

NEWER COMBINATION OF ACETYL SALICYLIC ACID AND NICOTINIC ACID IN BILAYER MATRIX TABLETS FOR DYSLIPIDEMIA: DESIGN AND EVALUATION THEREOFF

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ABSTRACT

Nicotinic acid (NA) although known since decades, as an antidyslipidemic drug has not become a first-line treatment due to the strong side effect called flushing. The combination product of acetyl salicylic acid (ASA) in immediate release (IR) layer and NA in sustained release (SR) layer to design a bilayer matrix tablets (BMTs) is conceptualized based on the fact that, in clinical practice, ASA is used as "the drug" to prevent or reduce the severity of NA-related flushing. IR of ASA was more than 80% within one hour which is attributed to the Sodium starch glycolate. SR of NA will remain intact upto 2 hours even in pH 1.2 due to eudragit and hydroxyl propyl methylcellulose phthalate and its release is not only initiated but tact fully retarded upto 12 hours which is solely attributable to the hydroxyl propyl methylcellulose. All prepared BMTs were found to be superior in physical properties, dissolution characteristics and drug content uniformity. The *in vitro* NA release data justifies the release mechanism follows Case-II and anomalous transport and was found to be a mixed pattern of first order and Korsmeyer-Peppas release models. Accelerated stability studies of optimal formulation FA3 made it clear that the drug content degradation of both the drugs was very negligible. Release pattern was almost unaffected and could be claimed to be stable at the end of six months. The f_1 and f_2 analysis before and after storage of optimal formulation, suggests that the dissolution profile of NA is superimposable with each other.

Keywords: Nicotinic acid, Acetyl salicylic acid, Bilayer matrix tablets and Stability studies.

INTRODUCTION

Today cholesterol-lowering medications are the 2nd most prescribed drug class; (behind only pain relievers). Since a long time, NA has been continuously under consideration to tackle the CVDs by treating dyslipidemia. Of all potent lipid-modifying drugs, Nicotinic acid (NA) has been named 'the broad-spectrum lipid drug'.¹ However, its usefulness has been limited due to a very disturbing side effect i.e., flushing, which is a prostaglandin D₂-mediated vasodilation. This flushing can be prevented in two best ways, of which one is the use of Acetyl salicylic acid (ASA) as is well known. Yet, one another way is to enable the extended release of NA itself. The extended release NA gives rise to much less flush than immediate release NA and has the same broad spectrum lipid effects as immediate release NA.²

From times in memoriam ASA has been used as an analgesic, antipyretic and also as a panacea to many illness like pericarditis, acute myocardial infarction^{5,6} heart attacks, strokes, blood clot⁵ and migraine.⁷ Nevertheless it is a highly effective inhibitor of prostaglandin synthesis, the best choice to prevent or reduce the severity of NA-related flushing.^{7,8} Since ASA can inhibit and modify the COX-2 enzyme it can be used to permit the use of NA without flushing.⁹

The bilayer sustained release matrix tablets (BSRMTs) were prepared such that ASA is contained in the first layer to obtain an immediate release there by giving a high serum concentration in a short period of time. The second layer in which NA is contained is a prolonged-release matrix, to maintain an effective plasma level for a prolonged period of time.¹⁰⁻¹²

Hydrophilic matrix system has often proved to be popular among the oral controlled drug delivery (OCRDD) technologies because of its simplicity of formulation, low cost, ease of manufacturing, FDA acceptance, and applicability to drugs with wide range of solubility.¹³⁻¹⁵ While considering preparations of OCRDD system the most widely and successfully used hydrophilic retarding agent is Hydroxypropyl Methylcellulose (HPMC).¹⁶ HPMC when comes in contact with gastrointestinal fluid, swells, gels, and finally dissolves slowly.¹⁷ Hydrophilic swellable polymer HPMC along with the enteric coating polymer hydroxypropyl methyl-cellulose phthalate

(HPMCP) or Eudragit RS100 has been used for coating the second layer, so that the release of NA in the gastric fluid is by far prevented.

Aim of the study

Now the focus of attention would be to use NA by cleverly handling the flush. At this juncture the entry of acetyl salicylic acid (ASA) has been taken to give the best result. May it be recalled that "People with heart disease should be on ASA anyway." The usual prescription for NA is always accompanied with ASA in variably so as to be taken half an hour before the administration of NA. This means there is a duplication of efforts of taking two concomitant drugs one following the other. Instead, the designing of a single dosage form that can give a combination of the two separate drugs (NA and ASA) with exclusivity of release mechanism is the theme of the present research.

1). By and large reports reveal that, so far there have been no formulations of BSRMTs for dyslipidemia that have used a combination of ASA and NA. Hence, the curiosity to explore the feasibility of such a formulation for dyslipidemia has become the theme of the present research work. As such, ASA as first layer (Immediate release) and NA as second layer (extended release) have been selected for formulations. 2). The BSRMTs of ASA and NA, to achieve the effective release of NA at simulated intestinal fluid only and that; the ASA has been released completely in the gastric fluid already. 3). Is also aimed to evaluate the prepared tablets with respect to preformulation studies, physicochemical parameters, *in vitro* drug release studies, stability studies, surface morphological studies.

MATERIALS AND METHODS

Nicotinic acid and Acetyl salicylic acid, the model drugs for this study have been procured from Western India, Pvt Ltd, Rajasthan, India. HPMC K100M, HPMC K15M, Eudragit S100 Polyvinylpyrrolidone (PVP-K30) and Sodium starch glycolate (SSG) from S.D. Fine Chemicals, Mumbai, India. Triethyl citrate (TEC), Magnesium stearate, Talc and Microcrystalline cellulose (MCC) from Loba chemie, Pvt Ltd, Mumbai, India. All the other ingredients used throughout the study are of analytical grade.

Method

Preparation of Bilayer tablets

Preparation of the controlled release layer

The composition of the tablets in controlled release layer (CRL) is given in Table 1.a., formulations FA1, FA2, FB1 and FB2, containing NA, HPMC and an enteric coating polymer HPMCP were prepared by wet granulation using varying concentrations of PVP-K30 (as granulating agent) in isopropyl alcohol. The formulations FA3, FA4, FA5, FB3, FB4 and FB5, containing NA and HPMC were prepared by wet granulation using varying concentrations of Eudragit S100 (as

enteric coating polymer), TEC (60%) and 1M ammonia and talc (as anticaking agent) in isopropyl alcohol.¹⁸ Dough mass was passed through sieve No.12 (sieve opening: 1,680 µm), dried by hot air oven and were again passed through sieve No. 20 (sieve opening: 840 µm) superimposed on sieve No.40 (sieve opening:420 µm). The 20/40 fraction of granules were blended with sieved and weighed lubricants and manually fed into the die in a 10-station rotary tablet compression machine (Rimek Mini Press-1, Ahmadabad, India), equipped with concave punches of 9.5mm diameter. Nine die cavities were blocked with stainless steel solid blocks and then compressed.

Table 1: (a) Different composition of Immediate release Formulation, (b) Different composition of Controlled release Formulation.

Ingredients (mg/tab)	FA1	FA2	FA3	FA4	FA5	FB1	FB2	FB3	FB4	FB5
a. Composition for Controlled release layer										
NA	250	250	250	250	250	250	250	250	250	250
HPMC K100M	210	185	220	215	175	-	-	-	-	50
HPMC K15M	-	-	-	-	50	210	185	220	215	175
HPMCP	20	40	-	-	-	20	40	-	-	-
PVP K 30	25	25	-	-	-	25	25	-	-	-
Eudragit S100	-	-	20	15	10	-	-	20	15	10
TEC	-	-	12	9	6	-	-	12	9	6
Talc	-	-	4	3	2	-	-	4	3	2
IPA	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
Mag stearate	04	04	04	04	04	04	04	04	04	04
b. Composition for Immediate release layer										
ASA	80	80	80	80	80	80	80	80	80	80
SSG	10	10	10	10	10	10	10	10	10	10
Mag stearate	02	02	02	02	02	02	02	02	02	02
MCC	04	04	04	04	04	04	04	04	04	04

Preparation of immediate release layer

For the preparation of the two-layer tablets, the die of the tableting machine was filled with granules and a pre compression was done followed by filling of the immediate release constituents into the die cavity and then compressed to the final tablet. The accurately weighed and sieved ingredients of Table 1.b were manually fed into the die on CRL and then compressed to the final tablet.

Evaluation of pre and post compression parameters of formulations¹⁹⁻²¹

Pre compression test

Bulk density (Db), tapped density (Dt), Percentage compressibility (PC), Hausner ratio (HR) and the angle of repose of granules were determined (Table 2). Db and Dt were determined by USP method I using a Tapped density tester (ETD 1020, Electrolab, Mumbai, India). Percent compressibility and hausner ratio were calculated using Equation (1) and (2).

$$\text{Percent compressibility} = \{(Dt - Db) / Dt\} \times 100 \text{ ----- (1)}$$

$$\text{Hausner ratio} = Dt / Db \text{ ----- (2)}$$

Where, Dt and Db are tapped and bulk densities.

Post Compression Tests

For the determination of weight variation, tablets of each batch, were randomly sampled and individual weight of tablets was taken in analytical balance (Sartorius Model TE-214 S (d=0.0001) Germany). Thickness and diameter of tablets was measured individually using digital vernier caliper (Mitutoyo, Japan). The crushing strength of each tablet was measured using a Monsanto hardness tester (Campbell Electronics, Mumbai). The friability was measured using Friabilator (EF-2 Friabilator (USP) Electrolab, Mumbai), after which tablets weighed from each batch were rotated

for 4 min at 25 rpm and re-weighed to test the percentage loss of weight.

Estimation of drug content

Content of ASA and NA in the prepared tablets was determined by randomly taking ten tablets that were weighed and subsequently powdered using a pestle and mortar. Powder equivalent to the mass of one tablet was quantitatively transferred into a volumetric flask containing simulated gastric fluid (SGF) (pH 1.2 ± 0.1) for ASA and NA. Simulated intestinal fluid (SIF) (pH 6.8 ± 0.1) is only for NA. Following sonication the sample was filtered through Cellulose acetate Filters, 0.45 µm, (Millipore®), suitably diluted and analyzed at a λ max of 228 for ASA and at 261 and 263nm for NA using UV-Vis double beam spectrophotometer (UV-1800 ENG 240V Soft, Shimadzu, Japan). For each batch, the assay procedure was performed in triplicate.

In vitro release rate studies

The *in vitro* release studies of ASA and NA from prepared tablets were carried out using USP Type II dissolution test apparatus. (TDT-08L Dissolution Tester (USP) with automatic temperature controller, ETC-11L, Electrolab, Mumbai). Drug release was carried out in SGF (pH 1.2±0.1) from 0 to 2 hrs for ASA and NA and in SIF (pH 6.8±0.1) for NA only from 2 to 24 hrs. Rotation speed of 50 rpm at a temperature of 37±0.5° and a dissolution medium of 900 ml was maintained throughout the experiment. At predetermined time intervals, 10 ml of sample was withdrawn and replaced with the same volume of prewarmed (37± 0.5°) fresh dissolution medium. The samples withdrawn were filtered through Cellulose acetate Filters, 0.45 µm, (Millipore®) suitably diluted and the absorbance of the solution was measured at 228 for ASA and at 261 and 263nm for NA by using a, UV-Vis double beam spectrophotometer (UV-1800 ENG 240V Soft, Shimadzu, Japan). The mean of six determinants was used to calculate the amount of drug released from the samples. The amounts of drug dissolved were plotted versus time as percent

dissolved drug. These drug release profiles were fitted into several mathematical models to get a better understanding about the release mechanism of ASA and NA from the prepared tablets.

Kinetic modeling of drug release:²²⁻²⁴

The release pattern of all the prepared formulations were evaluated to check the goodness of fit for zero-order release kinetics, First-order release kinetics, Higuchi's square root of time equation, and Korsmeyer- Peppas' power law equation and finding the R² values of the release profile corresponding to each model, such that the best possible release mechanism of ASA and NA could be identified.

Drug release data were fitted according to the exponential Eq. (3).

$$M_t/M_\infty = kt^n \text{ ----- (3)}$$

Where, M_t/M_∞ is the fractional drug released at time t ; k is a constant incorporating the properties of the macromolecular polymeric system and the drug, and 'n' is a kinetic constant which depends on and is used to characterize the transport mechanism. For example, $n=0.45$ for Case I or Fickian diffusion, $n=0.89$ for Case II transport, $0.45 < n < 0.89$ for anomalous behavior or non-Fickian transport, and $n > 1.0$ for Super Case II transport.²⁵ Under some experimental situations the release mechanism deviates from the Fick equation, following an anomalous behavior (non-Fickian). In these cases a more generic equation can be used:

$$M_t / M_\infty = at^n \text{ ----- (4)}$$

A modified form of this equation²⁶⁻²⁸ was developed to accommodate the lag time (l) in the beginning of the drug release from the pharmaceutical dosage form:

$$M(t-l)^n / M_\infty = a(t-l)^n \text{ ----- (5)}$$

Independent-model method (data analysis)^{29,30}

In order to compare dissolution profiles, model-independent methods are used. The *in vitro* release profiles of NA in the optimized formulation before the stability studies was considered as reference formulation and the profiles after the stability studies are considered as test formulation. Model independent pair-wise approach, which involved the calculation of 'difference factor' (f_1) and 'similarity factor' (f_2) were calculated using Microsoft Excel 2007. f_1 and f_2 provide a simple measure of similarity between pairs of dissolution profiles. The difference factor is the percentage difference between two dissolution profiles at each time interval. This can be represented in the form of the following equation

$$f_1 = \{[\Sigma | R_t - T_t |] / \Sigma R_t\} \times 100 \text{ ----- (6)}$$

Where,

R_t = The released amount of drug of reference formulation.

T_t = The released amount of drug of test formulation.

If $f_1 = 0$ the dissolution profile is said to be superimposed, the factor value increases when the differences between dissolution profiles also increase. From a practical point of view, values of f_1 ranging between 0 and 15 can be considered as superimposed dissolution profiles.

The similarity factor can be calculated using the following expression:

$$f_2 = 50 \times \log \{ [1 + (\Sigma (R_t - T_t)^2 / N)]^{1/2} \} \times 100 \text{ ----- (7)}$$

Where,

N = Number of experimental data.

Values of f_2 between 50 and 100 can be considered as superimposed dissolution profiles.

Fourier transforms infrared radiation measurement (FT-IR)

The drug-polymer compatibility studies were carried out using a Shimadzu FT-IR 8300 Spectrophotometer (Shimadzu, Tokyo, Japan) in the wavelength region of 4,000 to 400 cm^{-1} . The procedure

consisted of dispersing a sample (drug alone or mixture of drug and excipients) in KBr and compressing into pellets by applying pressure 15kg/cm^2 using Hydraulic pellet press.

Scanning Electron Microscopy (SEM)

Optimized formulation FA3 was removed from the dissolution apparatus at predetermined time intervals and sectioned through an undisturbed portion of the gel formed at the flat face of the tablet. The specimen was then positioned on the sample holder so as to present a cross-section of the tablet to the microscope. Samples were coated with gold and visualized under SEM (Leica, Bensheim, Switzerland).

Stability studies³¹

To assess the stability of tablets, the tablets of optimized formulations FA3 were packed in strips of 0.04-mm thick aluminum foil laminated with polyvinyl chloride. 07 separate groups in different containers were stored in International Conference Harmonization (ICH) certified stability chambers maintained at $40^\circ \pm 2^\circ / 75\% \text{ RH} \pm 5\% \text{ RH}$ and subjected to accelerated stability studies as per ICH guidelines for 6 months, as India falls under climatic Zone III. The samples were withdrawn monthly (from 0 month to 6th Month) and evaluated for the different physico-chemical parameters viz., Physical appearance, % drug content and dissolution characteristics after each month for 6 months. The assay and dissolution study of ASA and NA followed the same procedure as previously described in this work.

RESULTS AND DISCUSSION

Effect of Pre-compression parameters

As shown in Table.2, the granules of different formulations were evaluated for Db, Dt, PC, HR and angle of repose. The Db and Dt of granules of prepared formulations is ranged from 0.29 ± 0.032 to $0.44 \pm 0.101\text{g/ml}$ and 0.34 ± 0.132 to $0.51 \pm 0.121\text{g/ml}$ respectively. The PC and HR of granules is ranged from 7.9 ± 0.121 to $21.95 \pm 0.011\%$ and 1.08 ± 0.004 to 1.26 ± 0.103 . Angle of repose of granules is ranged from $28.6^\circ \pm 0.101$ to $37.3^\circ \pm 0.1002$. As is known PC values upto 15% result in good to excellent flow properties, but readings above 25% indicates poor flowability. The values of angle of repose from 25° to 30° indicate excellent and 20° to 40° indicate good. As such all the results obtained indicate that the formulated granules match the compressibility and flow properties satisfactorily.

Effect of Post-compression parameters

As shown in Table.2, the results of thickness and diameter of prepared tablets using 10-station rotary tablet compression machine ranged from 5.34 ± 0.202 to $5.92 \pm 0.123\text{mm}$ and 9.49 ± 0.01 to $9.51 \pm 1.02\text{mm}$ respectively. All prepared formulations showed uniform thickness and diameter. The evaluation of the prepared tablets showed that the drug content of ASA is ranged from 97.0 ± 1.234 to $100.8 \pm 1.0434\%$, and NA is ranged from 93.1 ± 0.1021 to $100.9 \pm 1.132\%$, indicating a uniform contents in the formulations. The results indicate that all the tablets prepared in this study meet the USP 29 requirements for weight variation tolerance. The hardness and friability of prepared tablets is ranged from 5.4 ± 1.01 to $6.9 \pm 1.023 \text{ Kg/cm}^2$ and 0.30 ± 0.1302 to $1.2 \pm 0.007\%$ respectively. The final comparison revealed that the prepared tablets were superior in hardness accompanied with very negligible amount in percentage weight loss.

Drug release kinetics

The BSRMTs were prepared such that ASA is contained in the first layer to obtain an immediate release and the second layer in which NA is contained is a prolonged-release matrix.

Immediate release layer (IRL)

The IRL of the BSRMTs successfully disintegrated and released only ASA. All prepared formulations released more than 80% of ASA content within 60 min and complete release was at almost 2 hours as shown in Fig.1 and Fig. 2. A concentration of 9.6% of sodium starch glycolate (Table 1.b) was found to be optimum in all

formulations for disintegration of IRL. The effect of disintegration of the IRL did not have any effect on characteristics of the controlled release layer.

Controlled release layer (CRL)

The release of NA was found to be a function of the polymer concentration and all formulations of CRL retarded the release of NA

for 12 hours as shown in Fig.3 and Fig.4. The effect of hydrophilic polymer HPMC K100M and HPMC K15M (alone or in combination, ranging from 35% to 45%) along with the enteric coating polymer HPMCP (ranging from 4% to 8%) or Eudragit S100 (ranging from 2% to 4%) (Table 1.a) has been used for coating the CRL, so that the release of NA in the gastric fluid is by far prevented.

	FA1	FA2	FA3	FA4	FA5	FB1	FB2	FB3	FB4	FB5
Bulk density (gm/ml) ±SD (n=03)	0.32 ±0.0102	0.29 ±0.032	0.34 ±1.102	0.44 ±0.101	0.39 ±0.001	0.40 ±0.041	0.31 ±0.011	0.39 ±0.121	0.40 ±1.102	0.35 ±0.22
Tapped density (gm/ml) ±SD (n=03)	0.41 ±0.012	0.34 ±0.132	0.38 ±0.012	0.51 ±0.121	0.46 ±0.022	0.48 ±1.012	0.39 ±1.021	0.44 ±1.02	0.44 ±1.212	0.38 ±0.003
Compressibility (%)	21.95	14.7	10.52	13.72	15.22	16.67	20.51	11.36	9.09	7.9
Hausners ratio	1.3	1.17	1.12	1.16	1.18	1.2	1.26	1.13	1.1	1.08
Angle of Repose (°)	29.32°	31.12°	37.3°	35.65°	27.8°	33.25°	28.6°	31.13°	37.1°	29.8°
±SD (n=03)	±1.001	±0.0102	±0.1002	±0.012	±0.002	±0.032	±0.101	±0.1003	±0.212	±0.230
Post compression Parameters	FA1	FA2	FA3	FA4	FA5	FB1	FB2	FB3	FB4	FB5
Thickness (mm) ±SD (n=03)	5.59 ±0.102	5.50 ±0.022	5.44 ±0.2002	5.70 ±0.203	5.92 ±0.123	5.67 ±0.054	5.6 ±1.11	5.68 ±0.211	5.45 ±1.004	5.34 ±0.202
Diameter (mm) ±SD (n=03)	9.51 ±1.012	9.50 ±0.132	9.51 ±0.011	9.49 ±0.01	9.51 ±0.022	9.50 ±1.212	9.51 ±1.021	9.51 ±1.02	9.51 ±1.212	9.50 ±0.001
Hardness (Kg/cm ²) ±SD (n=10)	6.8 ±1.011	5.9 ±0.102	5.8 ±1.243	6.8 ±0.001	5.6 ±0.021	5.9 ±0.021	6.9 ±1.023	5.4 ±1.01	6.8 ±0.121	5.8 ±1.213
Friability (%) ±SD (n=03)	1.1 ±0.2002	0.3 ±0.1302	0.7 ±0.004	0.9 ±0.004	0.1 ±0.1002	0.3 ±0.032	0.9 ±0.101	1.1 ±0.1003	0.8 ±0.212	1.2 ±0.007
Drug Content of ASA (%) ±SD (n=03)	98.6 ±1.123	99.2 ±0.21	100.8 ±1.032	97 ±1.234	100.8 ±1.434	99.2 ±0.074	97.8 ±1.144	100.8 ±1.07	100.6 ±0.332	100.4 ±1.083
In vitro release of ASA (%) ±SD (n=03)	97.6 ±0.011	91.6 ±0.201	98.9 ±0.001	96.7 ±0.11	95 ±0.211	98.4 ±0.234	96.5 ±0.02	99.5 ±0.01	98.6 ±1.01	98.9 ±0.02
Drug Content of NA (%) ±SD (n=03)	95.6 ±0.12	93.1 ±0.021	99.7 ±1.012	100.2 ±0.0012	96.9 ±1.224	91.7 ±1.3001	97.6 ±1.1042	98.4 ±0.0001	99.7 ±1.01	100.9 ±1.132
In vitro release of NA (%) ±SD (n=03)	71.9 ±0.02	77.6 ±0.001	98.6 ±0.0	82.3 ±0.012	94.9 ±0.101	75.3 ±0.034	81.5 ±0.24	96.7 ±0.21	86.6 ±0.03	99.4 ±0.01

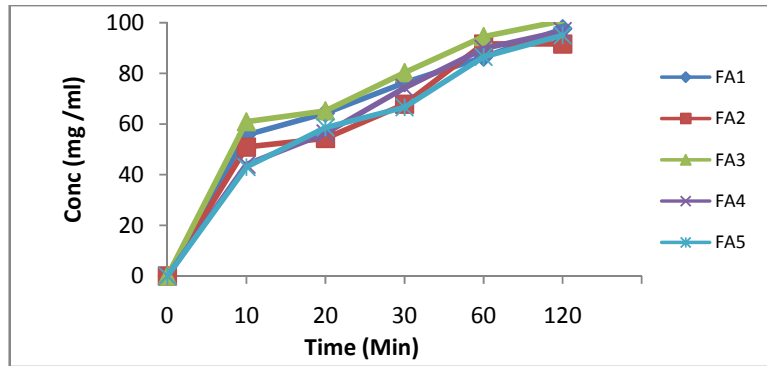


Fig. 1: In Vitro release profile of ASA (Immediate release layer) from formulations FA1 to FA5

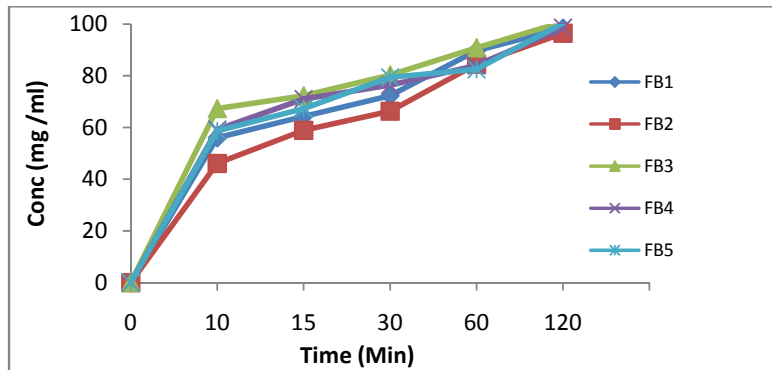


Fig. 2: In Vitro release profile of ASA (Immediate release layer) from formulations FB1 to FB5

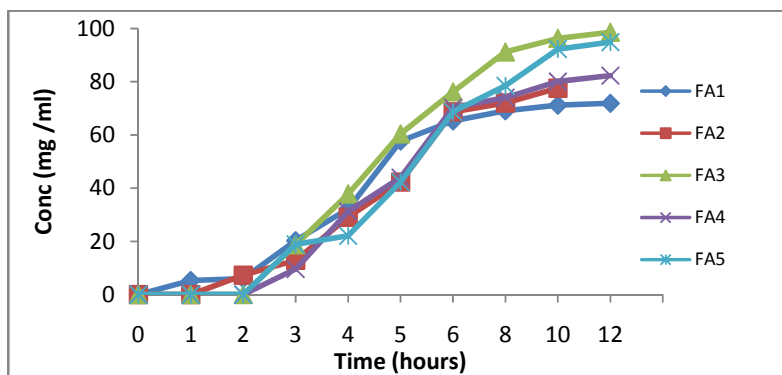


Fig. 3: *In Vitro* release profile of NA (Controlled release layer) from formulations FA1 to FA5

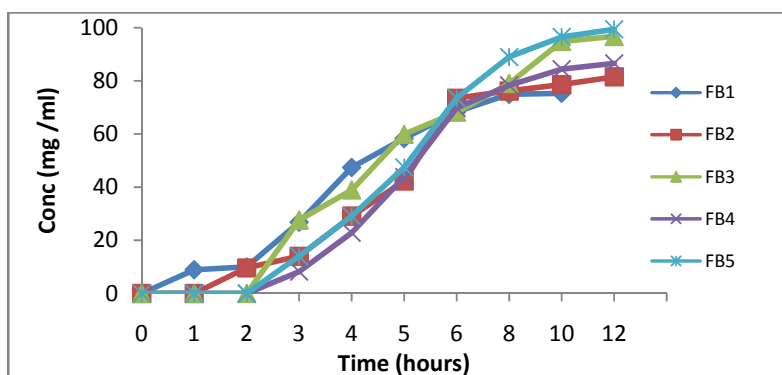


Fig. 4: *In Vitro* release profile of NA (Controlled release layer) from formulations FB1 to FB5

To study the release mechanism of CRL of all formulations, the release data were fitted into different mathematical models. The rate constant and correlation coefficient (R^2) values for zero order, first order, Higuchi and Korsmeyer-Peppas and "n" value for Korsmeyer-Peppas were evaluated. The criteria employed to select the "best fit model" was the one with the highest correlation coefficient determination. Considering the R^2 values as obtained from the different kinetic equations, the drug release from most of the formulated tablets were found to follow first order as well as Korsmeyer-Peppas. As shown in Table.3, Formulations FA1, FA3 and FB1, FB2 and FB3 follow Korsmeyer-Peppas. Formulations FA1, FA3 and FB1, FB2 and FB3 follow Korsmeyer-Peppas. Formulations FA2, FA4, FA5, FB4 and FB5 follow first order. The correlation coefficient (R^2) values of formulations that fall under first order is ranged from 0.959 to 0.984 and formulations that fall under Korsmeyer-Peppas model is ranged from 0.916 to 0.985. The release exponent "n" value for all formulations is ranged from 0.58 to 1.0 except for formulation FA1. Formulation FA1 showed the diffusional "n" value of 0.16 which is less than 0.5. The smaller the values of release exponent ($n < 0.5$) it may be attributed to partial drug diffusion through a swollen matrix and water filled pores in the formulations. Formulations FA3, FA4

and FB1, FB2 and FB3 show "n" value is from 0.58 to 1.0 which is in between 0.5 to 1.0, which indicate the anomalous transport kinetics that means the drug is released by the combined mechanism of pure diffusion controlled and swelling controlled drug release. Formulations FA2, FA5, FB4 and FB5 show "n" value is from 0.90 to 1.0 which is indicative of Case-II Transport.

Characterization of the optimal formulation

Of all the prepared BSRMTs, the formulation FA3 is identified as optimized formulation and hence was subject to detailed characterization in terms of FTIR, SEM, and stability studies for six months.

Fourier transforms infrared radiation measurement (FT-IR)

The characteristic band peaks acquired were taken from the prepared drug-polymer mixtures. The interaction study between drug and polymer was evaluated. The pyridine ring of the NA was present in all the IR spectra of the samples conforms the stable nature of the drug in the polymer mixture (Figure 5).

Table 2: Model fitting for CRL of NA:

Formulations	Zero Order		First Order		Higuchi model		Korsmeyer- Peppas		Release mechanism	Best Fit Model
	R^2	K_0	R^2	K_r	R^2	K_h	R^2	n		
FA1	0.827	3.206	0.9	0.028	0.046	14.45	0.971	0.16	($n < 0.5$)	Korsmeyer- Peppas
FA2	0.935	4.302	0.977	0.042	0.025	10.78	0.935	1	Case-II transport	First Order
FA3	0.955	4.436	0.947	0.069	0.044	18.29	0.985	0.84	Anomalous transport	Korsmeyer- Peppas
FA4	0.888	4.006	0.959	0.035	0.009	7.746	0.948	0.58	Anomalous transport	First Order
FA5	0.895	4.723	0.974	0.080	0.014	11.42	0.760	1	Case-II transport	First Order
FB1	0.812	3.945	0.898	0.036	0.043	13.86	0.916	0.70	Anomalous transport	Korsmeyer- Peppas
FB2	0.897	3.790	0.956	0.044	0.041	15.49	0.973	0.88	Anomalous transport	Korsmeyer- Peppas
FB3	0.902	4.289	0.917	0.078	0.047	18.78	0.976	0.58	Anomalous transport	Korsmeyer- Peppas
FB4	0.926	4.208	0.984	0.043	0.023	12.86	0.901	1	Case-II transport	First Order
FB5	0.941	4.725	0.963	0.074	0.030	16.17	0.945	0.90	Case-II transport	First Order

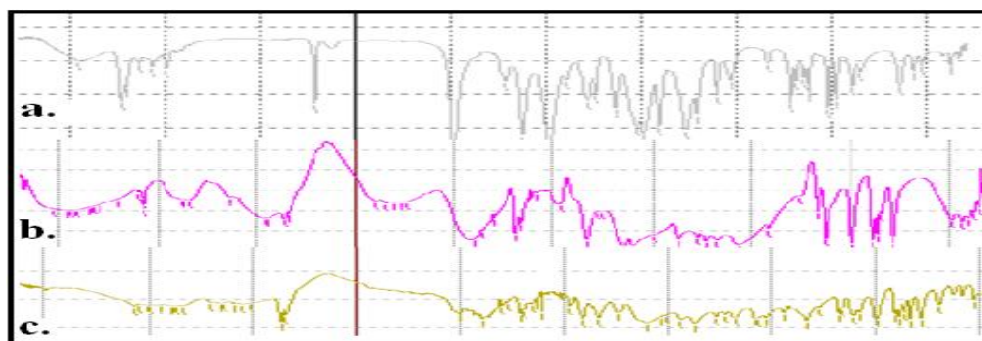


Fig. 5: FTIR of a). Pure drug (Nicotinic acid) b). Nicotinic acid + HPMC c) Optimal formulation (FA3)

Scanning electron microscopy

SEM studies of the optimized formulation FA3 were carried out to assess the surface morphology and to confirm the mechanism of drug release. SEM photomicrographs of tablets at 04 hours and after 10 hours of dissolution studies are shown in Fig.6. The surface of the tablet at 04 hours did not show any pores at $\times 1000$

magnification; but at 10th hour the surface showed pores with increasing diameter. These photomicrographs revealed formation of gelling structure indicating the possibility of the swelling of the tablet. Hence, the formation of both pores and gelling structure on tablet surface indicates it to be the result of both erosion and diffusion mechanisms.

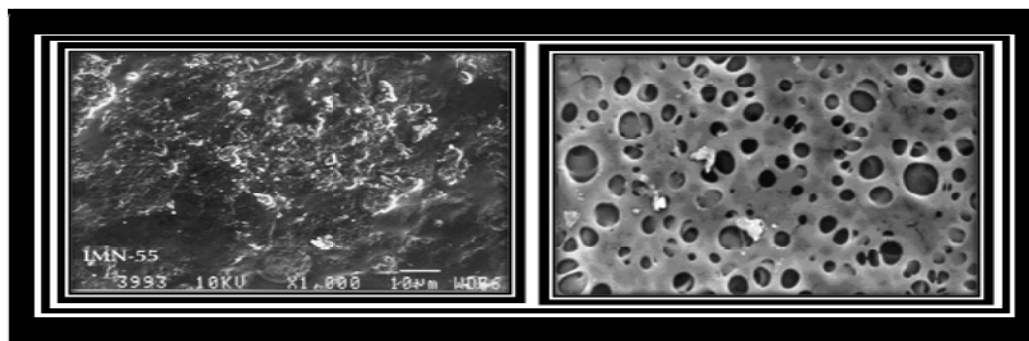


Fig. 6: SEM photomicrographs of optimized tablet (FA3) showing surface morphology after 04 hours and 10 hours of dissolution study

Stability studies

The BSRMTs of optimized formulations FA3 were subject to accelerated stability studies for 6 months as per ICH guidelines. The parameters like color, % drug content and % drug release were evaluated as shown in Table.4. Accelerated stability test shows: As is common the color was prone to vary in the tablet dosage form; a gradual shift in color from the initial white color to pale white in 6th month was noticed. Initial drug content of ASA and NA in optimized formulation FA3 is 100.8 ± 1.101 and $99.7 \pm 0.002\%$ respectively both the drug contents remained intact upto 3rd month and a negligible amount of drug content degradation i.e., 0.7% in ASA and 1.1% in NA sets in from the 4th month onwards. The drug content degradation in 5th month was 1.6% and 1.9% respectively and in 6th

month was 2.1% and 2.8% respectively. Initial drug release of ASA and NA in optimized formulation FA3 is $98.9 \pm 0.011\%$ and $98.6 \pm 0.011\%$ both the drug release remained intact upto 3rd month and a negligible amount of drug release degradation i.e., 0.9% in ASA and 1.4% in NA sets in from the 4th month onwards. The drug release degradation in 5th month was 2% and 2.3% respectively and in 6th month was 2.6% and 3.1% respectively. The accelerated stability studies of ASA and NA of optimized formulations FA3 made it clear that only negligible amount of drug content degraded, release pattern was almost unaffected and could be claimed to be stable at the end of six months. The analysis CRL containing NA showed f_1 is 8.85 and f_2 is 83.94 which is superimposable dissolution profile before and after the period of six months storage as shown in Fig.7.

Table 3: Stability studies

Condition		40 ° ± 2 ° / 75 % RH ± 5% RH						
Sampling period		0 Month	1 st Month	2 nd Month	3 rd Month	4 th Month	5 th Month	6 th Month
Parameters Evaluated (n=3)	Color	White	White	White	White	White	Pale yellow	Pale yellow
	Drug Content of ASA in (%)	100.8 ±1.01	100.8 ±1.002	100.8 ±0.001	100.8 ±1.002	100.7 ±0.002	99.2 ±0.032	98.7 ±0.022
	Drug Content of NA in (%)	99.7 ±0.002	99.7 ±0.102	99.7 ±0.02	99.7 ±0.001	98.6 ±0.031	97.8 ±1.01	96.7 ±0.042
	Drug Release of ASA in (%)	98.9 ±0.011	98.9 ±0.002	98.9 ±0.002	98.9 ±0.002	98.0 ±0.002	96.9 ±0.002	96.3 ±0.002
	Drug Release of NA in (%)	98.6 ±0.011	98.6 ±0.202	98.6 ±0.132	98.6 ±1.01	97.2 ±1.03	96.3 ±1.12	95.5 ±0.02

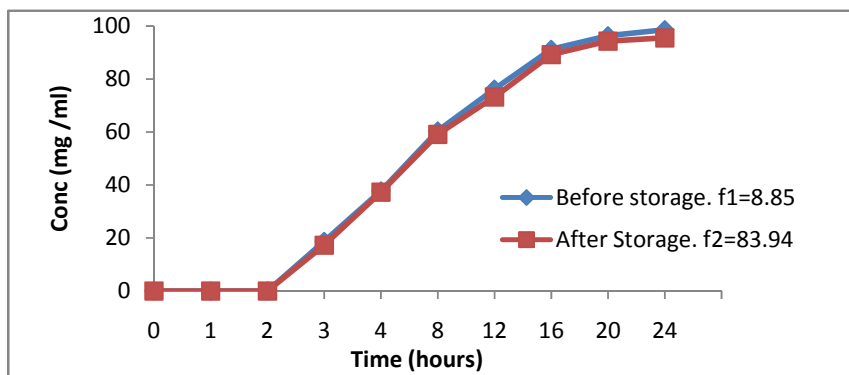


Fig. 7: Comparative *in vitro* release profile of NA from Optimized formulation FA3 before and after storage

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