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Research Article

Accelerated stability studies of niacin and green tea extract sustained release bilayer tablets with different polymers

Arun Kumar A*[1], Sivaraman G. K [1], Venkatesan P [2], Valliappan K[2]

[1]Apex Laboratories Private Limited, Chennai, Tamil Nadu, India
[2]Faculty of Engineering and Technology, Annamalai University, Annamalainagar, Tamilnadu - 608 002, India

ABSTRACT

Niacin and Green tea extract are used for maintaining the lipid profile in Hyperlipidemia. Currently Statins are extensively used in the treatment of Hyperlipidemia which is known to cause rhabdomyolysis. The combination of Niacin and Green tea extract as a sustained release bilayer tablets will help to reduce or avoid the statin therapy. There are many polymers available to control the release of the drugs which includes Hypromellose (K4M), Guar Gum and Sodium Carboxymethyl Cellulose. In our present study we designed to evaluate the formulations containing different polymers by accelerated stability studies and examined for the parameters of hardness, dissolution and assay for drug concentration in formulation after one, three and six months duration at controlled tropical conditions of temperature and relative humidity. From the accelerated stability study results it was observed that the formulation containing Hypromellose (K4M) as a polymer founds to be more stable.

Keywords: Accelerated stability study; Assay; Bilayer tablets; Dissolution; Green Tea Extract; Hypromellose; Niacin; Sustained release.

INTRODUCTION

Stability of pharmaceutical product means the physical and chemical integrity of dosage form (Shakeel F et al., 2008). Pharmaceutical products adopt various pathways of chemical degradation. Accelerated stability studies are performed in order to predict the long term stability of pharmaceutical products (Fitzpatrick S et al., 2002). They also help to identify the major degradation products; degradation pathways and stability indicating potential of analytical procedure used (ICH, 2003). These studies are performed by exposing the representative sample of pharmaceutical product to stress conditions of temperature, humidity, light and radiations. Niacin and Green tea extract are used for maintaining the lipid profile in Hyperlipidemia (Creider JC et al., 2012; Maki Inoue-Choi et al., 2010). The combination of Niacin and Green tea extract as a sustained release bilayer tablets will help to reduce or avoid the statin therapy. The aim of this study is to be conducted the accelerated stability studies of Niacin and Green Tea Extract sustained release bilayer tablets containing different polymers which includes Hypromellose (K4M), Guar Gum and Sodium Carboxymethyl Cellulose in order to evaluate the parameters of dissolution, hardness and assay (WHO guidelines for stability testing, 2006) at different time intervals of 1, 3 and 6 month as function of temperature and relative humidity at tropical conditions according to ICH guidelines, 2003.

* Corresponding Author
Email: arhavishaa@gmail.com
Contact: +91-9894050871
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MATERIALS & METHODS

Reagents and chemicals

Niacin was obtained from Lonza, Switzerland. Green Tea Extract obtained from Novanat, China. Hypromellose (HPMC K4M) was obtained from DOW Chemical Company, United States. Guar gum was obtained from Ashland Aqualon Functional Ingredients, United States. Sodium Carboxymethyl Cellulose was obtained from C P Kelco, United Kingdom. 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. Three batches of Niacin 500 mg with Green tea extract 500 mg sustained release bilayer tablets, containing Hypromellose (K4M), Guar Gum and Sodium Carboxymethyl Cellulose as polymers in each batch. Chemicals used for analysis are UPLC grade.

Instruments

Hardness tests were performed on DHT-250 Campbell Electronics and dissolution tests performed on, USP Type 2 (14L) Electrolab Autosampler (Paddle) respectively. Assay for concentration of Niacin and Epigallo

Table 1: Niacin sustained release granules with different polymers

S No	Ingredients	Formulation Code		
		NG1	NG2	NG3
1	Niacin	500 mg	500 mg	500 mg
2	Hypromellose (K4M)	100 mg	-	-
3	Guar Gum	-	100 mg	-
4	Sodium Carboxymethyl Cellulose	-	-	100 mg
5	Povidone K 30	25 mg	25 mg	25 mg
6	Stearic acid	40 mg	40 mg	40 mg
7	Microcrystalline Cellulose	30 mg	30 mg	30 mg
8	Colloidal Silicon dioxide	5 mg	5 mg	5 mg
Total		**700 mg**	**700 mg**	**700 mg**

Table 2: Green tea extract sustained release granules with different polymers

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

Table 3: Hardness of sustained release bilayer tablets with different polymers

Formulation Code	Hardness (average) (kg/cm^2)			
	Initial	1M	3M	6M
NGT1	15.9	16.2	16.8	17.2
NGT2	17.1	17.9	19.4	22.6
NGT3	13.6	13.8	14.1	15.8

Table 4: In-vitro release of Niacin and Green tea extract from sustained release bilayer tablets containing Hypromellose (K4M) as polymer (Formulation Code: NGT1)

Time (hr)	Cumulative % release							
	Niacin				Green tea extract			
	Initial	1M	3M	6M	Initial	1M	3M	6M
0	0	0	0	0	0	0	0	0
1	27.24	27.17	26.81	24.45	29.65	29.45	27.81	25.85
2	31.51	31.07	29.54	28.54	33.54	32.46	31.05	28.43
3	44.18	43.08	42.35	39.54	47.64	46.40	45.65	43.15
4	53.15	52.94	53.43	50.08	55.68	55.91	54.54	53.18
5	57.51	57.09	56.45	51.24	59.87	52.54	58.04	56.27
6	63.48	63.18	61.24	60.55	65.08	65.24	64.24	63.10
7	67.70	67.48	65.64	62.08	68.53	68.53	66.55	64.54
8	74.09	73.24	72.24	70.54	75.08	74.50	74.24	73.08
9	78.08	77.80	74.12	73.19	80.24	79.24	79.24	78.87
10	83.30	82.81	82.65	80.27	84.81	84.15	82.35	79.25
11	86.97	86.38	83.16	80.54	88.24	88.07	87.84	87.02
12	98.67	98.01	96.54	93.54	99.04	98.24	97.55	96.50

Table 5: In-vitro release of Niacin and Green tea extract from sustained release bilayer tablets containing Guar gum as polymer (Formulation Code: NGT2)

Time (hr)	Cumulative % release							
	Niacin				Green tea extract			
	Initial	1M	3M	6M	Initial	1M	3M	6M
0	0	0	0	0	0	0	0	0
1	27.65	26.58	24.56	20.84	29.43	28.63	25.25	22.44
2	31.54	30.75	27.48	24.77	33.64	31.52	29.68	25.97
3	44.61	42.63	40.52	35.84	47.18	45.08	43.77	40.63
4	53.65	51.45	50.42	46.74	55.83	54.87	52.69	50.94
5	57.12	56.18	54.81	47.53	59.23	57.54	56.37	53.08
6	63.27	62.39	59.35	56.41	65.45	64.81	62.30	60.55
7	67.19	66.56	63.78	58.12	68.92	67.98	64.61	61.34
8	74.20	72.37	70.06	66.43	75.59	73.71	72.83	70.81
9	78.45	76.69	72.31	69.21	80.41	78.32	77.54	75.12
10	83.51	81.13	80.91	76.51	84.30	83.78	80.95	76.45
11	86.58	85.72	81.56	76.13	88.05	87.92	85.21	84.81
12	98.27	97.54	94.41	89.61	99.50	97.53	95.45	93.10

Table 6: In-vitro release of Niacin and Green tea extract from sustained release bilayer tablets containing Sodium carboxymethyl cellulose as polymer (Formulation Code: NGT3)

Time (hr)	Cumulative % release							
	Niacin				Green tea extract			
	Initial	1M	3M	6M	Initial	1M	3M	6M
0	0	0	0	0	0	0	0	0
1	27.89	29.85	32.45	36.91	29.42	31.88	33.00	37.21
2	31.12	33.81	35.94	40.78	33.23	34.96	37.45	40.57
3	44.65	45.67	48.53	51.85	47.82	48.74	51.23	55.86
4	53.65	54.21	59.65	62.78	55.44	57.45	60.87	65.78
5	57.89	59.57	62.78	63.78	59.23	61.32	64.52	68.38
6	63.98	65.98	67.85	72.88	65.85	67.74	70.45	75.32
7	67.42	69.32	71.51	74.66	68.74	70.63	72.93	76.91
8	74.65	75.62	78.89	82.47	75.45	76.21	80.12	85.78
9	78.65	79.61	80.98	85.26	80.65	81.45	85.97	90.74
10	83.95	84.21	88.74	92.88	84.74	86.98	88.56	91.94
11	86.53	88.43	89.53	92.73	88.69	90.54	93.12	99.87
12	98.72	100.84	99.89	100.04	100.50	99.84	99.97	100.03

Table 7: Assay of Niacin and Green tea extract sustained release bilayer tablets with different polymers

Formulation Code	Assay (%)							
	Initial		1M		3M		6M	
	Niacin	GTE	Niacin	GTE	Niacin	GTE	Niacin	GTE
NGT1	100.28	99.45	98.05	97.19	95.18	95.35	91.15	92.24
NGT2	99.42	100.16	96.28	95.24	91.28	92.15	87.14	89.15
NGT3	100.05	99.24	94.04	93.15	88.24	87.24	85.15	82.54

catechin gallate (a component of Green tea extract) performed on Waters Acquity UPLC.

Preparation of niacin and green tea extract sustained release bilayer tablets with different polymers

Binder solution is a hydro alcoholic solution of IPA and purified water (2:1) containing the polymer and binder. Povidone K30 is used as a binder and we use three different polymers in three trials (Table 1 and Table 2) which include Hypromellose (K4M), Guar Gum and Sodium Carboxymethyl Cellulose. 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 Si eve using vibro sifter and transferred to the fluidized bed processor (FBP). Binder solution was sprayed through FBP. After drying, the granules were passed through 16 mesh SS Sieve. Stearic acid and Colloidal Silicon dioxide

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. Binder solution was sprayed through FBP. After drying, the granules were passed through 16meshSS Sieve. Stearic acid and Colloidal Silicon dioxide 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.

ACCELERATED STABILITY STUDIES

Niacin 500mg with Green Tea Extract 500 mg sustained release bilayer tablets with three different polymers (NGT1, NGT2 and NG3 with Hypromellose (K4M), Guar Gum and Sodium Carboxymethyl Cellulose respectively) were placed in stability chamber with controlled temperature and humidity of class IV climatic conditions as recommended by ICH guidelines. Temperature was maintained at 40±2°C and relative humidity at RH 75±5%.

Tablet hardness

Hardness of tablets was determined by placing them in plungers of Hardness Tester, measuring the average force in kg/cm^2 by triplicate of tests.

Dissolution studies

In vitro drug release studies were performed by dissolution test USP Type II for 12 hours, the first two hours in Hydrochloric acid buffer at pH 1.20 ± 0.05 followed by 10 hours in phosphate buffer at pH of 6.80 ± 0.05 maintained at 37±2°C as dissolution medium for sustained release bilayer tablet. Sample of 5ml was first taken after every 1 hour and replaced by fresh dissolution medium to maintain the volume. Concentration of drug in sample was measured, after filtration and dilution, and percentage drug release was measured using Ultra Performance Liquid Chromatography method and the separation technique adopted for both the components is by gradient method. Two mobile phases used for dilution and to elude the components in chromatography termed as Mobile Phase A and Mobile Phase B. Mobile Phase A comprises of 3.5 mL Orthophosphoric acid, 50 mL Methanol which is diluted to 1000 mL with Water. Mobile Phase B comprises of Acetonitrile and Methanol in ratio of 95:5 (% v/v). Peak areas were recorded for both Epigallocatechin gallate (a component of Green Tea Extract) and Niacin at 278 nm. The flow rate was maintained at 0.5 mL/min during the separation.

Assay

Percentage drug content was measured using Ultra Performance Liquid Chromatography method and the separation technique adopted for both the components is by gradient method. Two mobile phases used for dilution and to elude the components in chromatography termed as Mobile Phase A and Mobile Phase B. Mobile Phase A comprises of 3.5 mL Orthophosphoric acid, 50 mL Methanol which is diluted to 1000 mL with Water. Mobile Phase B comprises of Acetonitrile and Methanol in ratio of 95:5 (% v/v). Peak areas were recorded for both Epigallocatechin gallate (a component of Green Tea Extract) and Niacin at 278 nm. The flow rate was maintained at 0.5 mL/min during the separation.

RESULTS AND DISCUSSION

Tablet hardness

It was observed that the hardness of the bilayer tablet increases in all the three batches (Table 3). Hardness of the bilayer tablet considerably increased during storage in the batch in which Guar gum was used as polymer when compared to the other two batches.

Dissolution studies

It was observed that the dissolution of the bilayer tablet decreases in batches where Hypromellose (K4M) and Guar gum whereas it increases in batch containing Sodium Carboxymethyl Cellulose as polymer (Table 4 to Table 6). It was also observed that the release was considerably decreased during storage in the batch containing Guar gum as polymer when compared to the batch which contains Hypromellose (K4M) as polymer on storage.

Assay

It was observed that the assay of Niacin and Green tea extract in the final bilayer tablets decreases in all the three batches (Table 7). It was also observed that the release was considerably decreased during storage in the batch containing Guar gum and Sodium carboxymethyl cellulose as polymer when compared to the batch which contains Hypromellose (K4M) as polymer on storage.

CONCLUSION

The Niacin and Green tea extract sustained release bilayer tablets which contain Hypromellose as polymer provides better control of release till the end of accelerated stability studies when compared to the other trials containing Guar gum and Sodium carboxymethyl cellulose as a polymer. The stability of the bilayer tablets manufactured using Hypromellose (K4M) is comparatively higher than the other two formulations containing Guar gum and Sodium carboxymethyl cellulose.

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