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Formulation Development and *In-Vitro* Evaluation of Gabapentin Matrix Tablets

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ABSTRACT

A controlled release system is designed to provide constant or nearly constant drug levels in plasma with reduced dose, frequency of administration and fluctuations in plasma concentrations via slow release over an extended period of time.One of the least complicated approaches to the manufacture of controlled release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Gabapentin is an anti epileptic drug used for the treatment of epileptic seizures and in treatment of post therapeutic neuralgia. In this study controlled released Gabapentin matrix tablets were prepared by using different matrix forming polymers which include hydrophilic polymers like HPMC K15M, HPMC K100M, Xanthan gum and hydrophobic polymer like Ethylcellulose in various ratios to retard the release of drug upto 12hrs. The formulations containing the combination of hydrophilic and hydrophobic polymer combinations (HPMC K100M with Ethycellulose) and the formulations prepared with the combination of two hydrophilic polymers of synthetic and natural origin (HPMC K100M with Xanthan Gum) exhibited maximum drug release(99%) upto12hrs during *in vitro* dissolution studies with optimum swelling characteristics.

Keywords: Gabapentin, matrix systems, HPMC K15M, HPMC K100M, EC

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INTRODUCTION

An ideal drug delivery system (DDS) should be able to deliver an adequate amount of drug, preferably for an extended period of time for its optimum therapeutic activity. Most of the drugs are inherently not long lasting in the body and require multiple daily dosing[1] to achieve the desired blood concentration to produce therapeutic activity. To overcome such a problem, controlled release (CR) and sustained release (SR) delivery systems are receiving considerable attention from the Pharma industry world-wide[2]. A CR-DDS not only prolongs the duration of action, but also results in predictable and reproducible drug-release kinetics. Among the different approaches, matrix systems still appear as one of the most attractive from the economic as well as the process development and scale-up points of view[3,4,5]. Gabapentin is an antiepileptic (GABA analogue) used in the treatment of epilepsy and neuropathic pain[6,7]. Gabapentin is well absorbed in the small intestine by a combination of diffusion and facilitated transport.Its transport from the gut is facilitated by its binding to an, as yet unidentified, receptor linked to a saturable L-amino acid transport mechanism[8]. As this carrier mediated transport is saturable, the bioavailability of Gabapentin varies inversely with dose. It is not appriciably metabolized in the liver. The relative bioavailability of Gabapentin from a 300mg tablet was 60%[9,10]. The elimination half-life of Gabapentin is 5-7 hrs. The degree of binding of Gabapentin to human plasma is less than 3%. Based on the biopharmaceutical properties Gabapentin is selected as a drug candidate for the formulation of controlled release matrix tablets.

Table 1 : Formulation of Gabapentin Matrix Tablets

Ingredients	**F1** (mg)	**F2** (mg)	**F3** (mg)	**F4** (mg)	**F5** (mg)	**F6** (mg)	**F7** (mg)	**F8** (mg)	**F9** (mg)	**F10** (mg)
Drug	300	300	300	300	300	300	300	300	300	300
HPMC K 15M	**105 (15%)**	**140 (20%)**	**175 (25%)**	_	_	_	**87.5**	_	**87.5**	_
HPMC K100M	_	_	_	**105 (15%)**	**140 (20%)**	**175 (25%)**	_	**87.5**	_	**87.5**
Ethylcellulose	_	_	_	_	_	_	**87.5**	**87.5**	_	_
Xanthan gum	_	_	_	_	_	_	_	_	**87.5**	**87.5**
MCC	281	246	211	281	246	211	211	211	211	211
Mag.stearate	14	14	14	14	14	14	14	14	14	14
Total weight	700	700	700	700	700	700	700	700	700	700

MATERIALS AND METHODS

Materials:

Gabapentin was purchased from Cheminor drugs Ltd, Hyderabad, HPMC K15M, HPMC K100M were obtained as a gift sample from S.R. pharma, Vijayawada, Ethylcellulose,

Microcrystalline cellulose,Magnesium. Stearate were procured from SD Fine Chemicals Ltd,Mumbai, Xanthan gum was procured from Sigma Aldrich,, Mumbai.

Methods:

Matrix embedded controlled release tablets of Gabapentin were prepared by direct compression technique[11,12,13] using various concentrations and combinations of hydrophilic (HPMC K15M and HPMC K100M) and hydrophobic polymers (Xanthan Gum)[14,15,16]. Required quantities of materials as per the formulae were weighed and triturated in a mortar. The blended powder was accurately weighed into individual units and then compressed into tablets using 16 station tablet punching machine using 12mm punches. Each tablet contained 300mg of Gabapentin and other pharmaceutical ingredients as listed in table 1.

Evaluation of pre-compressed powder blends for micromeritic physical parameters:

All the prepared powdered blends were evaluated for Angle of repose, Bulk density, Compressibility index and Hausner's ratio[17,18] and the results were given in table 2.

Physical characterization of the designed tablets:

The properties of the compressed matrix tablets, such as hardness, friability, weight variation, thickness and % drug content19 were determined using reported procedure and the results were given in table 3.

Evaluation of swelling behaviour:

Swelling index of the prepared Gabapentin matrix tables was determined. Swelling index was calculated with respect to time. The swelling index of formulations F1-F10 were shown in Table4.

***In vitro* Dissolution Studies:**

Dissolution studies for each formulation were performed in a calibrated 8 station dissolution test apparatus (LABINDIA), equipped with paddles (USP apparatus II method) employing 900ml of 6.8 pH phosphate buffer as a dissolution medium. The paddles were operated at 50 rpm and the temperature was maintained at 37± 0.50C throughout the experiment. Samples were withdrawn at regular intervals upto 12hrs and replaced with equal volume of dissolution medium to maintain the constant volume throughout the experiment. Samples withdrawn at various time intervals were suitably diluted with same dissolution medium and the amount of drug released was estimated by double beam UV spectrophotometer at 208nm. The dissolution studies on each formulation were conducted in duiplicate. The dissolution profiles for all the formulations were given in table no 5.

Evaluation of Release Kinetics:

Pharmacokinetic parameters such as zero order rate constant, first order rate constant, higuchi constant, erosion and peppas constants were calculated from the dissolution data obtained from various formulations.

RESULTS AND DISCUSSION:

Gabapentin controlled release matrix tablets were formulated by using various polymers as HPMC K15M, HPMC K100M, EC and Xanthan Gum. All prepared powder blends were evaluated for Angle of repose, Bulk density, Tapped density, Carr's index and Hausner's ratio.all the values exhibited good flow characteristics for all formulations. Ten formulations (F1-F10) of Controlled released matrix tablets of Gabapentin were prepared by direct compression process and the prepared tablets were evaluated for physical parameters such as thickness, %weight variation, hardness, friability and % drug content. All the values for all compressed tablets were within the limits as per U.S.P. The tablets of all ten formulations were also evaluated for swelling index. The order of swelling index for the polymers used in the study was found to be HPMC K100M+Xanthan Gum >HPMC K100M+EC>HPMC K15M+Xanthan Gum> HPMC K15M+EC >HPMC K100M>HPMC K15M. This order would indicate the rate at which the polymers were able to absorb water and swell. The direct relationship was observed between swelling index and polymer concentration in case of formulations F1-F6. The formulations F7-F10 exhibited greater swelling index values resulting far diffusional path lengths. The formulation F10 had high swelling index among all formulations.The *in vitro* dissolution studies were carried out for all the matrix tablet formulations. The retardation of drug release from Gabapentin Matrix Tablets containing various polymers were found to be in the order of HPMC K100M+Xanthan Gum >HPMC K100M+EC>HPMC K15M+Xanthan Gum> HPMC K15M+EC >HPMC K100M>HPMC K15M. The release rate of drug found to be decreased with the increased concentration of polymer in respective formulations of F1-F6 and the retardation was more in formulations containing hydrophilic-hydrophobic polymer combinations (F7 & F8) and in formulations containing synthetic- natural polymer combinations (F9 & F10).

When the R^2 values for First-order and Zero-order were considered, it was evident that the drug release from matrix tablet formulations followed Zero-order kinetics. Comparing the R^2 values of Higuchi and Erosion models, the Higuchian plots (cumulative %drug released Vs square root time) for all the matrix tablet formulations were found to be linear with R^2 values in the range of 0.987 to 0.998. According to Korsmeyer-Peppas model, the release exponent 'n' values of all matrix tablet formulations were in between 0.5-1.0, which it indicates that all the Gabapentin matrix tablet formulations followed Non-Fickian diffusion or Anomalous diffusion mechanism.

Table 2:Micromeritic properties of the physical mixture of Gabapentin formulations

Formulation code	Angle of repose (^{0})	Bulk Density(g/cc)	Tapped density(g/cc)	Compressability index (%)	Haussner's ratio
F1	26.564±0.012	0.564±0.076	0.584±0.042	14.63±0.534	1.14±0.017
F2	27.639±0.074	0.520±0.023	0.621±0.065	14.75±0.365	1.19±0.036
F3	25.664±0.013	0.558±0.068	0.657±0.098	14.58±0.356	1.15±0.045
F4	25.893±0.035	0.543±0.052	0.648±0.064	15.08±0.048	1.21±0.020
F5	28.223±0.064	0.586±0.011	0.632±0.018	14.56±0.461	1.18±0.032
F6	27.782±0.011	0.564±0.064	0.683±0.026	14.91±0.751	1.15±0.062
F7	29.146±0.082	0.580±0.025	0.625±0.014	15.04±0.246	1.16±0.074
F8	26.164±0.076	0.574±0.053	0.653±0.054	14.42±0.343	1.14±0.045
F9	26.897±0.065	0.580±0.076	0.678±0.037	15.08±0.512	1.18±0.051
F10	27.432±0.056	0.532±0.065	0.642±0.045	15.01±0.321	1.16±0.086

*All the values represent mean ± standard deviation (SD),n=3

Table 3 : Evaluation of Physical Properties of The Matrix Tablets

S.No	Formula	Thickness (mm)	%Weight Variation	Hardness (kg/cm²)	Friability (%)	%Drug content
1	F1	3.44±0.02	0.142±0.26	6.7±0.3	0.49±0.012	99±0.082
2	F2	3.45±0.01	0.146±0.22	6.8±0.2	0.36±0.013	99±0.031
3	F3	3.42±0.02	0.144±0.18	6.7±0.3	0.42±0.012	100±0.012
4	F4	3.46±0.03	0.143±0.26	6.9±0.2	0.38±0.014	99±0.033
5	F5	3.47±0.02	0.143±0.12	6.8±0.3	0.46±0.016	101±0.016
6	F6	3.45±0.02	0.145±0.37	6.7±0.3	0.51±0.012	99±0.015
7	F7	3.45±0.01	0.144±0.25	6.9±0.1	0.47±0.013	99±0.034
8	F8	3.44±0.02	0.143±0.21	6.9±0.1	0.45±0.012	99±0.051
9	F9	3.46±0.03	0.142±0.35	6.7±0.3	0.39±0.012	100±0.032
10	F10	3.43±0.02	0.144±0.19	6.8±0.2	0.43±0.013	99±0.061

*All the values represent mean ± standard deviation(SD),n=3

Table 4: Swelling index (%) of Gabapentin Matrix Tablets

Time(hrs)	Swelling Index (%)									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
0	0	0	0	0	0	0	0	0	0	0
1	4.587	8.571	11.42	5.71	11.42	17.14	20.00	25.71	21.42	27.14
2	7.142	15.71	24.28	12.85	15.71	42.85	52.00	60.00	55.71	62.85
3	10.00	24.28	28.57	18.57	32.85	60.00	64.28	94.28	68.57	97.14
4	20.00	30.00	37.14	37.14	52.85	70.12	81.42	111.42	84.28	110.00
5	25.71	38.57	41.42	50.00	62.84	80.01	101.4	131.42	94.28	130.00
6	32.85	41.42	48.57	65.71	74.28	87.14	112.8	137.14	111.4	145.71
7	40.00	54.28	64.28	72.85	91.42	108.5	122.8	148.57	120.0	161.42
8	37.14	40.00	57.14	91.42	102.4	125.7	138.5	165.71	141.4	172.85
9	31.42	35.71	40.00	82.85	97.14	110.0	144.2	174.28	150.0	**177.14**
10	-	-	22.85	75.71	94.28	101.4	140.0	**182.85**	138.5	165.71
11	-	-	-	-	-	-	132.8	172.85	130.0	158.57
12	-	-	-	-	-	-	124.2	167.14	125.7	154.28

*All the values represent mean ± standard deviation(SD),n=3

Table 5:In Vitro Cumulative % Drug Released From Gabapentin Matrix Tablets

Time (hrs)	Cumulative % Drug Released									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
0	0	0	0	0	0	0	0	0	0	0
1	32.17	31.59	19..46	24.06	17.23	17.08	28.49	19.22	26.41	22.28
2	40.49	47.93	29.35	47.78	29.57	23.38	35.81	40.19	39.58	33.45
3	49.95	40.71	32.78	53.08	37.98	34.83	40.04	50.17	46.83	39.67
4	58.31	56.08	41.66	59.44	46.46	43.19	49.89	58.10	49.40	47.05
5	72.15	69.48	56.87	66.12	59.60	54.67	61.62	62.57	61.53	59.86
6	84.21	85.77	60.27	74.72	65.26	60.88	70.92	71.60	68.96	61.31
7	90.06	91.77	68.32	79.22	77.84	67.34	79.34	73.80	78.48	64.22
8	98.20	94.68	74.11	88.22	82.16	79.80	84.61	79.37	82.62	69.27
9	-	98.69	81.30	99.24	89.96	86.29	88.80	85.10	88.34	77.20
10	-	-	97.37	-	97.59	98.29	94.31	90.45	91.31	89.90
11	-	-	-	-	-	-	97.22	92.32	98.14	95.02
12	-	-	-	-	-	-	-	**99.18**	-	**99.36**

*All the values represent mean ± standard deviation (SD),n=3

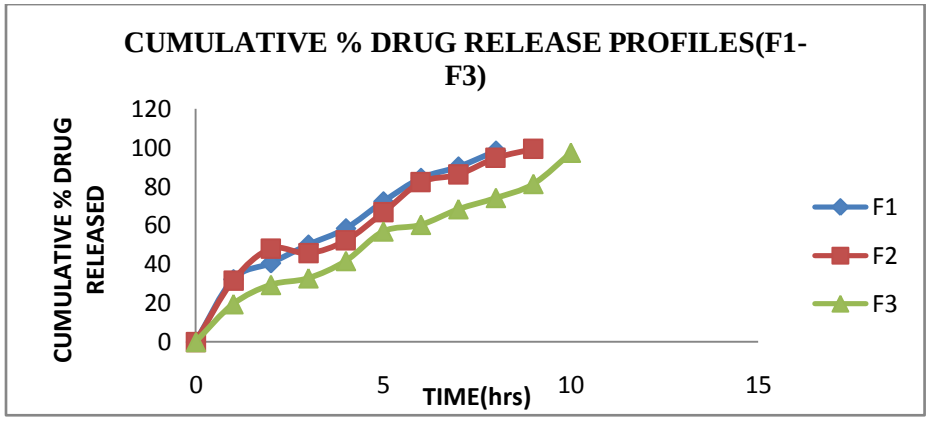

Figure 1:Cumulative Percentage Drug Release Profiles of Gabapentin Matrix Tablets (F1-F3)

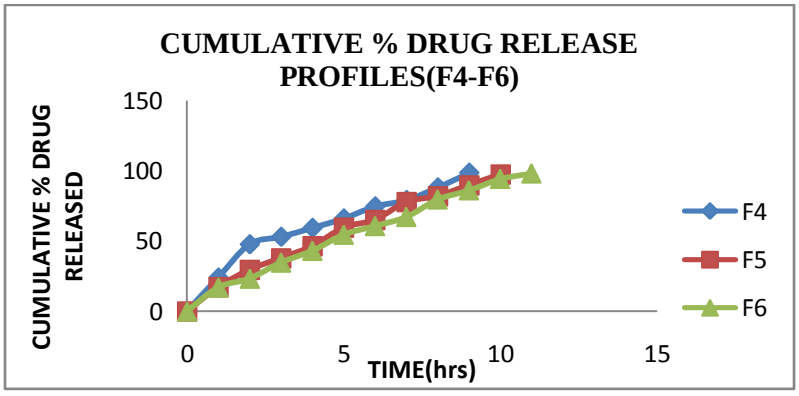

Figure2: Cumulative Percentage Drug Release Profiles of Gabapentin Matrix Tablets (F4-F6)

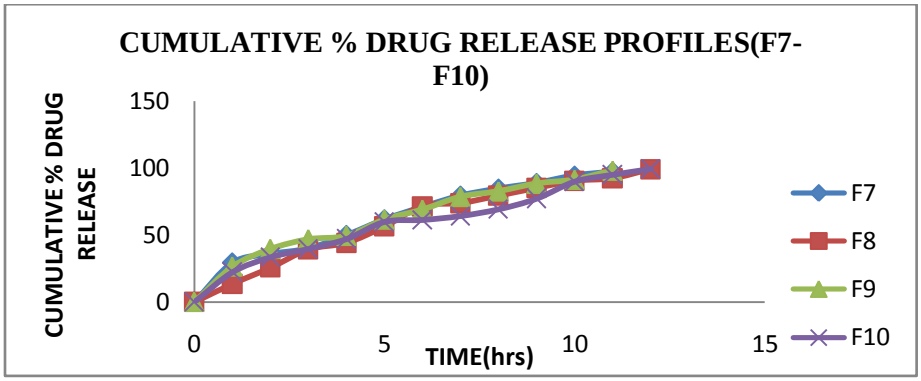

Figure3: Cumulative Percentage DrugRelease Profiles of Gabapentin Matrix Tablets (F7-F10)

Table 6:Evaluation of release kinetics:

Formulation code	Zero order	First order	Higuchi model	Erosion model	Peppas model	K_0 (hrs^{-1})	T50 (hrs)	T90 (hrs)
	R^2	R2	R2	R2	n			
F1	0.914	0.847	0.975	0.25	0.897	10.27	14.60	26.29
F2	0.909	0.898	0.964	0.25	0.906	10.46	14.34	25.81
F3	0.960	0.745	0.928	0.12	0.794	9.780	15.33	27.60
F4	0.911	0.872	0.984	0.24	0.894	11.08	13.53	24.36
F5	0.966	0.853	0.941	0.07	0.783	10.52	14.25	25.66
F6	0.991	0.839	0.925	0.10	0.766	9.667	15.51	27.93
F7	0.961	0.831	0.977	0.50	0.904	10.67	14.05	25.30
F8	0.923	0.854	0.949	0.60	0.897	9.382	15.98	28.77
F9	0.901	0.862	0.989	0.49	0.914	10.20	14.70	26.47
F10	0.985	0.815	0.967	0.50	0.874	9.074	16.53	29.75

CONCLUSION:

Controlled release matrix tablets of Gabapentin were successfully formulated. All formulations exhibit good flow characteristics and all the selected excipients were compatiable with the drug. According to the promising results obtained from the study, it can be concluded that, formulation F8 containing hydrophilic-hydrophobic polymer combination (HPMC K100M+EC) and formulation F10 containing hydrophilic (synthetic-natural) polymer combinations (HPMC K100M+Xanthan Gum) were the best formulations with maximum *in-vitro* drug release in 12hrs, with desired physico-chemical characteristics and with optimum swelling properties.

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