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# Formulation, development and *in vitro* evaluation of effervescent tablets of niacin for dyslipidemia

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**ABSTRACT**

*The literature and market survey reveal that so far there is no preparation of n*iacin *in the form of effervescent tablets (ET) and it is still available in the market as only a conventional tablet. Even this conventional tablet is prepared hardly by a handful of pharmaceuticals.* The present study was aimed to formulate the niacin in the form of ET dosage form as an alternative to the available marketed few conventional tablets. *ET was made up of* effervescent granules (EG). *EG are prepared by* wet granulation method with non-reactive liquids using PVP as a binder with concentration ratios of 1: 2: 4. As the concentration of PVP is increased, the dissolution profile of niacin was decreased. The formulation F8 containing citric acid, tartaric acid and sodium bicarbonate in the ratio of 1:1:1 was considered to be the best formulation. All the prepared EG and ET are evaluated for the official tests and found to be within limits. In- vitro dissolution studies of formulation F8 shows good release by about 95.2% in 3.30 hours. All prepared formulations are slightly acidic (pH 4.0 to 4.2) to augment the taste of the solution. IR Spectra of formulation F8 shows, there is no interaction between niacin and excipients used. And the formulation F8 was most stable at temperature 25°C to 40°C. It conclude that, niacin can prepared in the form of "pleasantly flavored effervescent drink" of ET by compressing EG, which is prepared by wet granulation method with non-reactive liquids.

**Key words:** Niacin, effervescent tablet, polyvinylpyrrolidine, sodium bicarbonate, dyslipidemia.

## INTRODUCTION

The purpose of this study is to explore the possibility in the formulation of novel, flavored effervescent drink of niacin in the form of effervescent tablets (ET) for Dyslipidemia. The formulation and evaluation of ET of niacin was taken up with the following aim: As is common with most of the dosage forms, niacin in the form of conventional tablet is associated with not only gastric irritation, but also poor absorption. To reduce this gastric irritation and to enhance absorption of drug, niacin can be given in the form of ET and to provide a suitable dosage form as an alternative to the available marketed few conventional tablets of niacin. Efficiently administering medicine is of utmost importance in order to obtain good therapeutic results. The most common way to give patients their medicine is by oral administration, through pills, tablets, capsules and syrups,[1] that have some drawbacks. However, especially concerning pills, tablets and capsules, for example, all three take time to dissolve in the stomach and release the active ingredient. This increases the time that is needed to transport the drug from the intestine into the bloodstream. Dissolving the pill, tablet or contents of the capsule in water prior to ingestion is a common way to avoid this extra step in the stomach. Yet, the obtained solution is seldom clear and contains un-dissolved material, which remains

unused in the dispensed containers, thereby assuring cent percent drug has not been given to the patient.

One pill alternative is the formulation of active ingredients as ET. When dissolved in water, the basic excipient (a carbonate) and the acid excipient (an organic acid) will react with each other, liberating carbon dioxide. Due to the dynamics of this process, turbulence is created and the active ingredient will dissolve more rapidly[1] in the water, without any un-dissolved material in the solution. Thereby, assuring cent percent drug transportation into the blood stream.

Since, niacin is so far known to be a best example for drug that is sparingly soluble in water; effervescence is the method of choice in formulating active ingredients (niacin) with poor water solubility.

Niacin was first reported to affect lipids in 1955 [2], is one of the oldest drugs used to treat Dyslipedemia and was most versatile in that favorably affect virtually all lipids parameters. Niacin was the best agent available for increasing HDL-C (increments of 30% to 40%); it also lowers triglycerides 35% to 45% (as effectively as fibrates and the more potent statins) and reduces LDL-C levels by 20% to 30%. Niacin is also the only lipid-lowering drug that reduces Lp(a) levels significantly, by about 40%. The pharmacological doses of regular (crystalline) niacin (>1 g per day) used to treat Dyslipedemia are almost completely absorbed, and peak plasma concentration (upto 0.24mM) are achieved within 30 to 60 minutes.[3]

The National Pharmacy Cardiovascular Council (NPCC) recommends niacin as first-line therapy for patients with hypertriglyceridemia (without diabetes) and for patients with isolated low HDL-C. Furthermore, the NPCC recognizes that niacin's favorable effects on the overall lipid profile make it a valuable treatment option for patients with atherogenic or mixed Dyslipidemia, a condition characterized by elevated LDL-C and triglycerides.[4] Despite its salutary effects niacin has its own side effects also. Historically, the use of niacin has been limited by cutaneous flushing, which is a prostaglandin D2-mediated vasodilation characterized by sudden warmth, redness, itching, and/or tingling on the face and truncal regions and is usually evident one to two hours after taking a dose of niacin.[5] Flushing can be reduced by giving aspirin and taking the medication with meals.[3]

## MATERIAL AND METHODS

### Materials

USP Niacin RS, (Reference Standard) (Dry the Niacin at 105°C for 1 hour before using), tartaric acid, citric acid (anhydrous), sodium carbonate, sodium bicarbonate, polyvinylpyrrolidine (PVP), aspartame, sodium saccharine, talc, sod benzoate, polyethylene glycol 6000, magnesium stearate, sodium chloride, colors (Sunset Yellow), flavors, (orange booster) and all other chemicals AR grade, provided by Jagdale scientific research foundation, Bangalore.

### Methods

#### Processing of effervescent granules (EG) and effervescent tablet (ET)

EG and ET requires special environmental conditions: low relative humidity (RH) and moderate -to- cool temperatures in the processing areas are essential to prevent the granulations or tablets from sticking to machinery and from picking up moisture from the air, which may lead to tablet instability. In the present processing a maximum of 25% RH at a controlled room temperature (RT) of 25°C or less, was found to be satisfactory to avoid the problem due to atmospheric moisture [6].

#### Preparation of effervescent granules (EG)

EG were prepared by wet granulation method with nonreactive liquids. First sieve all the ingredients with a # 60 sieve. Weigh and collect the required quantity of sieved ingredients (Table 1), (except flavor and the lubricants.) and weigh the clinically relevant dosage strength of 500 mg niacin. Both were placed in a tray and mixed with liquid binder, such as PVP (5% in anhydrous ethanol) to make a coherent mass. This mass was immediately passed through sieve no. 16, which was superimposed sieve no. 44, then spread out on a tray, and dried in a oven at 50°C for 1 hour. These EG were immediately transferred to suitable dessicator, and tightly closed[6].

**Preparation of effervescent tablets**

Blend the thus obtained EG thoroughly with the weighed and sieved flavor and lubricants (Table 1). Now the ET can be prepared by compressing the lubricated EG on single punch tablet machine at a RH of 25% and RT of 25$^0$C, using 13 mm in diameter and flat faced, beveled edge die and punch set, ET weighing 3.165g each. pass through curing oven; cool; and package in aluminum foil [6].

**Evaluation of effervescent granules**

**Angle of repose**

Angle of repose was determined by using funnel method [7]. EG were poured from the funnel, that can be raised vertically until a maximum cone height, h , was obtained. diameter of heap, D, was measured. The repose angle $\theta$ was calculated by formula:

$$\tan \theta = 2h / D.$$

**Bulk density**

Apparent bulk density was determined by placing presieved EG into a graduated cylinder and measuring the volume and weight "as is"[8].

**Tapped density**

It was determined by placing a graduated cylinder, containing a known mass of EG on mechanical tapping apparatus, which was operated for fixed number of taps until the EG bed volume has reached a minimum. Using the weight of EG bed in a cylinder and this minimum volume, the tapped density was computed[8].

**Compressibility index and Hausner ratio**

This was measured for the property of EG to be compressed. As such they are measured for relative importance of interparticulate interactions [9]. Compressibility index was calculated by the following equation

$$\{(Dt - Db)\} \times 100$$

Where Dt = Tapped Density. Db = Bulk Density

Hausner ratio was calculated by the following equation $Dt / D_0$

Where Dt = Tapped Density. $D_0$ = Bulk Density.

**Evaluation of effervescent tablets**

**Physical parameters**

**Weight variation**

Twenty ET were selected at random and weighed individually. The average weight and standard deviation of all twenty ET was calculated [10].

**Thickness**

The thickness of the ET was measured by using a sliding caliper scale, twenty ET was selected at random in a holding tray and total crown thickness was measured.

**Hardness**

Hardness of ET was measured using Monsanto hardness tester [10].

**Friability**

Twenty ET were weighed and placed in the Roche friabilator. It revolves at 25 rpm, dropping the ET at a distance of six inches with each revolution. The ET were then dusted and reweighed [10].

**Disintegration time**

Place an ET in a beaker containing 200 ml of water at 15$^0$C to 25$^0$C; numerous bubbles of gas are evolved. When the evolution of gas around the ET or its fragments ceases, the ET has disintegrated in the water. No agglomerate of particles remains. The test was repeated for five other ET [11].

**Chemical parameters**

**Solution pH**

Solution pH is measured with digital pH meter in standardized water volume and temperature. Place an ET in a beaker containing 200ml of water at 15$^0$C to 25$^0$C. The pH was measured after complete disintegration of the ET [6].

**Drug content determination**

Drug content was determined by dissolving the ET in 200 ml of water. Transfer an accurately weighed quantity of the liquid equivalent to about 500 mg of Niacin to a volumetric flask; and heat on a steam bath for 30 minutes. Sonicate for 2 minutes, shake by mechanical means for 15 minutes, and cool to room temperature. Dilute with water to volume, mix and filter. Transfer 1.0 ml of this solution to a100-ml volumetric flask, dilute with water to volume, and mix. Concomitantly determine the absorbance of this solution and a solution of niacin in the same medium, at a concentration of about

20 mcg/ml, in 1-cm cells at a wavelength of maximum absorbance at about 262 nm, using UV Spectrophotometer [12].

***In-vitro* drug release study**

*In-vitro* release studies were carried out using USP Type 1 apparatus at 100 rpm, 0.1N hydrochloric acid: 900 ml was used as dissolution medium. Temperature of dissolution medium was maintained at 37 ± 0.5°C. The release study was carried out for 3.30 hrs. Aliquot of dissolution medium was withdrawn at specific time interval and was filtered. Then absorbance was measured at about 262 nm, with UV Spectrophotometer. The data presented were the mean of three determinations [12].

**IR spectra**

The best Formulation F8 (Table 1) was subject to IR – analysis by KBr pellet method using Perkin Elmer IR-Spectrophotometer. The solvent

**Table 1: Formulation of effervescent tablets**

| Name of theIngredients | Quantity/Tablet (mg) Formulation codes | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** |
| Niacin | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 |
| Citric acid (Anhydrous) | 1550 | - | 1550 | | 775 | 775 | 775 | 775 |
| Tartaric acid | - | 1550 | | 1550 | 775 | 775 | 775 | 775 |
| Sod carbonate | 1000 | - | 500 | 500 | 1000 | 500 | 700 | 1000 |
| Sod bicarbonate | - | 1000 | 500 | 500 | | 500 | 300 | - |
| Sod saccharin | 40 | 40 | 40 | 40 | 20 | - | - | - |
| Aspartame | - | - | - | - | 20 | 40 | 40 | 40 |
| PVP (5% in Anhydrous Ethanol) | 0.016 | 0.016 | 0.016 | 0.008 | 0.008 | 0.004 | 0.004 | 0.004 |
| Sod benzoate | 05 | 05 | 05 | 05 | 05 | 20 | 20 | 20 |
| Talc | 40 | 40 | 40 | - | - | - | - | - |
| Polyethylene glycol 6000 | - | - | - | 35 | 35 | - | - | - |
| Magnesium stearate | 10 | 10 | 10 | 10 | 10 | 25 | 25 | 25 |
| Sod chloride | 10 | 10 | 10 | 15 | 15 | 20 | 20 | 20 |
| Color (Sunset yellow) | 05 | 05 | 05 | 05 | 05 | 05 | 05 | 05 |
| Flavor (Orange booster) | 05 | 05 | 05 | 05 | 05 | 05 | 05 | 05 |

**Table 2: Results of evaluation tests for effervescent granules**

| Formulation codes | Parameters Angle of Repose (0)* | Bulk Density ($g/cm^3$)* | Tapped Density ($g/cm^3$) * | %Compressibility* | Hausner Ratio* |
|---|---|---|---|---|---|
| F1 | 30.680±0.199 | 1.124±0.007 | 1.306±0.070 | 19.200±0.006 | 1.170±0.045 |
| F2 | 30.060±0.077 | 1.092±0.001 | 1.292±0.055 | 20.000±0.013 | 1.183±0.009 |
| F3 | 30.180±0.090 | 1.084±0.002 | 1.296±0.045 | 21.200±0.002 | 1.195±0.014 |
| F4 | 30.990±0.190 | 1.104±0.009 | 1.284±0.068 | 18.000±0.009 | 1.163±0.198 |
| F5 | 30.030±0.079 | 1.076±0.006 | 1.288±0.059 | 21.200±0.007 | 1.197±0.009 |
| F6 | 29.960±0.026 | 1.092±0.077 | 1.296±0.049 | 20.400±0.010 | 1.186±0.000 |
| F7 | 30.050±0.096 | 1.096±0.097 | 1.308±0.086 | 21.200±0.018 | 1.193±0.190 |
| F8 | 29.950±0.020 | 1.080±0.011 | 1.296±0.044 | 21.600±0.010 | 1.200±0.120 |

The values are presented as arithmetic mean ±standard deviation of 3 determinations.

**Table 3: Results of evaluation tests for effervescent tablets**

| Parameters | | Formulation codes | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
| Physical Parameters | Weight Variation (gm) * | 3.149±0.0008 | 3.160±0.0012 | 3.169±0.0076 | 3.171±0.0001 | 3.160±0.0024 | 3.170±0.0000 | 3.161±0.0006 | 3.165±0.0012 |
| | Thickness (mm) * | 4.990±0.0001 | 5.020±0.000 | 5.010±0.0002 | 5.020±0.004 | 4.990±0.0001 | 5.000±0.000 | 5.010±0.0001 | 5.010±0.000 |
| | Hardness ($Kg/cm^2$) * | 5.000±0.0002 | 5.100±0.354 | 5.500±0.646 | 5.200±0.928 | 5.100±0.220 | 4.900±0.289 | 4.900±0.301 | 4.900±0.279 |
| | Friability (%)* | 0.490±0.032 | 0.460±0.026 | 0.340±0.038 | 0.430±0.041 | 0.450±0.045 | 0.650±0.033 | 0.470±0.029 | 0.630±0.030 |
| | Disintegrating Time (Sec) * | 104 | 105 | 99 | 88 | 82 | 75 | 76 | 73 |
| Chemical Parameters | Solution pH * | 4.200 ±0.006 | 4.100 ±0.008 | 4.200±0.301 | 4.200±0.003 | 4.000±0.009 | 4.200±0.004 | 4.200±0.008 | 4.000±0.008 |
| | Assay (%Drug Content) * | 99.300±0.050 | 100.300±0.040 | 98.600 ±0.000 | 98.000 ±0.020 | 101.200±0.010 | 98.600±0.070 | 98.500±0.060 | 99.600 ±0.010 |

The values are presented as arithmetic mean ±standard deviation of 10 determinations

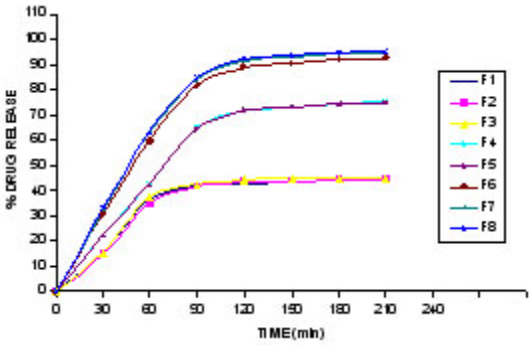


**Fig. 1: Dissolution profile of all formulations**

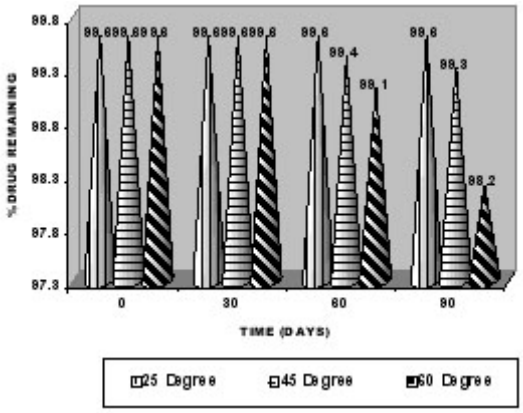


**Fig. 2: Accelerated stability studies of the best formulation 08 at 25±2°C, 45±2°C, & 60±5°C, for 90 Days**

used was Nujol and the IR Spectra was taken directly on KBr window.

**Accelerated stability studies**

The Accelerated stability studies at 25 ± 2°C, 45 ± 2°C, & 60 ± 5 °C, for 90 days, were carried out for the best formulation F8 (Table 1). The general appearance & drug content was evaluated.

## RESULTS AND DISCUSSION

ET was prepared by compressing EG that were successfully prepared by wet granulation method with non-reactive liquids [a concentration of 5% polyvinylpyrrolidine (PVP) in anhydrous ethanol produced a granulation of good compressibility and vigorous effervescence with rapid disintegration of the resulting tablets] using acid source like citric acid, tartaric acid, and carbonate sources like sodium carbonate and sodium bicarbonate. The formulation f8, (table 1), containing citric acid, and tartaric acid and sod bicarbonate in the ratio of 1:1:1 was the best among all the 08 formulations.

When the ET was dropped in water, the basic excipient (a carbonate) and the acid excipient (an organic acid) will react with each other, liberating carbon dioxide. Due to the dynamics of this process, turbulence is created and the active ingredient will dissolve more rapidly in the water, without any undissolved material in the solution. Thereby assuring cent percent drug transportation into the blood stream.

Lubricants like talc, sodium benzoate, polyethylene glycol 6000, magnesium stearate, and sodium chloride, were used in the formulations (table 1). Talc was used in the formulations F1, F2&F3 (table 1), acts as both lubricant and glidant. It facilitates glidency of granules during material flow, eliminates binding in the die and minimizes picking and sticking to punch-face surface on compression. It retards little disintegration of ET from 99 to 104 Sec (Table 1). And when single ET was dropped in a glass of water it disintegrate and leaves a thin layer of talc at the bottom of the glass after keeping the solution for 10 minutes without disturbing, because of the insolubility of talc in water.

Polyethylene glycol (PEG) 6000 was used as the water-soluble lubricant in formulations F4 & F5 (Table 1). The disintegration time was good (82 to 88 sec) (Table 1), and also the final solution was clear without any sediment. But it was having little sticking to punch face surface on compression, and

at the end of every sip of the drink it gave bad flavor and was unfit for drinking.

A combination of water-soluble lubricants like sodium benzoate, magnesium stearate, and sod chloride was used in the formulations F6, F7& F8 (Table 1). The disintegration time was good (73 to 76 sec) (Table 1), the final solution was crystal clear without any sediment and finally gives pleasantly flavored drink. So this combination of the lubricants was considered to be the best for the formulation of ET.

Sodium saccharine was used in the formulations F1, F2, F3 & F4 (Table1) as a sweetening agent. But at the end of every sip of drink it gives bitter taste. When aspartame was used as a sweetening agent in the formulation F6, F7& F8 (Table1) gave pleasant taste without any bitterness. Natural coloring agent (sunset yellow), and flavor (orange booster) of orange, have been used correspondingly to give a "pleasantly flavored orange drink".

All prepared EG and ET were evaluated for the tests like, angle of repose, bulk density, tapped density, compressibility and Hausner ratio (table 2) for EG and weight variation, thickness, hardness, friability, and disintegration time, solution pH and drug content for ET (Table 3) were found to be within limits.

The consistent measurement of solution pH is a sign of good distribution of raw materials within the ET. The pH of the solution was important for taste reasons in a product meant for ingestion. All 08 formulations are slightly acidic (pH 4.0 to 4.2) (Table 3) to augment the taste of the solution.

*In-vitro* release studies were evaluated for drug release by using USP-XXI dissolution test apparatus. The release of niacin significantly decreased with increase in the concentration of PVP, (Fig 1) The formulations F1, F2, & F3 at 0.016 concentration of PVP release the niacin 44.4% to 45.2 % for 3.30 hrs, The formulations F4& F5, at 0.008 concentration of PVP release the niacin 74.9% to 75.3% for 3.30 hrs, The formulations F6, F7, & F8 at 0.004 concentration of PVP release the niacin 92.1% to 95.2% for 3.30 hrs. This reveals that formulation F8 shows good release as compared to the rest of the formulations. Assay of ET shows that all formulations are of required purity and match the USP specifications

From the IR Spectra (not shown) of best formulation F8 (Table 1) it is clear that there is no significant shift in the major peaks, which indicates that there is no interaction between the excipients and the niacin used, and this formulation F8 was in compliance with the I.P. specifications.

Accelerated stability studies of best formulation F8 (table1) was exposed at 25 ± 2 $^0$C, 45 ± 2$^0$C, & 60 ± 5 $^0$C, temperature for 90 days and was found most stable at temperature between 25$^0$C and 45$^0$C. There was no change in appearance. The Drug content at 25$^0$C and 45$^0$C for 90 days did not show any remarkable changes, but at 60$^0$C for 90 days fell down a negligible amount 1.6% (initial concentration 99.6% and final concentration 98%. (Fig. 2).

This study confirms that niacin can be successfully prepared in the form of "pleasantly flavored effervescent drink" of ET by compressing EG that were prepared by wet granulation method with non-reactive liquids. This technique was more applicable to industrial practice and production.

## CONCLUSION

Effervescence technology provides a novel dosage form for nutritional supplements and pharmaceuticals. The ability to incorporate large dosages of a wide variety of active ingredients in an easy-to- swallow liquid, plus increased absorption of the active ingredient, offers advantage over conventional tablets.

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