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Formulation and Evaluation of Niacin Sustained Release Matrix Tablets

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ABSTRACT

The present study was aimed to develop twice daily sustained release matrix tablets of Niacin using various polymers like Guar gum, HPMC K4M, HPMC K15M, HPC, PVA, and PVP individually and in combinations of these polymers in different proportions. Both hydrophilic and hydrophobic matrices were selected in order to sustain the drug release. The optimized formulations N5, N7, and N8 were selected and further coated in order to prolong drug release time period and also to improve the appearance. The coated formulations showed improved *in-vitro* dissolution profiles compare to uncoated formulations. The drug release of N5, N7, and N8 formulations were sustained to 12h,18h and 28h respectively. These optimized formulations did not show any remarkable changes after three months stability studies. The drug release was found to be dependent on the relative proportions of polymer with a drug used in the tablet matrix.

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INTRODUCTION:

Niacin (Nicotinic acid or Vitamin B_3) is highly water soluble vitamin, which has been used as a lipid lowering agent and is rapidly absorbed from the human gastrointestinal tract. Delayed and slow release formulations of Niacin 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 hypocholesterolemic 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 hyperlipoproteinemias were related to prolonged exposure rather than high plasma levels of Niacin. For Niacin, the high load (500mg) and high water solubility aspects are challenging in terms of formulation development, especially using simple matrix technology for twice a day sustained release delivery. The drug is freely soluble in water and hence the judicious selection of release retarding excipients is necessary to achieve a constant *in-vivo* input rate of the drug.

The matrix tablets composed of a drug and release-retarding material (polymer), offers the simplest approach in designing a sustained release system. Hydrophilic polymers form a gel-like structure around the tablet core which controls the drug release. The use of hydrophilic polymer alone for controlling the drug release of highly water-soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel layer. Use of hydrophobic polymers will retard the drug release of such drugs with high water solubility. Thus hydrophobic polymers are suitable, along with a hydrophilic matrix for developing sustained release dosage forms.

Hence, in the present work, an attempt has been made to develop sustained release matrix tablets of Niacin using hydrophilic matrix materials such as Guar gum alone and in combination with HPMC K4, HPMC K15M. Eudragit S100 was used as coating polymer.

MATERIALS AND METHODS:

Niacin and Hydroxypropyl methylcellulose K4M, were obtained as a gift sample from Natco Pharma Pvt Ltd, Sodium hydroxide, Monobasic potassium phosphate, Xanthan gum, Guar gum, Microcrystalline cellulose PH101, Lactose monohydrate, Magnesium stearate, PEG 4000, Acetone, Isopropyl alcohol and PEG 4000 was a gift sample from S D Fine Chem. Ltd,

Hydroxypropyl cellulose, Polyvinyl alcohol, Polyvinyl pyrrolidone K90 and Eudragit S 100 were obtained as gift sample from Oxford laboratories, Hydroxypropyl methyl cellulose K15Mwas obtained as a gift sample from Taian Ruitai Cellulose Co. Ltd.

Preparation of matrix tablets:

SR matrix tablets of Niacin of different doses (350mg, 500mg) were prepared by wet granulation technique. The powder blend was evaluated for flow properties prior to granulation. The prepared granules were lubricated, weighed and evaluated for flow properties prior to punching and weighed as per individual tablet weight in order to adjust the die cavity and compressed with proper punches of appropriate fill quantity of different sizes using 10 station tablet compression machine. The composition of all tablets tried is shown in Table 1. The best formulations were selected based on the desired release profiles. An empty capsule filled with pure drug Niacin of dose 500mg is prepared in order to compare the sustained release profiles with the pure drug.

Coating of prepared matrix tablets:

1. **Preparation of coating solution of PEG 4000 8% w/v:**

2 gm PEG 4000 was taken and dispersed in 25ml of acetone and stirred for 15 to 20 minutes on a magnetic stirrer in a glass beaker covered with aluminum foil to prevent evaporation of the solvent. Stirring was continued until a uniform dispersion is obtained.

2. **Preparation of coating solution of Eudragit S100 12.5% w/v:**

3.125gm of Eudragit S100 was taken and dispersed in 25ml of acetone and stirred for 15 to 20 minutes on magnetic stirrer maintained at a temperature of 40^{o}C in a glass beaker covered with aluminum foil to prevent evaporation of the solvent. Stirring was continued until uniform clear dispersion is obtained.

3. **Coating process:**

Different batches of tablets were prepared with varying concentrations of drug and polymer were initially coated using 8% solution of PEG 4000 and later using 12.5% solution of Eudragit S100

by dip coating technique and dried at room temperature. These coated tablets were used for further evaluation.

Table1: Composition of SR matrix tablets

Formulation ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Niacin	500	500	500	500	350	500	500	500
HPMC K4M	138	-	-	-	-	-	-	-
HPMC K15M	-	138	-	-	-	100	-	-
HPC : Xanthan gum	-	-	1 : 2.5	1: 2.5	1: 2.5	-	-	-
HPC : Guar gum	-	-	-	-	-	-	-	-
HPMC K15M : Guar gum	-	-	-	-	-	-	1:1	1:2
MCC PH 101	44	44	-	-	-	44	44	44
Lactose	82	82	-	-	-	-	-	-
PVA : PVP K90	-	-	-	1:1	1:1	-	-	-
PVP K90 : Guar gum	-	-	1:1	-	-	1:3	-	-
Drug : Matrix mixture	-	-	1:0.5	1:0.5	1:1	1:1	-	-
Magnesium stearate	6	6	6	6	6	6	6	6
Water	Qs	Qs	-	-	-	-	-	-
IPA	-	-	Qs	Qs	Qs	-	-	-
IPA and water (1:1)	-	-	-	-	-	Qs	Qs	Qs
Sieve number used	30	30	18	18	18	18	18	16
Punch size in mm	14.5	14.5	14.5	14.5	14.5	14.5	14.5	16
Punch shape	Caplet	Caplet	Caplet	Caplet	Caplet	Caplet	Caplet	Caplet
Total tablet weight	770	770	750	750	700	750	750	850

Evaluation of tablets:

The prepared matrix tablets were evaluated for hardness, weight variation, thickness, friability and drug content. The hardness of the tablets was tested using Monsanto tester is used for testing all formulations except F8 for which Strong Cobb tester is used from Natco Pvt. Ltd, Hyderabad. Friability of the tablets was determined in a Rochefriabilator. The thickness of the tablets was measured by vernier calipers. Weight variation was performed according to the official method of USP30-NF25.

***In-vitro* drug release studies:**

The formulated matrix tablets were subjected to the USP dissolution apparatus type -1 (paddle method) using 900ml pH 7 Phosphate buffer solution as dissolution medium. The dissolution was performed at 50rpm at37^0C ± 0.5^0C temperature. 5 ml of the sample was withdrawn at predetermined intervals and replaced with the same volume of fresh dissolution medium. The samples withdrawn were filtered through a cotton plug and drug content in each sample was analyzed by UV spectrophotometer at 262 nm after suitable dilution. All experiments were run in triplicate and averages were accounted.

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 this study, four kinetic models as Zero order equation, First order equation, Higuchi equation and Korsmeyer-Peppas equation were used.

RESULTS AND DISCUSSION:

Physical properties:

The powder mixtures of different formulations were evaluated for angle of repose, bulk density (apparent and tapped), and compressibility index for selected formulations (F5, F7, F8). The apparent bulk density and tapped bulk density values for powders ranged from 0.45 to 0.49 and 0.97 to 0.99andwhereas for granules ranged from 0.43 to 0.45 and 0.5 to 0.56 respectively. The results of angle of repose and compressibility index (%) for powders ranged from 50.5 to 57 and

1.476 to 1.595 and whereas for granules ranged from 14 to 24.5 and 2.1804 to 2.1867 respectively. The results of angle of repose and compressibility index indicate poor flow properties of the powder mixture and good flow properties for granules. The results of flow properties were given in Table 2.

Table2: Results of flow property studies

Parameters tested	**Powders**			**Granules**		
	F5	**F7**	**F8**	**F5**	**F7**	**F8**
Angle of repose	50.5	56	57	14	23	24.5
Bulk density	0.45	0.43	0.49	0.43	0.40	0.45
Tapped density	0.97	1.0	0.99	0.5	0.53	0.5
Carr' index	53.6	57	50.5	14	24.5	19.6
Hausner's ratio	2.1	2.3	2.0	1.16	1.25	1.24
Flow property	**Poor**	**Poor**	**Poor**	**Good**	**Poor**	**Passable**

The hardness of the tablets was found to be in the range of 5 to 8.7 kg/cm^2. It was found that crushing strength of tablets was dependent on a number of polymers. As the concentration of HPC, HPMC in polymer mixture increased the crushing strength of tablets also gets increased.

Another measure of tablets strength is friability. All the selected formulations showed loss less than 0.5%. Hence they were acceptable.

The selected tablets were subjected to drug content and weight variation. The tablets were found to contain 98.1 to 99.6% of the formulated dose. In weight variation test, the pharmacopeia limit for the tablets of more than 324 mg is 5%. All selected formulations showed weight variation less than 5%. Hence they were acceptable.

All tablets comply with the pharmaceutical quality control standards for weight variation, drug content, hardness and friability and they are within the prescribed limits. The results were given in Table 3.

Table3: Results of evaluated parameters of niacin SR matrix coated tablets

Parameters tested	Formulation code		
	F5	**F7**	**F8**
Weight variation (n = 20)	0.13% < 5%	0.15% < 5%	0.14 < 5%
Hardness (n = 5)	5 kg/cm^2	6.3 kg/cm^2	8.7 kg/cm^2
Friability%	0.12% < 0.5 %	0.1% < 0.5%	0.16% < 0.5%
Drug content (n = 5)	498 mg (99.6%)	494mg (98.9%)	490mg (98.1%)
% Drug released	99.6% in 12 hrs	98.9% in 19 hrs	98.1% in 28 hrs

***In-vitro* release kinetics:**

Among all the formulations F1 released the drug in 6hrs, F2 released the drug in 8hrs, F3 released the drug in 6hrs, F4 released the drug in 7hrs, F5 released the drug in 11hrs, F6 released the drug in 6hrs, F7 released the drug in 18 hrs and F8 released the drug in 10hrs.

Based on the above release profiles F5, F7, F8 were selected as the best formulations as the drug release is prolonged for required period of time.

These formulations contained HPC: Xanthan gum in ratio of 1:2.5 with a dose of 350mg of Niacin in F5, HPMC K15M: Guar gum in ratio of 1:1 with a dose of 500mg of Niacin in F7, HPMC K15M: Guar gum in ratio of 1:2 with a dose of 500mg Niacin in F8 respectively. As a combination of hydrophilic and hydrophobic polymers was used they prolonged the drug release as compared to pure drug.

In order to further prolong the release of these selected formulations; they were coated with 8% solution of PEG. As it was a hydrophilic polymer no significant change in drug release was observed. Hence the formulations were coated with 12.5% solution of Eudragit S100 by dip coating technique. Eugragit S 100 coating prolonged the drug release up to 13hrs with 97.4% of drug release for F5 formula, for F7 it was observed to be 96.7% drug release up to 19hrsand for F8 it was observed to be 97.6% drug release up to 28hrs.

The correlation coefficient (r^2) values obtained was ranging from0.9826 to 0.9918.From the correlation coefficient (r^2)values it can be concluded that the drug release follows Zero order kinetics.

The mechanisms of drug release were Non-fickian diffusion (super case-II) since they fitted well with Korsmeyer peppas models as their correlation coefficient (r) values in the range of 0.9887 to 0.9891 with n value greater than 1. This indicates that drug release depends on swelling, relaxation and erosion of polymer with zero order release kinetics.

Table4: Correlation coefficients of all formulations before coating

Formulation code	Zero order plot	First order plot	Higuchi plot	Koresmeyer's plot
Pure drug	0.8154	0.9707	0.9562	0.8857
F1	0.9735	0.9509	0.9561	0.9824
F2	0.9458	0.9095	0.8229	0.8631
F3	0.9468	0.9863	0.9079	0.9424
F4	0.6216	0.7915	0.8783	0.7129
F5	0.9604	0.6643	0.8853	0.9039
F6	0.9209	0.8545	0.8552	0.8174
F7	0.9464	0.8074	0.9007	0.9236
F8	0.9819	0.8286	0.9615	0.9486

Table5: Correlation coefficients of all coated formulations after coating

Formulation code	Zero order plot	First order plot	Higuchi plot	Koresmeyer's plot
F4	0.9551	0.6263	0.9233	0.8934
F5	0.9966	0.7428	0.9001	0.9912
F7	0.9667	0.8055	0.9356	0.9727
F8	0.9819	0.8554	0.8385	0.9895

Table6: Correlation coefficients of selected coated formulations after stability test

Formulation code	Zero order plot	First order plot	Higuchi plot	Koresmeyer's plot
F5	0.9918	0.999	0.9006	0.9887
F7	0.9887	0.9155	0.8836	0.9821
F8	0.9826	0.781	0.8799	0.9891

Table7: n values of all formulations

Formulation code	Uncoated formulations	Coated formulations	Coated formulations after one-month stability test
Pure drug	0.5502	-	-
F1	0.7782	-	-
F2	0.9174	-	-
F3	0.9424		
F4	0.1777	0.4964	-
F5	0.4795	1.0721	1.0949
F6	0.8174	-	-
F7	0.6093	1.267	1.3476
F8	0.9615	1.6594	1.9972

TABLE 8: Percent cumulative drug release of selected formulations

Formulation code	% Cumulative drug released		
	Before coating	After coating	After stability study
F5	97.3% in 11 hrs	99.6% in 12 hrs	97.4% in 13 hrs
F7	99.2% in 18 hrs	99.8% in 19 hrs	96.7% in 20 hrs
F8	96% in 10 hrs	97.6% in 28 hrs	97.61% in 28 hrs

Preliminary stability studies:

The optimized tablets from batch F5, F7, F8 were subjected for stability studies. Results given in Table 9 respective for F5, F7 and F8 showed that there was no change in drug release and the formulations were stable.

Formulations were analyzed for the assay and dissolution studies. Average drug content of the tablets was found to be 97.4%, 96.7%, 97.6%respectively of the labeled claim. *In-vitro* dissolution profile showed that there was no significant change in the release rate of the drug from optimized tablets at the end of one month. From all the above results it can be made clear that the attempt made to formulate SR tablets was achieved.

Table9 : *In-vitro* dissolution data

Formulation code	Coated formulations before stability test		Coated formulations after stability test	
	t_{50}hrs	t_{90} hrs	t_{50}hrs	t_{90}hrs
F5	5.8	10.3	4.7	10.9
F7	7.8	15.5	7	16.2
F8	18.5	26.5	17	26.5

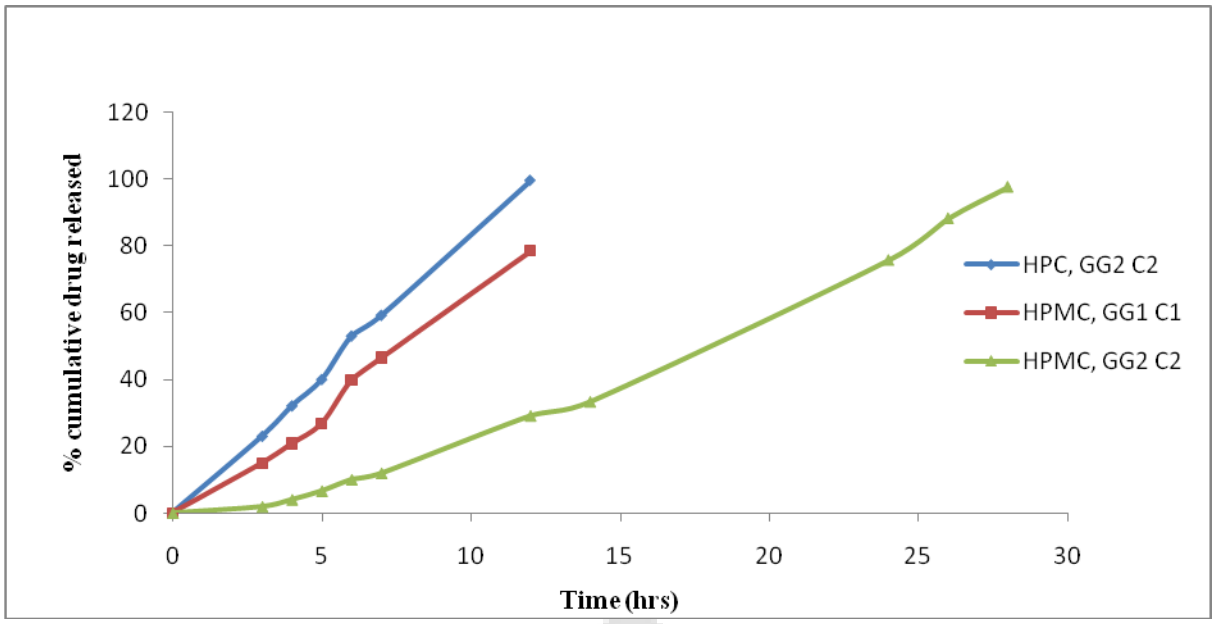

Figure 1: Zero order plots of matrix SR coated formulations selected before stability test

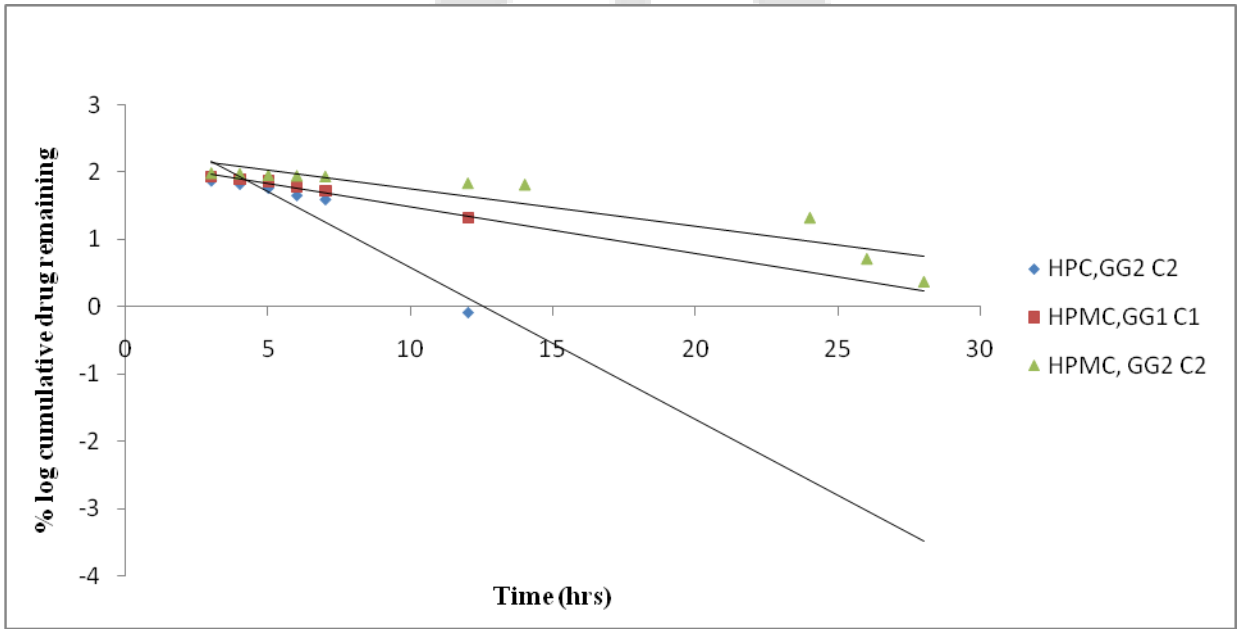

Figure 2: First order plots of matrix SR coated formulations before stability test

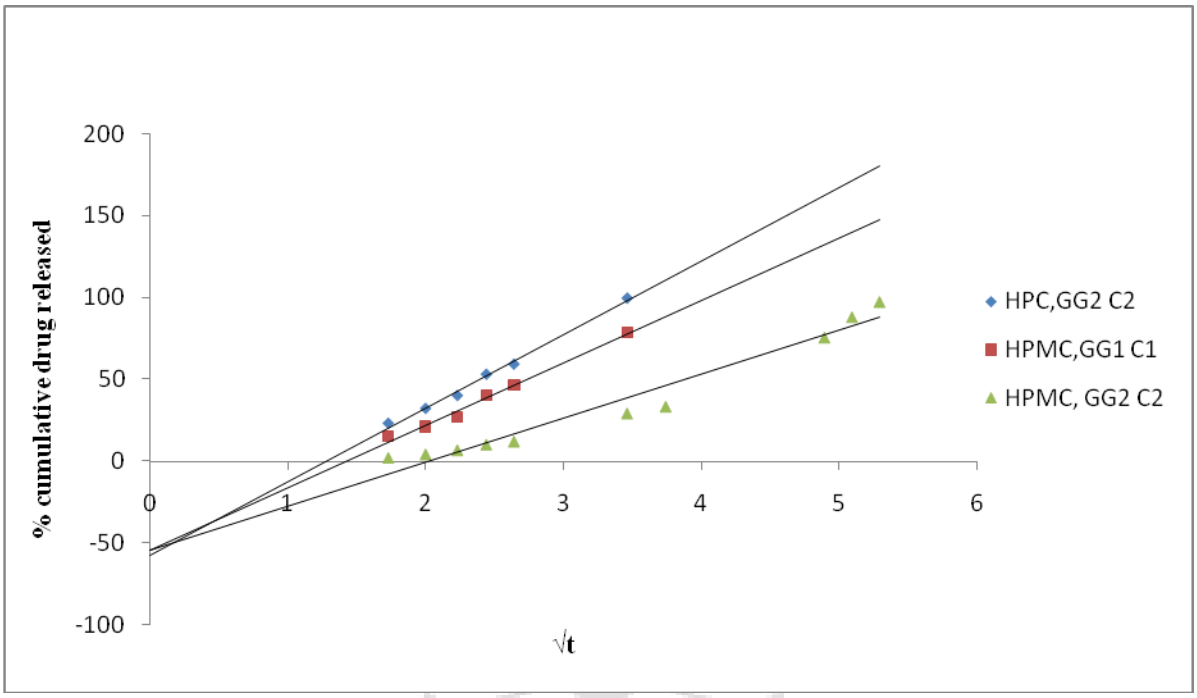

Figure 3: Higuchi plots of matrix SR coated formulations before stability test

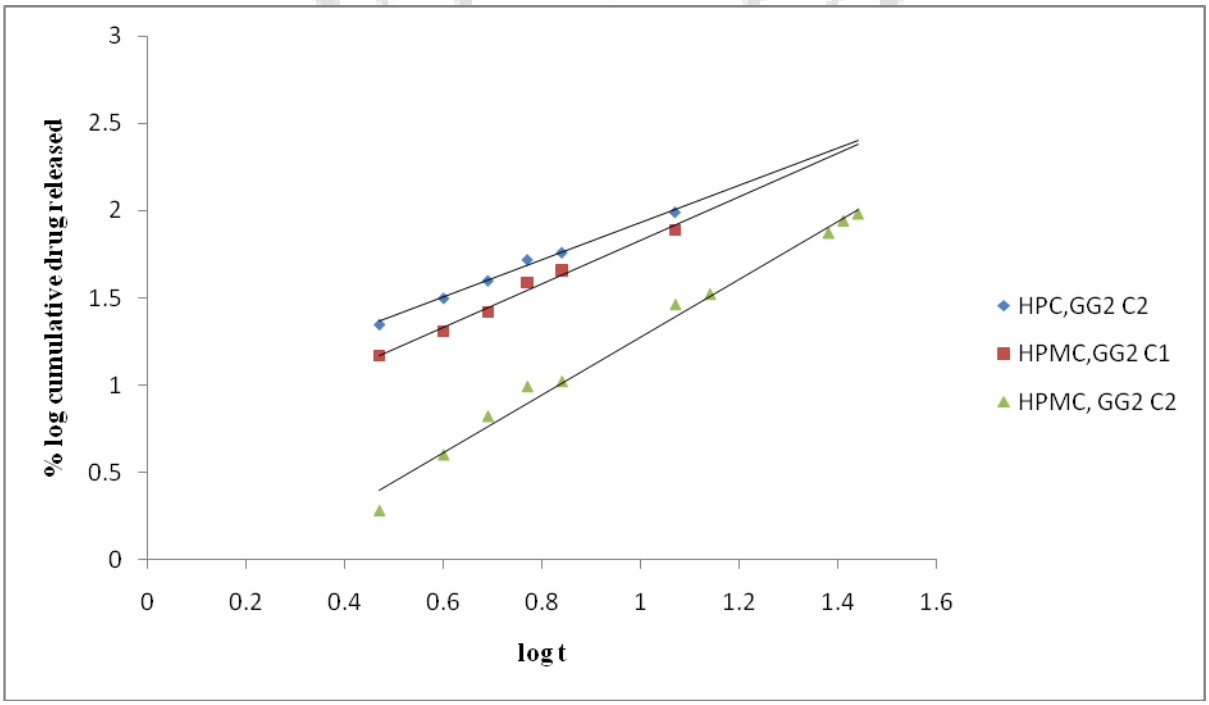

Figure 4: Koresmeyer's peppas plots of SR coated formulations before stability test

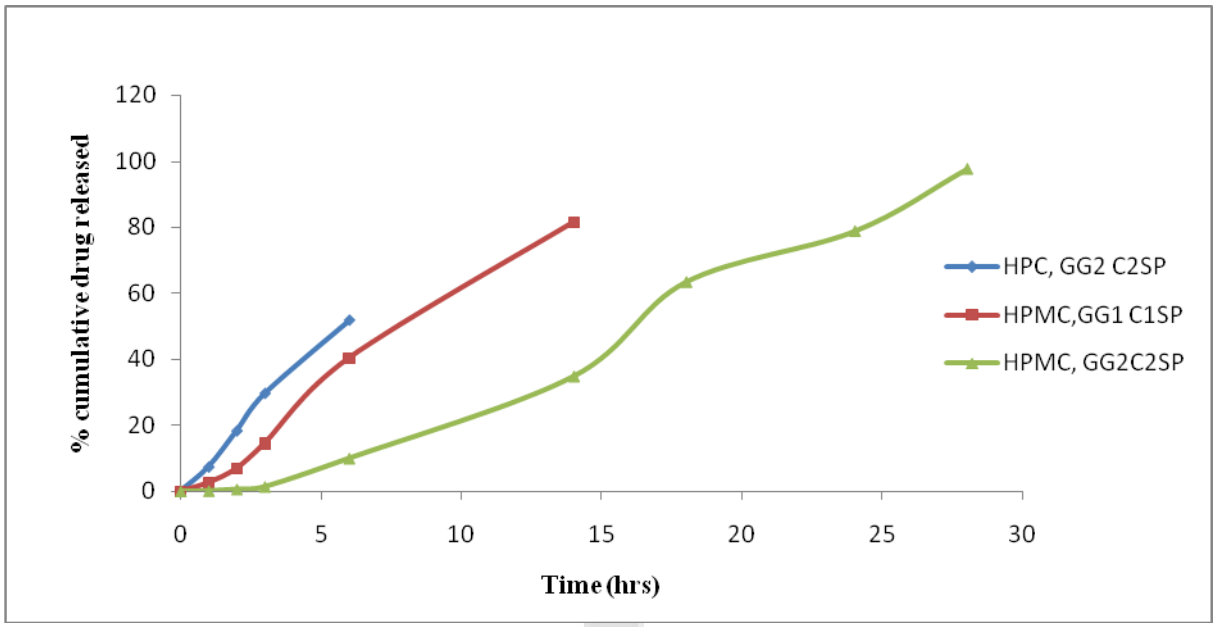

Figure 5: Zero order plots of matrix SR coated formulations after stability test

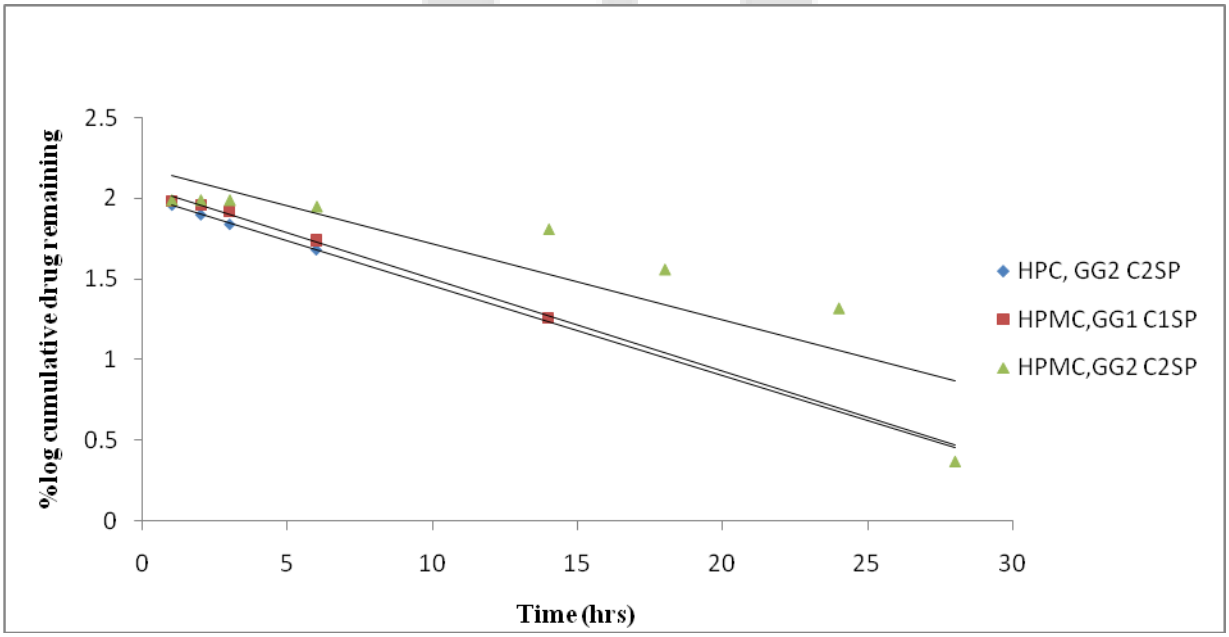

Figure 6: First order plots of matrix SR coated formulations after stability test

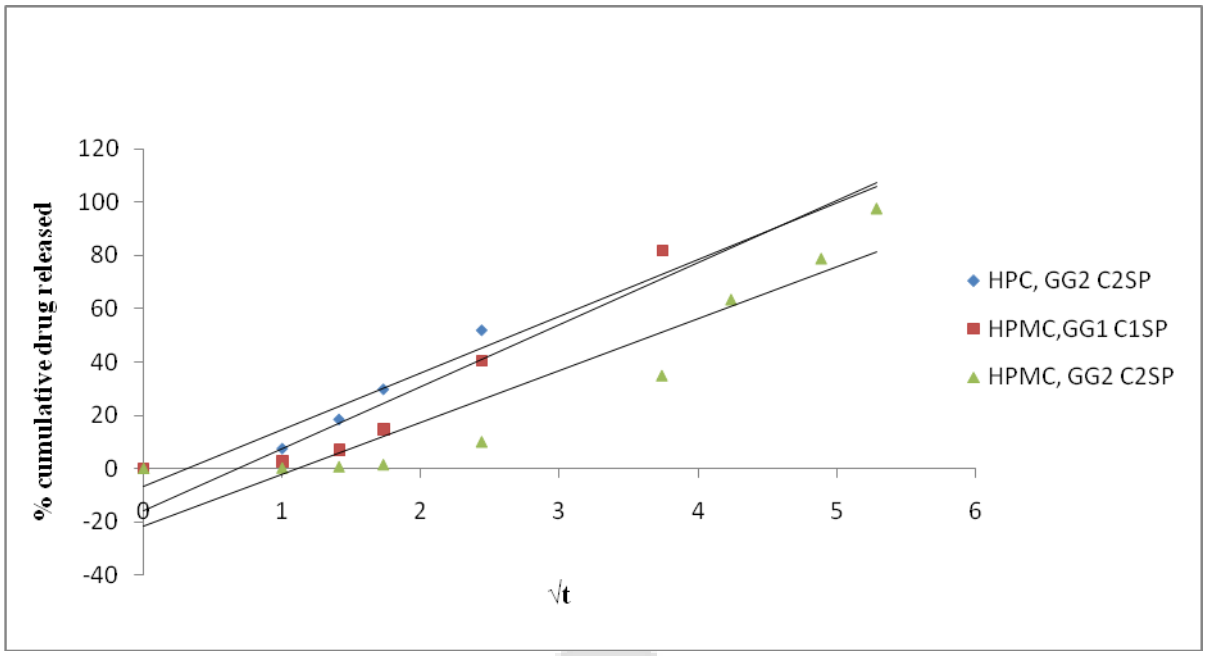

Figure 7: Higuchi plots of matrix SR coated formulations after stability test

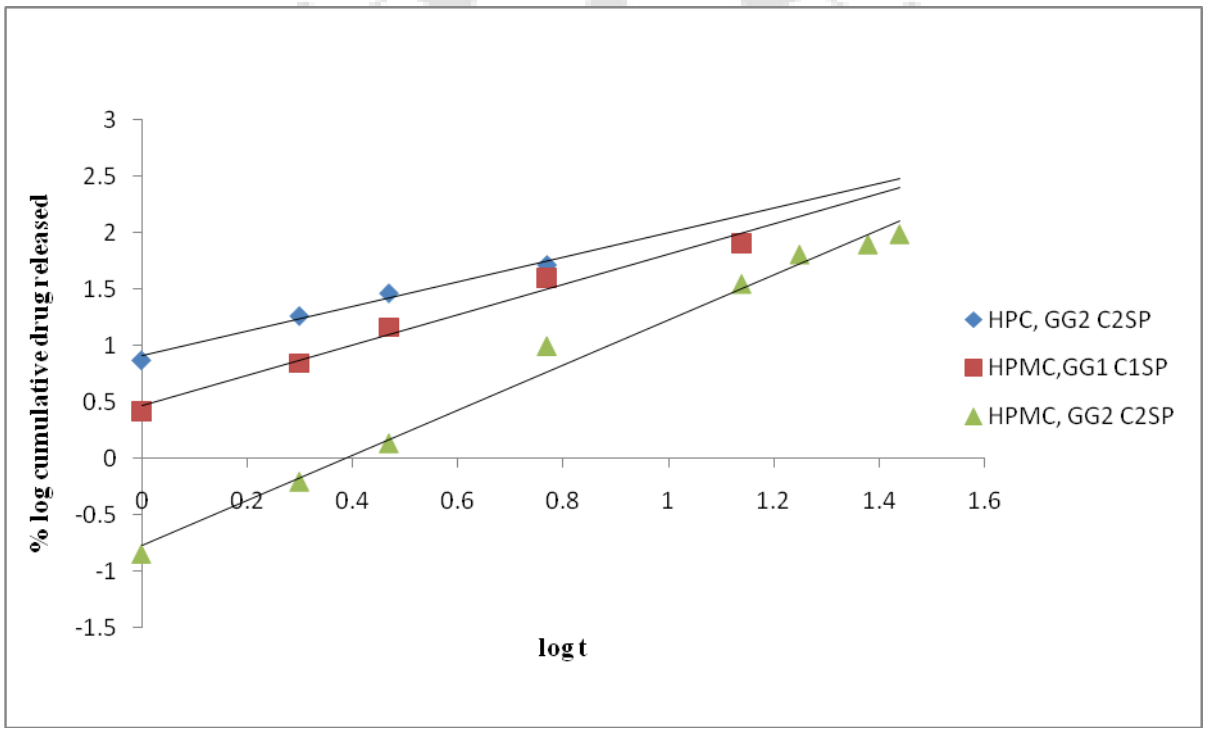

Figure 8: Koresmeyer's plots of matrix SR coated formulations stability test

CONCLUSION:

In comparison with the pure drug the selected formulations showed greater sustained release of the drug. Coating with a hydrophobic polymer like Eudragit S100 has further prolonged the drug release when compared with uncoated tablets. The combination of hydrophilic and hydrophobic polymers like HPC, HPMC, and Guar gum has been proved as a better matrix for formulating Niacin as SR matrix tablet. As these polymers were already proved safe for matrix formulations they can be used in varying concentrations with increased doses of Niacin. From stability data, it can be concluded that there was no degradation observed in the formulation under predetermined conditions of temperature and humidity. Hence it can be concluded that the aim of preparing SR matrix tablets for prolonged release of the drug is achieved.

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