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Design and Development of Extended Release Tablet of Nicotinic Acid

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ABSTRACT

Nicotinic acid (NA) although known since decades, as an lipid lowering agent drug has not become a first-line treatment due to the strong side effect called flushing occurs when given in Immediate release (IR)dosage form. In the present research, an attempt has been made to formulate extended release matrix tablets of Nicotinic acid (NA). The tablets were prepared by wet granulation method and the prepared tablets of NA will remain intact up to 2 hrs even in pH 1.2 due to eudragit L 100-55 and its release is not only initiated but tact fully retarded up to 12 hrs and were found to be superior in physical properties, dissolution characteristics, and drug content uniformity. The *in vitro* NA release data justified the release mechanism to be Case-III and dissolution control release was found to be a mixed pattern of zero order and Korsmeyer-Peppas release models. Moreover, lactose shows moderately affected drug release due to channeling action and hence causing drug release at desired rate and amount.

Keyword: Nicotinic acid (NA), Extended release (ER), HPMC K15M. Eudragit L 100-55, di calcium phosphate (DCP).

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INTRODUCTION:

Hyperlipidemia (HPL) is a major cause of atherosclerosis and atherosclerosis-associated conditions, such as coronary heart disease (CHD), ischemic cerebrovascular disease, and peripheral vascular disease. These conditions account for the majority of morbidity and mortality among middle-aged and older patients. HPL and low levels of high-density-lipoprotein cholesterol (HDL-C) are major causes of increased atherogenic risk; both genetic disorders and lifestyle contribute to the HPL seen in developed countries around the world[1].

NA has been used to treat HPL for more than 50 years. In pharmacologic doses, NA has multiple effects on lipoprotein metabolism. In adipose tissue, NA inhibits the lipolysis of triglycerides by hormone sensitive lipase. In the liver NA reduces triglyceride synthesis by inhibiting both the synthesis and esterification of fatty acids, effects that increase apoB degradation. NA also enhances LPL activity, which promotes the clearance of chylomicrons and VLDL triglycerides. NA raises HDL-C (good cholesterol) levels by decreasing the fractional clearance of apoA-Iin HDL rather than by enhancing HDL synthesis.

In clinical practice, however, the use of NA has been limited by poor tolerability, primarily due to cutaneous flushing. Flushing occurs in nearly all patients treated with immediate-release NA. ER formulations were developed to reduce flushing and improve tolerability. IR dosage form of NA is required to administer three times per day after meals. While such a regimen does produce cutaneous flushing. A method of avoiding or reducing the side effects associated with immediate release of drugs like NA is the use of ER formulations. ER formulations are designed to slowly release the active ingredient from the tablet, which allows a reduction in dosing frequency as compared to the typical dosing frequency associated with conventional or immediate dosage forms. The extended drug release reduces and prolongs blood levels of the drug, and thus minimizes or lessens the cutaneous flushing side effects that are associated with conventional or immediate release NA products. The oral route of drug delivery is the most popular, desirable and preferred method of administering therapeutic agents for systemic effects because it is convenient for the patient, and cost effective to manufacturing process. Tablets are the most popular oral formulations available in the market and preferred by the patients and physicians Alike[2].

ER tablet formulations are much desirable and preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and

increase safety margin for high potency drugs[3]. The most commonly used method of modulating the drug release is to include it in a matrix system[4].

The aim of this present work is to formulate an extended release matrix tablet of Nicotinic acid by wet granulation method using polymer such as HPMC K-15M. NA has a short biological half life of 20-48 min. and rapid first pass metabolism which necessitates multiple daily dosing hence the present study was aimed to develop an extended release formulation of NA. The best formulation is to be selected on the basis of evaluation characteristics. To provide a drug delivery system for prolong release of drug at controlled rate and maintains the therapeutic blood plasma concentration for a required period of time.

METHODOLOGY

Construction of standard curve for NA

A. Preparation of Standard Calibration Curve of NA in pH 1.2[5]

Preparation of Stock Solution: 100mg of NA was dissolved in 100ml of pH 1.2 buffers so as to get a stock solution of 1000 µg/ml concentrations.

Table 1: Standard Calibration Curve of NA in pH 1.2

Conc.(µg/ml)	Absorbance(Avg.)
5	0.228
10	0.453
15	0.654
20	0.848
25	1.082

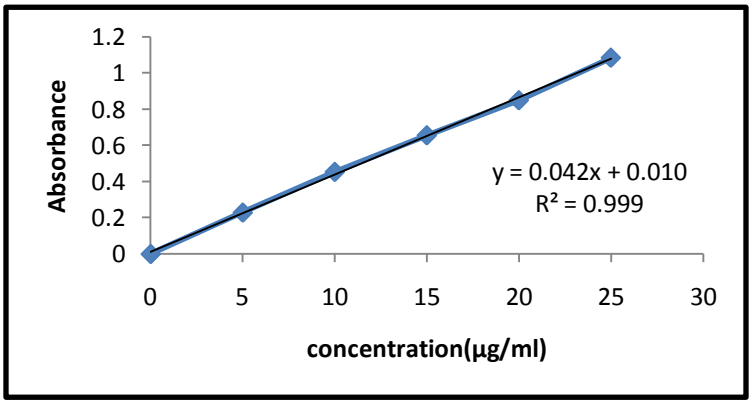

Figure. 1: standard calibration curve NA in pH 1.2

Preparation Standard Solution:

1ml of stock solution was diluted to 100ml with pH 1.2 buffer in 100ml volumetric flask this gives a concentration of 10 µg/ml. Aliquot of standard drug solutions were prepared by withdrawing 5, 10, 15, 20, 25ml and transferred in to 10ml volumetric flask and were diluted up

to the mark with pH 1.2 buffer. This gives the final concentration of 5, 10, 15, 20, 25µg/ml of NA respectively. The absorbances of the solution were measured against pH 1.2 as blank at 261nm using UV visible spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

B. Preparation of Standard Calibration Curve of NA in pH 6.8 Preparation Stock Solution[5]

100mg of NA was dissolved in 100ml of pH 6.8 buffers so as to get a stock solution of 1000 µg/ml concentration

Preparation Standard Solution:

5ml of stock solution was diluted to 100ml with phosphate buffer pH 6.8 this gives a concentration of 50 µg/ml. Aliquot of standard drug solution ranging from 1ml to 7ml were transferred in to 10ml volumetric flask and were diluted up to the mark with pH 6.8 phosphate buffer. Thus the final concentration ranges from 5-35 µ/g/ml. Absorbance of each solution was measured at 262 nm against phosphate buffer pH 6.8 as a blank. A plot of concentrations of drug vs. absorbance was plotted.

Table 2: Standard Calibration Curve of NA in pH 6.8

Conc.(µg/ml)	Absorbance(Avg.)
5	0.13
10	0.264
15	0.366
20	0.494
25	0.610
30	0.728
35	0.820

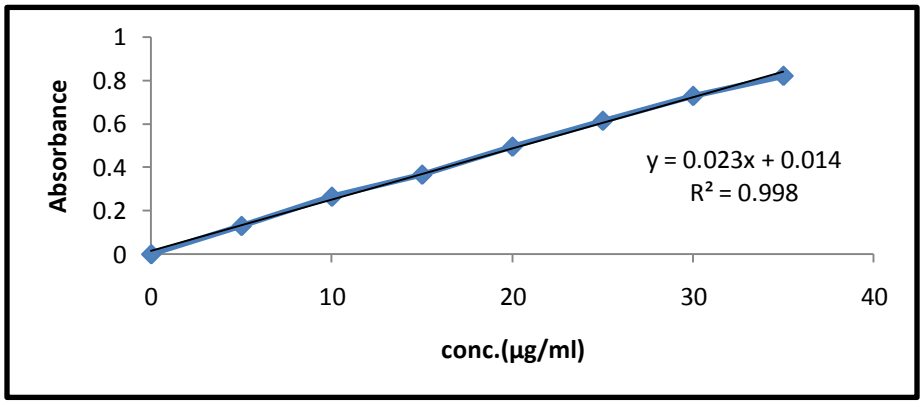

Figure. 2: standard calibration curve NA in pH 6.8

Preparation of NA Matrix Tablets

Extended release tablets of NA were prepared by wet granulation technique using variable concentrations of polymer HPMC K15M. Different steps in Wet Granulation.

a) Weighing and blending: Specified quantity of all materials was weighed and then active ingredient (NA) and polymers were mixed by mortar pestle.

b) Preparation of dump mass: A liquid binder solution of PVP K30 is added to the mixture to facilitate adhesion. A damp mass resembling dough is formed and used to prepare the granulation.

c) Screening the dump mass into pellets or granules: The wet mass was pressed through a 10 number sieve to prepare the granules. This is done by hand. The resultant granules are spread evenly on large pieces of paper in shallow trays and dried

d) Drying the granulation: Granules were dried in hot air oven at 60^0c for 1 to 2 hrs

e) Sizing the granulation by dry screening: Here granules were passed through sieve number 20. Sizing of the granules is necessary so that the die cavity for tablet compression may be completely and rapid filled by the free flowing granulation.

f) Adding lubricant and blending: After completion of dry screening the granules were mixed with magnesium stearate and aerosil which acts as lubricants which prevents the adhesion of the tablet formulation to the punches and dies during compression.

Forming tablets by compression:

After blending with the polymers the granules were subjected to the compression using 10 stations tablet punching machine (Rimek mini press-1 Karnavati Engineering Ltd, Mehsana, Gujarat.) formulation shown in table 3

Coating of prepared tablet:

The prepared tablets were coated using deep coating with Eudragit L 100-55. 12% Eudragit L 100-55 solution in Acetone with 6% concentration of plasticizer

(PEG 400) with respect to Eudragit L 100-55 dry powder. And each tablet coated with Eudragit L 100-55 to gain 4% weight of tablet.

Table 3: Tablet composition of different formulations of NA matrix tablets containing HPMC K15M as extended release polymer using 3^2 factorial.

Ingredient(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nicotinic acid	500	500	500	500	500	500	500	500	500
HPMC K15M	100	100	100	125	125	125	150	150	150
DCP	50	-	-	50	-	-	50	-	-
Lactose	-	50	-	-	50	-	-	50	-
MCC	-	-	50	-	-	50	-	-	50
Mg. Stearate	1%	1%	1%	1%	1%	1%	1%	1%	1%
Aerosil	1%	1%	1%	1%	1%	1%	1%	1%	1%
Total(mg)	**663**	**663**	**663**	**688.5**	**688.5**	**688.5**	**714**	**714**	**714**

- All tablet were prepared using PVP K30 (10%) solution in IPA.
- All tablet were coated with Eudragit L 100-55(12%) solution in Acetone using deep coating method.

3^2 full factorial designs		
Independent variables		Dependent variables
X1	X2	Y
Concentration of HPMC 15M	Excipients	Drug release at 4,6,8,10 hrs, k, n

Evaluation Parameter [6, 7]

Pre and post Compression Parameters: Parameters like bulk density (BD), tapped density (TD), Carr's index (CI), housner's ratio, angle of repose were evaluated before compression. And the parameters like weight variation, hardness(Monsanto Hardness Tester),thickness(Digital Vernier Caliper, Mitutoyo, Chaina), fribility (using Friabilator USP EF-2), were evaluated after compression of the tablet.

Uniformity of drug content:

Five tablets of various formulations were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in Phosphate buffer pH 6.8, the drug content was determined measuring the absorbance at 262 nm after suitable dilution using a UV/Visible Spectrophotometer (UV-1800).

In-vitro release study:

Apparatus:	USP XXIV dissolution testing apparatus II (paddle method)
Dissolution medium:	Phosphate buffer pH- 6.8
Temperature:	37± 0.5 ^{0}C
RPM: `	50
Vol. withdrawn and replaced:	5ml every 1 hour
λ max:	261 in pH1.2 and 262 nm in pH6.8
Blank solution:	Phosphate buffer pH- 6.8
Duration of study:	12 hours
Volume of dissolution media:	900ml

Procedure:

The release rate of NA from tablets was determined using The United States Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle type). The dissolution test was performed using 900 ml of pH 1.2, for first 2 hours then in phosphate buffer pH 6.8 for rest of the hours at 37 ± 0.5°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 hours, and the samples were replaced with fresh dissolution medium.

The samples diluted to a suitable concentration with respected dissolution medium. Absorbance of these solutions was measured using a UV-Visible Spectrophotometer (UV-1800). Cumulative percentage of drug release was calculated.

Drug-polymer compatibility studies:

Studies were carried out using FTIR spectrophotometer (FTIR 8400S Spectrophotometer Shimadzu, Japan) by KBr pellet method.

RESULTS AND DISCUSSION

Compatibility studies:

Study is carried out using FTIR spectrophotometer (FTIR 8400S Spectrophotometer Shimadzu, Japan) by KBr pellet method, the spectra of drug with excipients and polymers confirms that drug is compatible with all excipients (figure3-4).

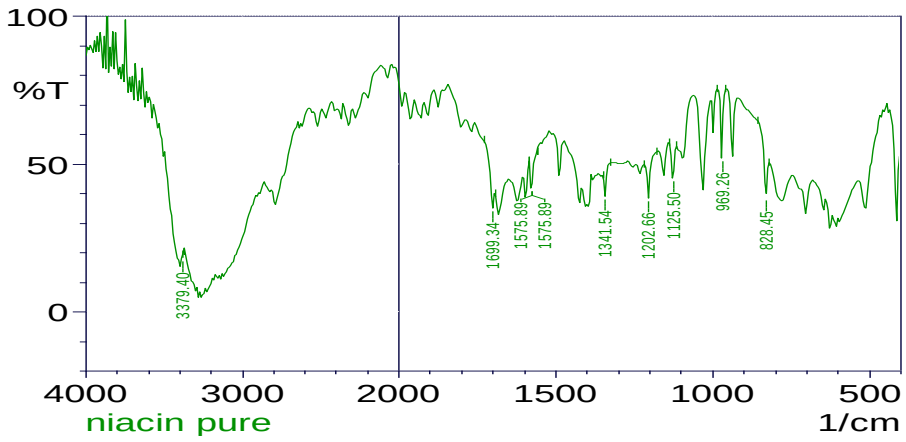

Figure. 3: FTIR spectrum of pure NA

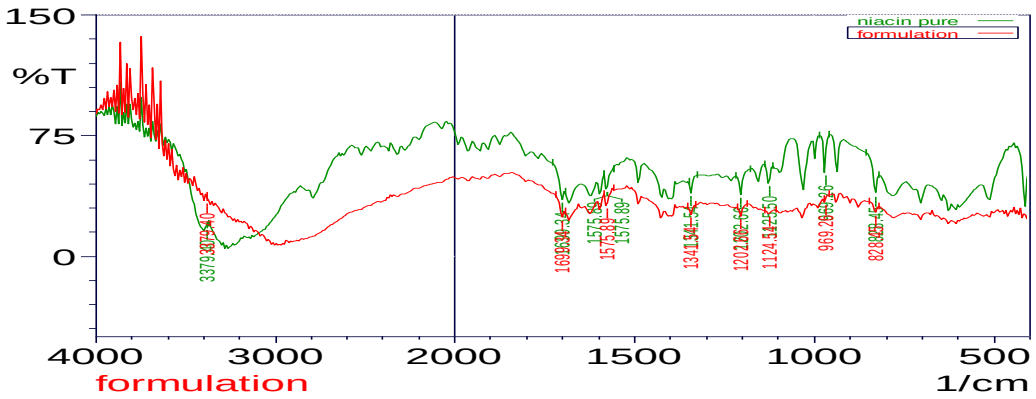

Figure. 4: FTIR spectrum of formulation

Pre and Post compression parameters:

Granules prepared by wet granulation method were evaluated for pre compression parameters measurement of bulk density and angle of repose, Hausner's ratio, compressibility index and

drug content. The results of angle of repose (<30) indicate good flow properties and the values for prepared formulations ranges from 24.32-29.59. Generally Hausner's ratio less than 1.25 shows good flow property and values for all formulation were between the ranges of 1.17-1.23. Compressibility index values up to 15% result in good to excellent 9.54%-13.46%. All these results obtained indicate that the granules possessed satisfactory flow properties, compressibility, (Result shown in Table 4). Drug content for all the formulations were in the ranges from 97.26-100.23% (Table 6). The tablet formulations were subject to various post evaluation tests (Table 5) such as thickness, diameter, uniformity of weight, drug content, hardness, friability. All the parameters pass the pharmacopoeial limits.

Table 4: Pre Compression Parameters

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Angle of repose	25.22	26.25	24.65	25.15	26.45	28.59	27.64	26.33	24.32
Tapped density[TD](g/ml)	0.284	0.278	0.228	0.248	0.234	0.278	0.276	0.246	0.297
Bulk density[BD](g/ml)	0.254	0.246	0.211	0.234	0.215	0.246	0.248	0.215	0.259
Carre's index (%)	10.56	11.51	7.46	5.6	8.12	11.51	10.14	12.60	12.79
Hausner's ratio	1.11	1.13	0.97	1.06	1.08	1.13	1.11	1.14	1.15

- Standard deviation values of Angle of repose of all batches are within the limit of $\pm$ 5.
- Standard deviation values of bulk density of all batches are within the limit of $\pm$ 0.008.
- Standard deviation values of tapped density of all batches are within the limit of $\pm$0 .004
- Standard deviation values of Carre's index of all batches are within the limit of $\pm$0.95
- Standard deviation values of hausner's of all batches are within the limit of $\pm$ 0.02

Table 5: Post Compression Parameters

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Thickness(mm)	7.01	7.11	7.08	7.04	7.06	7.1	7.13	7.09	7.08
Hardness(kg/cm^2)	7.2	7.5	6.8	6.7	7.4	6.7	7.8	7.5	7.6
Friability (%)	0.06	0.05	0.07	0.07	0.06	0.07	0.04	0.05	0.05

Table 6: Drug Content Uniformity

Tablet formulation	Calculated value(mg)	%drug content
F1	500	99.11
F2	500	98.45
F3	500	99.85
F4	500	97.65
F5	500	98.25
F6	500	100.23
F7	500	97.26
F8	500	100.12
F9	500	96.23

Dissolution study:

Dissolution study is carried out using USP-2 apparatus result shown in the table 7, the release of the formulation F8 shows the release up to 12hrs. And it can be drawn that release rate decreases as the concentration of the polymer increases. Correlation coefficients of different mathematical

models for formulations F-1 to F-9 was calculated (Table 8), and graphs of optimized formula F8 were plotted. Model fitting for formulation F8 was shown in figure 5. ANOVA for dependent variables from experimental design of F8 formulation was shown in Table 9 and Response surface plots was shown in figure 6.

Table 7: Percentage drug release of formulations F1-F9

Time(Hrs.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	4.67	7.63	10.17	3.99	6.27	9.27	3.34	5.41	8.62
1	13.26	18.63	22.14	11.59	16.15	21.11	8.65	14.63	20.21
2	19.07	24.85	29.84	17.36	23.49	29.27	14.36	21.44	26.29
3	26.58	35.95	42.99	21.37	34.28	41.95	21.55	30.70	40.14
4	34.36	53.40	61.84	29.12	49.06	58.75	24.97	39.40	55.77
5	45.19	65.90	82.97	28.90	61.26	81.70	33.48	50.73	77.76
6	53.07	76.15	99.04	44.97	67.46	93.88	37.35	58.16	89.37
7	62.43	83.59		50.13	80.17	99.24	44.53	68.71	94.22
8	70.14	83.59		59.06	87.90		49.45	74.13	98.01
9	76.24	92.16		67.16	95.68		55.85	82.30	
10	82.93	100.77		71.54	98.51		63.04	89.98	
11	87.67			77.18			70.34	94.76	
12	92.65			84.07			77.13	99.90	

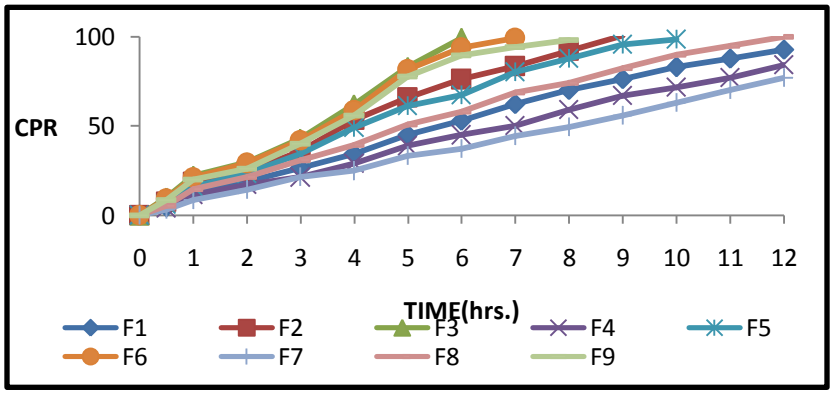

Figure. 4: In-vitro dissolution profile of F1 to F9 formulations

Table 8: Correlation coefficients of different mathematical models for formulations

Formulation	Zero order R^2	First order R^2	Higuchi's R^2	Korsmeyer-peppas	
				R^2	n value
F1	0.9249	0.8568	0.9620		
F2	0.9943	0.9263	0.9899	0.9813	0.7917
F3	0.9929	0.9654	0.9688	0.9934	0.8741
F4	0.9981	0.9155	0.9852	0.9894	0.8745
F5	0.9931	0.9125	0.9921	0.9934	0.9064
F6	0.9922	0.9490	0.9787	0.9951	0.9049
F7	0.9989	0.9256	0.9778	0.9923	0.8892
F8	0.9956	0.9054	0.9927	0.9968	0.9378
F9	0.9859	0.9341	0.9818	0.9954	0.8836
				0.9910	0.8840

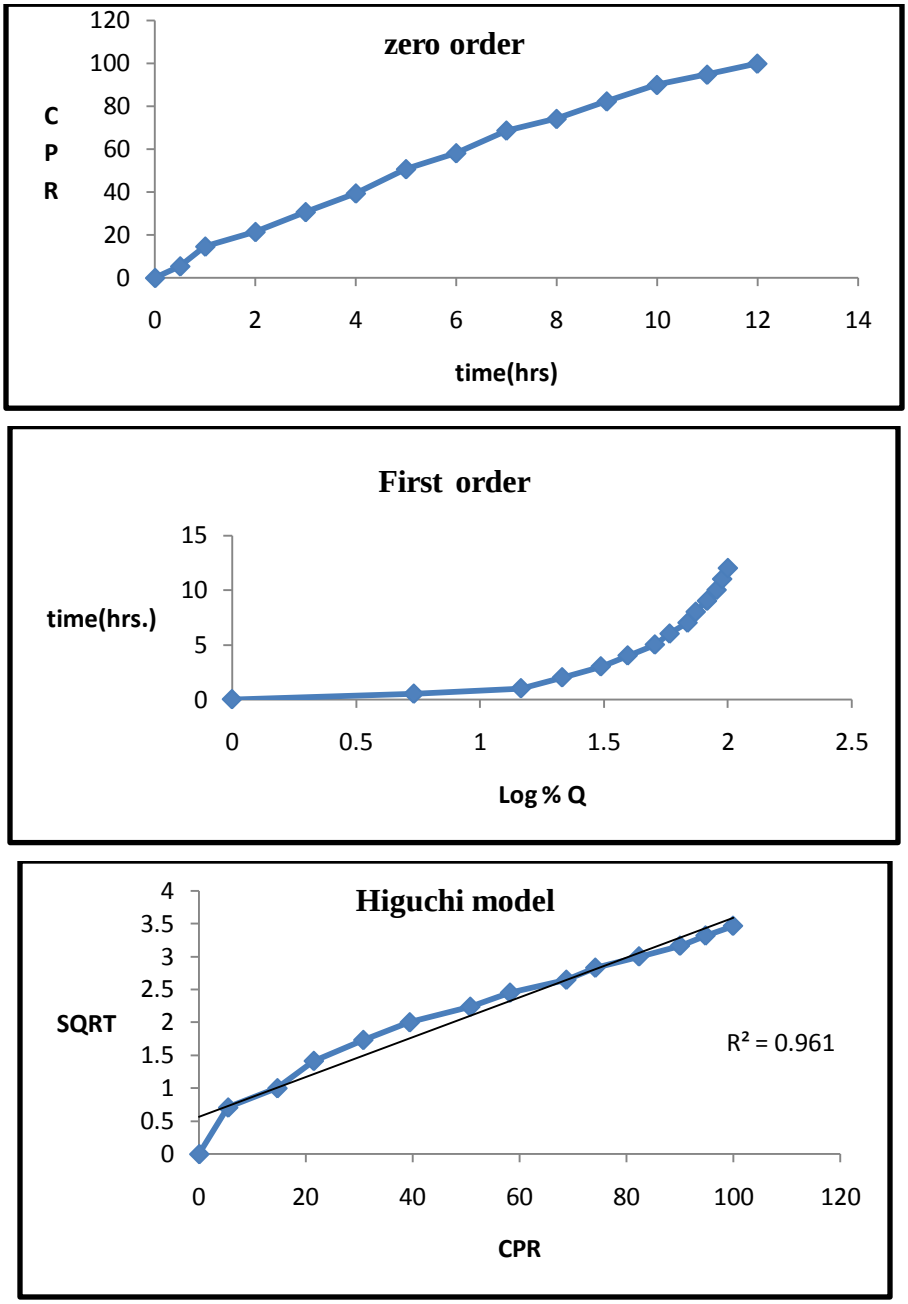

Figure: 5 Model fitting for formulation F8:

Table: 9 ANOVA for dependent variables from experimental design of F8 formulation.

	DF	SS	MS	F	p	R^2
Q4	5	1455.717	291.1433	51.00998	0.004212	0.988374
Q6	5	3930.159	786.0319	248.8804	0.0004	0.997595
Q8	5	2545.019	509.0037	32.57007	0.008126	0.981911
Q10	5	1231.709	246.3417	9.828576	0.044455	0.942466
n	5	0.002673	0.000535	2.608702	0.229923	0.813009
k	5	0.013537	0.002707	359.8089	0.00023	0.998335

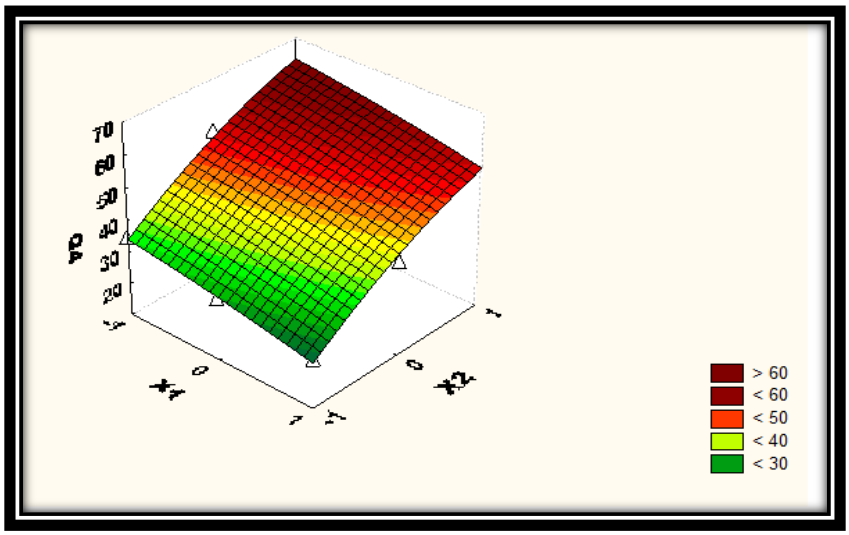

Figure: 6 Response surface plots:

Q4: CPR at 4 hrs, **X1**: HPNC K15M, concentration, **X2**: excipients

CONCLUSION:

In this study matrix tablet of NA were prepared by wet granulation technique, using HPMC K-15M, polymer as retardant. The drug-polymer ratio was found to influence the release of drug from the formulations. It was found that increase in the concentration of HPMC K-15M in polymeric ratio decreases the drug release. The formulations F-5, and F-8 showed good drug release with good matrix integrity but the formulation F-5 showed the release up to 10hr (i.e.98.51% release at the end of 10hr) while the formulation F-8 showed the release of 99.90% at the end of 12hr so the formulation F-8 selected as the optimized formula . The enteric coated polymer Eudragit L100-55 was used to avoid the drug release in stomach because the drug is quiet unstable in stomach and the aim of the work is to release the drug in intestine.

Use of different excipients has significant effect on drug release, because DCP retarded the release due to hydrophobic nature, on the contrary MCC increased drug release for its swelling property and causing burst release, and lactose moderately affected drug release due to channeling action and hence causing drug release at desired rate and amount. The formulation F-8 showed good drug release with good matrix integrity. Different parameters like hardness, friability, weight variation, drug content uniformity, *in-vitro* drug release were evaluated. Based on these results formulation F-8 was found to be the most promising formulations. The regression coefficient (R^2) of Higuchi plot of optimized formula F-8 shows that the drug releases through the matrix was diffusion and slope (n) value of peppas plot confirms that non-Fickian diffusion (dissolution control transport) was the main mechanism. The regression coefficient (R^2) values of zero order of the optimized formulation F-8 was greater than the R^2 release

kinetics. The results suggest that the developed extended-release matrix tablets of NA could perform better than conventional dosage forms, leading to improve efficacy and better patient compliance. Thus the aim of this study was achieved. Further preclinical and clinical studies are required to evaluate the efficacy of these formulations of NA in the management of Hyperlipidemia.

REFERENCE:

1. Goodman and Gilman's the pharmacological basis of therapeutics, 10th edition, 2001: 991-992 1758-1760.
2. Brahmankar DM, Jaiswal SB. "Biopharmaceutics and pharmacokinetics a treatise" 1st ed. Vallabh prakashan; New Delhi: 1995: 64-70
3. Sallsa T. Veiga F, Pina ME. Oral controlled - release dosage forms Cellulose ether polymers in hydrophilic - matrices. Drug Dev Ind Pharm 1997; 23: 929 - 938.
4. Alderman DA. A review of cellulose ethers in hydrophilic matrices for oral controlled - release dosage forms. Int S Pharm Tech Prod Manuf 1984; 5:1-9.
5. Singh A, Mohamed R. Design and Evaluation of controlled release tablet of Lipid lowering agents for hyperlipidemia. Int J Pharm Pharma Sci 2011;3(4):201-08.
6. Lachman Leon, Lieberman Herbert A. Pharmaceutical Dosage Forms: Tablets. In: The Theory and Practice of Industrial Pharmacy. Lea and Febiger, U.S.A, 1991; 3rd edition: 293-345.
7. Subrahmanyam CVS.Textbook of physical pharmaceutics. 2nd ed. Delhi : Vallaba prakashan;2003.p.180-234.
8. Modern pharmaceutics, revised and expanded, edited by Gilbert S. banker, Christopher T. Rhodes. 2002.
9. Chein YW. Oral Drug delivery and delivery systems. In: Novel drug delivery systems. Marcel Dekker, Inc., New York, 2002; 50; 3rd edition: 139-96.
10. Gohel MC, Patel TP, BarigyaSH. Studies in preparation and evaluation of pH independent sustained – release matrix tablets of Verapamil Hcl using directly compressible Eudragits. Pharam Dev Technol, 2003; 8: 323 – 333. Pubmed Dol: 10. 1081 / PDT – 120024686.
11. Anroop B. Nair, Hiral vyas, Ashok Kumar. Controlled release matrix uncoated tablets of enalapril maleate using HPMC alone, J Basic Clinical Pharm 2010; 1(2).
12. Shantveer V. Salger, Lingaraj S. Danki, Abdul Sayeed , Shivanand Hiremath.Formulation and *in-vitro* evaluation of sustained release matrixtablets of anti-hypertensive drug

propranolol hydrochloride, Scholars Research Library. Der Pharmacia Lettre, 2010;2(5):12-22.

13. Yadav Amit.S, Ashok Kumar P, Vinod R, Someshwara Rao B, Suresh V Kulkarni. Design and Evaluation of Guar Gum Based Controlled Release Matrix Tablets of Zidovudine. J Pharma Sci Technol 2010; 2(3):156-162
14. Marikanti R, Kiran Joshi, Vidya Sagar P, Venkateswara reddy CH. Kiran kumar BA, Nagaraju I, Srinivasa Rao, Ravi kiran. Formulation and evaluation of controlled release matrix tablets of Trimtazidine Dihydrochloride. J Chem Pharm Res 2010; 2(3):746-753.
15. Raju Manda, K Sundaramoorthy, Vetrichelvan T. Formulation and In-Vitro Evaluation of sustained release Matrix Tablets of Aceclofenac by using different natural polymers. Res J Pharma Chem Sci 2010:279-91.
16. Santanu Ghosh, Barik BB. Preparation and evaluation of aceclofenac sustained release formulation and comparison of formulated and marketed product. Int J Medicine Medical Sci 2009;1(9):375-382.
17. Kar RK, Mohapatra S, Barik BB. Design and characterization of controlled release matrix tablets of zidovudine. Asian J Pharma Clinical Res 2009; 2(2).
18. Korsemeyer RW, PeppasNA. Macromolecular and modeling aspects of swelling – controlled Systems. In: Mansdrofsz, Roseman TJ, ad, Controlled Release Delivery systems. New – York, NY: Marcel Dekker; 1983:77.