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Research Article

Preparation and evaluation of sustained release niacin and green tea extract bilayer tablets

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ABSTRACT

The aim of present study was to formulate and evaluate the Niacin and Green Tea Extract Sustained release matrix bilayer tablets. Both the sustained release layer contains Hydoxypropylmethyl cellulose, a cellulose polymer derivative used as retardant material and Polyvinyl pyrollidone used as a binder along with other excipients like Colloidal Silicondioxide, Microcrystalline Cellulose and Stearic acid. The effects of process conditions such as flow properties of granules and physical parameters of the tablets on the characteristics of sustained release bilayer tablets were investigated. The in-vitro drug release studies were evaluated using USP-II (Paddle type), carried out in Hydrochloric acid buffer at pH 1.2 as dissolution media for two hours followed by phosphate buffer pH 6.8 as a dissolution media for ten hours. The release rate of Niacin and Green Tea Extract was around 30% in pH 1.2 after two hours and not less than 90% after ten hours in pH 6.8 followed by two hours in pH 1.2 when the drug to polymer ratio is 1:0.2.

Keywords: Bilayer tablets; Green Tea Extract; Hypromellose; Niacin; Sustained release.

INTRODUCTION

Drug delivery systems (DDS) had an enormous impact on health care as it can precisely control the release rates. The goal of any drug delivery system is to maintain the desired drug concentration and to provide therapeutic amount of drug in a sustained manner (Arthur SW, 1999). When two or more active drugs are presented as a single dosage form is termed as fixed dose combinations (Roger Collier, 2012). These fixed dose combinations provide the advantages of combination therapy which helps to improve the patient compliance and attendant administrative costs. It also helps to reduce the number of prescriptions. Niacin is an organic compound. It is also known as Vitamin B_3 and Nicotinic acid which is used primarily for the treatment of hypercholesterolemia. Green Tea Extract is used as an adjuvant used for maintaining the cholesterol levels in the body. IUPAC name of Niacin is Pyridine-3-carboxylic acid. Lipid profile is controlled by several mechanisms by Niacin which includes the following (1) DGAT2 is directly inhibited which is a key enzyme for the synthesis of triglyceride (2) It has the ability to decrease triglyceride synthesis by binding with the receptor HCAR2 (3) increased apoB catabolism (4) It decreases CETP mass and activity, and this synergistic effect with the decrease in triglyceride levels, can indirectly raise HDL cholesterol levels (Creider JC et al., 2012). Green Tea Extract on the other hand is herbal derivative obtained from green tea leaves which contains the major component Epigallocatechin gallate (EGCG) comprising 50% in the extract. COMT is inhibited directly by EGCG. It is considered that the concentration of circulatory catecholamine will be increased which in turn increase the SNS. This stimulates the lipolysis through adrenergic receptors and potentially increasing the oxidation of fat (Maki Inoue-Choi et al., 2010). In today's market more than 75% of the sustained release tablets are based on hydrophilic matrix tablets and this is applicable on a broad range of therapeutic categories. Matrix systems gained its popularity as we can use the conventional equipment and processes for following the system and it is well understood. It is also have a broad regulatory acceptance. Hypromellose is biodegradable, biocompatible, nontoxic semi synthetic polymer and widely used in oral formulation (Williams RO et al., 2001). The main objective of this work was to investigate the possibility of obtaining a sustained release formulation of Niacin and Green Tea Extract bilayer tablets by using Hypromellose in various drugs, polymer ratios (1:0.12, 1:0.20, and 1:0.27). The various physicochemical characteristics and the *in-vitro* release rates from these bilayer tablets were thus examined.

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MATERIALS & METHODS

Niacin was obtained from Lonza, Switzerland. Green Tea Extract obtained from Novanat, China. Hypromellose (HPMC K4M) was obtained from DOW Chemical Company, United States. Stearic acid and Povidone (PVP K30) were obtained from BASF, Germany. Colloidal Silicon dioxide obtained from Evonik Industries, Germany. Microcrystalline Cellulose (MCC) was obtained from FMC Biopolymer, United States. Isopropyl Alcohol (IPA) was obtained from Merck, India.

Preparation of Niacin and Green Tea Extract Sustained Release Bilayer Tablets

Wet granulation using hydro alcoholic solution of IPA and purified water (2:1) containing the polymer and binder in various ratio and Stearic acid as lubricants in various ratio incorporated in various permutation combinations to the drug (Table 1). In this method, PVP K30 was dissolved in Purified water and HPMC K4M was dissolved in IPA. Then both the solutions were mixed together and used as a binder solution. This binder solution was used for wet granulation of drug. Stearic acid used as lubrication. The preparation of binder solution and granulation was performed individually for Niacin and Green Tea Extract.

Preparation of Niacin sustained release granules

Niacin and MCC were passed through 40mesh SS Sieve using vibro sifter and transferred to the fluidized bed processor (FBP). PVP K30 was dissolved in water and HPMC K4M was dissolved in IPA separately. Once after dissolving both the solutions were mixed together to form a hydroalcholic binder solution. This resulting binder solution was sprayed through FBP. After drying, the granules were passed through 16mesh SS Sieve. Stearic acid and Colloidal Silicondioxide were added to the dried granules after passing through 60mesh SS Sieve.

Preparation of Green Tea Extract sustained release granules

GTE and MCC were passed through 40mesh SS Sieve using vibro sifter and transferred to the FBP. PVP K30 was dissolved in water and HPMC K4M was dissolved in IPA separately. Once after dissolving both the solutions were mixed together to form a hydroalcholic binder solution. This resulting binder solution was sprayed through FBP. After drying, the granules were passed through 16meshSS Sieve. Stearic acid and Colloidal Silicondioxide were added to the dried granules after passing through 60 mesh SS Sieve.

Compression of Niacin and Green Tea Extract sustained release granules into bilayer tablets

The granules were compressed using 21 x 10 mm caplet shaped punch. Niacin granules was compressed as the first layer with thickness 5.2 ± 0.2 mm followed by Green Tea Extract granules with final thickness of 7.2 ± 0.2 mm. The prepared bilayer tablets were packed in aluminium foil and evaluated for various parameters.

Physicochemical characterization of the bilayer tablets

Evaluation of Granules

To assess physicochemical properties and release characteristics of the granular blend, both Niacin and Green Tea Extract sustained release granules mentioned in **Table 2** and **Table 3** are subjected to pre-formulation studies like bulk density, tapped density, Angle of repose, compressibility index, Hausner's ratio and particle size distribution.

Angle of Repose

This is the maximum steepest angle possible between the surface of a pile of granules and the horizontal plane.

$$\theta = tan^{-1}\,(h / r)$$

Where, θ = angle of repose

h = height of the heap

r = radius of the heap

Particle size distribution of granules

Sieve analysis method used for measuring the particle size distribution.

Bulk Density (BD) & Tapped Density (TD) of granules

The bulk density is measured by measuring the volume (V_o) of a known mass of granules (M) into a graduated measuring cylinder as referred in USP <616> Bulk Density, Method I. The unit of measurement of bulk density is gm/ml.

$$BD = M/Vo$$

Tapped bulk density is measured after tapping the above measuring cylinder containing the granules (M) mechanically. The tapping is continued until there is little change in volume (V_1) observed as referred in USP <616> Tapped Density, Method I. The unit of measurement of tapped density is gm/ml.

$$TD = M/V1$$

Compressibility of granules

The compressibility index was determined by Carr's compressibility index and Hausner's ratio.

$$Carr's\ index = TD - BD\ X\ 100\ /\ BD$$

$$Hausner's\ ratio: Hausner's\ ratio = TD\ /\ BD$$

The prepared bilayer tablets were evaluated (Lachmen L et al., 1987) for its weight variation, dissolution test, thickness, hardness and friability. The weight variation test is performed by weighing 20 bilayer tablets individually, calculating the average weight and comparing

Table 1: Ratio of HPMC K4M, PVP K30 and Stearic acid to drug used

Niacin Sustained release granules				Green Tea Extract Sustained release granules			
Drug	HPMC K4M	PVP K30	Stearic acid	Drug	HPMC K4M	PVP K30	Stearic acid
1	0.27	0.01	0.05	1	0.27	0.01	0.05
1	0.20	0.05	0.08	1	0.20	0.05	0.08
1	0.12	0.03	0.11	1	0.12	0.03	0.11

Table 2: Various trials taken for Sustained release granules of Niacin

S No	Ingredients	Formulation Code		
		NG1	NG2	NG3
1	Niacin	500 mg	500 mg	500 mg
2	Hypromellose (HPMC K4M)	135 mg	100 mg	60 mg
3	Povidone K 30	5 mg	25 mg	15 mg
4	Stearic acid	25 mg	40 mg	55 mg
5	Microcrystalline Cellulose	30 mg	30 mg	65 mg
6	Colloidal Silicon dioxide	5 mg	5 mg	5 mg
Total		700 mg	700 mg	700 mg

Table 3: Various trials taken for Sustained release granules of Green Tea Extract

S No	Ingredients	Formulation Code		
		GG1	GG2	GG3
1	Green Tea Extract	500 mg	500 mg	500 mg
2	Hypromellose (HPMC K4M)	135 mg	100 mg	60 mg
3	Povidone K 30	5 mg	25 mg	15 mg
4	Stearic acid	25 mg	40 mg	55 mg
5	Microcrystalline Cellulose	30 mg	30 mg	65 mg
6	Colloidal Silicon dioxide	5 mg	5 mg	5 mg
Total		**700 mg**	**700 mg**	**700 mg**

Table 4: Evaluation of sustained release granules of Niacin and Green Tea Extract

Formulation Code	Parameters				
	Angle of re-pose (θ)	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility Index (%)	Hausner's Ratio
NG1	29.46	0.50	0.57	14.00	1.14
NG2	26.57	0.46	0.51	10.87	1.11
NG3	26.15	0.45	0.50	11.11	1.11
GG1	28.24	0.61	0.70	14.75	1.15
GG2	27.78	0.50	0.56	12.00	1.12
GG3	26.68	0.49	0.55	12.24	1.12

Table 5: Evaluation of sustained release bilayer tablets of Niacin and Green Tea Extract

Formulation Code	Hardness (kg/cm^2)	Friability (% w/w)	Weight variation (mg)	Thickness (mm)
NGT1	18.7	0.10	1415 ± 0.03	7.25
NGT2	15.9	0.16	1408 ± 0.04	7.27
NGT3	9.8	0.28	1412 ± 0.07	7.37

the individual weights to the average. The hardness of each batch of bilayer tablet was checked by using hardness tester. The hardness was measured in terms of kg/cm^2. The hardness of 6 bilayer tablets was determined. The Friability was determined by initially weighing 10 bilayer tablets after dusting and placing them in a friability tester (Roche friabilator), which was rotated for 4 min at 25 rpm. After the test, the total remaining mass of bilayer tablet was recorded after dusting and the percent friability was calculated. The thickness was measured with Varnier Caliper for 10 tablets.

In- vitro Drug Release

The USP II dissolution rate testing apparatus was employed to study the release of Niacin and Green Tea Extract (Chakraborty S and Khandai M, 2008) using Hydrochloric acid buffer at pH 1.2 as dissolution media

Table 6: In-vitro release of Niacin and Green Tea Extract from bilayer tablets

Time (hr)	Cumulative % release					
	Niacin			Green Tea Extract		
	NGT1	NGT2	NGT3	NGT1	NGT2	NGT3
0	0	0	0	0	0	0
1	23.54	27.24	30.68	25.16	29.65	33.46
2	30.54	31.51	33.75	30.34	33.54	37.14
3	41.18	44.18	50.75	44.41	47.64	52.13
4	50.54	53.15	60.48	52.43	55.68	60.50
5	52.15	57.51	65.45	54.31	59.87	65.26
6	55.58	63.48	70.48	60.43	65.08	70.41
7	60.47	67.70	75.09	63.84	68.53	72.10
8	65.18	74.09	80.54	70.74	75.08	79.02
9	68.27	78.08	87.02	76.65	80.24	85.64
10	74.15	83.30	90.52	79.90	84.81	88.91
11	78.18	86.97	94.12	82.65	88.24	93.47
12	90.68	96.15	99.68	91.15	99.04	99.72

for two hours followed by phosphate buffer pH 6.8 as a dissolution media for ten hours. Dissolution test was being carried out at 50 rpm maintained at 37°C ± 0.5°C. 5ml of sample were withdrawn at specific time interval for 12 hours. The sample volume was replaced by an equal volume of fresh medium. The concentration was determined spectrophotometrically at 278 nm. The same procedure was repeated for other formulations also. The percentage of drug release at various time intervals was calculated and plotted against time.

Stability Studies

The optimized formulation was subjected for two month stability study according to ICH guidelines. The selected formulations were packed in aluminium foils, which were in wide mouth bottles closed tightly. They were then stored at Room Temperature 40ºC / 75% RH for 2 months and evaluated for their permeation study.

RESULTS AND DISCUSSION

Evaluation of Blend

The micromeritic properties such as of bulk density, tapped density, Angle of repose, compressibility index, Hausner's ratio and particle size distribution of Niacin and Green Tea Extract sustained release blend were studied. The overall results were shown in **Table 4**. The value of bulk density indicates good packing characteristics. The compressibility index of the formulation found to be below 15 indicating excellent flow properties of granules which were further confirmed by determining the angle of repose, it is in the range of 26° to 30° which indicates good flow properties.

Evaluation of Tablets

The compressed Tablets were evaluated for hardness, friability, weight variation and thickness. The results of all the 3 formulations (NGT1, NGT2 and NGT3) are shown in **Table 5.**

In vitro Dissolution Study

The in-vitro dissolution characteristics of Niacin and Green Tea Extract bilayer tablets are shown **Table 6**. Based on the in-vitro release profile of drug formulations of NGT1, NGT2 and NGT3, the formulation NGT2 showed better drug release, which was achieved by optimizing the polymer concentration along with binder and lubricant concentration in a controlled rate at regular time intervals in appropriate concentrations as per the limits. Hence formulation NGT2 was selected for further studies.

SUMMARY AND CONCLUSION

The matrix sustained release bilayer tablets of Niacin and Green Tea Extract were successfully prepared. The formulation NGT2 shows better control over the in-vitro dissolution release of Niacin and Green Tea Extract. The ratio of drug to polymer in three formulations was found to be in the range of 1:0.12 1:0.27. It was observed that the drug to polymer ratio of 1:0.20, drug to binder ratio of 1:0.05 and drug to lubricant ratio of 1:0.08 showed better release profile.

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