International Journal of Pharmacy and Pharmaceutical Sciences
ISSN- 0975-1491 Vol 2, Issue 4, 2010

Research Article

DEVELOPMENT OF MATRIX TABLETS BY EXTRUSION/SPHERONIZATION PROCESS USING LABORATORY EXTRUDER: STUDY OF THE EFFECTS OF THE PROCESS PARAMETERS

R.K. MOHAMED MUTAHAR[1, 2], B.M. DINESH[3], S.B. SATEESHA[2], SHAHISTA OMER[4] AND L.V.G. NARGUND[2]

[1]Dept. of Pharmaceutics, Karpagam University, Coimbatore, Tamil Nadu, India, [2]Dept. of Pharmaceutics, Nargund College of Pharmacy, Bangalore, Karnataka, India, [3]Dept. of Pharmaceutics, K.L.E.S. College of Pharmacy, Bangalore, Karnataka, India, [4]Dept. of Pharmacology, Sonia College of Pharmacy, Dhardwad, Karnataka, India Email: profmutahar@gmail.com

Received: 07 Jun 2010, Revised and Accepted: 16 July 2010

ABSTRACT

The main aim of this research is to formulate and evaluate matrix tablets (MTs) of Nicotinic acid by extrusion/Spheronization process using extruder. Where in, the effects of the process parameters have also been focused for a close study. Extruded MTs were first prepared directly from extruder rod die and again by direct compression of extruded granules by Spheronization using mixed polymers and compared with the MTs prepared by direct compression of powders. These extruded MTs exhibited extended release pattern and were found to be superior in physical properties, dissolution characteristics, and drug content uniformity. The *in vitro* drug release data justifies the release process is diffusion-controlled as all the formulations best fitted into first order release kinetics and Higuchi's equation. To confirm diffusion mechanism results, the data were fit into Korsmeyer- Peppas model, which revealed anomalous transport kinetics. The release rate result $t_{20\%}$, $t_{50\%}$, and $t_{80\%}$, of formulations tend to show similar to market product (MP) release rate. The model independent pair-wise approach f_1 and f_2 analysis suggests that the dissolution profile of formulations is superimposable with the MP profile. The accelerated stability studies of optimized formulations GEM.2 and TEM.2 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. Thus it may be concluded that extrusion/Spheronization as a method for the preparation of MTs has better prospects.

Keywords: Extrusion, Spheronization, Matrix tablets, Nicotinic acid, Stability studies.

INTRODUCTION

Extrusion is a process originating from the plastic industry and has recently found its place in the array of pharmaceutical manufacturing operations. It is a process of converting raw material into a product of uniform shape and density by forcing it through a die under controlled conditions[1] The process of preparing spherical granules of approximately 1mm in diameter by extrusion/spheronization (E/S) was introduced during the late 1960s. It involves forming the powder into a wet mass, which is forced through a restricted area (extrusion) to form strands of extrudate that are broken into short lengths and rounded by placement on a rotating plate within a cylinder.[2] In the present research work the E/S process was carried out using Nargund laboratory extruder (NLE), keeping in view the making of both granules and tablets for laboratory scale. NLE 'the one and only one of its kind' has been designed and engineered on 09/09/09 in laboratory, P.G. Dept of Pharmaceutics, Nargund College of Pharmacy, Bangalore.

In this research, Nicotinic acid (NA) is used as model drug. NA when taken for the first time is always known for inducing flush - an intensive cutaneous vasodilation starting in the face, spreading to the upper body, sometimes even down to the feet. This unpleasant effect has greatly limited the use of NA in the treatment of dyslipidemia in spite of its excellent broad spectrum effect of raising high density lipoproteins and lowering all atherogenic lipoproteins.[3] The latest available extended release tablet of NA gives rise to much less flush than immediate release NA tablet and has the same broad spectrum lipid effects as immediate release NA.[4]

Matrix tablets (MTs) are an interesting option when developing an oral controlled release formulation. The most convenient way to achieve controlled release of active agent involves physical blending of drug with polymer matrix, followed by direct compression, compression molding, injection molding, extrusion, or solvent casting which results either in monolithic device or in swellable hydrogel matrix.[5-9] The MTs composed of drug and the release retarding material (polymer), offers the simplest approach in designing an extended-release system.[10] In the present research, polymer combinations have been extensively studied in order to achieve the desired release kinetics. As is well established a Hydrophilic polymer i.e. Hydroxypropyl Methylcellulose (HPMC) and Hydrophobic polymer i.e. Ethyl Cellulose (EC) are polymeric excipients best suited to produce MTs using extrusion process.[11,12] Hydrophilic matrix systems are most popular because of the simplicity of formulation, ease of manufacturing, low cost, FDA acceptance, and applicability to drugs with wide range of solubility.[13-15] However the use of hydrophilic polymer alone for controlling the release of drug is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel layer. Rather, the use of hydrophobic polymer along with the hydrophilic polymer can retard the drug release as desired. Thus hydrophobic polymers are suitable, along with a hydrophilic matrix for developing extended-release dosage forms.[16] Since EC is a hydrophobic polymer and cannot swell in a manner similar to HPMC, it was considered that an admixture of HPMC with EC could change the permeability of the matrix and consequently modify the drug release rate.[17]

Aim of the study

For a controlled release dosage form to be effective and efficient it is very important to use minimum number of excipients with minimum processing steps in order to reduce the tablet-to-tablet and batch-to-batch variations.[18] E/S is the best method of choice to satisfy "minimum number of excipients with minimum processing steps" Hence, in the present research work, an attempt has been made, to develop MTs of NA by E/S method using HPMC and EC in different ratio combinations. Direct compression method known so far as being the most popular and easily up-scalable technique is here being compared with E/S method to explore the possibilities of opting/preferring E/S over direct compression. To confirm the hypothesis estimated above, MTs of NA prepared using the NLE and tablet punching machine are compared with those of the marketed product of NA (Sustained release).

To develop the MTs of NA prepared from granules spheronization method and tablet extrusion method using NLE such that, the superiority in physical properties, dissolution characteristics, and drug content uniformity attained may achieve a status of rank.

MATERIALS AND METHODS

Nicotinic acid (NA) the model drug for this study has been procured from Western India, Pvt Ltd, Rajasthan, India. HPMC (E4M) and EC (20 cps) from S.D. Fine Chemicals, Mumbai, India

Polyvinylpyrrolidone (PVP-K30), Magnesium stearate and Talc from Loba chemie, Pvt Ltd, Mumbai. India. All the other ingredients used throughout the study are of analytical grade.

Nargund Laboratory Extruder (NLE)

NLE 'the one and only one of its kind' has been designed and engineered on 09/09/09 in laboratory, P.G. Dept of Pharmaceutics, Nargund College of Pharmacy, Bangalore; for the purpose of making both granules and tablets for Laboratory scale. There are other benefits to using E/S over traditional processing techniques. These include fewer unit operations, better content uniformity, an anhydrous process, a dispersion mechanism for poorly soluble drugs, a low energy alternative to high shear granulation, and less processing time compared to conventional wet granulation.[19] As shown in Fig 1, names of the different parts of the NLE are 1). Cylindrical Steel Barrel, 2). Sieve Screen, 3). Handle, 4). Barrel cap, 5). Steel conveyer, 6). Shaft, 7). Rod die (Standard Calibrated pipe), 8). Sharp stainless steel blade, 9). Stand with metal clamps.

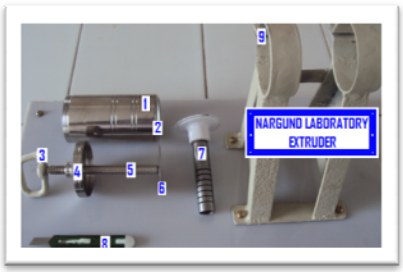

Fig. 1: Different parts of Nargund Laboratory Extruder

Description of the different parts of the NLE

Barrel: Cylindrical steel Barrel (Fig 2A) measuring 6inches in length and 57.85mm in diameter fixed firmly to the stand with clamps. The position of the barrel may be kept either horizontal or vertical, one end of the barrel is open to accommodate the barrel cap, and the other end is for rod die.

Conveyer: A steel conveyer (Fig 2B) with handle at one end and the shaft on the other; barrel cap is in the middle.

Tablet Extruder Die: Rod die (Standard calibrated pipe) (Fig 3A) with six equal intersections of 5.14mm thickness and 14.23mm inner diameter giving 6 tablets in one batch as shown in Fig 3B and Fig 3C respectively.

Granules Extruder Die: Sieve screen of 57.84mm in diameter with a sieve size of approximately 1.5mm for Granules by spheronization.

Sharp Blade: sharp stainless steel blade of the required thickness is used to run between intersections of the rod pipe to cut the coherent mass into uniform size tablets.

Fig. 2: A. Cylindrical steel Barrel, B. Steel conveyer

Table 1: Composition of Matrix Tablets of Nicotinic Acid.

Ingredients	Formulations								
	Granules extrusion method			Tablet extrusion method			Direct compression method		
	GEM.1	GEM.2	GEM.3	TEM.1	TEM.2	TEM.3	DCM.1	DCM.2	DCM.3
NA (mg/tab)	250	250	250	250	250	250	250	250	250
HPMC-E4M (%)	80%	75%	60%	80%	75%	60%	80%	75%	60%
EC (20 cps) (%)	20%	25%	40%	20%	25%	40%	20%	25%	40%
PVP- K30 (%)	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	—	—	—
Mag stearate (%)	1%	1%	1%	—	—	—	1%	1%	1%
Talc (%)	1%	1%	1%	—	—	—	1%	1%	1%

METHODS

Preparation of MTs of NA

MTs of NA have been prepared by three methods. Each method utilizes1:1ratio of NA and mixed polymers (HPMC E4M and EC (20 cps), 4:1, 3:1, and 3:2) as shown in Table 1.

Granules extrusion/spheronization (GE) method

The process of extrusion in the form of spheronization has been used to produce a wide variety of engineered, controlled release drugs, since the past few decades.

Step I: Mixing: Sieve all the ingredients with a # 60 sieve. Weigh and collect the required quantity of sieved ingredients (Table 1) (except lubricants), place in a mortar and mix with liquid binder, such as PVP- K30 in anhydrous ethanol to make a coherent mass (CM).

Step II: E/S: Extrusion: The CM was placed in the cylindrical barrel (CB) and forced out through a sieve screen where it was continuously formed into extrudates of uniform shape and size. Spheronization: The wet extrudates were placed in a spheronizer, where a gridded, fast spinning disc, breaks them into smaller particles and rounds them to form spheres.

Step III: Drying: These wet spheres (sometimes referred to as "beads" or "beadlets") are spread out on a tray, and dried in a hot air oven at 50^0 for 24 hrs. These dried spheres were immediately transferred to a dessicator, and tightly closed before tableted in tablet punching machine.

Tablet extrusion (TE) method

Step I: Same as said above in step-I under GE method.

Step II: The CM was placed in the CB and forced out through the rod die (Fig 3A) giving continuous rod like shaped CM. Now a sharp blade is run between each intersection of the rod die to give tablets (Fig 4) of uniform size and shape (5.14mm in Thickness and 14.23mm in Diameter).

Step III: These Tablets were immediately dried in a hot air oven at 50^0 for 24 hrs.

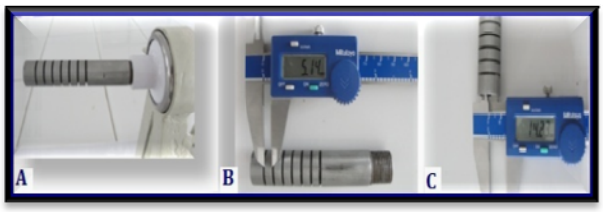

Fig. 3: Tablet extruder rod die.

Direct compression (DC) method

For the purpose of comparison the identical formulations evolved as a result of the TE method and GE method are used in DC method (Table 1). Here the tablets are prepared by compressing the sieved and weighed ingredients in a 10-station rotary tablet compression machine (Rimek Mini Press-1, Ahmadabad, India), equipped with concave punches of 12.5mm diameter. Nine die cavities were blocked with stainless steel solid blocks.

Evaluation of pre and post compression parameters[20,21]

Pre compression test

Such as bulk density (BD), tapped density (TD), Carr's compressibility index (CI).The prepared MTs of NA were evaluated for hardness, weight variation, thickness, diameter, CCI), and the angle of repose of powder and granules of NA were determined (Table 2). BD and TD were determined by USP method I using a Tapped density tester (ETD 1020, Electrolab, Mumbai, India). The CI was calculated from Hausner's ratio and Carr's index (Table 2).

Post compression tests

For the determination of weight variation of each batch, tablets 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 the NA in the prepared MTs 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) and simulated intestinal fluid (SIF) (pH 6.8 ± 0.1) respectively. Following sonication, the sample was filtered through Cellulose acetate Filters, 0.45 µm, (Millipore®), suitably diluted and analyzed at a λ max of 261 and 263nm respectively 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* drug release studies of prepared MTs of NA were carried out using USP Type II dissolution test apparatus, (TDT–08L Dissolution Tester (USP) with automatic temperature controller, ETC–11L, Electrolab. Mumbai) in SGF (pH 1.2±0.1) from 0 to 2 hrs and SIF (pH 7.4±0.1) from 2 to 24 hrs. Rotation speed of 100 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 261 and 263nm 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 an idea about the release mechanism of NA from the MTs.

Kinetic modeling of drug release

After completing the *in vitro* dissolution of all formulations, the release/dissolution of drug i.e. NA from MTs was evaluated by kinetic models. These drug release profiles were compared by different model methods

Dependent-model method (data analysis)[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. Such that the best possible release mechanism of MTs of NA could be identified.

Zero order: If the release rate of a drug is independent of its concentration, it is zero order and can be expressed as follows.

$$Q_t = Q_o + K_o t \quad \text{---------- (1)}$$

Where,

Q_t= Amount of drug dissolved in time "t".

Q_o = Initial amount of drug in the solution, which is often zero, and

K_o= zero order release constant. If the zero order drug release kinetic is obeyed, then a plot of Q_t versus t will give a straight line with a slope of K_o and an intercept at zero.

First order: If the release rate of a drug is concentration dependent, it is first order and can be expressed as follows.

$$\text{Log } Q_t = \log Q_o + k_t / 2.303 \quad \text{-------- (2)}$$

Where,

k = first order release constant.

If the first order drug release kinetic is obeyed, then a plot of log (Q_o-Q_t) versus t will be straight line with a slope of k_t / 2.303 and an intercept at t=0 of log Q_o.

Higuchi model: If the release rate of a drug is proportional to square root of time, it is Higuchi model and can be expressed as follows.

$$M_t / M_\infty = k_H t^{1/2} \quad \text{---------- (3)}$$

Where,

M_t and M_∞ = Cumulative amounts of drug release at time t and infinite time, and

k_H= Higuchi dissolution constant.

If the Higuchi model of drug release (i.e. Fickian diffusion) is obeyed, then a plot of M_t and M_∞ versus $t^{1/2}$ will be a straight line with slope of k_H.

Korsmeyer-Peppas model (Power Law): If the release rate of a drug deviates from Fickian diffusion, it is Korsmeyer-Peppas model and can be expressed as follows.

$$M_t \text{ and } M_\infty \; kt^n \quad \text{---------- (4)}$$

$$\text{Log } [M_t \text{ and } M_\infty] = \log k + n \log \quad \text{------- (5)}$$

Where,

K= constant.

n= diffusional release exponent.

To characterize the release mechanism, the dissolution data { M_t and M_∞ <0.6} are evaluated. A plot of log { M_t and M_∞ } versus log t will be linear with slope of 'n' and intercept gives the value of log k. Peppas used the "n" value in order to characterize different release mechanisms. This equation has two distinct physical realistic meaning in the two special cases of n = 0.5 (indicating diffusion-controlled drug release) and n = 1. 'n' between 0.5 and 1 can be regarded as an indicator for the superposition of both phenomena (anomalous transport). If 'n' approaches to 1, the release mechanism can be zero order and on the other hand if 0.5<n<1, non-Fickian (anomalous) transport could be obtained. Anomalous (non-Fickian) transport generally refers to the drug release by the summation of both diffusion and erosion of the polymeric matrix. The criteria employed to select the ''best model'' was the one with the highest coefficient correlation (R^2).

Independent-model method (data analysis): [25] In order to compare dissolution profiles, model-independent methods are used. The release profile of NA in MTs of all prepared formulations were compared with MP using model independent pair-wise approach, which involved the calculation of 'difference factor' (f_1) and 'similarity factor' (f_2). The difference factor f_1 and similarity factor 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

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

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:

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

Where,

N = Number of experimental data.

Values of f_2 between 50 and 100 can be considered as superimposed dissolution profiles. The mean release profile (n=06) of all formulations was compared with that of the Marketed Product (MP) using the model independent pair-wise approach with Microsoft excel.

Other release parameters: [26] Other parameters used to characterize drug release profile are $t_{x\%}$**,** sampling time. The $t_{x\%}$ parameter corresponds to the time necessary to the release of a determined percentage of drug and sampling time corresponds to the amount of drug dissolved in that time.

Drug–polymer compatibility studies

The drug–polymer compatibility studies were carried out using IR-Spectrophotometer (FTIR-8400S, Shimadzu, Tokyo, Japan) by KBr pellet Method, pellets were prepared at 15kg/cm ^{2} using Hydraulic pellet press, Bombay, India.

Stability studies[27]

To assess the stability of MTs of NA, the tablets of optimized formulations (GEM.1and TEM.2) 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° ± 2° / 75% RH ± 5% 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, % age drug content and dissolution characteristics after each month for 6 months. The assay of NA and the dissolution study followed the same procedure as previously described in this work.

RESULTS AND DISCUSSION

Effect of Pre- compression parameters

The granules/powders of different formulations were evaluated for BD, TD, CCI, HR and angle of repose. The BD and TD of granules in GEM.1 to GEM.3 formulations ranged from 0.42 ± 0.013 to 0.52 ± 0.0221g/ml and 0.49 ± 0.1004 to 0.58 ± 0.121g/ml respectively. Similarly the BD and TD of powders in DCM.1 to DCM.3 formulations ranged from 0.22 ± 1.0023 to 0.49 ±0.0012g/ml and 0.28 ± 1.0201 to 0.56 ±0.1021g/ml respectively as shown in Table 2. The CCI and HR of granules in GEM.1 to GEM.3 formulations ranged from 10.34 ±0.0413 to 14.3±0.013 % and 1.12 ± 0.011 to 1.7 ± 0.01 respectively. Similarly the CCI and HR of powder in DCM.1 to DCM.3 formulations ranged from 12.5 ± 0.1201 to 21.43 ± 0.1001% and 1.14 ± 0.111 to 1.3 ± 0.201 respectively as shown in Table 2. Angle of repose of granules in GEM.1to GEM.3 formulations ranged from 25.96 ± 0.0011 to 28.62 ± 0.0111^o and was found to be lower than angle of repose of powder in DCM.1 to DCM.3 formulations which ranged from 36.73 ± 0.001 to 38.6 ± 1.032^o as shown in Table 2. As is known CCI 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^o to 30^o indicate excellent and 20^o to 40^o indicate good.[28] As such all the results obtained indicate that the formulated granules/powders match the compressibility and flow properties satisfactorily.

Effect of post- compression parameters

The results of thickness and diameter of tablets prepared by both GE and DC methods using 10-station rotary tablet compression machine ranged from 4.66 ± 0.0121 to 4.55 ± 0.021 mm and 12.41 ± 0.001 to 12.49 ± 0.003mm respectively. The results of thickness and diameter of tablets prepared by TE method using Nargund laboratory extruder ranged from 5.12 ± 0.013 to 5.13 ± 0.122 mm and 14.21 ± 0.01 to 14.22 ± 0.122 mm respectively as shown in Table 2. All prepared formulations showed uniform thickness and diameter. As summarized in Table 2, the evaluation of the prepared MTs containing NA showed that the drug content of all prepared formulations ranged from 95.8 ± 0.0131 to 102.2 ± 0.031%, indicating a uniform amount of NA in the formulations. The results indicate that all the tablets prepared in this study meet the USP 29 requirements for weight variation tolerance.

Table 2: Evaluation of pre and post compression parameters of formulations

FORMULATIONS	Pre compression parameters					Post compression parameters						
	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility Index(%)	Hausners ratio	Angle of Repose (^{o})	Thickness(mm)	Diameter(mm)	Average Weight (mg)	Hardness (Kg/cm^{2})	Friability (%)	Drug content (%)	% Drug Release
	±S.d (n=10)	±S.d (n=10)	±S.d (n=01)	±S.d (n=01)	±S.d (n=03)	±S.d (n=03)	±S.d (n=03)	±S.d (n=20)	±S.d (n=10)	±S.d (n=03)	±S.d (n=03)	±S.d (n=06)
GEM.1	0.43 ±0.0102	0.49 ±0.123	12.24 ±1.013	1.14 ±1.001	26.89 ±0.1422^{o}	4.57 ±0.001	12.45 ±0.002	506.7 ±0.012	6.2 ±0.021	0.2 ±0.113	95.8 ±0.0131	95.6 ±0.131
GEM.2	0.52 ±0.0221	0.58 ±.0121	10.34 ±0.0413	1.12 ±0.011	25.96 ±0.0011^{o}	4.62 ±0.0102	12.41 ±0.001	504.9 ±0.012	6.8 ±0.212	0.5 ±0.032	102.2 ±0.031	96.2 ±0.121
GEM.3	0.42 ±0.013	0.49 ±0.1004	14.3 ±0.013	1.17 ±0.01	28.62 ±0.0111^{o}	4.66 ±0.0121	12.45 ±0.013	505.4 ±0.021	7.1 ±0.04	0.3 ±0.002	98.7 ±0.003	98.6 ±0.001
DCM.1	0.49 ±0.0012	0.56 ±0.1021	12.5 ±0.1201	1.14 ±0.111	36.73 ±0.001^{o}	4.59 ±0.002	12.49 ±0.003	508.1 ±0.111	4.9 ±0.001	1.2 ±0.131	100.6 ±0.121	99.6 ±0.111
DCM.2	0.32 ±0.0213	0.39 ±0.1112	17.95 ±0.1003	1.22 ±0.022	38.6 ±1.032^{o}	4.55 ±0.021	12.48 ±0.133	503.3 ±0.112	4.2 ±0.021	1.6 ±0.013	96.3 ±0.102	96.1 ±0.032
DCM.3	0.22 ±1.0023	0.28 ±1.0201	21.43 ±0.1001	1.3 ±0.201	38.33 ±0.102^{o}	4.58 ±1.022	12.48 ±1.232	507.2 ±1.001	4.6 ±0.002	1.7 ±0.123	99.4 ±0.002	96.9 ±0.012
TEM.1	NA	NA	NA	NA	NA	5.12 ±0.013	14.22 ±0.122	503.1 ±0.032	10.8 ±0.013	0.0	97 ±0.021	96.2 ±0.041
TEM.2	NA	NA	NA	NA	NA	5.13 ±0.131	14.22 ±0.012	505.4 ±0.013	10.3 ±0.122	0.0	98.2 ±0.1001	97.7 ±0.012
TEM.3	NA	NA	NA	NA	NA	5.13 ±0.122	14.21 ±0.01	507.2 ±0.112	10.6 ±0.002	0.1 ±0.211	96.3 ±0.021	96 ±0.021
MP				Not applicable							99.8 ±0.002	99.8 ±0.121

Effect of hardness

The hardness effect of MTs of NA prepared by GE and TE method on the release rate was evaluated and the results compared with the MTs of NA prepared by DC method. Usually an increase in hardness of a tablet is accompanied by a decrease in release rate, due to a decrease in porosity of the tablet. A comparison of the hardness values of the tablets is shown in Fig 5, which depicts that the formulations prepared by GE and TE method are having higher hardness value (Table 2).The hardness and friability of MTs of NA in TEM.1 to TEM.3 formulations ranged from 10.3 ± 0.122 to 10.8 ± 0.013 Kg/cm ² and 0.0 to 0.1 ± 0.211% respectively. GEM.1to GEM.3 ranged from 6.2 ± 0.021 to 7.1 ± 0.04 Kg/cm ² and 0.2 ± 0.113 to 0.5 ± 0.032% respectively. DCM.1 to DCM.3 ranged from 4.2 ± 0.021 to 4.9 ± 0.001 Kg/cm ² and 1.2 ± 0.131 to 1.7 ± 0.123% respectively (Table 2).The results of hardness and friability in MTs of NA prepared by TE method using NLE and those prepared by GE method using 10-station rotary tablet compression machine were compared with MTs of NA prepared by DC method. The final comparison revealed that the MTs of NA prepared by TE method were superior in hardness accompanied with very negligible amount in percentage weight loss (Friability).

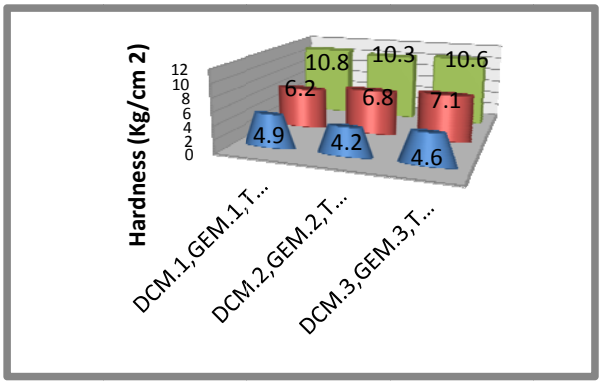

Fig. 5: Comparison of the Hardness of Matrix Tablets of Nicotinic Acid.

Effect of polymers

All formulations of MTs of NA were prepared with a combination of polymers - HPMC E4M and EC (20 cps). Content increase of HPMC in formulations GEM.1, TEM.1 and DCM.1 exhibited controlled drug release rate, and as time progresses swelling of HPMC occurs there by prolonging the duration of drug release. This may be attributed to structural reorganization of hydrophilic HPMC polymer. HPMC

polymer when exposed to aqueous medium undergoes rapid hydration and chain relaxation to form viscose gelatinous layer (gel layer). Failure to generate a uniform and coherent gel may cause rapid drug release.[29] To check this rapid release of the drug even more control is required. Hence an attempt with EC was undertaken in the present research. The presence of hydrophobic EC provides a complimentary environment in controlling the drug release from the matrix. However the increase in concentration of EC does not seem to influence the release profile as shown in the formulations GEM.3, TEM.3 and DCM.3, which is predominantly influenced by the increased HPMC content. Nevertheless, the combination effect of HPMC and EC slows down the diffusion process which is found to be relatively uniform between the 08th to 24th hour.

Evaluation of methods adopted

MTs of NA are prepared by three methods like, GE, TE and DC using NA and mixed polymers (HPMC E4M and EC) in the ratio of 1:1. Each method utilizes HPMC E4M and EC in different proportion such as (4:1, 3:1, and 3:2) as shown in Table 1.

Method I: - Granules extrusion: Granules by spheronization in GEM.1, GEM.2 and GEM.3 formulations were prepared using NLE. Compression of these granules was done in 10-station rotary tablet compression machine (Rimek Mini Press-1, Ahmadabad, India). The compression force was adjusted so that the crushing strength of the tablets prepared was in the range of 6.2 - 7.1kg/cm² .The average weight and the drug content of the prepared tablets was adjusted to 505 mg and 250 ± 5 mg respectively.

Method II: - Tablet extrusion: Coherent mass in TEM.1, TEM.2 and TEM.3 formulations was prepared using Nagund laboratory extruder rod die (Fig 3).

Method III:- Direct compression: Powder in DCM.1, DCM.2 and DCM.3 formulations were compressed in 10-station rotary tablet compression machine (Rimek Mini Press-1, Ahmadabad, India), equipped with concave punches of 12.5mm diameter. The compression force was adjusted so that the crushing strength of the tablets prepared was in the range of 4.2 - 4.9kg/cm². The average weight and the drug content of the prepared tablets were adjusted to 505 mg and 250 ± 5 mg respectively. Off all the prepared formulations, GEM.2 and TEM.2 were selected for comparison with DCM.2. All three formulations (optimized formulation GEM.2, TEM.2 and comparative formulation DCM.2) contain same concentration of NA and mixed polymer (HPMC E4M 75%: EC 25%). In the present research work the results of pre or post compression parameters of GEM.2 and TEM.2 as shown in Table-II, tend to show better results in comparison with the formulation DCM.2. The anticipated time required for the complete release of NA from the prepared MTs of NA is 24 hrs. Accordingly GEM.2 and TEM.2 and DCM.2 (Fig 7) give results corresponding to the requirement. The GEM.2, TEM.2 and DCM.2 are now taken for comparison with the marketed product (sustained release prepared by direct compressed) (Fig 9), looking into the release rate of NA (Table 2), its kinetic mechanism (Table 3), and model independent pair-wise approach (Difference factor (f_1) and similarity factor (f_2) analysis dissolution pairs) (Table 4), the MP, GEM.2, TEM.2 and DCM.2 formulations show no significant difference. The results of these studies help in establishing that MTs of NA prepared using GE and TE method stand a good chance against those prepared by DC method. Finally it is concluded that Nargund laboratory extruder with its unique and novel features - most importantly the precision aspects needed for fabricating tablets can be successfully employed in laboratory scale tablet preparation.

Effect of *In vitro* release rates

The release rate of NA in GEM.1, TEM.1 and DCM.1 formulations using mixed polymers (HPMC E4M 80% and EC 20%) (Table 1) is 28.9, 27.8 and 33.6% respectively in SGF for 2hrs, and 95.6 ± 0.131, 99.6 ± 0.111 and 96.2 ± 0.041% respectively in SIF for approximately 22 hrs (Fig 6).The release rate of NA in GEM.2, TEM.2 and DCM.2 formulations using mixed polymers (HPMC E4M 75% and EC 25%) (Table-I) is 36.0, 34.5 and 35.4% respectively in SGF for 2hrs, and 96.2 ± 0.121, 96.1 ± 0.032 and 97.7 ± 0.012% respectively in SIF for approximately 22 hrs (Fig 7). No significant differences in release rates were observed in prepared formulations, despite the difference in the method of preparation and polymer combination ratios (4:1 and 3:1). The release rate of NA in GEM.3, TEM.3 and DCM.3 formulations using mixed polymers (HPMC E4M 60% and EC 40%) (Table 1) is 40.2, 41.2 and 43.5% respectively in SGF for 2hrs. But a noteworthy point in GEM.3 and TEM.3 is that the release rate of NA in SIF i.e. 98.6 ± 0.001and 96.0 ± 0.021 could not be prolonged beyond 18 hours and in DCM.3 release rate of NA in SIF being 96.9 ± 0.012% for 12 hrs could be prolonged upto 12 hrs only (Fig 8). thus, it may be concluded that mixed polymers (HPMC and EC) in the ratio of 4:1and 3:1gave the most effective drug release rate as anticipated, and mixed polymers (HPMC and EC) in the ratio of 3:2 could not meet the expectations which may be due to the burst effect on the drug release because of excess of EC and less amount of HPMC.

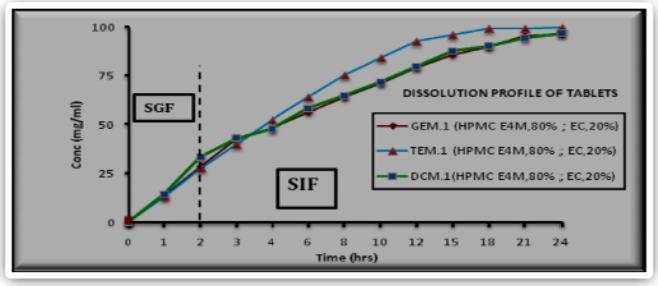

Fig. 6: Release profiles of GEM.1, TEM.1, and DCM.1, formulations.

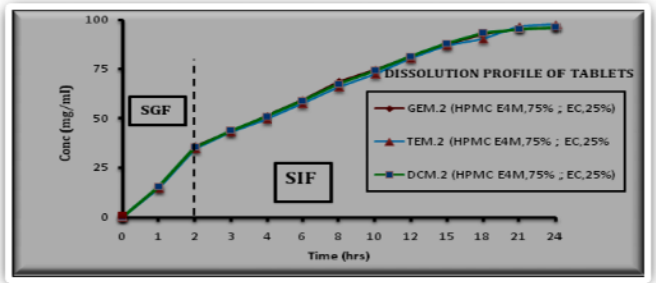

Fig. 7: Release profiles of GEM.2, TEM.2, and DCM.2, formulations.

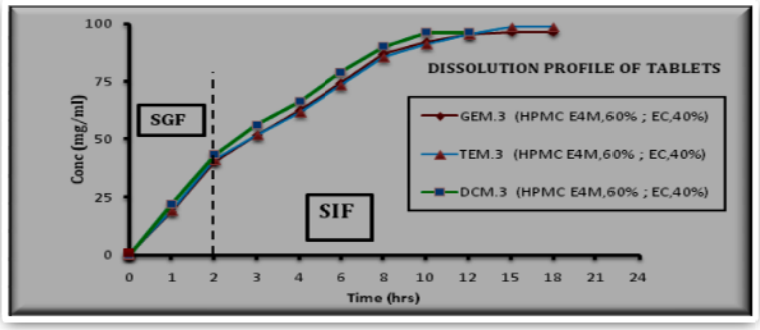

Fig. 8: Release profiles of GEM.3, TEM.3, and DCM.3, formulations.

Drug release kinetics

In order to describe the kinetics of the release process of drug in all the formulations as well as in the marketed product, various equations were used, such as the zero-order rate equation, which describes the systems where the release rate is independent of the concentration of the dissolved species. The first-order equation describes the release from systems where dissolution rate is dependent on the concentration of the dissolving species. The Higuchi square root equation describes the release from systems where the solid drug is dispersed in an insoluble matrix, and the rate of drug release is related to the rate of drug diffusion. The Korsmeyer-Peppas equation is used to analyze the release of pharmaceutical polymeric dosage forms, when the release mechanism is not well known or when more than one type of release phenomena could be involved. The applicability of all of these equations was tested in the present research work. The kinetics data for all the models is shown in Table 3. It is evident from Table 3, that the drug release process is not zero-order in nature. This indicates that the dissolution rate of the drug is independent of the amount of drug available for dissolution and diffusion from the matrix. The dissolution data of all formulations when fitted in accordance with the first-order equation showed good linearity ranging from (R^2: 0.919 to 0.992) (Table 3). It is evident that a linear relationship was obtained with 'R^2' (correlation coefficient) value close to unity and higher than 'R^2' obtained from the zero-order equation for all formulations, showing that the release is an apparent first-order process. All the formulations in this investigation could be best expressed by Higuchi's equation, as the plots showed high linearity (R^2: 0.924 to 0.977) (Table 3). The linearity of the plots indicates that, the release process is diffusion-controlled. To confirm the diffusion mechanism, the data were fit into Korsmeyer-Peppas model. All the formulations showed exponent "n" value that ranged from 0.89 to 0.95 (Table 3). The diffusional exponent; "n" between 0.5 and 1.0 which indicate the anomalous transport kinetics (non-Fickian diffusion kinetics) that means the drug is released by the combined mechanism of pure diffusion controlled and swelling controlled drug release.

Table 3: Fitting of drug release data of formulation according to various mathematical models.

Formulations	Zero order				First order				Higuchi model				Korsmeyer- Peppas			
	R^2	Intercept	Slope	K_0, (%hr-1)	R^2	Intercept	Slope	K_r, (%hr-1)	R^2	Intercept	Slope	K_H, (%hr-1)	R^2	Intercept	"n" Value	Release mechanism
GEM.1	0.854	3.646	24.63	24.63	0.992	-0.051	1.974	1.974	0.977	20.94	1.978	1.978	0.667	0.925	0.89	*AT
GEM.2	0.824	3.548	27.67	27.67	0.924	-0.103	2.131	2.131	0.966	20.64	4.914	4.914	0.635	0.901	0.93	AT
GEM.3	0.789	5.029	29.04	29.04	0.919	-0.172	2.225	2.225	0.95	25.41	4.705	4.705	0.6	1.013	0.95	AT
TEM.1	0.85	7.526	22.62	22.62	0.948	-0.186	2.128	2.128	0.974	30.33	0.255	0.255	0.585	1.188	0.92	AT
TEM.2	0.85	3.63	26.05	26.05	0.922	-0.084	2.087	2.087	0.977	20.89	3.369	3.369	0.647	0.909	0.92	AT
TEM.3	0.828	3.571	27.44	27.44	0.951	-0.093	2.091	2.091	0.968	20.73	4.645	4.645	0.636	0.902	0.93	AT
DCM.1	0.797	3.951	27.26	27.26	0.985	-0.092	2.050	2.050	0.942	23.08	1.651	1.651	0.688	0.970	0.88	AT
DCM.2	0.763	4.922	29.61	29.61	0.972	-0.164	2.126	2.126	0.933	25.08	5.286	5.286	0.601	1.015	0.95	AT
DCM.3	0.846	3.598	25.88	25.88	0.988	-0.061	1.988	1.988	0.975	20.74	3.313	3.313	0.649	0.910	0.91	AT
MP	0.759	3.855	30.66	30.66	0.907	0.114	2.047	2.047	0.924	22.85	4.777	4.777	0.656	0.945	0.92	AT

*AT = Anomalous Transport.

Statistical analysis of dissolution data

Release profile of MTs of NA needed to be fine-tuned to achieve a uniformly prolonged release pattern. So, release profile of a market product was taken as the target profile. The proximity of release profiles of MTs of NA were compared by calculating two statistically derived mathematical indices, difference factor (f_1) and similarity factor (f_2) using marketed product as the reference standard. The f_1 and f_2 analysis (Table 4) suggests that the dissolution profile of GEM.2 and TEM.2 is almost superimposable with the market product profile (Figure 9). Hence GEM.2 and TEM.2 are adopted as ideal formulations for further studies.

The $t_{x\%}$ parameter used to characterize drug release profile at $t_{20\%}$, $t_{50\%}$, and $t_{80\%}$, and sampling time, were determined from the dissolution profiles for each formulation. The percentage release rate at predetermined time points extending over the entire dissolution period up to approx. 80% of drug release was compared (Table 5). All prepared formulations release rate result of $t_{20\%}$, $t_{50\%}$, and $t_{80\%}$, and sampling time tend to show similar to MP. Where as the optimized formulations GEM.2 and TEM.2 release rate and sampling time results are in unison with MP.

Drug–polymer compatibility studies

On seeing Fig12, the IR Spectra of pure NA and mixture of NA with polymers, it was concluded that there is no significant shift in the major peaks, which indicates that there is no interaction between the polymers and the NA used. Hence it may be construed and affirmed that the polymers selected are suitable for the intended formulations.

Table 4: Difference factor (f_1) and Similarity factor (f_2) analysis of various dissolution pairs formulations.

Formulations		Dissolution pairs	Difference factor (f_1)	Similarity factor (f_2)
Optimized Formulations	GEM.2	GEM.2 Vs MP	9.89	87.2
	TEM.2	TEM.2 Vs MP	10.8	86.9
Other Prepared Formulations	GEM.1	GEM.1 Vs MP	11.9	86.4
	GEM.3	GEM.3 Vs MP	27.73	84.91
	TEM.1	TEM.1 Vs MP	53.47	80.9
	TEM.3	TEM.3 Vs MP	9.89	87.22
	DCM.1	DCM.1 Vs MP	3.7	90.52
	DCM.2	DCM.2 Vs MP	28.6	84.4
	DCM.3	DCM.3 Vs MP	11.29	86.7
	GEM.2	GEM.2 Vs MP	9.89	87.2
	TEM.2	TEM.2 Vs MP	10.8	86.9

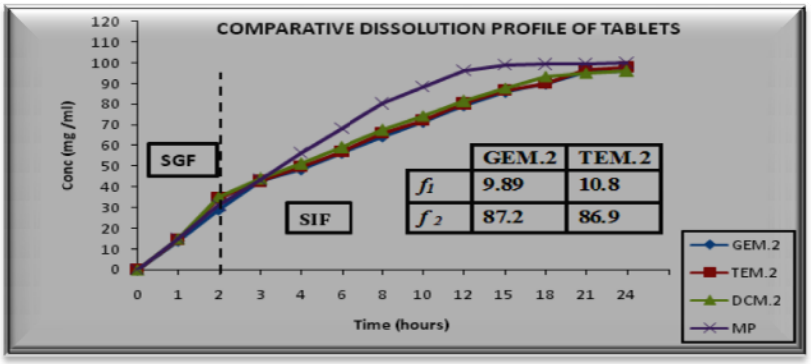

Fig. 9: Comparative release profiles of optimized formulations GEM.2, TEM.2, and DCM.2, of Matrix Tablets of Nicotinic Acid and MP.

Table 5: Release rate and sampling time of formulations.

	Formulations	$t_{20\%}$	$t_{50\%}$	$t_{80\%}$
Marketed product	MP	1.17	3.3	6.57
Optimized Formulations	TEM.2	1.15	3.52	10.38
	GEM.2	1.12	3.33	10.22
Other Prepared Formulations	GEM.1	1.25	3.58	10.42
	GEM.3	1.3	2.45	6.25
	TEM.1	0.56	2.21	4.47
	TEM.3	1.17	3.35	10.28
	DCM.1	1.27	3.45	8.28
	DCM.2	1.02	2.41	6.12
	DCM.3	1.25	4.05	9.55

.

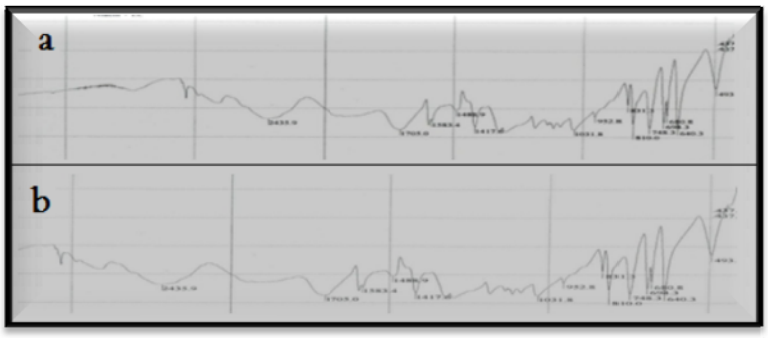

Fig. 4: IR spectra of a). Pure NA and b). Mixture of NA with polymers (NA+HPMC+EC)

Characterization of the optimal formulation

Two formulations GEM.2 and TEM.2 among all those prepared are identified as optimal MTs of NA, formulation GEM.2 (HPMC E4M 75%; EC 25%) prepared from GE method and TEM.2 (HPMC E4M 75%; EC 25%) prepared from TE method were subjected to a detailed characterization in terms of release kinetics, and statistical analysis of dissolution data, in comparison with the formulation DCM.2 (HPMC E4M 75%; EC 25%) prepared by DC method and then finally compared all three formulations with marketed product. These two optimized formulations gave satisfactory results on the formulation of MTs of NA, finally they were subjected to accelerated stability studies for 6 months as per ICH guidelines (Table-6) and formulations were stable after six months study.

Stability studies

The tablets of optimized formulations GEM.2 and TEM.2 were subjected to accelerated stability studies for 6 months as per ICH guidelines. The parameters like color, % drug content, % drug release and difference factor (f_1) and similarity factor (f_2) were evaluated (Table 6). 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 5th month onwards in GEM.2 and 4th month onwards in TEM.2 was noticed. Initial drug content in GEM.2 is 102.2 ± 0.031 remained intact upto 5th month and only a negligible amount of drug content 1.1% degradation sets in, from the 6th month and degradation rate was found to be 6.1×10^{-03}/day. In TEM.2 initial drug content is 98.2 ± 0.1001 remained intact upto 3rd month and a negligible amount of drug content 0.6% degradation sets in from the 4th month onwards, 5th and 6th month 0.8% and 01% respectively and the degradation rate was found to be 5.6×10^{-03}/day. Initial drug release in GEM.2 is 96.2 ± 0.002 remained intact upto 5th month and only a negligible amount of drug release 0.6% decreased in the 6th month. In TEM.2 initial drug release is 97.7 ± 0.112 remained intact upto 3rd month and a negligible amount of drug release 1.6% starts decreasing from the 4th month onwards and in 5th month 1.8% and 6th month 2.2%. The accelerated stability studies of optimized formulations GEM.2 and TEM.2 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 f_1 and f_2 analysis of GEM.2 (Fig 10) and TEM.2 (Fig 11) showed a superimposable dissolution profile before and after the period of six months storage.

Table 6: Evaluation of optimized formulations at accelerated stability studies.

	Parameters Evaluated (n=3)										
	Optimized Formulations GEM.2						Optimized Formulations TEM.2				
Condition	Sampling period	Color	Drug content (%)	Drug release (%)	f_1 and f_2 analysis before and after storage		Color	Drug content (%)	Drug release (%)	f_1 and f_2 analysis before and after storage	
					f_1	f_2				f_1	f_2
40 ° ± 2 ° / 75 % RH ± 5% RH	0 Month	White	102.2 ±0.031	96.2 ±0.002	9.89	87.2	White	98.2 ±0.101	97.7 ±0.012	10.8	86.9
	1st Month	White	102.2 ±1.001	96.2 ±0.131			White	98.2 ±0.021	97.7 ±0.101		
	2nd Month	White	102.2 ±0.022	96.2 ±0.011			White	98.2 ±0.103	97.7 ±0.013		
	3rd Month	White	102.2 ±0.032	96.2 ±0.21			White	98.2 ±0.021	97.7 ±0.022		
	4th Month	White	102.2 ±0.101	96.2 ±0.133			White	97.6 ±0.111	96.1 ±0.03		
	5th Month	Pale yellow	102.0 ±0.001	96.2 ±0.123			Pale yellow	97.4 ±0.001	95.9 ±0.014		
	6th Month	Pale yellow	101.1 ±0.102	95.4 ±0.002	11.6	85.9	Pale yellow	97.0 ±0.012	95.5 ±0.022	11.3	86.1

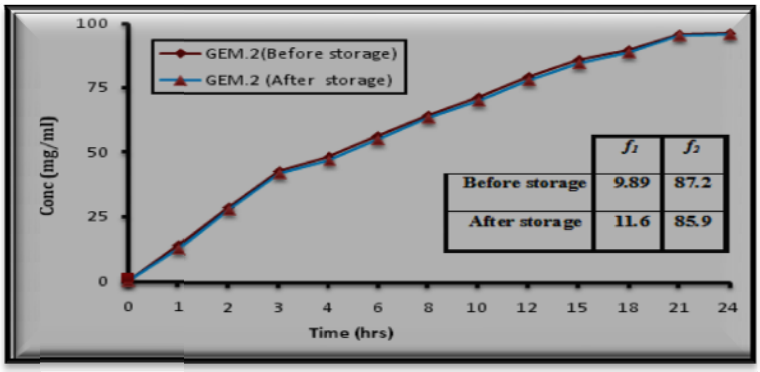

Fig. 50: Comparative release profiles of optimized formulation GEM.2 before and after storage.

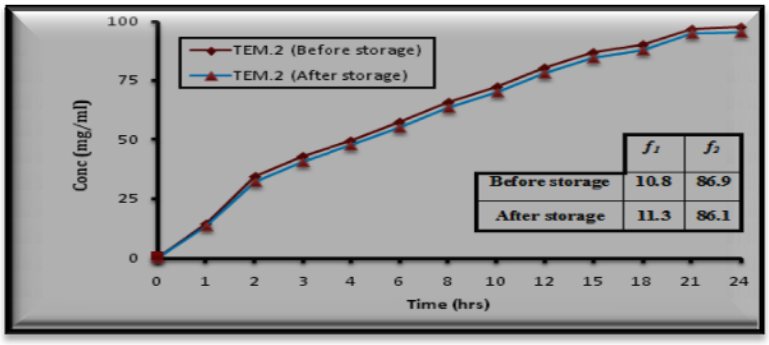

Fig. 6: Comparative release profiles of optimized formulation TEM.2 before and after storage.

ACKNOWLEDGEMENTS

The Authors are grateful to the Chairman, Dr. L.V.G. Nargund and the H.O.D. Dept. of Pharmaceutics Dr.C.S.R. Laxmi, Nargund College of Pharmacy, Bangalore, for providing facilities necessary for the project undertaken and their constant encouragement.

REFERENCES

1. Rauwendaal. *Ch. Polymer Extrusion.* Munchen: Hanser publishers; 1986. 20-25.
2. Reynolds AD. A New Technique for the Production of Spherical articles. Manuf Chem.1970; 41(6): 40-43.
3. Carlson LA. The broad spectrum hypolipidaemic drug nicotinic acid. J Drug Dev. 1990; 3(Suppl.1):223-26.
4. Carlson LA. Niaspan, the prolonged release preparation of nicotinic acid (niacin), the broad spectrum lipid drug. *Int J Clin Pract.* 2004; 58:706-13.
5. Heller J. Use of polymers in controlled release of active agents. In: Robinson J R, Lee V H L. Editor's. Controlled Drug Delivery — Fundamentals and Applications: Drugs and the Pharmaceutical Sciences. 2nd ed. New York: Marcel Dekker INC; 1987; 29: 179–212.
6. Santos H, Veiga F, Pina M E, Sousa J J. Compaction, compression and drug release characteristics of xanthan gum pellets of different compositions. Eur J Pharm Sci. 2004; 21: 271–281.
7. Al-Saidan S M, Krishnaiaha Y S R, Satyanarayanab V, Bhaskarc P, Karthikeyan R S. Pharmacokinetic evaluation of guar gum-based three-layer matrix tablets for oral controlled delivery of highly soluble metoprolol tartrate as a model drug. Eur J Pharm Biopharm. 2004; 58: 697–703.
8. Shlieout G, Zessin G. Investigation of ethyl cellulose as a matrix former and a new method to regard and evaluate the compaction data. Drug Dev Ind Pharm.1996; 22:313–319.
9. Tobyn M J, Staniforth J N, Baichwal A R, McCall T W. Prediction of physical properties of a novel polysaccharide controlled release system. Int J Pharm. 1996; 128:113–122.
10. Nellore RV, Rekhia GS, Hussain AS, Tillmand LG, Augsburger LL. Development of metoprolol tartrate extended-release matrix tablet formulations for regulatory policy consideration. J Control Release 1998;50:247-56.
11. Coppens K, et al. Hypromellose, Ethylcellu-lose, and Polyethylene Oxide Use in Hot Melt Extrusion – A Review Article. Pharmaceutical Technology. January 2006.
12. Selim Rezal Md, Mohiuddin Abdul Qadir and Syed Shabbir Haider. comparative evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled release drug delivery. J. Pharm. Pharmaceut Sci. 2003; 6(2): 274-291.
13. Durig T, Fassihi R. Guar-based monolithic matrix systems: Effect of ionizable and non-ionizable substances and excipients on gel dynamics and release kinetics. J Control Release. 2002; 80: 45–56.
14. Sako K, Sawada T, Nakashima H, Yokohama S, Sonobe T. Influence of water soluble fillers in hydroxypropylmethylcellulose matrices on in vitro and in vivo drug release. J Control Release. 2002; 81:165– 172.
15. Williams III RO, Reynolds TD, Cabelka TD, Sykora MA, Mahaguna V. Investigation of excipient type and level on drug release from controlled release tablets containing HPMC. Pharm Dev Technol. 2002;7: 81–193.
16. Raghuram KR, Mutalik S, Reddy S. Once-Daily sustained-release matrix tablets of nicorandil: Formulation and In Vitro Evaluation. AAPS Pharm Sci Tech. 2003; 4:61.
17. Dabbagh MA , Ford JL , Rubinstein MH , Hogan JE . Effects of polymer particle size, compaction pressure and hydrophilic polymers on drug release from matrices containing ethylcellulose. Int J Pharm. 1996; 140:85-95.
18. Chikhalikar K, Moorkath S. Carbopol Polymers: A versatile range of polymers for pharmaceutical applications. Pharmabiz. 2002.
19. Ghebre-Sellassie I, Martin C. Pharmaceutical Extrusion Technology. New York: Marcel Dekker INC; 2003.
20. Aulton ME, Wells TI. Pharmaceutics: The science of dosage

form design. London, England: Churchill Livingstone; 1998. 647-9.
21. Cooper J, Gunn C. Powder flow and compaction. In: Carter SJ, editor. Tutorial Pharmacy. New Delhi: CBS Publishers and Distributors; 1986. p. 211-33.
22. Higuchi T. Mechanismof sustained-action medication: Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci. 1963; 52: 1145–1149.
23. Korsmeyer RW, Gurny R, Doelker EM, Buri P, Peppas NA. Mech anism of solute release from porous hydrophilic polymers. Int J Pharm. 1983; 15:25-35.
24. Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. Pharm Acta Helv. 1985;60:110-111
25. Lin Ju H, Liaw SJ. On the assessment of similarity of drug dissolution profiles: A simulation study. Drug Inf J. 1997; 31: 1273-89.
26. Costa P, Lobo JMS. Modeling and comparison of dissolution profiles. Eur J Pharm Sci. 2001; 13:123-133.
27. Carstensen JT. Solid state stability. In: Carstensen JT, Rhodes CT, editors. Drug stability: Principles and practices. New York: Marcel Dekker INC; 2000. p. 145-89.
28. Marshall K. Compression and consolidation of powdered solids. In: Lachman L, Lieberman H, Kanig J. editors. The theory and practice of industrial pharmacy. Mumbai: Varghese Publishing House; 1987. p. 66-99.
29. Rajabi-Siabhoomi AR, Melia CD, Davies MC, Bowtell RW, Mcjury M, Sharp JC et.al. Imaging the internal structure of the gel layer in hydrophilic matrix systems by NMR microscopy. J Pharm Pharmacol. 1992; 44:1062.