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FORMULATION AND EVALUATION OF NICORANDIL COMPRESSED COATING TABLETS

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ABSTRACT

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery system for the more obivous advantage of the oral routes of the administration. Such systems release the drug with constant or variable release rates. Pulsatile Drug Delivery systems (PDDS) are basically time-controlled drug delivery systems in which the system controls the lag time and drug is released in an immediate or extended fashion. The formulations developed using HPMC K 100M as rate retarding polymers doesn't exhibit a satisfactory drug release near to lag time, formulation with Eudragit RS 100 exhibits a satisfactory drug release near lag time.

Keywords: Pulsatile Drug Delivery System, Eudragit RS 100 and controlled release.

INTRODUCTION

Oral controlled drug delivery systems represent the most popular form ofcontrolleddrugdeliverysystemforthemoreobiv ousadvantageoftheoral routes of the administration. Such systems release the drug with constant or variable release rates.

These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance.

However, there are certain conditions for which such a release pattern is not suitable. These conditions demand release of drug after a lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration. Such a release pattern is known as pulsatile release

The release of the drug as a pulse after a lag time (an interval of no drug release) has to be designed in such a way that a complete and rapid drug release follows the lag time.

In chronopharmacotherapy (timed drug therapy) drug administration is synchronized with biological rhythms to produce maximal therapeutic effect and minimum harm for the patient.

DRUG PROFILE

NICORANDIL

Nicorandil is a potassium channel opener with nitrovasodilator (NO donor) actions, making it both an arterial and a venous dilator.

Chemical Formula

$C_8H_9N_3O_4$

Molecular Weight

211.177

IUPAC Name

2-[(pyridin-3-yl)formamido]ethyl nitrate

Mechanism of Action

Nicorandil mediates its therapeutic efficacy via two main mechanisms. Nicorandil is an activator and opener of ATP-sensitive (ATP-dependent) potassium channels (KATP

channels) KATP channel- dependent membrane hyperpolarization can also lead to vasodilation via reduction in Ca2+ influx through the voltage-gated Ca2+ channels and regulation of intracellular Ca2+ mobilization in smooth muscle cells.

EXCIPIENT PROFILE

It mainly contains
1.crosspovidone
2.hydroxypropyl methyl cellulose
3.Ethyl Cellulose
4.Eudragit S100 And Eudragit L100
5.Microcrystalline Cellulose
6.Purified Talc
7.MagnesiumSterate

METHODOLOGY

I. Analytical Method Development

Preparation of buffers

a)Preparation of 0.1 N Hcl Solution

0.1NHcl was prepared by diluting 8.5mL of concentrated Hydrochloric acid to 1000 mL distilled water.

b)Preparation of 6.8 pH phosphate buffer solution

27.22g of monobasic potassium phosphate was weighed and diluted up to 1000 ml to get stock solution of monobasic potassium phosphate. 8g Sodium hydroxide was weighed and diluted upto 1000ml to get 0.2Msodium hydroxide solution.50ml of the monobasic potassium phosphate solution was taken from the stock solution in a 200-mLvolumetric flask and 22.4ml of sodium hydroxide solution from stock solution of 0.2M sodium hydroxide solution was added and then water was used to make up the volume.

Formulation of Nicorandil PDDS tablets

Preparation of core Tablets

- All the excipients except Talc & Magnesium stearate were cosifted through # 40 ASTM & blended in a motor and pistle for 10min.
- To the above mixture #60ASTMpassedTalc&Magnesiumste aratewere added & lubricated by blending in a motor and pistle for 5min

Preparation of coating layer

- All the excipients except Mg.stearate were cosifted through # 40ASTM & blended in a poly bag for 10min

Compression coating of core tablet

- Prepared coating layer was used for shell formation.
- Press coating of tablet was performed. Half the amount of powder from every formulation (one by one) were filled into the die to form a powder bed. In center core, tablet formulation is placed. Over this remaining half of the granules was filled into die and contents were compressed using concave punches of 10mm diameter. Hardness of tablet was maintained between 6-8 kg/ cm^2.

II. EVALUATION OF TABLETS

The formulated tablets were evaluated for the following Pre, post compression quality control studies and dissolution studies

A) Pre-Compression studies

1. Angle of Repose

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

$= \tan^{-1}$ (h/r)

2. Carr's Index

Compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down[19]. The formula for Carr's index is as below:

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Post compression studies

1.General appearance

The formulated tablets were assessed for its general appearance and observations were made for shape, colour, texture and odour.

2. Average weight/ Weight Variation

20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to assure whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage.

Average weight = weight of 20 tablets
20

3. Thickness
Thickness of the tablets (n=3) was determined using a vernier calipers

4. Hardness test
Hardness of the tablet was determined by using the Monsanto hardness tester(n=3) the lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

5. Friability test
This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Initial weight of 20 tablets is taken and these are placed in the Friabilator, rotating at 25rpm for 4min.
%Friability = [(W1-W2)/W1] X 100
Where, W_1= weight of tablets before test, W_2 = weight of tablets after test

2.In vitro Dissolution Study
900ml of 0.1NHCl was placed in the vessel and the USP-II apparatus (Paddle method) was assembled. The medium was allowed to equilibrate to temperature of $37^0C \pm 0.5^0C$. A tablet was placed in the vessel and was covered; the apparatus was operated up to 2 hrs at 50 rpm. At definite time intervals, 5 ml of dissolution medium was withdrawn; filtered and again replaced with 5 ml of fresh medium to maintain sink conditions. Suitable dilutions were done with dissolution medium and were analyzed spectrophotometrically at λ_{max}=262 nm using a UV-spectrophotometer (Lab India). Then remove the 0.1N Hcl and replace with 6.8 phosphate buffer and continue the dissolution with the above procedure from 2nd hour.

RESULTS AND DICUSSION
1. Construction of Standard calibration curve of Nicorandil in 0.1NHCl
The absorbance of the solution was measured at 262nm, using UV spectrometer with 0.1NHCl as blank.The values are shown in table. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 3 to 15µg/ml.

2. Construction of Standard calibration curve of Nicorandil in 6.8 phosphate buffer
The absorbance of the solution was measured at 262nm, using UV spectrometer with 6.8 as blank. The values are shown in table no 20. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 3 to 15µg/ml.

Inference
The standard calibration curve of Nicorandil in 6.8 phosphate buffer showed good correlation with regression value of 0.999.

Pre Compression studies
Inference

- The thickness of tablets was found to be between 4.9-5.2mm.
- The prepared tablets were evaluated for their flow properties; the results for the blends of compression tablets were shown in Table.
- The bulk density and the tapped density for all formulations were found to be almost similar.
- The Carr's index and Hausner's ratio were found to be in the range of ≤ 18 and 1.0 respectively, indicating good flow and compressibility of the blends.
- The angle of repose for all the formulations was found to be 11.14 which indicating passable flow (i.e. incorporation of glidant will enhance its flow).

Post compression studies
Inference

- The blends prepared for direct compression of tablets were evaluated for their flow properties; the results for the blends of compression tablets were shown in Table:
- The bulk density and the tapped density for all formulations were found to be almost similar.
- The Carr's index and Hausner's ratio were found to be in the range of ≤ 18and1.0to1.23respectively, indicating good flow and compressibility of the blends.
- The angle of repose for all the formulations was found to be in the range of 25.35-34.96˚ which indicating passable flow (i.e. incorporation of glidant will enhance itsflow).

Post compression studies of Nicorandil coating tablets
Inference

- The variation in weight was within the range of ±7.5% complying with pharmacopoeia specifications of USP.

- The hardness for different formulations was found to be between 5.56 to 6.63 kg/cm^2, indicating satisfactory mechanical strength
- The friability was < 1.0% W/W for all the formulations, which is an indication of good mechanical resistance of the tablet.
- The drug content was found to be within limits 98 among the different control release polymers Eudragit RS 100 was showing highest drug release retarding capacity.
- F8 was showing the satisfactory results and having better sustainability.

SUMMARY AND CONCLUSION

From the experimental data, it can be concluded that

- Eudragit RS100 was respectively showed better pulsatile drug release of Nicorandil.
- When drug: polymer concentration increases the release rate decreases this is because of reason when the concentration of polymer increases the diffusion path length increases
- Formulated tablets showed satisfactory results for various Post compression evaluation parameters like: tablet thickness, hardness, weight variation, content uniformity and *in vitro* drugr elease.
- FormulationF8gavebetter-pulsatiledrugreleaseandincomparisont othe other formulations.
- The most probable mechanism for the drug release pattern from the formulation was Anomalous (Non-Fickian) diffusion.

Table 1: Formulation of core tablets for inner and outer

Ingredients	IRT
Nicorandil	10
Crospovidone	5
MCC	81
Talc	2
Magnesium stearate	2
Total weight (mg)	100

Table 2: Preparation of coating layer

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
HPMC K15M	60	75	90	--	--	--	--	--	--
Ethyl cellulose	--	--	--	60	75	90	--	--	--
Eudragit RS 100	--	--	--	--	--	--	60	75	90
MCC	180	165	150	180	165	150	180	165	150
Talc	6	6	6	6	6	6	6	6	6
Mg. Stearate	4	4	4	4	4	4	4	4	4
Total Weight (mg)	250	250	250	250	250	250	250	250	250

Table 3: Dissolution parameters

Parameter	Details
Dissolution apparatus	USP -Type II (paddle)
Medium	0.1N HCl. upto 2hrs and 6.8 phosphate buffer 3hr-8hr
Volume	900 ml
Speed	50 rpm
Temperature	37± 0.5 ºC
Sample volume withdrawn	5ml
Time points	1,2,3, 4, 5, 6, 7 and 8hrs
Analytical method	Ultraviolet Visible Spectroscopy
λ_{max}	262 nm

Table 4: Standard Calibration graph values of Nicorandil in 0.1N Hcl at 262 nm

Concentration (µg/ml)	Absorbance
3	0.079
6	0.155
9	0.233
12	0.309
15	0.393

Table 5: Standard Calibration graph values of Nicorandil 6.8 phosphate buffer at 262 nm

Concentration (µg/ml)	Absorbance
3	0.076
6	0.159
9	0.262
12	0.304
15	0.381

Table 6: Pre compression studies of Nicorandil core tablets

Bulk density (Kg/cm^3)	Tapped density (Kg/cm^3)	Cars index	Hausners ratio	Angle of repose (˚)
0.37	0.41	9.75	1.1	11.14

B) Post compression studies

Table 7: Post compression studies of Nicorandil core tablets

% Weight variation	Thickness	% Friability	%Drug Content	Hardness (Kg/cm^2)
Pass	3.03	0.132	99.6	3.63

Table 8: Pre compression studies of Nicorandil compressed coating tablets

Formulation Code	Bulk density (Kg/cm^3)	Tapped density (Kg/cm^3)	Cars index	Hausners ratio	Angle of repose (˚)
F1	0.40	0.48	16	1.2	32.73
F2	0.39	0.48	18	1.23	34.96
F3	0.50	0.58	13	1.16	28.58
F4	0.44	0.50	12	1.1	27.92
F5	0.37	0.41	9.75	1.1	25.35
F6	0.37	0.41	9.75	1.1	33.14
F7	0.36	0.39	7.6	1.0	27.03
F8	0.41	0.45	8.8	1.0	31.85
F9	0.39	0.48	18	1.23	28.96

Table 9: Post compression studies of Nicorandil coating tablets

Formulation Code	% weight variation	Thickness (mm)	% Friability	%Drug Content	Hardness (Kg/cm^2)
F1	Pass	5.06	0.145	98.9	5.62
F2	Pass	4.92	0.116	100.6	5.72
F3	Pass	5.01	0.144	101.3	5.56
F4	Pass	5.03	0.157	101.2	6.03
F5	Pass	5.07	0.621	100.1	6.00
F6	Pass	5.1	0.157	100.4	6.63
F7	Pass	4.98	0.231	99.2	5.97
F8	Pass	5.14	0.183	100.4	5.83
F9	Pass	5.06	0.169	99.5	5.98

Table 10: Dissolution data of Nicorandil colon targeted Tablets

Time (Hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	**0**	0
1	0	0	0	0	0	0	0	**0**	0
2	0	0	0	23	0	0	0	**0**	0
3	61	48	32	68	5	0	0	**0**	0
4	97	99	87	99	39	2	7	**0**	0
5			98		78	11	52	**0**	0
6					99	44	99	**1**	0
7						99		**38**	0
8								**99**	16

Table 11: R^2 and 'n' result table

Formulation code	R^2 values				'n' value
	Zero order	First order	Higuchi	Peppas	
F8	0.478	0.354	0.299	0.365	1.651

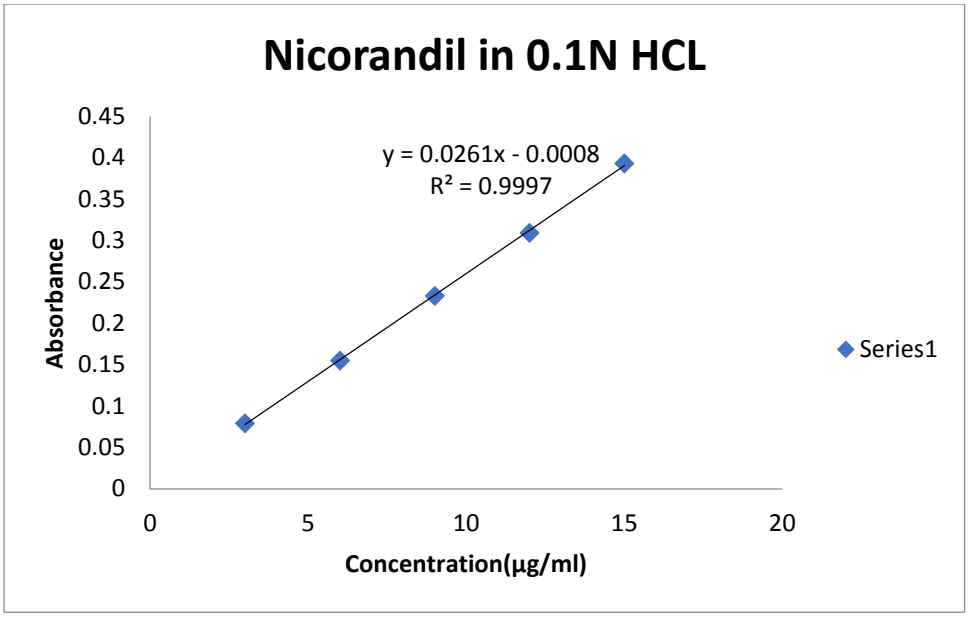

Fig. 1: Standard calibration curve of Nicorandil in 0.1N Hclat 262 nm

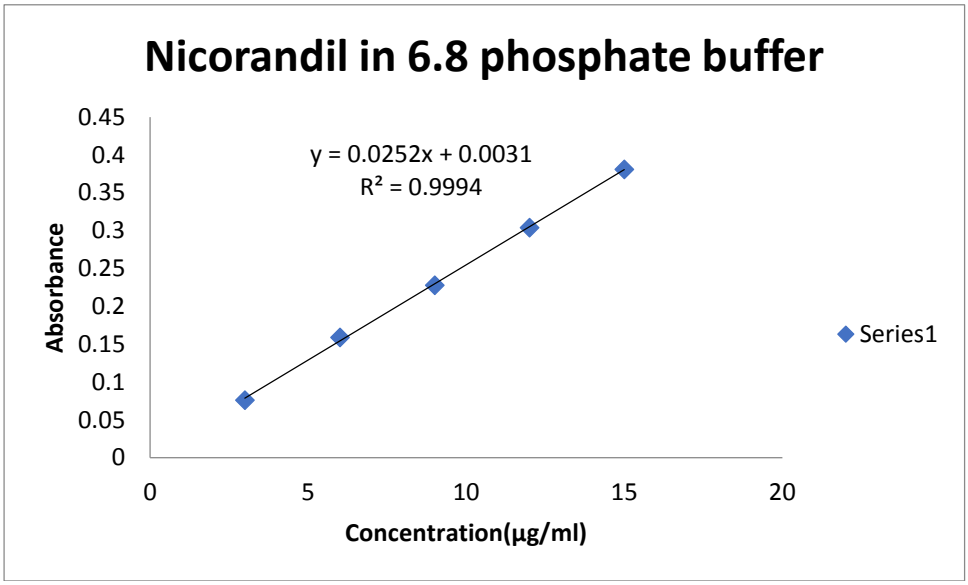

Fig. 2: Standard calibration curve of Nicorandil in 6.8 phosphate buffer at 262nm

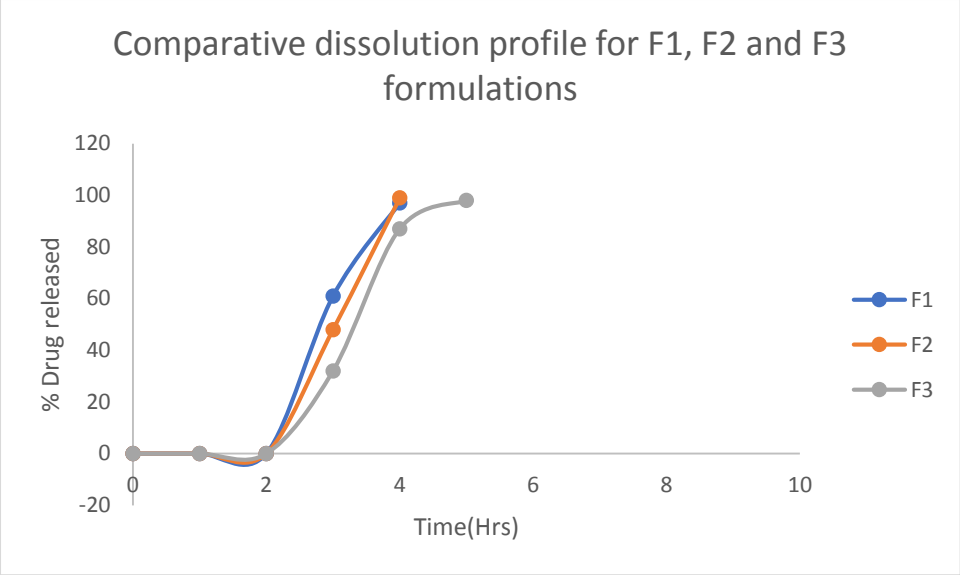

Fig. 3: Comparative dissolution profile for F1, F2 and F3 formulations

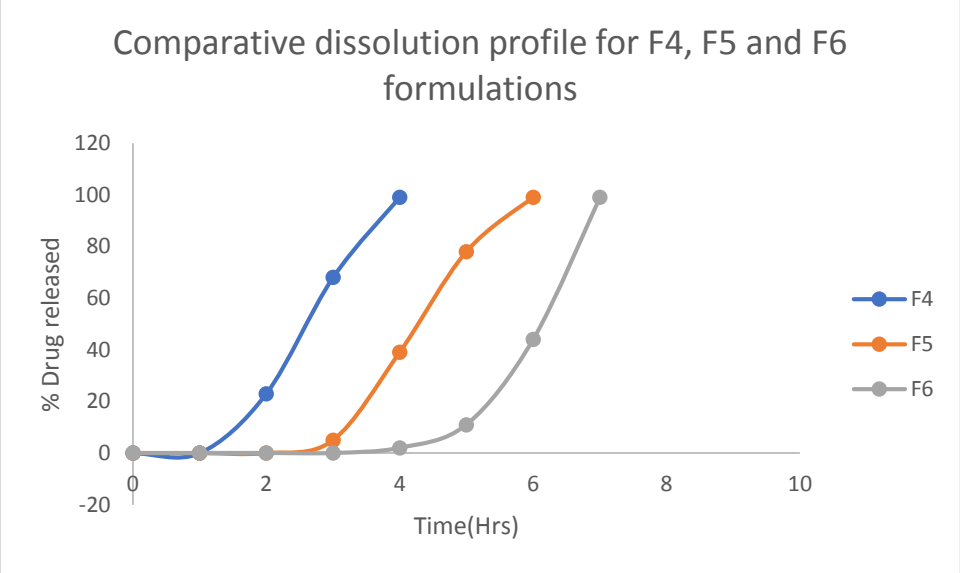

Fig. 4: Comparative dissolution profile for F4, F5 and F6 formulations

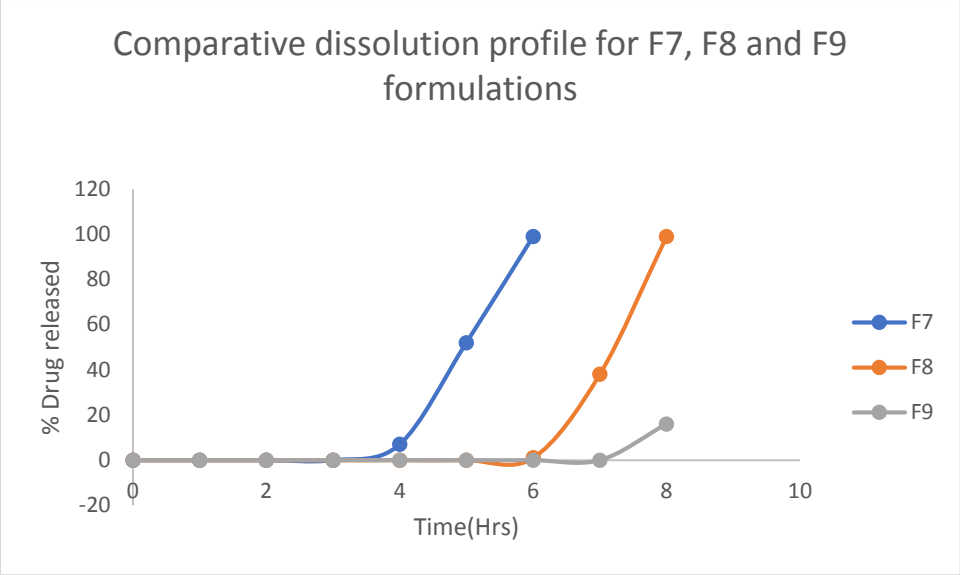

Fig. 5: Comparative dissolution profile for F7, F8 and F9 formulations

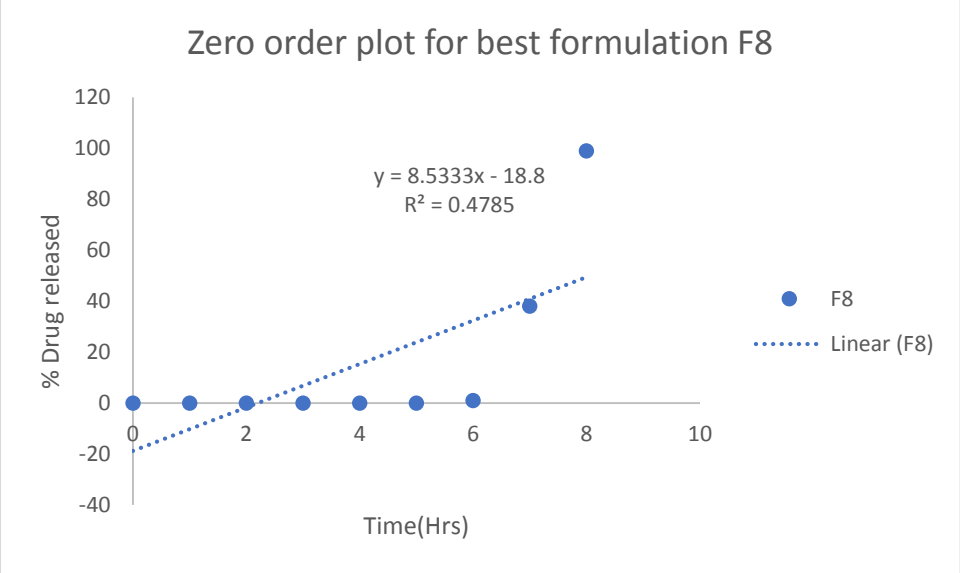

Fig. 6: Zero order plot for best formulation F8

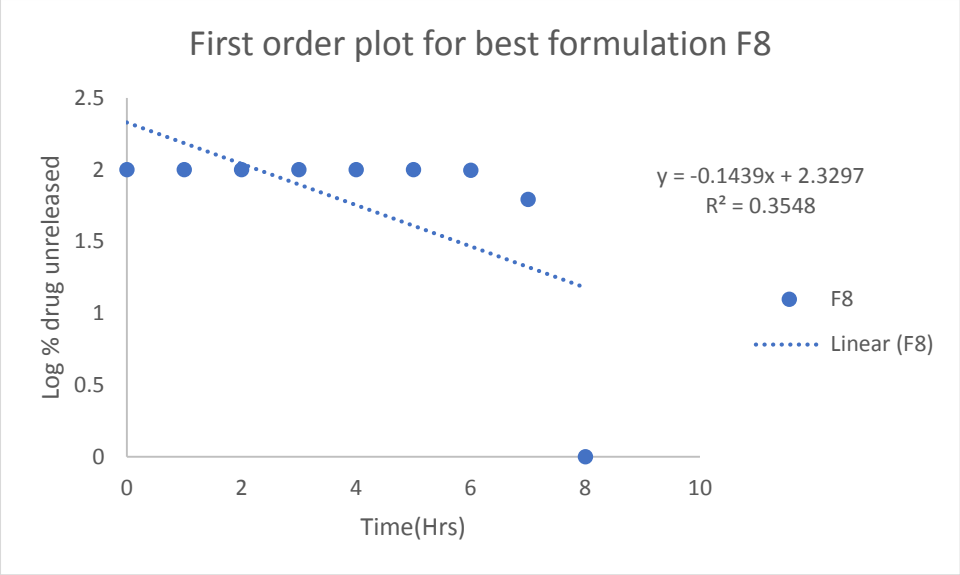

Fig. 7: First order plot for best formulation F8

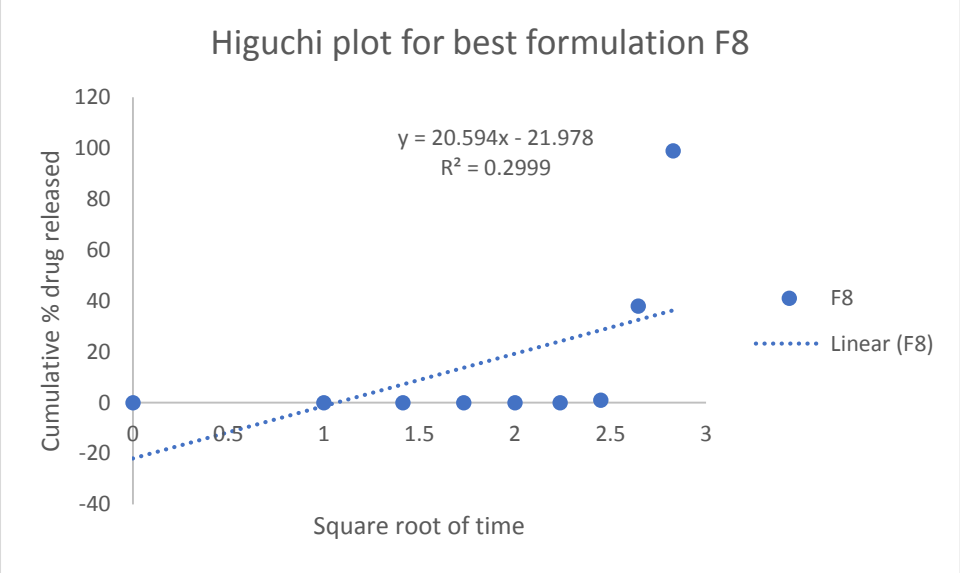

Fig. 8: Higuchi plot for best formulation F8

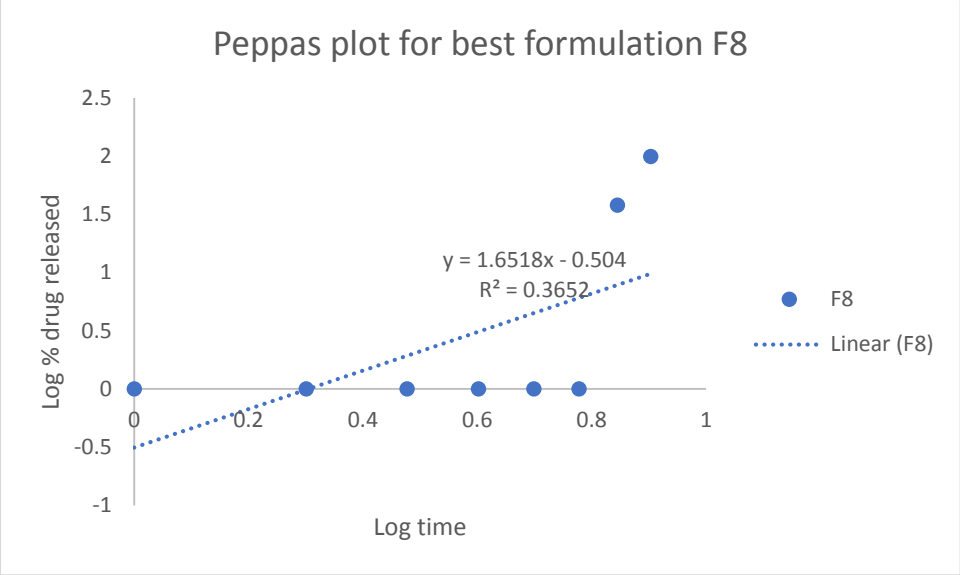

Fig. 9: Peppas plot for best formulation F8

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