flow. The bulk density and tapped density were also low, which needs to be improved. The compressibility index was found to be poor. So, nisoldipine

Table 8: Characteristics of Nisoldipine API Powder

S. No	Parameters	Results
1.	Angle of Repose	39.23°
2.	Bulk Density	0.5650 g/cc
3.	Tap Density	0.6978 g/cc
4.	Compressibility Index	25.90 %
5.	Hausner's Ratio	1.34

Table 9: Pre-Compression and Post-compression Evaluation of the Nisoldipine powder Blend and Extended-release Tablets

Evaluation Parameters	*Formulation Batches*								
	Direct Compression Method		Roll Compaction Method						
Pre-Compression	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7	Trial 8	
	Angle of Repose	38.21°	38.19°	38.19°	38.25°	38.23°	38.21°	38.20°	38.20°
	Bulk Density (g/mL)	0.5289	0.4683	0.595	0.5952	0.503	0.590	0.598	0.560
	Tapped Density (g/mL)	0.6284	0.5289	0.877	0.8064	0.509	0.702	0.673	0.672
	Compressibility Index (%)	18.81	29.68%	32.14	26.19	28.53	26.33	20.83	27.33
	Hausner's Ratio	1.18	1.35	1.47	1.35	1.41	1.31	1.26	1.43
	Average Weight (mg) ± SD	600 ± 10	600 ± 10	400 ± 10	600 ± 10	600 ± 10	600 ± 10	600 ± 10	600 ± 10
Post-Compression	Hardness (kp)	12 – 14	14.5 – 15.5	9 – 10	13.5 – 14.5	7 – 12	7 – 12	10 – 12	7 – 13
	Thickness (mm) ± SD	5.76 ± 0.5	6.12 ± 0.5	4.54 ± 0.2	6.75 ± 0.1	5.68 ± 0.2	6.28 ± 0.5	5.88 ± 0.5	6.70 ± 0.2
	Friability (% w/w)	0.112	0.125	0.152	0.110	0.233	0.152	0.183	0.175

pre-formulation characteristics like bulk density, tapped density, compressibility index and Hausner ratio should be improved to get a better formulation (Table 8).

3.4. Pre-Compression and Post-Compression Evaluation of the Nisoldipine Powder Blend and Extended-release Tablets

The pre-compression parameters of the nisoldipine powder blend and post-compression parameters of the nisoldipine tablets were evaluated. During the preparation of extended-release tablets, the blend's compressibility was not satisfactory, and the compressed tablets had shown capping tendency irrespective of the tablet hardness. Some of the tablets had failed in friability; as per USP. Dissolution profiles were not matching with marketed product. Therefore, the direct compression method was not suitable for the preparation of the tablets. Hence, roll compaction method was adopted from batch 3 to 8 selectively for the preparation of the tablet. The tablets were good and have not created troubles during compression. The finished dosage form is a yellow to pale yellow circular tablet. So, further trials were carried out by roll compaction method (Table 9).

Based on the above results, it has been inferred that around 40% of API having 250 µ sizes retained in #60 mesh. Similarly 7.94%, 7.44% and 19.85% of API having size of 400µ, 177µ and 74µ were retained in #40, #80, and #200 meshes respectively (Table 10).

3.5. *In Vitro* Dissolution Studies

From the results of the *in vitro* drug release of compressed nisoldipine tablets, the maximum release of drug was found to be 101.4 % within 24 hours of batch 5, whereas batch 7 released the drug 82.8% in 24 hours (Figure. 1 and Table 11).

3.6. Accelerated Stability Studies

Accelerated stability studies of prepared nisoldipine tablets is shown is Table 12.

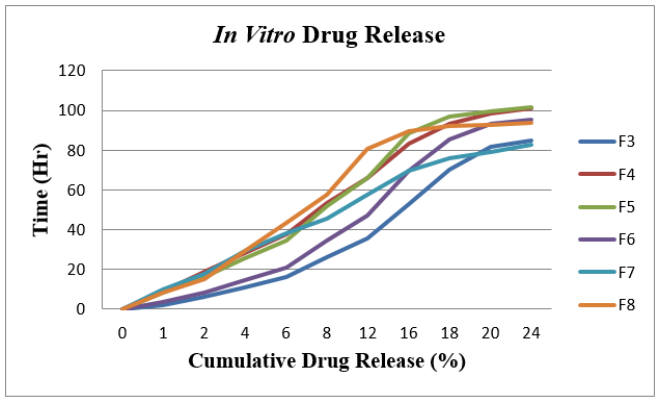

Fig. 1: *In Vitro* Dissolution Studies of Prepared Nisoldipine Tablets

Table 10: Particle Size Distribution of the Nisoldipine Powder Blend

Sieve No. (microns)	*Initial Wt. (g)*	*Final Wt. (g)*	*Sample Retained (g)*	*% Retained*	*Cumm. % Retained*
#20 (841µ)	398.90	399.00	0.1	0.50	0.50
#30 (595µ)	404.60	404.60	0.0	0.00	0.50
#40 (400µ)	307.30	318.90	1.6	7.94	8.44
#60 (250µ)	355.30	363.20	7.9	39.21	47.64
#80 (177µ)	361.20	362.70	1.5	7.44	55.09
#100 (149µ)	306.50	307.60	1.1	5.46	60.55
#200 (74µ)	352.00	356.00	4.0	19.85	80.40
Fines	415.90	419.80	3.9	19.35	99.75
Total			20.1	99.75	

Table 11: *In Vitro* Dissolution Studies of Prepared Nisoldipine Tablets

	Cumulative Drug Release (%)					
Time (Hr)	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*
0	0	0	0	0	0	0
1	2.3	9	8.1	3.6	10.1	8.4
2	6.4	18.7	16.4	8.4	17.6	15.1
4	11.2	28.3	25.5	14.6	29.4	29.2
6	16.1	37.8	34.5	21.1	38.2	43.6
8	25.9	53.4	51.6	34.4	45.5	57.6
12	35.5	66	66.1	47.2	57.4	80.8
16	53.1	83	88.4	69.7	69.7	89.5
18	70	93	97.1	85.4	75.7	92.3
20	81.7	98.3	99.7	93	78.9	92.7
24	84.8	101.3	101.4	95.4	82.8	93.9

Table 12: Accelerated Stability Studies of Prepared Nisoldipine Tablets

S. No.	Formulation 8	1st Month	2nd Month	3rd Month
1	Physical Appearance	Yellow to pale yellow circular tablet	Yellow to pale yellow circular tablet	Yellow to pale yellow circular tablet
2	Friability(% w/w)	0.175	0.174	0.175
3	Dissolution at 24 Hr (%)	93.8	93.8	93.5

4. DISCUSSION

The maintenance of drug content at the site of action is the primary concern with any formulation design. Controlled release tablet formulations are preferred over conventional drugs because they produce patient compliance, maintain steady state drug levels, dose reduction and increase the margin of safety for high-potency drugs.[2,5] The objective of a sustained release dosage form is to maintain plasma or tissue drug levels for a prolonged period.

Nisoldipine is a calcium channel blockers reversibly bind to the calcium channel, indicated for the treatment of hypertension. It is practically insoluble in water with an absolute bioavailability of 5%. The very poor aqueous solubility of nisoldipine causes difficulties in the design of pharmaceutical formulations, for which there is a need to improve rate of drug release. Hence, the study was carried out to design, formulate, and evaluate the sustained-release tablet formulation of nisoldipine.[7,8]

The micrometric properties of the prepared powder blend were studied by determining various parameters like the bulk density, tapped density, angle of repose, Hausner's ratio, and Carr's index (compressibility index). API was also analyzed for particle size distribution by means of a mechanical sieve shaker machine. Solubility studies were performed for nisoldipine API conducted at 37 ± 0.5 ^{0}C and 25 ± 0.2 °C. The results showed that nisoldipine has a maximum solubility in 0.1 N HCl with 0.5% SLS at 37°C.

The excipients' compatibility studies showed that the selected excipients have no significant interaction with the drug and physical observation of the samples did not show any atypical changes. Hence, it was concluded that the drug in powder mixture is free from any reactive product.

The micrometric properties of the prepared powder blend were studied by determining various parameters like the bulk density, tapped density, angle of repose, Hausner's ratio, Carr's index (compressibility index), and particle size distribution. The prepared nisoldipine powder blend's bulk density was in between 0.595-0.560 gm/mL, whereas the tapped density was in the range of 0.877-0.672 gm/mL. The compressibility values range from 32.14-27.33 %. The Hausner's ratio values of the formulations were found to be in between 400 - 600. It has been inferred from particle size distribution studies that 40% of API having 250 µ sizes retained in #60 mesh whereas 7.94%, 7.44%, and 19.85% of API having size of 400µ, 177µ and 74µ were retained in #40, #80, and #200 meshes respectively. From these observations, it can be concluded that the prepared powder blends had virtuous flow properties and can be subjected for direct compression. The matrix tablets were finally prepared by roll compaction method and film-coated with opadry white.

The post-compression parameters of prepared tablets were studied by determining various factors like the average weight, hardness, thickness, and friability. All the formulations prepared had hardness within the desired range of 9.0-14.5. Friability was found to be within limits of <1% and thickness was also in the accepted range. The weight variation results of the prepared tablets indicated that all the tablets are within the range. The drug release results from prepared compressed nisoldipine extended-release tablets showed a maximum release of drug content within 24 hours. The drug release rate was increased; from the formulation batch numbers 6, 7, 8, and the drug release of formulation batch 8 have showed a better rate of release compared to other formulations.

5. CONCLUSION

Nisoldipine is a strong anti-hypertensive drug with very poor aqueous solubility. Thus, there is a need to improve the rate of drug release and develop the controlled formulation. In the present research work, nisoldipine was effectively formulated as extended-release tablets using suitable polymers by roll compaction method. Batch 8 formulation was found with improved release rates compared to other nisoldipine formulations and stable after the stability studies. Therefore, it can be established that prepared nisoldipine formulation may be considered as an appropriate formulation to achieve the desired therapeutic concentration.

6. FUTURE PERSPECTIVE

To compare *in vivo* profile of nisoldipine extended-release tablets with that of the innovator.

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