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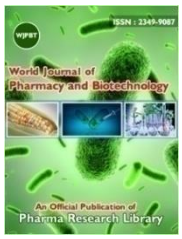

Formulation and *In-vitro* Evaluation of Nicorandi Tablet for Controlled Release Drug Delivery System

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A B S T R A C T
Nicorandil is a vasodilatory drug used to treat angina.Angina is chest pain that results from episodes of transient myocardial ischemia. This can be caused by diseases such as atherosclerosis, coronary artery disease and aortic stenosis. Angina commonly arises from vasospasm of the coronary arteries. There are multiple mechanisms causing the increased smooth muscle contraction involved in coronary vasospasm, including increased Rho-kinase activity.Aim of the present study was to develop controlled release formulation of Nicorandil to maintain constant therapeutic levels of the drug for over 12 hrs. Methocel K 15M, Gum karaya, Chitosan. Nicorandil dose was fixed as 10 mg. Total weight of the tablet was considered as 120 mg. Polymers were used in the concentration of 10mg, 20mg and 30 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F3) showed better and desired drug release pattern i.e., 98.07 % in 12 hours. It contains the natural polymer Nicorandil as controlled release material. It followed zero order release kinetics mechanism.
Keywords: Nicorandil, Chitosan, Methocel K 15M, karaya gum & Controlled release tablets.

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Nicorandil is vasodilator acting through an increase of both membrane potassium ion conductance and intracellular cGMP concentration in vascular smooth muscle. It is clinically used in the treatment of angina pectoris. Nicorandil is not metabolized significantly by the liver during passage through the portal system (lack of first-pass effect). Thus, it easily enters the systemic blood flow, resulting in almost complete bioavailability. After oral administration of a 5-, 10-, 20-, or 40- mg dose, there is a linear relationship between the doses and increases of maximum plasma concentrations and area under the curve, demonstrating that the pharmacokinetics of nicorandil are linear . Because of its short elimination half-life (1 hr), the drug has to be given frequently at 5 mg immediate-release (IR) tablet three times a day. To reduce the frequency of administration and to improve patient compliance, Controlled release formulation of nicorandil is desirable.

2. Materials and Methods

Materials: Nicorandil, Methocel K15M, Chitosan, Gum karaya, MCC pH 102, Magnesium stearate, Talc all the chemicals used were laboratory grade.

Method of Preparation:

Composition of preliminary trials for Nicorandil Controlled release Tablet by direct compression is shown in table 2. All the ingredients were weighed. Required quantity of drug and excipient mixed thoroughly in a polybag. The blend is compressed using rotary tablet machine-8 station with 6mm flat punch, B tooling. Each tablet contains 10 mg of Nicorandil and other pharmaceutical ingredients.

Evaluation of post compression parameters for prepared Tablets: The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

3. Results and Discussion

Analytical Method: Graphs of Nicorandil was taken in Simulated Gastric fluid (pH 1.2) and in p H 6.8 phosphate buffer at 298 nm and 296 nm respectively.

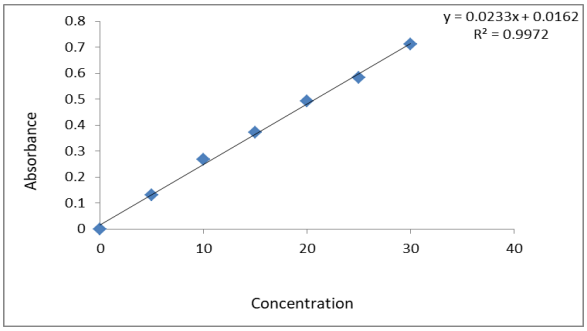

Fig 1: Standard graph of Nicorandil in 0.1N HCl

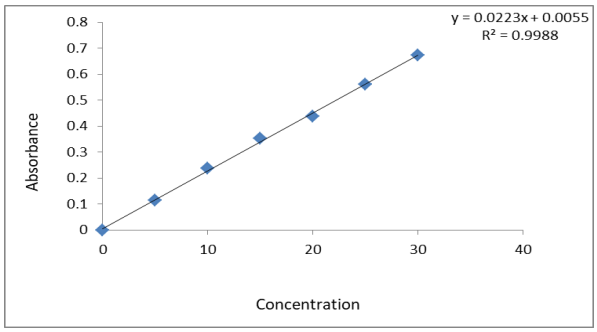

Fig 2: Standard graph of Nicorandil pH 6.8 phosphate buffer (232nm)

Pre formulation parameters of powder blend:

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.47 to 0.59 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.51 to 0.59 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which shows that the powder has good flow properties. All the formulations has shown the hausner's ratio ranging between 0.65 to 1.2 indicating the powder has good flow properties.

Quality Control Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the tablets. All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In-Vitro* Drug Release Studies:**

From the dissolution data it was evident that the formulations prepared with Chitosan and Karaya gum as polymer were unable to retard the drug release up to desired time period i.e., 12 hours.Whereas the formulations prepared with Methocel K15M retarded the drug release in the concentration of 30 mg (F3 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 98.07% in 12 hours with good retardation.From the dissolution data it was evident that the formulations prepared with Methocel K15M retarded the drug release in the concentration of 75 mg showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 98.12 % in 12 hours (Formulation F3) with good floating lag time and floating buoyancy time. The formulations prepared with Guar gum showed more retardation even after 12 hours they were not shown total drug release. Hence they were not considered.

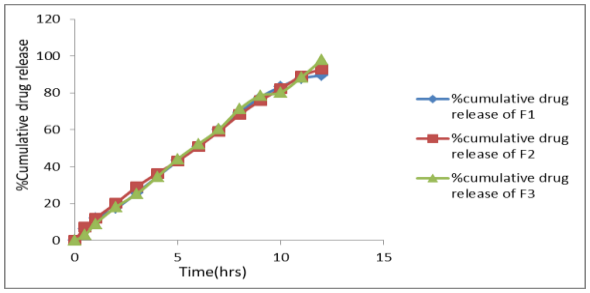

Fig 3: Dissolution graphs for the formulations F1,F2,F3

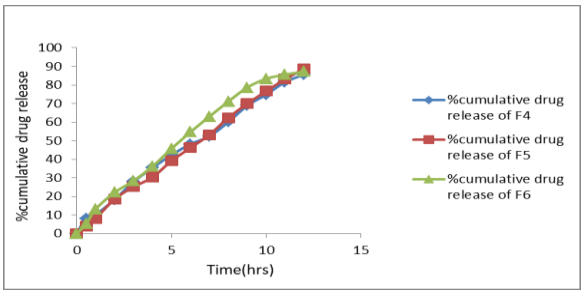

Fig 4: Dissolution graphs for the formulations F4,F5,F6

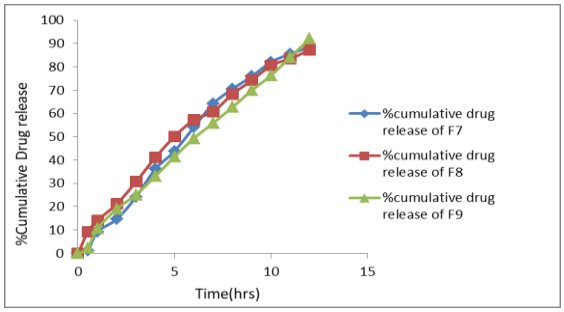

Fig 5: Dissolution graphs for the formulations F7,F8,F9

Application of Release Rate Kinetics to Dissolution Data: Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

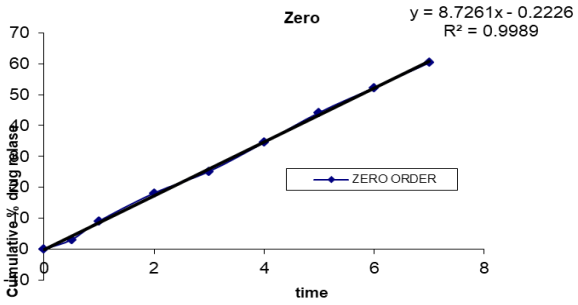

Fig 6: Zero order release kinetics graph

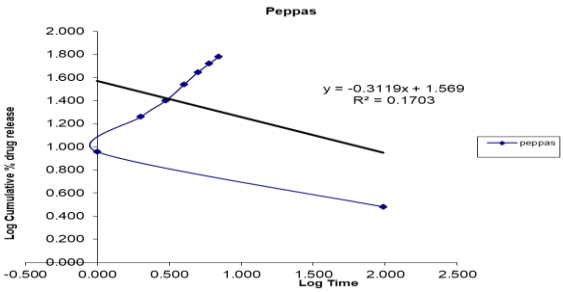

Fig 7: Higuchi release kinetics graph

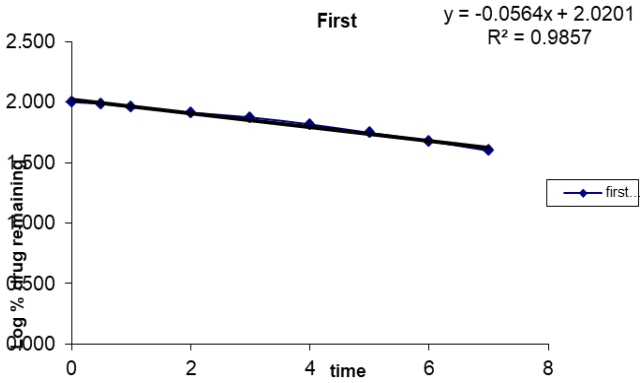

Fig 8: Kars mayer peppas graph

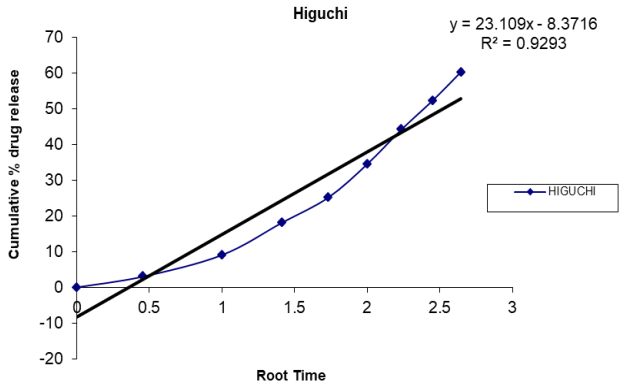

Fig 9: First order release kinetics graph

Table 1: Formulation of Nicorandil Controlled release tablets

INGREDIENT	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Nicorandil	10	10	10	10	10	10	10	10	10
Methocel K15M	10	20	30	-	-	-	-	-	-
Chitosan	-	-	-	10	20	30	-	-	-
Gum karaya	-	-	-	-	-	-	10	20	30
Talc	3	3	3	3	3	3	3	3	3
Mg. Stearate	3	3	3	3	3	3	3	3	3
MCC pH102	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
TOTAL	120	120	120	120	120	120	120	120	120

Table 2: Observations for graph of Nicorandil in 0.1N HCl (298nm)

Conc [µg/l]	Abs
0	0
5	0.132
10	0.268
15	0.372
20	0.493
25	0.582
30	0.712

Table 3: Observations for graph of Nicorandil in p H 6.8 phosphate buffer (232nm)

Conc [µg/l]	Abs
5	0.114
10	0.237
15	0.352
20	0.439
25	0.561
30	0.674

Table 4: Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	24.22	0.47	0.56	17.12	0.89
F2	23.61	0.53	0.54	17.13	0.91
F3	22.87	0.52	0.57	16.86	0.65
F4	23.75	0.58	0.52	16.84	1.10
F5	24.12	0.56	0.59	17.39	1.21
F6	25.19	0.54	0.51	16.21	1.04
F7	24.82	0.56	0.59	17.49	0.86
F8	23.72	0.59	0.55	16.55	1.18
F9	24.32	0.53	0.51	17.21	1.11

Table 5: Invitro quality control parameters for tablets

Formulation codes	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	122.5	4.4	0.51	1.9	98.45
F2	115.4	4.6	0.49	1.8	99.56
F3	118.6	4.5	0.52	1.9	97.42
F4	121.6	4.6	0.53	1.5	98.53
F5	119.4	4.3	0.55	1.8	97.49
F6	119.7	4.4	0.42	1.6	99.67
F7	118.3	4.6	0.53	1.6	97.08
F8	111.2	4.2	0.48	1.8	98.65
F9	118.3	4.6	0.51	1.3	99.09

Table 6: Cumulative percent drug release of Nicorandil Tablets

Time (Hrs)	% Drug release of F1	% Drug release of F2	% Drug release of F3	% Drug release of F4	% Drug release of F5	% Drug release of F6	% Drug release of F7	% Drug release of F8	% Drug release of F9
0.5	6.13	7.15	3.02	8.15	4.06	5.14	1.23	9.15	2.34
1	12.01	12.05	9.04	10.23	8.13	13.16	9.24	14.12	10.54
2	17.45	20.23	18.12	18.23	18.54	22.11	14.63	21.15	19.05
3	25.74	29.05	25.15	27.82	25.11	28.36	24.18	30.66	25.15
4	34.51	36.40	34.51	35.40	30.32	36.11	36.12	41.11	33.05
5	43.23	43.12	44.23	42.29	39.11	45.69	43.86	50.11	41.43
6	51.05	50.89	52.28	48.12	46.12	54.63	54.09	57.31	49.34
7	60.09	59.23	60.34	52.37	53.17	62.98	64.23	60.78	55.85
8	69.34	68.23	71.25	60.06	62.29	71.08	70.51	68.31	62.68
9	77.67	75.81	78.55	68.87	69.91	78.64	75.92	74.15	69.87
10	83.45	82.23	80.27	74.85	76.67	83.34	82.05	80.59	76.36
11	87.89	89.28	88.51	81.59	83.09	85.54	85.56	83.55	84.16
12	89.46	92.97	98.07	85.54	88.78	87.23	88.41	87.13	92.06

Table 7: Release kinetics data for optimized formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN
0	0	0			2.000
3.02	0.5	0.458	0.480	1.987	1.987
9.04	1	1.000	0.956	0.000	1.959
18.12	2	1.414	1.258	0.301	1.913
25.15	3	1.732	1.401	0.477	1.874
34.51	4	2.000	1.538	0.602	1.816
44.23	5	2.236	1.646	0.699	1.746
52.28	6	2.449	1.718	0.778	1.679
60.34	7	2.646	1.781	0.845	1.598
71.25	8	2.828	1.853	0.903	1.459

78.55	9	3.000	1.895	0.954	1.331
80.27	10	3.162	1.905	1.000	1.295
88.51	11	3.317	1.947	1.041	1.060
98.07	12	3.464	1.992	1.079	0.286

4. Conclusion

Aim of the present study was to develop controlled release formulation of Nicorandil to maintain constant therapeutic levels of the drug for over 12 hrs. Methocel K 15M, Gum karaya, Chitosan. Nicorandil dose was fixed as 10 mg. Total weight of the tablet was considered as 120 mg. Polymers were used in the concentration of 10mg, 20mg and 30 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F3) showed better and desired drug release pattern i.e., 98.07 % in 12 hours. It contains the natural polymer Nicorandil as controlled release material. It followed zero order release kinetics mechanism.

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