IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
May 2023 Vol.:27, Issue:2

Drug Release Profile of Antihypertensive Drug Based on Granulation

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Mohammed Hussain M*[1], Sangamesh Puranik[2]

[1]*Research Scholar Sunrise University, Alwar, Rajasthan, India*

[2]*Research Guide Sunrise University, Alwar, Rajasthan, India*

Submitted: 20 April 2023
Accepted: 26 April 2023
Published: 30 May 2023

Keywords: Hakea Gum, Psyllium Husk, Carbomer 940, Nicorandil,

ABSTRACT

This project aimed to develop sustained delivery buccal matrix tablet for Nicorandil by using natural polymers and semi-synthetic polymers like polycarbophils and carbomers. The controlled-release gastroretentive drug delivery systems which give prolonged & continuous input of the drug to the upper parts of the gastrointestinal tract (G.I.T) and improve the bioavailability of medications that are characterized by narrow therapeutic window. Also objective of the work was to evaluate the impact of granulation on the release profile of the tablets by wet granulation and direct compression. During the study, it was also evaluated impact of incorporating water-insoluble polymer along with the rate-controlling polymers on the dissolution rate profile. The granules and tablets were evaluated for flow properties, thickness, hardness, friability, drug content and invitro dissolution parameters. The in vitro release data and drug release mechanism of the optimized formulation followed the Higuchi kinetics and nonfickain type respectively. It can be concluded that the wet granulation is found suitable for the sustained delivery of Nicorandil over the direct compression method. Psyllium husk, Hakea gum can be promising polymers for gastroretentive floating drug delivery systems when designed with a hydrophobic polymer.

INTRODUCTION

The development of gastrointestinal bioadhesive drug delivery systems gastrointestinal retention of dosage forms through adhesion to the mucosa has been studied for over a decade now, mainly in vitro or ex vivo with few in situ or in vivo studies and even fewer trials in man. The oral route is the most preferred route of administration of drugs because of low cost of therapy, ease of administration, patient compliance and flexibility in formulation, etc. It is evident from the recent scientific and patent literatures that an increased interest in novel oral controlled release dosage forms that designed to be retained in the gastrointestinal tract (GIT) for a prolonged and predictable period exists today[1].

Nicorandil is highly hydrophilic and having a short elimination half-life.

It has various side effects such as headache, dizziness and one of the major side effects is ulceration. Although Nicorandil is one of the emerging molecules in the case of hypertension and angina, successful treatment means maintenance of blood pressure at a normal physiological level, for which a constant and uniform supply of drug is desired.[2,3] Nicorandil has a short half-life, and the usual oral dosage regimen is 5 to 40 mg taken 2 to 4 times a day. To reduce the frequency of administration and to improve patient compliance, a once-daily sustained-release formulation of Nicorandil is desirable. The drug is freely soluble in water, and hence the judicious selection of release-retarding excipients is necessary to achieve a constant in vivo input rate of the drug.

EXPERIMENTAL

CHEMICALS AND REAGENTS

Nicorandil was procured from Taj Pharma Limited, Mumbai, the polymers were was received as gift sample from different companies like Atlas Ind. Sidhpur for psyllium Husk, hakea gum from Green Earth Products Pvt. Ltd., New Delhi., All the other chemicals used were of standard grade.

Calculation of Theoretical Release Profile of Nicorandil from Sustained-Release Formulations

The total dose of Nicorandil for a once-daily sustained-release formulation was calculated by the following equa-tion[4]using available pharmacokinetic data.[5,6]

$$Dt = Dose\ (1 + 0.693 \times t/t1/2)$$

where, Dt = total dose of drug;

Dose = dose of the immediate release part (5.92 mg);

t = time (hours) during which the sustained release is desired (24 hours);

t1/2 = half-life of the drug (1.33 hours).

$$Dt = 5.92\ (1+ (0.693 \times 24)/1.33) \cong 80.0 \text{ mg}$$

Hence, the formulation should release 5.92 mg in 1 hour like conventional tablets, and 3.21 mg per hour up to 24 hours thereafter.

PREPARATION OF TABLETS BY WET GRANULATION:

All the powders were passed through # 30 mesh. Required quantities of drug, filler and polymer were mixed thoroughly, and a required quantity of binder was added slowly. After enough cohesiveness is obtained, the mass was sieved through # 22/44 mesh. The granules was dried at 40°C ± 3°C for about 8 - 10 h and thereafter. Once the granules are found dry, the granules retained on 44 mesh was mixed with 15% of fines (granules that passed through 44 mesh). Stearic Acid was added as lubricant and mixed for about 5 – 10 minutes. Granules thus obtained were compressed into tablets on a 10-station single-punch rotary tablet compression machine (Rimek). A flat-faced punch 11 mm in diameter was used for tableting. Compression force of the machine was adjusted to obtain the hardness of 5-7 kg/cm^2 for the prepared batches. The composition is presented in Table 1.

FORMULATIONS B

Nicorandil matrix tablets were prepared by direct compression technique. Drug was passed through 30#sieve. All other ingredients [except for stearic acid] were passed through 40# sieve. All ingredients were mixed for 15-20 min. After mixing, Stearic Acid (60# sieve), was added to mixer blend and mix again for 3-5 min. Prepared blend was compressed into tablets on a 10-station single-punch rotary tablet compression machine (Rimek). A flat-faced punch 11 mm in diameter was used for tableting. The compression force of the machine was adjusted to obtain the hardness of 3-5 kg/cm^2 for the prepared batches. The composition is presented in table 2.

Physical evaluation:

Evaluation of Granules

Angle of Repose

The angle of repose of granules will be determined by the fun-nel method. The accurately weighed granules will be taken in a funnel. The height of the funnel will be adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules will be allowed to flow through the funnel freely onto the surface. The diameter of the powder cone will be measured and angle of repose was calculated using the following equation[7]:

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

Where h and r are the height and radius of the powder cone.

Bulk Density

Both loose bulk density (LBD) and tapped bulk density (TBD) will be determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any ag- glomerates formed, will be introduced into a 10-mL measuring cylinder. After the initial volume is observed, the cylinder will be allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The tapping will be continued until no further change in volume is noted. LBD and TBD were calculated using the following formula[7]:

$$\text{LBD} = \text{weight of the powder/volume of the packing}$$

$$\text{TBD} = \text{weight of the powder/tapped volume of the packing}$$

Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index[8]:

$$\text{Carr's index (\%)} = [(\text{TBD} - \text{LBD}) \times 100]/\text{TBD}$$

Total Porosity

Total porosity was determined by measuring the volume occupied by a selected weight of a powder (V_{bulk}) and the true volume of granules (the space occupied by the powder exclusive of spaces greater than the intermolecular space, V)[9]:

$$\text{Porosity (\%)} = V_{bulk} - V/V_{bulk} \times 100$$

Drug Content

An accurately weighed amount of powdered nicorandil granules (100 mg) was extracted with water and the solution was filtered through 0.45-µ membrane (Nunc, New Delhi, India). The absorbance was measured at 262 nm after suit- able dilution.

FORMULATION STUDY:

Evaluation of Tablets

Thickness:

The thickness of the tablets will be determined using a thick- ness gauge (Mitutoyo, New Delhi, India). Five tablets from each batch will be used, and average values will be calculated.

Weight Variation Test

To study weight variation, 20 tablets of each formulation will be weighed using an electronic balance (Denver APX-100, Arvada, Colorado), and the test will be performed accord ing to the official method[10].

Drug Content

Five tablets were weighed individually, and the drug will be extracted in water. The drug content will be determined as de- scribed above.

Hardness and Friability

For each formulation, the hardness and friability of 6 tablets will be determined using the Monsanto hardness tester (Cad- mach, Ahmedabad, India) and the Roche friabilator (Camp- bell Electronics, Mumbai, India), respectively.

In Vitro Dissolution Release Studies[11]

The in vitro dissolution studies were carried out using USP apparatus type II (Tab-Machines, Mumbai, India) at 75 rpm. The dissolution medium consisted of 0.1N hydrochloric acid for the first 2 hours and the phosphate buffer pH 7.4 from 3 to 24 hours (900 mL), maintained at 37°C ± 0.5°C. The drug release at different time intervals was measured by diode array UV-visible spectrophotometer (Hewlett-Packard, Agilent Technologies, New Delhi, India) at 262 nm using Chemstation software (Agilent Technologies, New Delhi, India). It is ensured that that none of the ingredients used in the matrix formulations interfered with the assay. The re- lease studies will be conducted in triplicate (6 tablets in each set), and the mean values will be plotted versus time with SDs of less than 3, indicating the reproducibility of the results.

RESULTS AND DISCUSSION

The granules made of wet formulations were evaluated for angle of repose, bulk and tapped density, compressibility index, total porosity, and drug content (Refer Table 3). The results of angle of repose and compressibility index (%) ranged from 21.56 to 26.15 and 11.85 to 14.85 respectively. The results of bulk and tapped densities are ranged from 0.452 to 0.526 and 0.548 to 0.678 respectively. The results of percentage porosity of the granules ranged from 26.58 to 31.85. The drug content in a weighed amount of granules of all formulations ranged from 97.56 to 100.56%.

The blend meant for direct compression were evaluated for angle of repose, bulk and tapped density, compressibility index, total porosity, and drug content (Refer Table 4). The results of angle of repose and compressibility index (%) ranged from 22.82 to 26.15 and 14.63 to 16.58 respectively. The results of bulk and tapped densities are ranged from 0.359 to 0.394 and 0.461 to 0.501 respectively. The results of percentage-porosity of the granules ranged from 31.62 to 34.65. The drug content in a weighed amount of granules of all formulations ranged from 97.45to 99.81%.

The bulk density of granules prepared by using only ethanol as the granulating agent was found to be much higher than that of other granules.

The appearance of buccal tablets was smooth and uniform on physical examination of both granulation technologies.

The thickness of the tablets made from wet granulation was ranged from 4.16 ± 0.03 to 4.42 ± 0.01 mm. The average percentage deviation of 20 tablets of each formula was less than ±5%. Drug content was found to be uniform among different batches of the tablets and ranged from 96.89 to 99.56. The hardness and percentage friability of the tablets of all batches ranged from 4.0 ± 0.14 to 4.8 ± 0.24 kg/cm^{2}and 0.68 ± 0.12 to 0.88 ± 0.05%, respectively (Table 5).

The thickness of the tablets made from direct compression was ranged from 4.78 ± 0.04 to 4.92 ± 0.03 mm. The average percentage deviation of 20 tablets of each formula was less than ±5%. Drug content was found to be uniform among different batches of the tablets and ranged from 97.23 to 99.41. The hardness and percentage friability of the tablets of all batches ranged from 4.0 ± 0.14 to 4.1 ± 0.23 kg/cm^2 and 0.82 ± 0.05 to 0.91 ± 0.03%, respectively (Table 6).

The low values of standard deviation and coefficient of variation (< 2) in the drug content indicate the uniform distribution of the drug within the prepared buccal tablets.

The dissolution profile studies of formulations from NWTF1 to NWTF8 are shown in Table 7 and Fig 1. Formulation NWTF6, NWTF4 and NWTF2 released about 30%60%, and 90% of nicorandil at the end of 0 to 5 hours, 6 to 12 hours and 13 to 18 hours respectively. At the end of 24 hours, all three formulations showed about 98% of drug release.

The dissolution profile of formulation NWTF8 was also comparable to the above three formulation codes. However, the initial release profile of formulation code of NWTF8 was faster when compared to the above three formulation codes. Graphical representation of dissolution behavior is presented in figure 1.

The dissolution profile of other formulation codes like NWTF5, NWTF1, NWTF7 and NWTF3 were also satisfactory however, the release at the initial levels were high and about 9% and above was already released between 13 to 18 hours time interval.

The dissolution profile studies of formulations from NDTF1 to NDTF4 are shown in Table 8 and Fig 2. To check the impact of granulation on the dissolution profile, the tablets made by using direct compression were also tested for the profile using same conditions as that of tablets made using wet granulation [NWTF1 to NWTF8]. In the case of NDTF3, some control in the release was observed whereas the other formulation codes NDTF1, NDTF2 and NDTF4 release rate was faster. About 95% of the drug release was observed in these codes. A graphical representation of dissolution behavior is presented in figure 2.

CONCLUSION:

The bulk density of granules prepared by using only ethanol as the granulating agent was found to be much higher than that of other granules. The appearance of buccal tablets was smooth and uniform on physical examination of both granulation technologies. The hardness, thickness, weight variation, average weight of tablets of both the approach tablets was found satisfactory. However, the bulk density, tapped density, compressibility index, total porosity of granules using wet granulation was better when compared to the granule characteristics made using direct compression. Friability values of both tablets from wet granulation and direct compression less than 1% indicate good mechanical strength to withstand the rigors of handling and transportation. The dissolution profile of tablets made from wet granulation was able to control better when compared to the dissolution profile of direct compression. The

incorporation of cellulose acetate phthalate, a hydrophobic polymer via granulation was successful in controlling the drug release according to the requirement. The high dissolution rate observed with direct compression tablets [NDTF1 to NDTF4] could be due to its low swellability, However, processing factors including wetting on granulation, particle size, and hardness also affect the re-lease rate of drug from tablets. The NWTF6, 4 and 2 of wet granulation formulations can be considered successful since they showed little deviation from the theoretical release pattern throughout the dissolution profile study. Incorporation of a different concentration of hydrophobic polymer has better control on the drug release in a better manner, which could be attributed to the decreased penetration of the solvent molecules in the presence of hydrophobic polymer, leading to decreased diffusion of the drug from the matrix.

From the above study, it is evident that a matrix tablet prepared by a wet granulation with a hydrophobic polymer is a better system for once-daily sustained release for a drug candidate drug like Nicorandil.

TABLES

Table 1: Composition of Matrix Tablets of Nicorandil by Wet Granulation

Sl. No.	**Ingredients**	**Formulation Codes**							
	Quantity in mg/tablets	**NWTF1**	**NWTF2**	**NWTF3**	**NWTF4**	**NWTF5**	**NWTF6**	**NWTF7**	**NWTF8**
1	Nicorandil	80	80	80	80	80	80	80	80
2	Corn starch	40	40	40	40	40	40	40	40
3	Mannitol	50	50	50	50	50	50	50	50
4	Hakea Gum	160	240	-	-	-		-	-
5	Polycarbophil [Noveon AA1]	-		160	240	-		-	-
6	Carbomer 940P	-		-		160	240	-	-
7	Psyllium Husk	-		-		-		160	240
8	Cellulose Acetate Phthalate in Acetone solution	8% Wt/Vol							
9	Stearic Acid	5	5	5	5	5	5	5	5
10	Polyvinylpyrolidone K90	10% Wt/Vol							

Note:* Acetone added to dissolve CAP during the granulation will be removed during drying of granules.

Table 2: Composition of Matrix Tablets of Nicorandil by DIRECT COMPRESSION

Sl. No.	Ingredients	Formulation Codes			
	Quantity in mg/tablets	NDTF1	NDTF2	NDTF3	NDTF4
1	Nicorandil	80	80	80	80
2	Corn starch	40	40	40	40
3	Mannitol	50	50	50	50
4	Hakea Gum	240	-	-	-
5	Polycarbophil [Noveon AA1]	-	240	-	-
6	Carbomer 940P	-	-	240	-
7	Psyllium Husk	-	-	-	240
8	Cellulose Acetate Phthalate	16	16	16	16
9	Stearic Acid	5	5	5	5

Table 3: Powder evaluation*Physical and chemical evaluation of wet granulation

Sl. No.	Formulation Code	Angle of Repose	Bulk Density [g/mL]	Tapped Density [g/mL]	Total Porosity [%]	Comp. Index [%]	Drug Content [%]
1	NWTF1	26.15	0.498	0.598	31.85	14.85	98.75
2	NWTF2	23.33	0.512	0.678	30.85	13.85	97.85
3	NWTF3	25.82	0.475	0.568	29.87	13.85	99.36
4	NWTF4	22.82	0.499	0.624	28.45	13.01	98.56
5	NWTF5	23.82	0.526	0.698	27.45	12.85	100.56
6	NWTF6	21.56	0.501	0.621	26.58	11.85	98.58
7	NWTF7	24.58	0.498	0.586	28.98	13.98	97.56
8	NWTF8	22.65	0.452	0.548	28.45	12.98	98.63

Note: *All results are average of n = 3 observations

Table 4: Powder evaluation* Physical and chemical evaluation of Direct Compression:

Sl. No.	Formulation Code	Angle of Repose	Bulk Density [g/mL]	Tapped Density [g/mL]	Total Porosity [%]	Comp. Index [%]	Drug Content [%]
1	NDTF1	26.15	0.368	0.461	34.65	16.58	97.52
2	NDTF2	23.33	0.394	0.501	33.53	15.46	99.81
3	NDTF3	25.82	0.372	0.489	32.41	14.63	98.30
4	NDTF4	22.82	0.359	0.484	31.62	15.23	97.45

Note: *All results are average of n = 3 observations

Table 5: Tablets Evaluation [Wet Granulation]:

Sl. No.	Formulation Code	Thickness* (mm)	Friability‡ (%)	Hardness‡ (kg/cm2)	Drug Content* (%)	Average Weight of Tablets [mg]
1	NWTF1	4.42 ± 0.01	0.75 ± 0.02	4.5 ± 0.20	98.65	372.8 ± 0.80
2	NWTF2	4.31 ± 0.06	0.88 ± 0.05	4.0 ± 0.14	97.56	449.2 ± 1.40
3	NWTF3	4.25 ± 0.02	0.85 ± 0.06	4.0 ± 0.23	96.58	374.2 ± 0.90
4	NWTF4	4.28 ± 0.03	0.76 ± 0.03	4.5 ± 0.25	99.56	454.2 ± 1.20
5	NWTF5	4.22 ± 0.04	0.72 ± 0.05	4.6 ± 0.16	98.23	371.6 ± 0.90
6	NWTF6	4.19 ± 0.03	0.73 ± 0.04	4.6 ± 0.16	97.56	450.8 ± 1.10
7	NWTF7	4.23 ± 0.05	0.68 ± 0.12	4.8 ± 0.24	96.89	373.6 ± 1.30
8	NWTF8	4.16 ± 0.03	0.75 ± 0.06	4.5 ± 0.19	97.86	451.2 ± 0.92

* All values are expressed as mean ± SE, n = 5.

† All values are expressed as mean ± SE, n = 20.

‡ All values are expressed as mean ± SE, n = 6.

Table 6: Tablets Evaluation [Direct Compression]:

Sl. No.	Formulation Code	Thickness* (mm)	Friability‡ (%)	Hardness‡ (kg/cm2)	Drug Content* (%)	Average Weight of Tablets [mg]
1	NDTF1	4.89 ± 0.02	0.89 ± 0.02	4.1 ± 0.20	98.65	429.8 ± 0.70
2	NDTF2	4.92 ± 0.03	0.82 ± 0.05	4.0 ± 0.14	99.41	435.2 ± 1.10
3	NDTF3	4.78 ± 0.04	0.85 ± 0.06	4.1 ± 0.23	97.23	428.7 ± 1.10
4	NDTF4	4.89 ± 0.03	0.91 ± 0.03	4.0 ± 0.25	98.52	430.2 ± 0.90

***** All values are expressed as mean ± SE, n = 5.

† All values are expressed as mean ± SE, n = 20.

‡ All values are expressed as mean ± SE, n = 6.

Dissolution Profile

Table7: The in vitro release profiles of Nicorandil of Wet Granulation Formulation

Sl. No.	Formulation Code	% Drug Release Observed			
		0 to 5 Hrs	6 to 12 Hrs	13 to 18 Hrs	19 to 24 Hrs
1	NWTF1	0 to 40	41 to 66	69 to 96	--
2	NWTF2	0 to 30	31 to 60	61 to 90	91 to 98
3	NWTF3	0 to 42	43 to 68	66 to 98	--
4	NWTF4	0 to 29	30 to 59	60 to 88	89 to 97
5	NWTF5	0 to 37	38 to 62	63 to 93	94 to 99
6	NWTF6	0 to 26	27 to 58	59 to 89	90 to 98
7	NWTF7	0 to 42	43 to 71	71 to 97	--
8	NWTF8	0 to 33	34 to 63	64 to 91	92 to 98

Dissolution profile

Table 8: The in vitro release profiles of Nicorandil of Direct Compression Formulation

Sl. No.	Formulation Code	0 to 5 Hrs	6 to 12 Hrs	13 to 18 Hrs	19 to 24 Hrs
1	NDTF1	0 to 46	49 to 88	89 to 98	--
2	NDTF2	0 to 48	47 to 91	92 to 97	--
3	NDTF3	0 to 41	42 to 83	84 to 99	--
4	NDTF4	0 to 50	51 to 89	90 to 94	

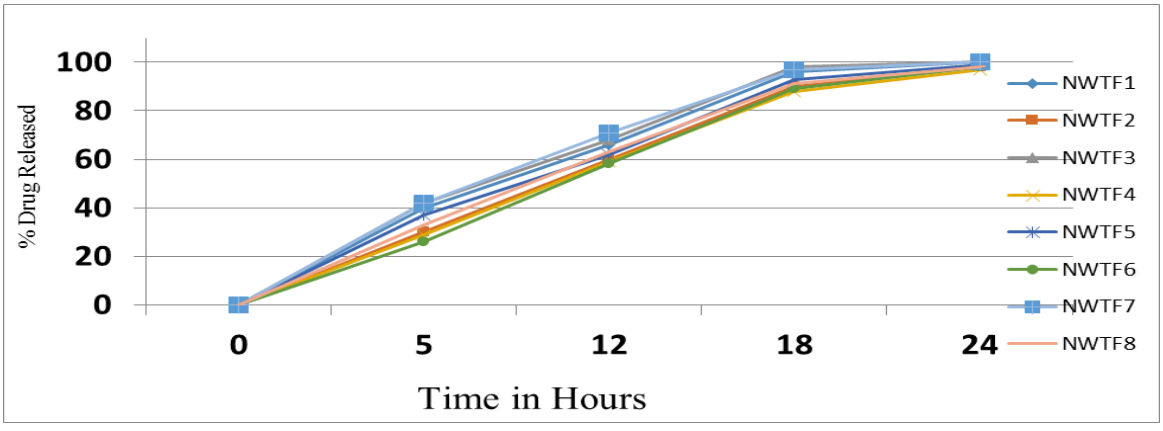

Figure 1: Graphical representation of invitro drug dissolution behavior of buccal tablets of wet granulation

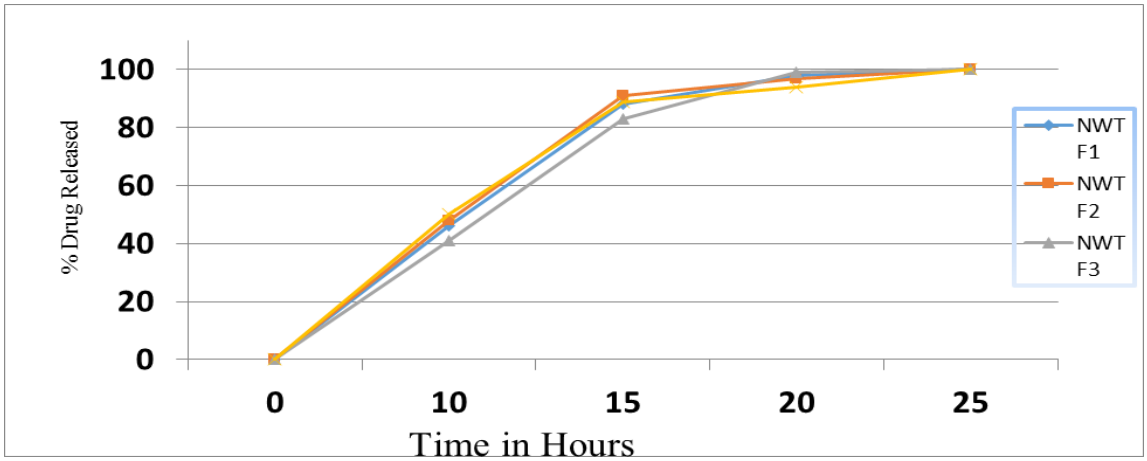

Figure 2: Graphical representation of invitro drug dissolution behavior of buccal tablets of direct compression

REFERENCES

1 Garg, R. and Gupta G.D., Progress in controlled gastroretentive delivery systems. Trop J Pharm Res., 7(3): 1055- 1066. 2008.

2. Leonetti G, Fruscio M, Gradnik R, Chianca R, Bolla GB, Prandi P, Zanchetti A. Nicorandil, a new vasodilator drug, in patients with essential hypertension. J Hypertens. 1989;7:S292-S293.

3. Camm AJ, Maltz MB. A controlled single-dose study of the efficacy, dose response and duration of action of nicorandil in angina pectoris. Am J Cardiol. 1989;20(63):61J-65J.

4. Rawlins EA. Bentley's Text Book of Pharmaceutics. London, England:Cassell and Collier MacMillan; 1977.

5.AnderssonKE.Clinicalpharmacologyofpotassiumchannelopeners. PharmacolToxicol.1992;70:244-254.

6.FramptonN.Reviewofnicorandilandpharmacologyandtherapeutic efficacyinangina.Drugs.1992;44:625-655.

7. Cooper J, Gunn C. Powder flow and compaction. In: Carter SJ, eds. Tutorial Pharmacy. New Delhi, India: CBS Publishers and Distributors; 1986:211-233.

8.AultonME,WellsTI.Pharmaceutics:TheScienceofDosageForm Design.London,England:ChurchillLivingstone;1988.

9.MartinA.Micromeritics.In:MartinA,ed.PhysicalPharmacy.Balti- more,MD:LippincottWilliams&Wilkins;2001:423-454.

10.PharmacopoeiaofIndia.NewDelhi:MinistryofHealthandFamily Welfare, Government of India, Controller of Publications;1996.

11. K Raghuram Reddy, Srinivas Mutalik, and Srinivas Reddy: Once-Daily Sustained-Release Matrix Tablets of Nicorandil: Formulation and In Vitro Evaluation AAPSPharmSciTech 2003; 4 (4) Article 61 (http://www.aapspharmscitech.org).