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FORMULATION AND EVALUATION OF BILAYER TABLET OF NIACINAMIDE EXTENDED RELEASE AND AMLODIPINE BESYLATE IMMEDIATE RELEASE

Sameer Asole *

Gurunanak College of Pharmacy, Nagpur University, Nagpur, India-440026.

ABSTRACT

The present study was aimed to develop bi-layer tablet of extended release matrix tablets of Niacinamide using various polymers like HPC, PEO AND PVP individually and combination with Amlodipine Besylate Immediate release of using MCC polymers in different proportions. HPC and PEO were selected as hydrophilic and hydrophobic matrix former respectively. The formulated tablets were also compared with a marketed product. The results of the dissolution study indicate that formulation FN4 showed maximum drug release up to 12 hr. that is similar to reference product. In case of formulations containing combination of HPC and PEO, the release of the drug was found to be dependent on the relative proportions of hydrophilic and hydrophobic polymers used in the bi-layer tablet.

Keywords: Niacinamide, Amlodipine, Extended Release, Immediate Release, Bi-layer Tablets.

INTRODUCTION

Niacinamide (nicotinamide) is a highly water-soluble vitamin, and Amlodipine is Anti hypertensive and calcium channel blocker, antianginal and niacinamide which has been used as a lipid-lowering agent and to controlled blood pressure respectively and also niacinamide is rapidly absorbed from the human GI tract. Delayed and slow-release formulations of niacinamide were originally developed to reduce or eliminate unwanted effects such as gastrointestinal disturbances, gastric irritation, and flushing of the skin, it was distinctly shown that slow absorption resulted in hypo cholesterolemic effect in a well-controlled clinical trial. Furthermore, it was shown that inhibition of very low density lipoprotein (VLDL) and subsequent reduction in LDL levels in the plasma of patients with a variety of hyper lipo-proteinemias were related to prolonged exposure rather than high plasma levels of niacinamide. For Niacinamide, the high load (250, 500 mg) and high water solubility aspects (1.7% at 25_C; p Ka = 4.8; MW= 123.11) are challenging in terms of formulation development, especially using simple matrix technology for bi-layer controlled-release delivery. The drug is freely soluble in water and hence judicious selection of release retarding excipients is necessary to achieve a constant in vivo input rate of the drug.[1-2] Thus hydrophobic polymers are suitable, along with a hydrophilic matrix for developing extended-release dosage forms.[1-9] Hence, in the present work, an attempt has been made to develop extended - release bi-layer tablets of niacinamide using polymer for controlled release materials such as HPC , alone and in combination with the PEO as the hydrophobic polymer, and to study the *In vitro* release characteristics. The prepared and evaluate [10].

MATERIALS AND METHODS

Amlodipine blend mixtures are formulated as immediate release layer and Niacinamide granules are formulated as extended release layer for bi-layer tablets. Niacinamide extended release granules were prepared using Wet granulation techniques.

Matrix System

Bi-layer tablets were prepared from both the immediate release and extended release formulations and compared.

Formulation of tablets

Preparation of Amlodipine besylate immediate release layer [11]

Amlodipine besylate immediate release tablets were prepared by using direct compression method. The microcrystalline cellulose, Dicalcium phosphate, sodium starch glycolate and the active ingredient were passed

Corresponding Author :- **Sameer Asole** Email:- sameerasole@gmail.com

through sieve no. 30 and mixed homogenously. Magnesium stearate and Aerosil were passed through sieve no.60 and added as a lubricant to the above dry mix and mixed well for 5 minutes. Finally the colorant was sieved through sieve no.100 mesh and then mixed with the dry mix homogenously to get uniform blend without mottling.

Preparation of Niacinamide sustained release layer

Niacinamide sustained release layer were prepared by wet granulation method. The hydroxyl propyl cellulose (HPC), PVP,PEO and Stearic Acid were passed through sieve no.30 and mixed homogenously. For the binder solution weighed amount of PVP was added little by little in isopropyl alcohol with continuous stirring to avoid lumps. The binder solution was slowly added to the above blend and mixed well to get a final coherent mass. These granules were air dried initially and passed through mesh no. 20.The resultant left on the sieve were milled through sieve of pore size 1.5mm. The granules were finally dried at 30ºC till a dried granules and homogenously mixed. Also we make the Niacinamide granules as per wel granulation method and we evaluate as per the standard procedure [1,3,6].

Weight Variation

Twenty (20) tablets from each batch were individually weighed in grams (gm) on an analytical balance. The average weight, standard deviation and relative standard deviation were reported. The tablet compression machine was suitably adjusted to produce tablets of uniform weight.

Tablet thickness

The thickness in millimetres (mm) was measured individually for 10 pre weighed tablets by using a starrett portable dial hand micrometer. The average thickness, standard deviation and relative standard deviation were reported.

Tablet hardness

Tablet hardness was measured using a Key hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kilopond (KP) and the average hardness, standard deviations, and relative standard deviations were reported. Tablets hardness was checked at the start and during the compression process to control an acceptable range of tablet hardness.

Friability

Twenty (20) tablets were selected from each batch and weighed. Each group of tablets were rotated at 25 rpm for 4 minutes (100 rotations) in the VanKel tablet friabilator. The tablets were then will dust and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets

***In vitro* drug release**

Evaluation of matrix tablets

Prepared matrix tablets were evaluated for hardness, weight variation, thickness, diameter, friability and drug content. Tablet hardness was determined for 10 tablets using a Monsanto hardness tester. The weight variation was evaluated on 20 tablets using an electronic balance and the test was performed according to the official method[15]. The thickness and diameter was determined for 10 tablets with the help of a Vernier caliper (Mitutoyo, USA). Friability was determined taking 20 tablets in a Roche Friabilator (Electrolab, Mumbai) for 4 min at 25 rpm. Drug content of the matrix tablets was determined by weighing and finely grinding 1 tablets of each batch. Aliquot of this powder equivalent to 500 mg of Niacinamide was accurately weighed, suspended in approximately 100 ml of distilled water and shaken for 15 min. and filtered. The final volume was made by taking 1 ml of above solution and diluted to 100 ml with distilled water. Absorbance of this solution was recorded at 262 nm using UV/Vis spectrophotometer (UV-1700 Shimandzu Co., Japan) against a reagent blank and the content was compared from a calibration curve prepared with standard Niacinamide in the same medium.

***In vitro* release rate studies**

The *In vitro* release rate studies were carried out in USP dissolution test apparatus Type I (Electro lab, Mumbai) in simulated gastric fluid (pH 1.2±0.1) from 0 to 2 h and simulated intestinal fluid (pH 7.2±0.1) from 2 to 24 h. Rotation speed of 50 rpm at temperature of 37±0.5oc and dissolution medium of 900 ml was maintained throughout the experiment. At predetermined time intervals, 1 ml of sample was withdrawn and replaced with the same volume pre -warmed (37±0.5oc) fresh dissolution medium. The samples withdrawn were filtered through 0.45 ì membrane filters, and drug content in each sample was analyzed after suitable dilution by UV /Vis spectrophotometer at 262 nm. The actual content in samples was read from a calibration curve prepared with standard Niacinamide. All dissolution studies were carried out in duplicate and repeated at least thrice. The same was carried out on marketed product for comparative evaluation.

Stability study: stability study is monitoring on 40ºC/75%RH condition for 2-3 months as per the ICH guidelines.

RESULTS AND DISCUSSION

Formulation of granules is the key factor in the production of tablet dosage form involving extended release of drug from matrix type particle. Physical parameters such as area, hardness, surface characteristics and size can significantly affect the rate of dissolution of drugs contained in a complex system. The selection of wet granulation technique for matrix tablet preparation was based on previously reported study which suggested that wet granulation results in harder tablets with lower matrix

porosity that give very low release rates when compared to direct compression. In our study 10% PVP in IPA was used as granulating agent. Non-aqueous granulating fluid was used, since it was thought to avoid the use of water and heat during drying of granules. The granules of different formulations were evaluated for LBD, TBD, compressibility index, angle of repose and moisture content. The LBD and TBD of granules ranged from 0.36±0.07 to 0.39±0.05 g/ml and 0.43±0.03 to 0.51±0.04 g/ml and 0.31±0.07 to 0.41±0.05 and 0.36±0.03 to 0.52±0.04 respectively. The compressibility index values ranging from 15±2.12 to 34.28±0.78 and 11.12±0.04 to 30.44±0.02. Generally, compressibility index values up to 15% result in good to excellent flow properties, but readings above 25% indicates poor flow ability. Angle of repose values of all formulations ranged from 28±0.15^o to 38.67±0.27 and 23±0.18^o to 40±0.25^o. Generally values of angle of repose are rarely less than 20^o and values up to 40^o indicate reasonable flow properties. All these results indicate that the formulated granules possessed satisfactory flow properties and compressibility. The moisture content of all formulations was found to be satisfactory. The results of hardness and friability of the prepared matrix tablets ranged from 2.8.0±0.35 to 3.730±0.21 kg/ cm2 to 3.0±0.02 to 3.89±0.03 and 0.89±0.03% to 1.102±0.07% and 0.89±0.03 to 1.101±0.04, respectively. The tablet formulations in all the prepared batches contained Niacinamide ranging from 80.76±1.12% to 96.22±0.74%. As such, all the batches of the fabricated tablets were of good quality with regard to hardness, friability and drug content. The results of thickness of tablets ranged from 3.03 ± 0.07 to 4.74 ± 0.03 and 3.02±0.05 to 4.44±0.03mm. Thus all formulations showed uniform thickness. Weight variation results of the matrix tablets ranged from 452±1.19 to 635±1.70 mg. The average percentage deviation of all tablet formulations was found to be within the above limit, in compliance with official standards. Figure 1 shows the in-vitro drug release of batch FA1 and FA7 containing MCC and di-Calcium phosphate as a immediate release modifying agents respectively. From the result, it was observed that 94.6% drug was released within 2hrs from the formulation FA3 and 100% drug was released within 2hrs from the formulation FA3. And also the modified release It indicates that release of drug from FN1 is slower and FN4 is faster than the reference product. The release of drug depends not only on the nature of matrix but also upon the drug polymer ratio. Therefore to control the release of drug further, combination of both polymers were used in the next batches. In formulation FN2 and FN7, mixture of HPC: PEO was used as per standard ratio of FN2 to FN7 respectively and shows 96.60% release in 12hrs. Figure 2 shows the comparison of *in-vitro* drug release of batch FA3 and FN4 with reference product, drug release was increased due to the fast release property of HPC. The combination of both polymers extends the drug release up to 14hr but the drug release was only 82%. So, further change in ratio of polymers has been required to achieve maximum drug release compare to reference product. Thus, in formulation FN4 polymer ratio was taken and *in-vitro* drug release has been carried out. The results (Figure 3) indicate the 100% of the drug release within 12 hrs in the dissolution medium. So we make the final bi-layer tablet in FA3 and FN4 combination and optimized the best result.

Table 1. Formulation of immediate release layer of Amlodipine besylate (mg)

Sr.No	Ingredients	Quantity Per Tablet (mg)						
		FAI	**FA2**	**FA3**	**FA4**	**FA5**	**FA6**	**FA7**
1	Amlodipine	5	5	5	5	5	5	5
2	MCC	55	57	58.5	60	59	59	61
3	Di cal. Phosphate	28	29	30	31	32	31	30
4	Sod. starch glycolate	6	5	3.5	2	2.5	3	2.5
5	Silicon dioxide	5	3	2	1	0.5	1	0.5
6	Mg. Stearate	1	1	1	1	1	1	1
Tablet Weight (mg)	100	100	100	100	100	100	100	100

Table 2. Formulation of sustained release layer of Niacinamide (mg)

Sr. No	Ingredients	Quantity Per Tablet (mg)						
		FNI	**FN2**	**FN3**	**FN4**	**FN5**	**FN6**	**FN7**
1	Niacinamide	250	250	250	250	250	250	250
2	Hydroxypropyl cellulose (HPC)	87.5	75	87.5	87.5	75	60	62.5
3	PVP	10	5	12.5	10	8	6	10
4	PEO	_	150	180	175	140	120	125
5	Stearic acid	4	5	5	4	2.5	7.5	5
6	Purified Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Tablet Weight (mg)		351.5	484	535	526.5	475	443	452.5

Table 3a. Pre-Formulation Evaluation of Amlodipine besylate blend powder mixture

Sr.No	Property (n=3)	Amlodipine Formulation code						
		FA1	FA2	FA3	FA4	FA5	FA6	FA7
1	Angle of repose	37.049	29.28	28.285	38.903	33.69	35.21	36.19
2	Bulk Density	0.3827	0.3686	0.3656	0.3909	0.3835	0.3662	0.3904
3	Tapped Density	0.5158	0.5090	0.4308	0.5050	0.5114	0.5035	0.4842
4	Hausner's ratio	1.3477	1.380	1.1783	1.2918	1.3335	1.3749	1.2402
5	Carr's Index (%)	34.77	27.58	15.13	22.594	25.009	27.26	19.37

Table 3b. Pre-Formulation Evaluation of Amlodipine besylate blend powder mixture

Sr.N	Property	Niacinamide Formulation code						
		FN1	FN2	FN3	FN4	FN5	FN6	FN7
1	Angle of repose	38.04	35.44	38.56	23.962	37.14	38.77	40.20
2	Bulk Density	0.3244	0.3823	0.4245	0.4617	0.3187	0.3653	0.3409
3	Tapped Density	0.3650	0.4632	0.5402	0.5293	0.4582	0.5115	0.4697
4	Hausner's ratio	1.1251	1.2116	1.1725	1.1464	1.4377	1.4002	1.3778
5	Carr's Index	11.12	17.46	21.41	12.77	30.44	28.58	27.42

Table 4a. Pre-formulation Evaluation of Niacinamide granules Evaluation of Tablets

Sr. No.	Formulation code	Test				
		Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
1	FA1	Within the limits	3.023	2.89	0.89	94.23
2	FA2	Within the limits	4.13	3.08	0.90	96.58
3	FA3	Within the limits	4.04	3.21	0.905	97.67
4	FA4	Within the limits	4.26	3.64	0.912	98.34
5	FA5	Within the limits	4.09	3.32	0.961	96.76
6	FA6	Within the limits	4.44	3.43	0.959	95.07
7	FA7	Within the limits	4.16	3.77	1.021	94.70

Table 4b. Pre-formulation Evaluation of Niacinamide granules Evaluation of Tablets

Sr. No.	Formulation code	Test				
		Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
1	FA1	Within the limits	3.03	3.0	0.92	94.11
2	FA2	Within the limits	4.37	3.22	0.89	93.49
3	FA3	Within the limits	4.51	3.11	0.90	93.88
4	FA4	Within the limits	4.69	3.41	0.94	98.23
5	FA5	Within the limits	4.32	3.89	0.97	96.97
6	FA6	Within the limits	4.74	3.39	0.91	95.98
7	FA7	Within the limits	4.16	3.81	1.011	96.03

Table 5. Post compression of Amlodipine besylate Tablet

Sr.No.	For. code	Test				
		Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
1	F3	Within the limits	4.054±0.061	3.27±0.015	0.95±0.16	97.12±0.78
2	F4	Within the limits	4.71±0.055	3.49±0.105	0.94±0.12	98.31±0.57

Table 6. Post-Compression Evaluation of Niacinamide Tablet FA3 and FN4 Evaluation

Sr.No.	For. code	Test				
		Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
1	F3	Within the limits	4.49	3.59	0.90	98.03

Table 7. Stability data of FA3 and FN4 Bi-layer Tablet

Storage condition→	**Room Temperature**	**40ºC/75%RH**		
Period→	Initial	Initial	Initial	3 Months
Formulations →	FA3	FN4	FA3/FN4	FA3/FN4
Parameters↓	**Observation**			
Physical Appearance	White	White	White	White
Hardness(kg/cm^2)	3.21±0.23	3.41±0.24	3.59±0.024	3.30±0.015
Assay (%)	97.67±0.25	98.23±0.52	94.03/96.84%	92.37% /s94.31%
Dissolution (%)	93.75±0.29	96.51±0.64	94.75% /96.84%	91.55% /94.12%

Fig 1. Amlodipine Dissolution profile(1.2 pH)

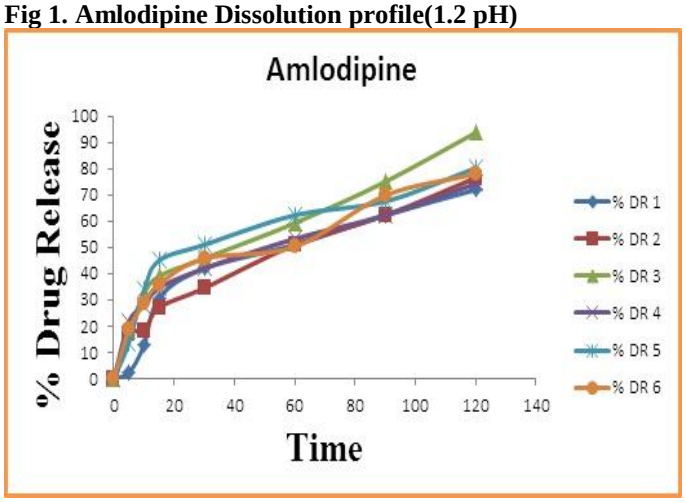


Fig 2. Niacinamide Dissolution profile(1.2 pH/6.8pH) controlled release Tablet

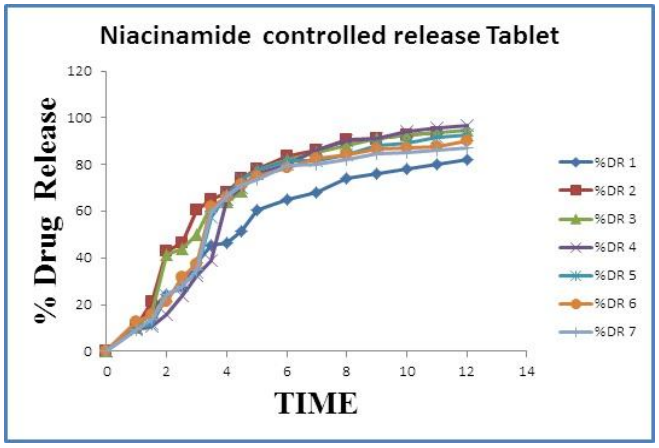


Fig 3. Bi-layer Tablet of FA3 and FN4 Composition

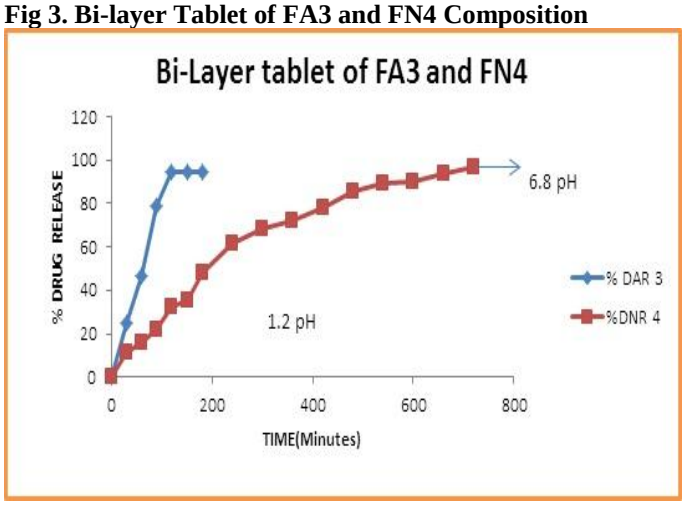
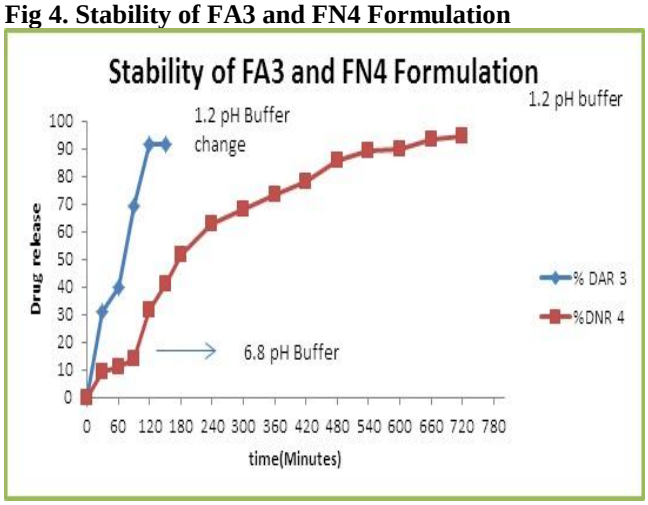


Fig 4. Stability of FA3 and FN4 Formulation



CONCLUSION

In present study attempt were made to formulate 500mg extended release formulation, which can provide effective drug release for 12 hours. Niacinamide Extended Release matrix tablets were prepared by wet granulation method. *In vitro* study showed Batch FN4 was well suited to extended release formulation. *In vitro* drug release was performed for the manufactured tablets according to the USP II "Dissolution procedure" over a 12-hour period for Niacinamide ER and 2-hour for Amlodipine IR, using an automated paddle dissolution system. A minimum of 1 tablet per batch were tested. The dissolution of Niacinamide ER and Amlodipine IR from bi-layer tablets was monitored using an automated USP II dissolution tester. The USP II (apparatus 2) paddle method was used at 50 rpm. The media used was 0.1N HCl at a pH 1.2 and 6.8 pH and a volume of 900 ml for the first 2 hours after which 150 ml of 0.2 M sodium phosphate, tribasic, was added to give a final pH of 6.8 and maintained at 37+ 0.5◦C. Amlodipine and Niacinamide release from each bi-layer tablet (in the

dissolution samples) was determined by Ultravoilet spectrophotometry (UV). The method employs the same detection wavelength, 262 and 363 nm, as the USP assay method for Amlodipine and Niacinamide. Different dissolution profiles were compared to establish the effect of formulation or process variables on the drug release as well comparison of the test formulations to the marketed product.

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