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RESEARCH ARTICLE

Formulation and Evaluation of Niacin Extended Release Tablets

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ABSTRACT

Present study aims to prepare and evaluate niacin extended release tablets. The Matrix tablets each containing 1000 mg of niacin are formulated employing ethyl cellulose (10cps & 50cps)/ eudragits (FS-30D, NE-40D, RL-30D) in various proportions as rate controlling polymers. All the matrix tablets are prepared by wet granulation method and are evaluated for hardness, friability, average weight, and dissolution rate. A total of 10 formulations are prepared and estimated for comparison, dissolution rate of innovator product (Niaspan) is also studied, among all formulations F10 is found to be the best as all properties including dissolution rate are similar to those of innovators product.

KEYWORDS

Niacin, Extended release, Ethyl cellulose, Eudragits, Wet granulation

INTRODUCTION

The concept of extended drug delivery has been explored for the delivery of drugs for prolong period of time for the past few years. This type of drug delivery has proved to provide a solution to several problems encountered in the repeated administration of such drugs. NIACIN is an antihyperlipedimic used for the treatment of hyperlipidemia which is available as immediate release and sustained release tablets[1]. In those immediate release formulations which are available in market causes cutaneous flushing, sustained release tablets causes hepatotoxicity[2]. To prevent both cutanious flushing and hepato toxicity caused by immediate and sustained release formulations an intermediate release i.e, extended release Niacin tablets 1000mg are formulated utilizing the concept of incorporating drug in to the polymer matrices and extend the drug release for prolong period of time, an attempt was made to design and evaluate extended release tablets of niacin.

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MATERIALS AND METHOD

Niacin was a gift from nakoda chemicals, Hyderabad, India, Avicel PH101 (loba chemie Pvt. Ltd, Mumbai), HPMC- E5, HPMC E15, Povidone K90 were gift sample from Signet chemical corporation, Mumbai. Ethyl cellulose grades were gift sample from Chemo, India, Mumbai. Eudragit grades were gift sample from Degussa Mumbai. Materials and excipients used in preparing tablets were of pharmaceutical grades. All other chemicals used were of analytical grade.

Preparation of Matrix Tablet

Matrix tablets (each tablet contains 1000 mg of niacin) were prepared by wet granulation method (Table 1). Where in F1 intra granular and extra granular concentration of EC is 1:1 in F2, F3, F4 the intra granular and extra granular concentration is in the ratio of 5:3, 3:1, 7:1.in all these formulas EC 10 cps grade was used. In F5 EC 50 cps was used in the concentration of 3:1 ratio, in F6 in place of EC polymer was replaced by eudragit (FS-30D). In F7 eudragit FS30D

was replaced with eudragit NE40D. In F8 eudragit NE40D replaced with RL30D in F9, F10 the compressed tablet was coated with different grades of HPMC i.e E15, E5.

In Vitro Drug Release Studies

The formulated matrix tablets were subjected to the USP APPARATUSII (PADDLE TYPE) using 900 ml of 0.1N HCl as dissolution medium. The dissolution was performed at 75 rpm and temperature was 37°C ± 0.5°C.

At six predetermined time intervals (1st hour, 3rd hour, 6thhour, 9^{th}, 12^{th} and 20^{th} hour) over 20 hours period, 5 milliliters of samples were withdrawn, centrifuged and assayed spectrophotometerically (Shimadzu UV spectrophotometer, UV-1650 PC) at 263 nm after suitable dilution. After each sampling, equal volume (5 ml) of fresh buffer solution with same temperature was replaced. All experiments were run as triplicate and averages were accounted.

Evaluation of Tablets

The prepared matrix tablets were evaluated for hardness, weight variation, thickness, friability and drug content. Hardness of the tablets was tested using a strong-Cobb hardness tester (Tab-Machine, Mumbai).

Friability of the tablets was determined in a Roche friabilator (Campbell Electronics, Mumbai). The thickness of the tablets was measured by vernier calipers. Weight variation test was performed according to the official method of British Pharmacopoeia. Drug content determination for Niacin (Nicotinic Acid) was carried out according to USP30-NF25

Release Kinetics

Based on *In-vitro* release studies, all data were fitted to various kinetic equations to find out the mechanism of drug release from the formulated matrix tablets.

In these study four kinetic models as Zero order equation, First-order equation, Square root of time equation or Higuchi equation and Korsmeyer-Peppas equation were used.

Zero Order Equation

The equation (Eq. 1) assumes that the cumulative amount of drug release is directly related to time. The equation is as follows,

$$C = K0\ t \ldots\ldots\ldots\ldots\ (1)$$

Where, *K0* is the zero order rate constant expressed in unit concentration/time and *t* is the time in hour.

First Order Equation

The release behavior of first order equation is expressed as log cumulative percentage of drug remaining verses time. The equation (Eq. 2) is as follows[3],

$$Log\ C = Log\ C0 - k\ t / 2.303 \ldots\ldots\ldots\ldots\ (2)$$

Where, *C* = The amount of drug undissolved at t time *C0* = Drug concentration at *t* = 0

k = Corresponding release rate constant.

Higuchi Equation

The Higuchi release model describes the cumulative percentage of drug release verses square root of time. The equation (Eq. 3) is as follows[4],

$$Q = K \sqrt{t} \ldots\ldots\ldots\ldots\ (3)$$

Where, *Q* = (100-*C*) the amount of drug dissolved at time *t*. *K* is the constant reflecting the design variables of the system. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Korsmeyer-Peppas Equation

Korsmeyer *et al* developed a simple, semi-empirical model, relating exponentially the drug release to the elapsed time[5].

The equation (Eq. 4) is as follows:

$$Q / Q0 = K\ t\ n \ldots\ldots\ldots\ldots\ (4)$$

Where, *Q / Q0* = The fraction of drug released at time *t k* = Constant comprising the structural geometric characteristics *n* = The diffusion exponent that depends on the release mechanism If $n \leq 0.5$, the release mechanism follows a Fickian diffusion, and if $0.5 < n < 1$, the release follows a non-Fickian diffusion or anomalous

transport. The drug release follows zero order drug release and case-II transport if n=1. But when n>1, then the release mechanism is super case-II transport. This model is used in the polymeric dosage form when the release mechanism is unknown or more than one release phenomena is present in the preparation[6]. Similarity factor in the range of 50-100 is acceptable according to US FDA. It can be computated using the formula

$$f2= 50\times\log \{[1+(1/n)\Sigma_{t=1}^{n}(R_t-T_t)^2]^{-0.5} \times 100\}.. (1)$$

Where, n is the number of dissolution sample times, R_t and T_t are the individual or mean percent dissolved at each time point, t, for the reference and test dissolution profiles, respectively. The similarity factor should be between 0 and 100. It is 100 when two comparative groups of reference and test are identical and approaches 0 as the dissimilarity increases.

Difference Factor (f1)

Difference factor focuses on the difference in percent dissolved between reference and test at various time intervals[7]. It can be mathematically computed by using

$$f1= \{[\Sigma_{t=1}^{n} |R_t-T_t|] / [\Sigma_{t=1}^{n} R_t]\} \times 100..... (2)$$

Therefore the factors directly compare the difference between percent drug dissolved per unit time for a test and a reference product.

RESULTS AND DISCUSSION

Physical Properties

The results of physical parameters (i.e., weight, hardness, thickness and friability) and drug content of the prepared matrix tablets were shown in Table no. 2. The hardness of tablets ranged from 24 kp to 28.6 and friability ranged from 0.49% to 0.76%.

The weight variations of prepared tablets found were complied with the pharmacopoeial specifications. The drug content of every formulation was found about to 100% of labeled content. All these results indicate that the granules possessed satisfactory flow properties, compressibility and drug content.

In Vitro Release Kinetics

Table no. 3 shows data analysis of release profile according to different kinetic models (Fig. 1, Fig. 2, Fig. 3, Fig. 4). The drug releases from tablets were found slow and extended over 20 hours. The initial formulation of niacin tablets were formulated with Ethyl cellulose 10cps, ethylcellulose (10cps)) with concentration of 8%. However satisfactory results were not obtained the polymer and it was decided to proceed further with high viscosity polymers which would effectively sustain the release of drug. The F2, F3, F4, F5 batches were formulated with ethyl cellulose (50cps) 8% and Povidone K-90 (6.5%).

where the amount of ethyl cellulose was added in the ratio of 5:3, 6:2, 7:1in internal and external granulation and in 4th ethyl cellulose (50cps) was used However the release was more from the dosage form and it was decided to replace EC (10cps) and EC (50cps) with high other polymer Ethyl cellulose N-50 (22 cps) no formula in the above batches achieved the desired f2 value. The F6 batch was formulated with Eudragit FS30D (3.6%). The desired f2 value was not achieved with this batch also. So Niacin in combination with EudragitNF40D AND Eudragit RL30D was used and release mechanism is checked. The F7 and F8 batches were taken with only Eudragit NF40D and Eudragit RL30D respectively.

The desired f2 value was not achieved with these batches also. But the release of drug with Eudragit RL30D was found very nearer to innovator product. The F9 batch was formulated with Eudragit RL 30D (08%) and HPMC E15 (5%) as film coating polymer. The F10 batch was formulated with Eudragit RL 30D (08%) and HPMC E5 (5%).

Eudragit RL 30D is pH independent sustained release polymer. The release of drug form the tablets which are film coated was very neater to that of the innovator. The desired f2 value was achieved with the formulation. Eudragit RL30D is insoluble in aqueous media but they are permeable and both have pH-independent release profiles.

Table 1: List of Ingredients Added in Different Formulations Prepared

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Niacin	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
Povidone (K90)	65	65	65	65	65	65	-	-	-	-
EC	40+40	50+30	60+20	70+10	60+20	-	-	-	-	-
Mg stearate	8	8	8	8	8	8	13	13	13	13
Aerosil	4	4	4	4	4	4	13	13	13	13
Avicel (PH 101)	143	143	143	143	143	143	79	79	79	79
Eudragit FS30D	-	-	-	-	-	40	-	-	-	-
Eudragit NE40D	-	-	-	-	-	-	48.75	-	-	-
Eudragit rl30d	-	-	-	-	-	-	-	65	65	65
HPMC E15	-	-	-	-	-	-	-	-	32.5	-
HPMC E5	-	-	-	-	-	-	-	-	-	32.5
PEG 4000	-	-	-	-	-	-	-	-	3.9	3’9
Iron oxide	-	-	-	-	-	-	-	-	0.163	0.163
Titaniumdioxide	-	-	-	-	-	-	-	-	0.163	0.163
water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Table 2: Evaluation Results of Prepared Formulations

Batch	Consolidation Index (Carr %)	Hausner’s Ratio	Angle of Repose	Hardness (Kp)	% Fraiability	Avg. wt	Assay
F1	22.05	1.333	34.25	24.3	0.76	1300.8±2.48	98.25±1.37
F2	20.15	1.158	31.78	24.2	0.68	1297.8±1.64	101.22±0.88
F3	19.75	1.89	30.75	22.9	0.73	1306.6±2.14	100.24±1.25
F4	20.25	1.394	30.56	23.3	0.54	1302.0±2.43	95.35±1.14
F5	21.63	0.912	31.89	25.4	0.49	1299.5±1.80	96.34±2.18
F6	23.05	1.351	32.87	24	0.71	1308.2±1.83	91.29±0.98
F7	19.84	0.991	31.69	28.6	0.67	1311.2±2.17	98.88±0.88
F8	20.13	1.336	31.48	26.2	0.49	1305.0±2.22	102.55±2.15
F9	21.47	1.261	30.12	27.7	0.65	1301.8±2.48	98.36±2.31
F10	21.38	1.254	30.08	26.8	0.57	1306.4±2.04	93.78±1.56

Table 3: Drug release kinetics of prepared formulations

Batch	Zero order		First order		Higuchi		Korsmeyer-Peppas	
	r^2	K_0 (mg/L/hr)	r^2	K_1 (h^{-1})	r^2	K_{Hg} (h^{-1})	r^2	n
INNOVATOR	**0.979**	**4.32**	**0.979**	**9.94**	**0.972**	**19.66**	**`0.821**	**1.184**
F1	0.895	4.97	11.45	0.88	0.972	24.21	0.704	1.144
F2	0.967	7.39	0.979	0.188	0.982	27.02	0.722	1.335
F3	0.884	8.44	0.99	0.387	0.964	32.07	0.679	1.355
F4	0.941	6.978	0.989	0.161	0.991	26.02	0.667	1.271
F5	0.979	7.341	0.007		0.979	26.67	0.7	1.299
F6	0.906	4.171	0.986	0.009	0.994	20.34	0.682	1.079
F7	0.934	3.041	0.988	0.048	0.995	14.57	0.712	1.019
F8	0.914	4.075	0.987	0.093	0.996	19.75	0.689	1.077
F9	0.92	3.663	0.983	0.071	0.996	17.7	0.706	1.062
10	0.95	3.91	0.985	0.081	0.991	18.54	0.721	1.079

Table 4: Differential factor (F1) and Similarity factor (F2) values of prepared formulations

Formulations	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
F1 values	39.27	58.80	60.72	100.28	61.60	36.16	15.66	16.50	3.38	3.57
F2 values	36.58	32.78	34.62	21.23	32.49	23.86	46.44	54.04	60.96	69.45

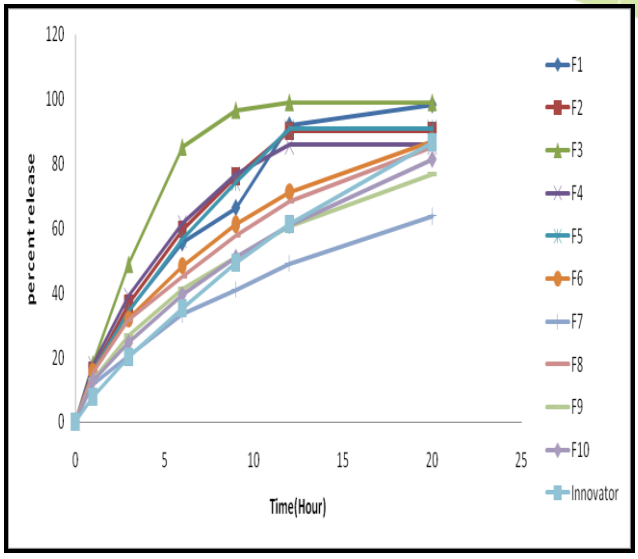

Figure 1: Zero-order release kinetics of formulation F1, F2, F3, F4, F5, F6, F7, F8, F9, F10 and Innovator

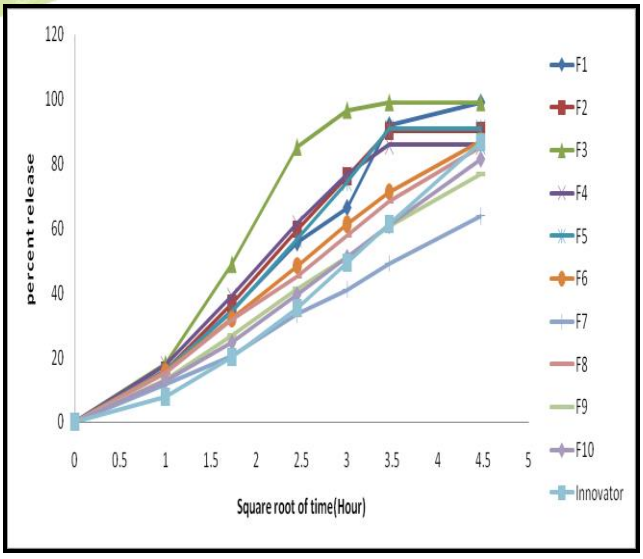

Figure 2: Higuchi release kinetics of formulation F1, F2, F3, F4, F5, F6, F7, F8, F9, F10 and Innovator

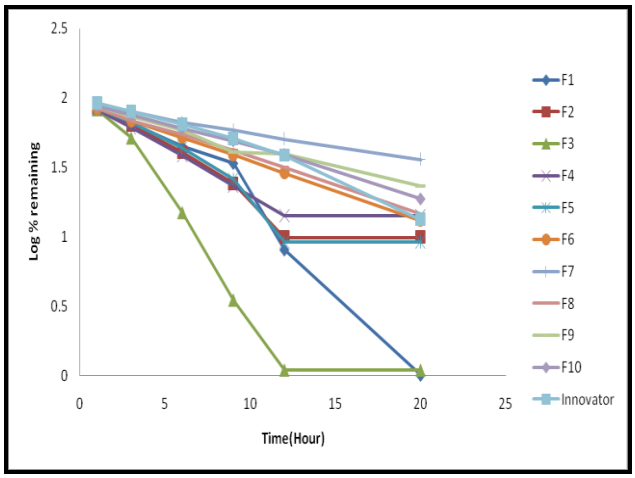

Figure 3: First order release kinetics of formulation F1, F2, F3, F4, F5, F6, F7, F8, F9, F10 and Innovator

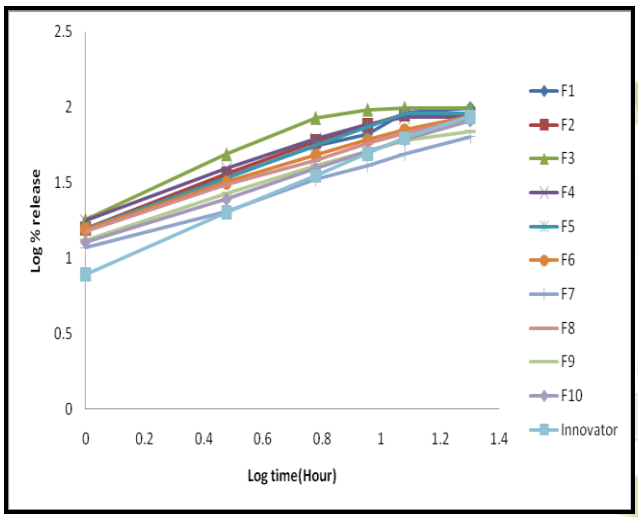

Figure 4: Korsmeyer peppa's plot of formulation F1, F2, F3, F4, F5, F6, F7, F8, F9, F10 and Innovator

The permeability of Eudragit RL30D in aqueous media is due to the presence of quaternary ammonium groups in their structure; Eudragit RL30D has a greater proportion of these groups so is more permeable. The combinations of this polymer and HPMC (E15) gave the drug release at initial times closer to innovator product. But later the release is less compared to innovator. So this time the next batch was formulated with less viscosity film coating polymer HPMC (E5). The F10, batch is formulated using Eudragit RL30D as drug releasing polymer and HPMC(E5) as film coating polymer the release is very close to innovator.

Release Mechanism

Based on the "n" value of 1.079 obtained for F10 formulation, the drug release was found to follow Fickian diffusion. Also, the drug release mechanism was best explained by first order equation, as the plots showed the highest linearity (r^2 = 0.985), followed by Higuchi's equation (r^2 = 0.991). As the drug release was best fitted in zero order kinetics, it indicated that the rate of drug release is concentration dependent. The dissolution profiles of formulation F10 and innovator product were compared by calculating differential factor (f1) and similarity factor (f2) (Table 4). The f1 and f2 were found to be within the limit when compared with the innovator product. Hence these two products were considered to be similar.

CONCLUSION

The prepared niacin tablets were evaluated or characterized based upon their physic chemical characteristics like Angle of repose, Compressibility index, Hausner ratio, Hardness, Friability and drug content. The in vitro release studies were performed. Good results were obtained both in physico chemical characteristics and in vitro studies. Hence the formulations of niacin tablets are promising one as the controlled drug delivery, improve bioavailability. It was concluded that F10 containing Avicel (PH101), Eudragit (RL30D), HPMC-E5, PEG 4000 can successfully be employed as a Extended release of niacin since it produced adequate properties due to the hydrophilic nature of polymers.

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