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RESEARCH ARTICLE

Development of Nicotinic Acid Controlled Release Tablets with Natural Phenolic Anti-oxidant Polymer by Encapsulation Technique

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Abstract

Nicotinic Acid (NA) is a cholesterol lowering agent used to treat dyslipidemia. Proanthocyanidins (PC) was selected as a drug and encapsulation material in which the later has a dual property of being a polymer as well as cholesterol lowering agent. The encapsulation of NA with different concentrations of (PC) was carried out by solvent evaporation technique. The encapsulated NA was converted to granules which were then compressed into tablets by wet granulation method. It was subjected to many pre-compression parameters evaluation such as flow properties, drug content and encapsulation efficiency. The tablets were evaluated for thickness, hardness, friability, *in vitro* release studies, release kinetics and stability studies. The evaluated parameters of the formulations showed compliance with pharmacopoeial standards. The encapsulation efficiency was 99.73% and 99.52% of drug content. The FT-IR spectrum did not show interaction between drug and polymer. The drug release in pH 1.2 was lesser than in pH 6.8 buffer. The encapsulated product released drug in controlled manner in alkaline medium. The drug release was 97.1% and release was extended up to 12 hrs. The optimized batch underwent stability studies as per ICH guidelines. It can be concluded that among all the formulations the F5 can be considered as optimized formulation. The optimized formulations showed non-fickian diffusion mechanism of release.

Keywords: Controlled, Delivery, Dyslipidemia, Compatible, Granulation

1. Introduction

There is an increase in the number of patients with chronic diseases off late., which necessitates taking drug for a longer time or multidrug together, which can lead to increase in non-compliance. The problem would be worse if half-life of drug is short. A dosage design offering gradual drug release might me one method to solve this problem. Controlled release dosage forms releases their active ingredients at a predetermined rate and time. The oral administration of pharmaceutical dosage forms is the more usual, convenient and comfortable route for active drug delivery to the body. Oral controlled release systems continue to be the most popular among the drug delivery systems since it has many advantages over the conventional systems. It improves the patient compliance since it reduces frequent drug dosage, fluctuation of steady state plasma level thereby helping in better control of disease condition[1,2]. There are various approaches to deliver the therapeutic agent to the target site in a controlled manner. One such approach is encapsulation of drugs. But, these formulations have less compliance since they have to be injected. Therefore, it is essential to develop an oral drug delivery system that is comfortable for patients.

The scientific community has so far well understood that Nicotinic Acid (NA) is the best drug for treating dyslipidemia. NA has been in usage since years for CVDs to treat dyslipidemia. Conventional formulations of NA are administered multiple times a day depending on

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the dose (500-mg thrice daily) due to its short half-life (t1/2 = 1 to 3 h). After oral administration, NA is rapidly absorbed from the GIT. The associated side effects are increased level of plasma of NA immediately after oral administration. The patients suffer facial and truncal blushing (prostaglandin mediated) during initial treatment with plain NA or Immediate Release (IR)[3]. These symptoms decrease slowly, but unfortunately, most of the patients stop the treatment before the development of tolerance. There are many unwanted effects like itching, diarrhea and irritation of the mucous membrane irritation. Also, NA IR (immediate release) requires multiple – doses (2 or 3 times a day)[4]. In 1960s the Sustained Release (SR) tablets containing NA was formulated in order to reduce the flushing. But the clinical use of SR-NA showed more hepatotoxicity and gastrointestinal intolerance[5]. Hence to overcome the side-effects of NA-IR and NA-SR delivery system, the Controlled Release (CR) NA formulations would be efficient.

PC is a condensed tannin consisting of oligomers and polymers of monomeric flavans. They are present in several berries, red grapes and their wines, and seeds, baking chocolate, cinnamon, pycnogenol, and *Ginkgo biloba*[6,7]. They are present more in vegetables and fruits. It contains catechin, epicatechin, and gallic acid esters[8]. PC is a strong natural antioxidant, containing multiple hydroxyl groups, and has attracted a considerable research interest in pharmaceutical preparations[9,10]. The investigations of PC attracted the scientists due to its numerous pharmacological properties, including antioxidant[11], anticancer[12], antimicrobial[13], antiangiogenic[14], lipoprotein lowering agent, cholesterol lowering agent, anti-atherosclerotic agent[15–17] and anti-inflammatory actions[18]. It has been reported that PC, even in high doses, is noncarcinogenic and nonteratogenic[19,20]. Encapsulation is a technique to entrap solids, liquids, or gases inside one or more polymeric coatings[21]. Microencapsulation protects the unstable core from its environment thereby improving its stability and extends the shelf life of core until its release[22,23]. One of the popular methods for the encapsulation of drugs is the solvent evaporation method. Hence PC polymer was used to develop control release system of NA, since PC itself is a lipoprotein (a) lowering agent, cholesterol lowering agent and an anti-atherosclerotic agent. PC coupled with NA, doubled the desired effects simultaneously reducing the undesirable side effects of NA. Hence NA was chosen as a drug to develop a dissolution controlled system of NA by encapsulation with PC, a natural phenolic antioxidant polymer for the treatment of dyslipidemia.

2. Materials

Nicotinic acid was obtained from SD Fine Chemicals Ltd, Bangalore and Proanthocyanidine from MMC health care, Chennai. SLS, PVP K30, Starch, Magnesium stearate and Talc were obtained from KAPL, Bangalore. All the chemicals and reagents used were of analytical grade.

3. Methodology

3.1 Preformulation Studies

The physicochemical characteristics of the drug and the drug in combination of excipients were investigated. These studies were initially performed before the development of dosage form.

3.1.1 Determination of Melting Point (Capillary Method)

One end of capillary tube was sealed and the fine powder of NA was filled in the other end, which was tied to a thermometer placed in Thais tube and placed on fire. The temperature at which the powder melted was noted.

3.1.2 Solubility

Solubility of NA was determined in pH 1.2 and 6.8 buffers spectrophotometrically (pH 1.2 blank at 260.5nm, pH 6.8 blank at 262.4nm).

3.1.3 Compatibility Studies

Compatibility study was carried out for the drug and its excipients by FTIR.

3.2 Encapsulation of NA with PC by Solvent Evaporation Method

Encapsulation of NA with PC by solvent evaporation method involved the following manner, the required quantity of PC (2% w/v) was dissolved in methanol and the active substance NA (250 mg) was dispersed uniformly into polymer solution with agitation. The resultant polymer and drug mixture was added manually drop wise at the rate of 1 ml/min into (3% w/v) sodium lauryl sulphate with agitation about 100 rpm and heat maintained at 100 °C. After addition of mixture, stirring was continued for 2 hours to achieve encapsulation of NA. The encapsulated NA was collected and dried in hot air oven at 40°C for 30 minutes to complete removal of moisture content. The different concentrations of polymer were used to estimate best drug release rate from dosage.

3.3 Evaluation of encapsulated NA

3.3.1 Drug Polymer Interaction (FTIR) Study

FT-IR spectroscopy was performed by Fourier transform infrared spectrophotometer. The drug and potassium bromide were compressed at 50 psi on KBr-press to form pellets. The spectra were scanned in the wave number range of 4000-600 cm^{-1}. FTIR study was carried on NA, physical mixture of NA and encapsulated NA.

3.3.2 Percentage Yield

Percentage yield was estimated to determine effectiveness of the method of preparation. Practical yield was calculated from the weight of the encapsulated nicotinic acid in comparison with the materials taken initially. The percentage yield of prepared encapsulated NA was determined.

3.3.3 Encapsulation Efficiency

Encapsulated NA (100mg) was powdered, dissolved in pH 6.8, sonicated for 30 minutes and filtered through 0.45µm membrane filter. The drug content was determined by UV spectrophotometer at 262 nm. The entrapment efficiency was calculated.

3.4 Formulation of Granules from Encapsulated NA

NA Granules containing the encapsulated NA was prepared by wet granulation technique with different concentrations of proanthocyanidin. Different steps followed for wet granulation are as follows, weighing of encapsulated NA, preparation of dump mass, screening the dump mass into granules, drying the granulation and sizing the granulation by dry screening. Specified quantity of encapsulated product was weighed. A 1%w/v PVP K30 was added to increase the cohesion. The resulting damp mass was used to prepare the granulation. Then it was pressed through the sieve (10 number) to prepare the granules manually. The prepared granules were spread uniformly on paper in trays and dried. Granules were dried in hot air oven at 60°C for 1 to 2 hours. The granules were sieved through number 20 sieve.

3.5 Evaluation of Pre-compression Parameters of Granules containing Encapsulated NA

The pre-compression parameters like angle of repose, bulk density and tapped density, Hausner's Ratio, Compressibility index (Carr's Index) were determined as per the standard protocol[25,26].

3.6 Formulation of Tablets of NA

The prepared granules were mixed with lubricants (magnesium stearate, talc) to avoid adhesion of tablet in punches and dies during compression (Table 1). The granules were compressed by 16 stations automatic tablet punching machine (MK1 – 16 stations punching machine (11mm concave punches).

3.7 Evaluation of Post-compression Parameters of NA Tablets

The prepared tablets were subjected to evaluation of properties including drug content uniformity, weight variation, tablet hardness, friability, thickness, disintegration study and *in-vitro* drug release with different media. The percentage of *in-vitro* drug release of NA from tablets was determined using the dissolution apparatus II of United States Pharmacopoeia (USP)

Table 1. Tablet composition of different formulations of nicotinic acid controlled release tablets

Ingredients (mg/tablet)	Code of Formulation									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Nicotinic acid	250	250	250	250	250	250	250	250	250	250
Proantocyanidine	250	250.5	260	260.5	270	270.5	280	280.5	290	290.5
SLS	87	82	77	72	67	62	57	52	47	42
PVP K30	sq	sq	sq	sq	sq	sq	sq	sq	sq	sq
Starch	04	04	04	04	04	04	04	04	04	04
Magnesium stearate	03	03	03	03	03	03	03	03	03	03
Talc	07	07	07	07	07	07	07	07	07	07
Total	600	600	600	600	600	600	600	600	600	600

* sq – Sufficient quantity

XXIV, paddle type with 900 ml of pH 1.2 buffer at 37°C for initial two hours followed by pH 6.8 phosphate buffer for the remaining hours at 50 rpm. 5 ml sample solution was taken for 12 hours in regular intervals and replaced with fresh dissolution medium. The samples were diluted to suitable concentrations with respective dissolution medium. The absorbance was measured using a UV-Visible Spectrophotometer (UV-1800) and the cumulative drug release percentage was calculated.

3.8 Kinetic Analysis of In-vitro Release Rates of Controlled Release Tablets

The *in-vitro* release profile of all the formulations were subjected to the data analysis of various models namely zero order kinetic model, first order kinetic model, Higuchi's model, Korsmeyer equation and/or Peppa's model.

3.9 Stability Studies

The stability studies were carried out as per ICH guidelines. These studies were designed to elevate degradation of the drug (physical and/or chemical) with increased storage properties. The formulations were tested by storing at various conditions of temperature and humidity.

4. Results and Discussion

4.1 Preformulation Studies

Preformulation testing was performed for drug substances alone and with pharmaceutical excipients.

4.1.1 Determination of Melting Point

The melting point of NA was found to be in the range 236.4–236.6 °C which was compiled with BP standards, indicating purity of the drug sample.

4.1.2 Solubility

NA was found to be more soluble in pH 6.8 phosphate buffer as compare to pH 1.2 and pH 7.4 phosphate buffer, i.e. it has optimum solubility at pH 6.8 (4.67 mg/ml). The solubility decreased to about (2.56mg/ml) at pH 1.2 and it was equal to (3.28mg/ml) at pH 7.4. (Table 2 and Figure 1)

Table 2. Solubility curve for Nicotinic acid

S. No.	Buffer pH	Solubility (mg/ml)
1	1.2	2.56±0.01
2	6.8	4.67±0.03
3	7.4	3.28±0.01

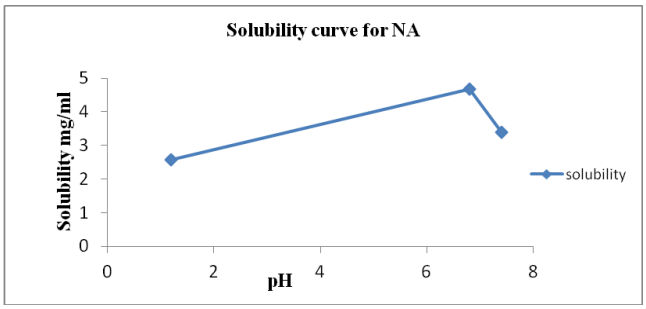


Figure 1. Solubility curve of NA at different pH.

4.1.3 Compatibility Studies

There were no chemical interactions between drug and the polymers. The FTIR spectra of mixture of drug and polymers (Figures 2, 3 and 4) did not show any changes in the main peaks, from which it is understood that there were no physical interactions. The peaks obtained in the spectrum of each polymer correlates with the peaks of drug spectrum (Table 3) which shows they are compatible.

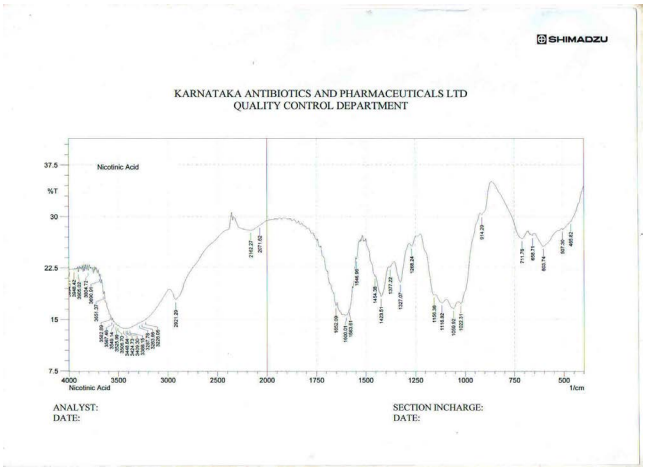


Figure 2. FT-IR Spectrum of pure NA.

Table 3. FT-IR of pure NA

S. No.	Functional group	Peak volume
1	-OH	3400cm-1
2	C=O	1662 cm-1
3	C-H aromatic strch.	2845 cm-1
4	C=C strch.	1596 cm-1

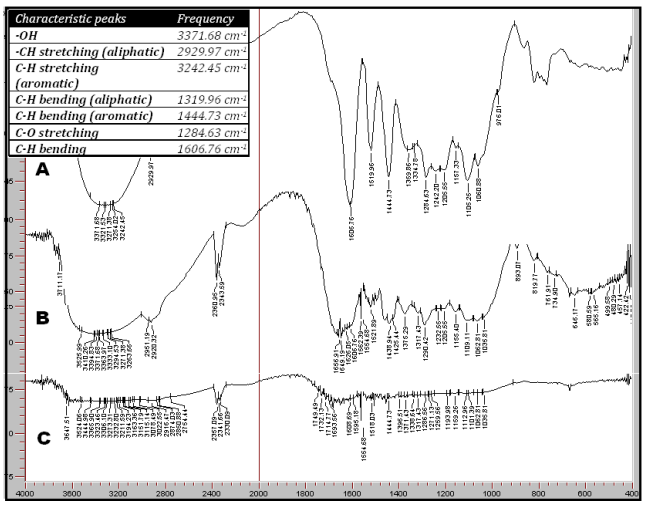


Figure 3. (A) FTIR spectra of PC (B) FTIR spectra of NA (C) FTIR spectra of both PC and NA.

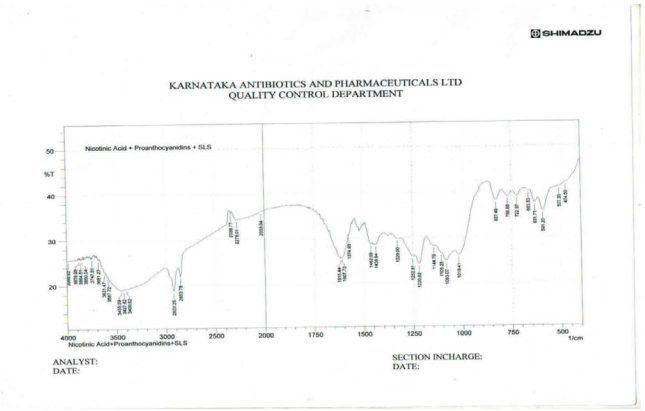


Figure 4. FTIR spectrum of mixture of NA, PC and SLS.

4.2 Encapsulation of NA with PC by Solvent Evaporation Method

NA was encapsulated with PC by solvent evaporation method.

4.3 Evaluation of Encapsulated NA

The physical mixture of NA and encapsulated NA was compatible. The percentage yield was satisfactory and within the limit as per the standard protocol. The resulted efficiency of encapsulation of NA with PC was appreciable.

4.4 Formulation of Granules from Encapsulated NA

NA Granules containing the encapsulated NA was prepared by wet granulation method with different concentrations of PC.

4.5 Evaluation of Pre-compression Parameters of Granules containing Encapsulated NA

Studyofflowpropertiesisveryessentialinpharmaceutical formulations, in particular in preparation of tablets, since variation in weight results due to improper flow. Values of Carr's Index (Compressibility) below 15% usually gives a good flow, rather above 25% indicate poor flow. The powders exhibited good flow properties, since the compressibility values were below 15%. The angle of repose values was rarely 20°. The values up to 40° indicated the reasonable flow properties. The Carr's Index was within the range of 8.0 to 18.0. The angles of repose of the powders were 23° to 28°, which indicated a good flow property of the powders. The results are given in the Tables 4, 5. Drug content and weight variation for all the formulations were within the standard limit. From the above data, formulation F-5 was selected as the optimized formulation.

4.6 Formulation of Tablets of NA

The granules were compressed in 16 stations punching machine containing 11 mm concave punches.

4.7 Evaluation of Post-compression Parameters of NA Tablets

The prepared NA tablets were evaluated for drug content uniformity, weight variation, tablet hardness, friability, thickness, disintegration study and *in-vitro* drug release[24]. The weight variation was found to be within the standard limits (Tables 6, 7). The thickness depended on the size of the die cavity, compression force and tablet weight. The thicknesses of the formulations were in the range of 4.14±0.0154 – 64±0.036 mm and the hardness was in the range 6.6±0.179 – 6.8±0.150 kg/cm^2 indicating good mechanical strength. Friability and drug content uniformity were found to be within official limits (Table 9). The dissolution studies were

Table 4. Data for blend evaluation of formulation (F-1 to F-5)

Pre- compression parameters	Code of the Formulations				
	F1	F2	F3	F4	F5
Angle of repose	23.92 + 1.24	24.16 + 1.21	26.34 + 1.49	27.23 + 1.22	28.64 + 1.64
Bulk density	0.247 +0.007	0.243 +0.009	0.029 +0.008	0.245+ 0.007	0.240 ± 0.007
True density	0.259+ 0.010	0.281 +0.018	0.260 ±0.013	0.259+ 0.011	0.270 ± 0.012
Car's index	9.60 + 0.69	12.59+ 1.80	11.69 ± 1.49	11.20 + 1.19	10.60 + 0.76
Hausner's ratio	1.31±0.02	1.18±0.02	1.24±0.01	1.23±0.02	1.19±0.01

Table 5. Data for blend evaluation of formulation (F-6 to F-10)

Parameters	Formulation code				
	F6	F7	F8	F9	F10
Angle of repose	27.46 + 0.488	24.90 +0.258	24.33 +0.370	26.92 +0.322	26.39 +0.139
Bulk density	0.34±0.01	0.35±0.02	0.36±0.02	0.38±0.01	0.35±0.01
True density	0.41±0.01	0.42±0.02	0.40±0.04	0.48±0.01	0.42±0.01
Car's index	16.73 ± 0.54	17.04 ± 0.79	14.00 ± 0.70	14.29 ± 1.25	16.79 ± 0.66
Hausner's ratio	1.21±0.01	1.24±0.02	1.23±0.01	1.19±0.01	1.22±0.01

carried out for 12 hours (Table 10 and Figures 5, 6). As per the result of dissolution study of formulation, F-4 and F-5 showed reasonable release of 91%, 97.23% respectively at the end of 12hrs. Formula F-5 has shown good drug release profile (97.23%) at 12 hours which showed excellent encapsulation integrity (Table 8) during the period of study when compared to the other formulations. Based on all these results, formulation F-5 was selected as the optimized formulation with 97.23% drug release.

Weight Variation Test

Table 6. Weight variation for tablet formulations (F-1 -to F-5)

S. No	F1	F2	F3	F4	F5
1	600.5	599.6	597.9	600.2	601.5
2	599.6	600.1	599.8	600.4	599.6
3	595.4	600.5	600.1	598.2	598.6
4	601.5	598.8	600.1	600.2	600.2
5	600.8	600.2	598.2	600	600.4
6	600.2	600.4	599.3	599.1	600.8
7	600.8	605.1	600.2	600.1	601.2
8	598.6	600.2	600.1	599.9	600.2
9	600.1	598.6	600.5	600.2	601.8
10	598.9	600.1	600.7	600.5	599.8
Average weight(mg)	599.4	600.24	599.69	599.88	600.41
Standard deviation	1.73282	1.84704	0.944516	0.703641	0.959687

Table 7. Weight variation for tablet formulations (F-6 to F-10)

S. No	F6	F7	F8	F9	F10
1	600.2	598.6	598.9	601.2	600.5
2	599.6	600.4	603.1	601.4	600
3	598.4	600.1	601	600.2	599.6
4	600.5	599.1	600.9	598.2	600.4
5	601.8	600.1	598.2	601	600.1
6	601.2	601.1	600.2	598.1	600.8
7	601.8	603.1	600.5	600.5	600.2
8	599.6	600.2	600.1	599.9	600.3
9	600.1	599.6	598.9	600.3	601.0
10	600.9	600.1	600.2	600.1	600.2
Average weight(mg)	600.27	600.25	600.2	600.07	600.31
Standard deviation	1.142172	1.222247	1.375177	1.106596	0.398469

Encapsulation Efficiency

Table 8. Encapsulation efficiency of formulations F1-F10

Tablet formulation	Calculated value(mg)	Estimated value	% Encapsulation efficiency
F1	600	598.4	99.73
F2	600	589.8	98.3
F3	600	593.2	98.8
F4	600	591.5	98.5
F5	600	597.7	99.58
F6	600	585.9	97.65
F7	600	592.7	98.70
F8	600	587.6	97.90
F9	600	589.3	98.21
F10	600	591.1	98.5

Table 9. Physical properties of tablet formulation (F-1 to F-10)

Formulation Code	Average weight(mg)	Thickness (mm)	Hardness (Kg/cm^2)	% Friability	% Drug content
F1	600.7±0.500	4.14±0.015	6.7±0.105	0.123	99.52
F2	599.8±0.527	4.28±0.009	6.8±0.138	0.092	99.13
F3	605.4±0.707	4.28±0.010	6.7±0.115	0.114	98.04
F4	600.3±0.881	4.29±0.010	6.8±0.091	0.125	98.08
F5	600.0.±0.500	4.25±0.014	6.8±0.121	0.111	98.06
F6	598.9±0.527	4.29±0.007	6.7±0.147	0.127	98.36
F7	603.2±0.707	4.28±0.019	6.8±0.150	0.105	97.64
F8	606.8±0.527	4.28±0.011	6.8±0.076	0.113	96.72
F9	600.4±0.667	4.27±0.030	6.8±0.089	0.105	98.20
F10	600.8±0.632	4.64±0.036	6.6±0.179	0.126	96.07

In-vitro Drug Release Studies

Table 10. Drug releases of F1-F5

S. No	Time in hrs	Code of the Formulations				
		F1	F2	F3	F4	F5
		pH 1.2				
1	1	11.1	9.02	7.11	7.89	7.78
2	2	17.37	14.11	9.8	10.65	9.89
		Phosphate buffer 6.8				
3	3	23.75	21.47	20.86	21.33	23.56
4	4	28.58	30.03	25.11	24.89	28.31
5	5	38.73	36.33	31.03	31.63	31.88
6	6	50.01	41.09	38.15	40.14	35.04

7	7	60.23	56.32	47.01	49.23	40.05
8	8	73.5	69.95	60.08	61.73	46.89
9	9	85.95	80.05	71.12	72.01	52.05
10	10	97.3	94.3	88.03	82.12	65.03
11	11	94.11	86.13	81	97.74	77
12	12	86.66	75	72.04	91	97.23

Table 11. Drug releases of F5 - F10

S. No.	Time (hrs)	Formulation code				
		F6	F7	F8	F9	F10
		pH 1.2				
1	1	7.49	7.56	8.77	8.63	8.63
2	2	10.1	10.87	11.19	10.6	9.97
		Phosphate buffer 6.8				
3	3	17.11	28.81	21.55	19.02	16.78
4	4	22.13	35.33	27.52	25.66	18.33
5	5	28.34	41.78	33.63	29.57	25.67
6	6	34.78	51.4	42.12	35.87	29.91
7	7	40.94	63.17	54.27	41.31	35.84
8	8	46.15	78.18	69.5	52.11	42.33
9	9	52.47	97.73	82.92	57.89	49.24
10	10	57.23	91.11	87.11	67.04	65.41
11	11	66.05	84.89	86.76	75	71.02
12	12	79.88	75	85.11	83.57	79.03

Drug Release Profiles

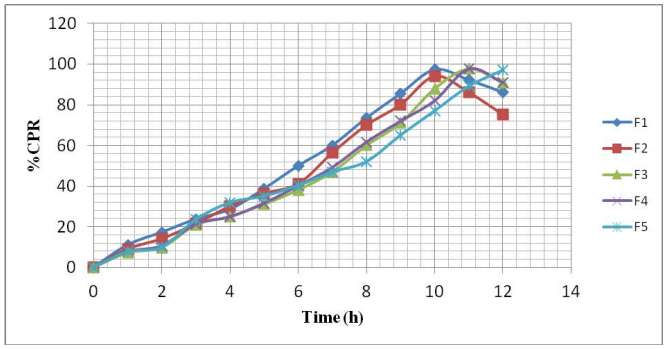


Figure 5. *In-vitro* dissolution profile of F1 to F5 formulations.

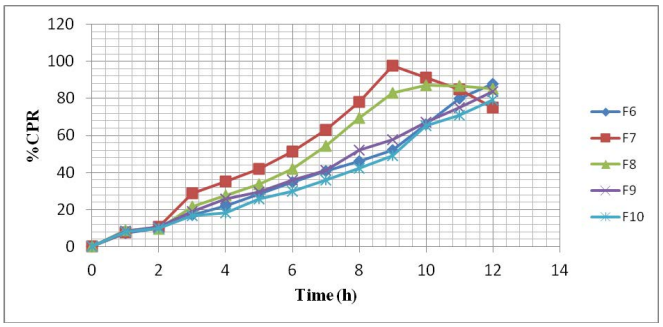
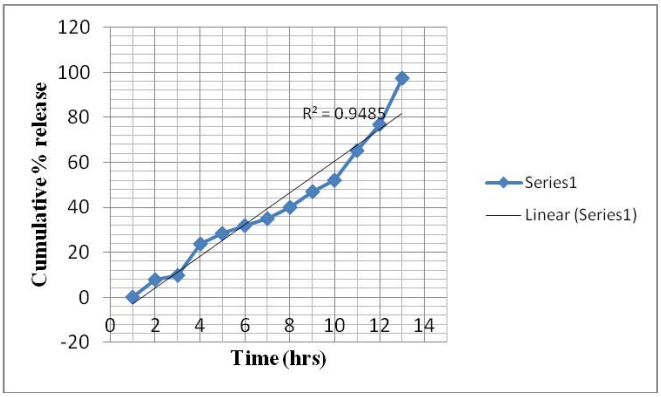


Figure 6. *In-vitro* dissolution profile of F6 to F10 formulations.

4.8 Kinetic Analysis of in-vitro Release Rates of Controlled Release Tablets

The release kinetics were fitted to different mathematical models like Zero order, Higuchi's and Korsmeyer-peppa's plot. The optimized Formulation F-5 followed Higuchi's plot since the regression coefficient is 0.833 which confirmed the drug release was through diffusion (Tables 12, 13 and Figures 7–10). The value of regression coefficient (R2) for zero order is more compared to the

value for first order for F5 from which it was confirmed that the drug release followed zero order.



4.9 Stability Studies

The optimized batch, F-5 was subjected to stability studies as per ICH guidelines. The tablets did not vary in integrity of the matrix at all temperature, significant changes were not found in the drug content. The hardness, friability and drug release values were within the limits (Tables 14–16) even after 90 days.

5. Conclusion

NA is a potent cholesterol lowering agent used in the treatment of dyslipidemia. NA has short biological half-life of 1-3 hours. The dissolution controlled system was

Table 12. Model fitting for formulation F-5

Time (h)	Cumulative % release	Log % un release	Log t	SQRT	Log Cum release
1	0.0	1.999522	0	0	0
2	7.78	1.964307	0	1	0.89098
3	9.89	1.954243	0.30103	1.414214	0.995196
4	23.56	1.882695	0.477121	1.73205	1.37275
5	28.31	1.854792	0.60206	2	1.45194
6	31.88	1.832573	0.69897	2.236068	1.503518
7	35.04	1.811910	0.778151	2.44949	1.544564
8	40.05	1.776992	0.845098	2.645751	1.602603
9	46.89	1.724276	0.903090	2.828417	1.67108
10	52.05	1.679791	0.954293	3	1.716421
11	65.03	1.542327	1	3.162278	1.813114
12	77	1.359646	1.041393	3,316625	1.886491
13	97.23	0.424882	1.079181	3.464102	1.987881

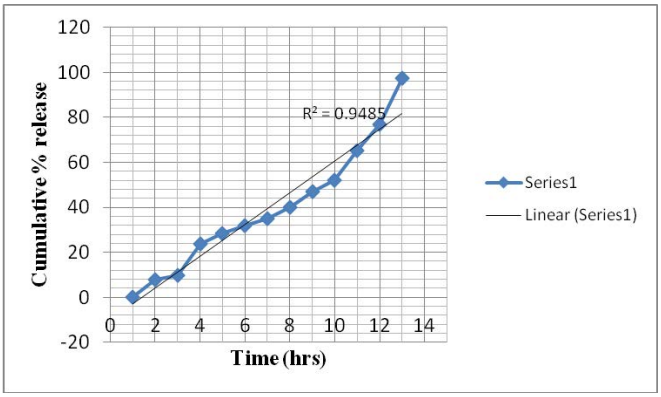


Figure 7. Zero order plot of formulation F5.

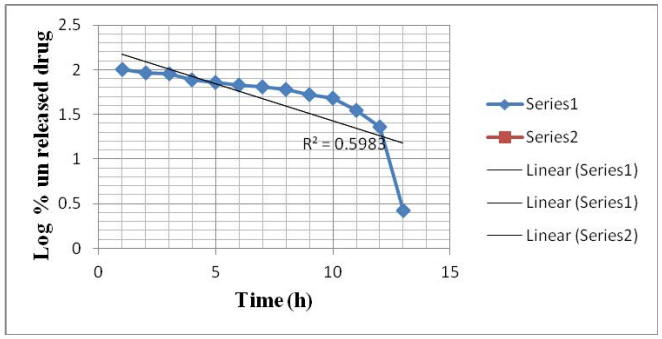


Figure 8. First order plot of formulation F5.

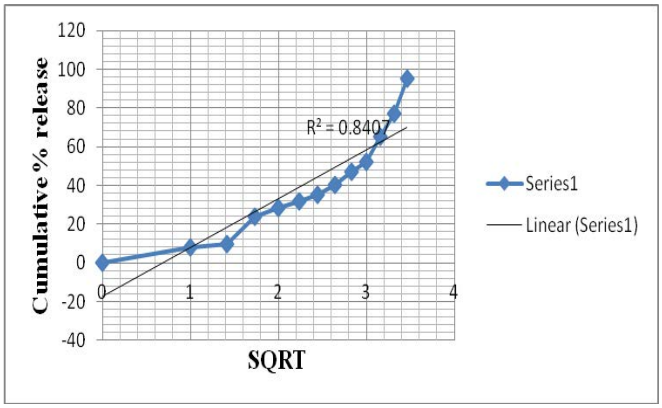


Figure 9. Higuchi plot of formulation F5.

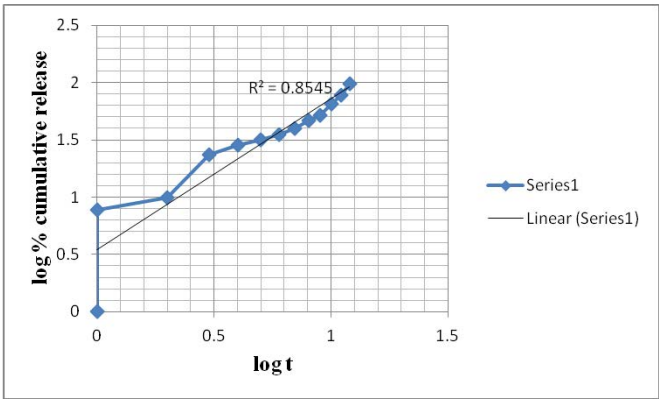


Figure 10. Korsmeyer - peppas plot of formulation F5.

Table 13. Coefficient of correlation using mathematical models (F-1 to F-10)

Model		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Zero order R^2		0.958	0.935	0.946	0.979	0.947	0.982	0.681	0.720	0.807	0.892
First order R^2		0.583	0.716	0.795	0.686	0.596	0.893	0.287	0.491	0.469	0.543
Higuchi's R^2		0.887	0.866	0.867	0.865	0.834	0.881	0.760	0.789	0.813	0.867
Korsmeyer – peppa's	**R^2**	0.973	0.977	0.976	0.974	0.946	0.986	0.861	0.871	0.917	0.941
	N	0.943	0.991	0.969	0.984	0.988	0.974	0.963	0.993	0.951	0.974

Table 14. Stability studies of optimized formulation (Physical parameter)

Temperature and relativeHumidity (± 2^{0}C, ± 5% RH)	Days				Parameters
	0	30	60	90	
25^{0}C/ 60% RH					
30^{0}C/ 65% RH		No change			Physical appearance
40^{0}C/75% RH					

Table 15. Stability studies of optimized formulation (Hardness, friability and drug content)

No of days	Physical parameters								
	Hardness (Kg/cm^2) (± 2^{0}C, ± 5% RH)			Friability % (± 2^{0}C, ± 5% RH)			% of Drug content (± 2^{0}C, ± 5% RH)		
	25°C/ 60%	30^{0}C/ 65%	40^{0}C/ 75%	25°C/ 60%	30^{0}C/ 65%	40^{0}C/ 75%	25°C/ 60%	30^{0}C/ 65%	40^{0}C/ 75%
Initial	6.8±0.121	6.82±0.101	6.89±0.112	0.111	0.121	0.098	99.58	99.23	99.04
30	6.81±0.12	6.87±0.111	6.90±0.890	0.109	0.110	0.095	99.58	99.12	99.12
60	6.7±0.011	6.89±0.122	6.92±0.121	0.099	0.100	0.084	99.46	99.12	99.10
90	6.7±0.120	7.05±0.101	7.10±0.121	0.089	0.089	0.081	99.10	99.04	99.12

Table 16. Stability study of optimized formulation (dissolution)

Time in hours	Cumulative drug release percentage								
	30 days later			60 days later			90 days later		
	25°C/ 60%	30°C/ 65%	40°C/ 75%	25°C/ 60%	30°C/ 65%	40°C/ 75%	25°C/ 60%	30°C/ 65%	40°C/ 75%
1	-	-	-	-	-	-	-	-	-
2	7.78	7.73	7.75	7.76	8.12	8.14	8.23	8.25	8.23
3	9.89	9.97	9.99	10.2	11.32	12.11	12.22	12.44	12.43
4	23.56	23.54	23.59	24.2	25.3	25.61	25.61	26.22	26.34
5	28.31	29.1	29.4	30.4	31.6	31.23	32.11	34.34	34.33
6	31.88	31.9	31.92	32.3	33.65	34.61	35.21	35.23	36.3
7	35.04	36.2	36.23	36.97	37.22	37.22	37.11	37.23	37.34
8	40.05	40.12	40.15	40.87	41.34	41.44	42.43	42.34	42.36
9	46.89	46.94	46.95	47.4	46.98	47.12	48.23	49.34	49.67
10	52.05	52.07	52.08	52.89	53.45	54.33	55.34	56.56	56.67
11	65.03	65.07	65.23	65.87	67.87	68.44	69.52	70.12	71.23
12	77	77.20	77.25	78.9	79.12	80.12	81.22	81.11	83.45
13	97.23	97.28	97.76	97.84	97.90	98.12	98.12	98.12	98.56

developed for NA by encapsulating with natural phenolic antioxidant polymer. This approach is to achieve stable drug level in plasma with reduced fluctuations via slow drug release over an extended period of time The F4 and F5 formulations resulted in good drug release and encapsulation efficiency. But formulation F-4 showed the release percentage of 97.74% for 11 hours whereas F-5 with 97.23% for 12 hours. The drug release followed zero order release. The results suggested that the formulated controlled-release tablets of NA through encapsulation can be effective than the conventional dosage forms and also better patient compliance. Preclinical and clinical studies can be further performed in order to evaluate the efficacy of NA controlled release formulations for the management of dyslipidemia.

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7. References

1. Harris D, Fell JT, Sharma HL, Taylor DC. GI transit of potential bioadhesive formulations in man. A scintigraphic study. Journal of Controlled Release. 1990; 12(2):45–53. https://doi.org/10.1016/0168-3659(90)90182-S
2. Shah SH, Patel JK, Patel NV. Stomach specific floating drug delivery system. International Journal PharmTech, Research. 2009; 1(3):623–33.
3. Knopp RH, Ginsberg J, Albers JJ, Hoff C, Ogilvie JT, Warnick GR, et al. Contrasting effects of unmodified time release forms of niacin on lipoproteins in hyperlipidemic subjects. Metabolism. 1985; 34(7):642–50. https://doi.org/10.1016/0026-0495(85)90092-7
4. Luria MH. Effect of low dose niacin on high density lipoprotein cholesterol and total cholesterol ratio. Archives of Internal Medicine. 1988; 148(11):2493–5. https://doi.org/10.1001/archinte.1988.00380110121025. PMid:3190381
5. Rang HP, Dale MM. Pharmacology, 5th ed. Elsevier Churchill Livingstone; 2007.
6. Cowan MM. Plant products as antimicrobial agents. Clinical Microbiology Reviews. 1999; 12:564–82. https://doi.org/10.1128/CMR.12.4.564. PMid:10515903 PMCid:PMC88925
7. Beecher GR. Proanthocyanidins: Biological activities associated with human health. Pharmaceutical Biology. 2004; 42(1):2–20. https://doi.org/10.3109/13880200490893474
8. Ding Y, Dai X, Jiang Y, Zhang Z, Li Y. Functional and morphological effects of grape seed proanthocyanidins on

peripheral neuropathy in rats with type 2 diabetes mellitus. Phytotherapy Research. 2014; 28(7):1082–7. https://doi.org/10.1002/ptr.5104. PMid:24343984
9. Devi SA, Chandrasekar BKS, Manjula KR, Ishii N. Grape seed proanthocyanidin lowers brain oxidative stress in adult and middle-aged rats. Experimental Gerontology. 2011; 46(11):958–64. https://doi.org/10.1016/j.exger.2011.08.006. PMid:21871550
10. Wang X-h, Huang L-l, Yu T-t, Zhu J-h, Shen B, Zhang Y, et al. Effects of oligomeric grape seed proanthocyanidins on heart, aorta, kidney in DOCA-salt mice: Role of oxidative stress. Phytotherapy Research. 2013; 27(6):869–76. https://doi.org/10.1002/ptr.4793. PMid:22903376
11. Engelbrecht AM, Mattheyse M, Ellis B, Loos B, Thomas M, Smith R, et al. Proanthocyanidin from grape seeds inactivates the PI3-kinase/PKB pathway and induces apoptosis in a colon cancer cell line. Cancer Letters. 2007; 258(1):144–53. https://doi.org/10.1016/j.canlet.2007.08.020. PMid:17923279
12. Zhang B, Kang M, Xie Q, Xu B, Sun C, Chen K. Anthocyanins from Chinese bayberry extract protect β cells from oxidative stress-mediated injury via HO-1 upregulation. Journal of Agricultural & Food Chemistry. 2011; 59(2):537–45. https://doi.org/10.1021/jf1035405. PMid:21166417
13. Lacombe A, Wu VCH, White J, Tadepalli S, Andre EE. The antimicrobial properties of the lowbush blueberry (*Vaccinium angustifolium*) fractional components against foodborne pathogens and the conservation of probiotic *Lactobacillus rhamnosus*. Food Microbiology. 2012; 30(1):124–31. https://doi.org/10.1016/j.fm.2011.10.006. PMid:22265292
14. de Rosso VV, Hillebrand S, Montilla EC, Bobbio FO, Winterhalter P, Mercadante AZ. Determination of anthocyanins from acerola (*Malpighia emarginata* DC.) and açai (*Euterpe oleracea* Mart.) by HPLC-PDA-MS/MS. Journal of Food Composition and Analysis. 2008; 21(4):291–9. https://doi.org/10.1016/j.jfca.2008.01.001
15. Masquelier J. United States Patent Number 3,436,407; 1969 April.
16. Das DK. Cardio protection of red wine: Role of polyphenolic antioxidants. Drugs under Experimental and Clinical Research. 1999; 25:115–20.
17. Sato M. Cardio protection with alcohol, role of both alcohol and polyphenolic antioxidants. Annals of the New York Academy of Sciences. 2002; 957:122–35. https://doi.org/10.1111/j.1749-6632.2002.tb02911.x. PMid:12074967
18. Martí M-P, Pantaleón A, Rozek A, Soler A, Valls J, Macià A, et al. Rapid analysis of procyanidins and anthocyanins in plasma by microelution SPE and ultra-HPLC. Journal of Separation Science. 2010; 33(17–18):2841–53. https://doi.org/10.1002/jssc.201000274. PMid:20730832
19. Scalbert A, Manach C, Morand C, Remesy C. Dietary of polyphenols and the prevention of diseases. Reviews in Food Science and Nutrition. 2005; 45(4):2872306. https://doi.org/10.1080/1040869059096. PMid:16047496
20. Mennen LI, Sapinho D, De Bree A, Arnault N, Bertrais S, Galan P, et al. Consumption of foods rich in flavonoids is related to a decreased cardiovascular risk in apparently healthy French women. Journal of Nutrition. 2004; 134(4):923–6. https://doi.org/10.1093/jn/134.4.923. PMid:15051848
21. Mathiowitz E, Kreitz MR, Brannon-Peppas L. Microencapsulation. Encyclopedia of controlled drug delivery. New York. John Wiley & Sons Inc.; 1999. p. 493–546.
22. Baruch L, Machluf M. Alginate-chitosan complex coacervation for cell encapsulation effect on mechanical properties and on long-term viability. J Biopolymers. 2006; (82):570–9. https://doi.org/10.1002/bip.20509. PMid:16552738
23. Vidhyalakshmi R, Bhakyaraj R, Subhasree RS. Encapsulation "The future of probiotics". A Review. Advances in Biological Research. 2009; (3):96–103.
24. Lachman L, Herbert AL. Compression coated and layer tablets. In: pharmaceutical dosage forms tablets. Marcel Dekker Inc. New York. 2002; (2)1:247–84.
25. Korsemeyer RW, Peppas NA. Macromolecular and modeling aspects of swelling-controlled systems. In: Mansdrofsz, Roseman TJ. Controlled release delivery systems. New York. Marcel Dekker; 1983. p. 77.
26. ICH Q1A (r2) stability testing guidelines: stability testing of new drug substances and products [Internet]. 2003. (cited 2008 (Nov 10). Available from: URL: http:// www.tga.health.gove.au/docs/pdf/euguide /inch/27699r 2en.pdf.