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Formulation development and evaluation of gabapentin controlled release tablets

Abstract

The objective of the present study was to develop a pharmaceutically equivalent, stable, robust, cost effective and quality improved formulation of Gabapentin controlled release tablets by using different grades of controlled release polymer. The design of dosage form was performed by choosing Hydroxypropyl Methyl Cellulose (HPMC K100MCR), Hydroxypropyl Methyl Cellulose (HPMC K15MCR), Microcrystalline Cellulose (MCC) and Di-calcium phosphate polymers as matrix builders. The drug-polymer compatibility studies were performed. Blend Uniformity was studied and accordingly the flowability was optimized for the powder blend. Tablets were prepared by direct compression with free flowing powder. The network formed by HPMC, MCC and DCP had been coupled satisfactorily with the controlled resistance, *in vitro* release and FT-IR. Mean dissolution time was also reported to compare various dissolution profiles. The formula was finalized by comparing the *in vitro* dissolution with that of the innovator SR and IR tablets. Optimized formulation of Gabapentin was formulated using 23% HPMC K100MCR and 10% of DCP. *In vitro* drug release profile was examined 98.69% within 12h. The releases of the formulation were fitting to Hixson Crowell model suggesting controlled zero order release from the formulation. The results suggested that direct compression is a suitable method to formulate controlled release Gabapentin tablets and it can perform therapeutically better than conventional immediate release dosage form.

Keywords: gabapentin, controlled release, *in vitro* release

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Abbreviations: API, active pharmaceutical ingredient; MEC, minimum effective concentration; CRDDS, controlled release drug delivery system; MSC, maximum safe concentration; PHN, post herpetic neuralgia; RH, relative humidity; HPMC, hydroxy propyl methyl cellulose; mg, milli gram; gm, grams; ICH, the international conference on harmonization; USP, united states pharmacopeia; NA, not applicable; SR, sustained release; IR, immediate release

Introduction

Immediate release/Conventional release tablets achieve a rapid onset of action, once they reach the Maximum Effective Concentration; they start to get eliminated from the body. Controlled release tablets of Gabapentin are often prescribed for chronic, severe neuronal pain caused as a result of certain long standing diseases. Controlled release tablets are used for a prolonged duration of action with minimal therapeutic effect. They are formulated with natural high intense polymer to achieve sustained release of the API.[1] Controlled release tablets are formulated with a loading dose and a maintenance dose.[2] The loading dose gives an immediate plasma concentration of the API to have immediate effect and the maintenance dose maintains the level of the drug in the plasma for the MEC.[1] Gabapentin is generally used as an anti-convulsant and an analgesic. Neuropathic pain is caused due to diseases affecting the somatosensory system. A common cause for such pain is Varicella. The disease is often localized to a single sensory dermatologic distribution and the pain is perpetuated by the resulting break down and the subsequent healing of the affected skin.[3]

Gabapentin is classified as a class II drug which is readily soluble in water and partially absorbed in the gut. Current studies on Gabapentin do not show the specific receptor for binding.[4] Hence, to treat the neuropathic pain, Gabapentin course is started with a dose of 300mg, 600mg or 1800mg/day.[5] Due to this high dose treatment, physicians often treat with lower doses further to avoid suicidal symptoms. Gabapentin has a ~~biological~~ half life of 5-7hours which gives the scope for the development of Controlled release tablets. Controlled release tablets will help to reduce the dose dependency and improve patient compliance.[6] Due to its crystalline properties, Gabapentin forms an intact matrix with the high viscous polymers.

Materials and methods-list of instruments used

Single Pan Electronic Weighing Balance - Sartorious BT 223S ; Hot air oven - Unilab, India; Blender- Rimek Kalweka HD- 400Ac, India, Rotary Compression Machine- GMI, Friability Test Apparatus- ElectroLab, EF-2, India, Monsanto Hardness Tester- Dr. Schleuniger Pharmatron, Dissolution Test Apparatus- Electrolab, Model-TDT-08L, USP, U.V-Spectrophotometer- Shimadzu Corporation, Japan, Perk Elimer, Sonicator- Spincotech Pvt. Ltd, Italy, pH-meter- Mettler, Toledo, Tap Density Apparatus- Electro Lab ETD - 1020, India, Moisture Balance (Halogen Moisture Analyzer)- Mettler Toledo, US, Vernier Caliper- Mitutoyo Corps, Japan.

Pre formulation study

The detailed physical and chemical properties of a drug substance, alone and in combination with excipient were evaluated in preformulation studies. The particle size distributions of the polymer powders were measured. Particle shape was analyzed microscopically.

Flow properties were assessed by utilizing a tap densiometer (Electro Lab ETD - 1020, India) and calculating the Hausner ratio.

Procedure for drug and excipient incompatibility study

Gabapentin drug was mixed with excipients in various ratios. Aliquots of these mixtures and the drug alone were kept in open 5mL glass vials, exposed to 40°C and 75% relative humidity for one month and, at intervals of 2 weeks and 4 weeks, the samples were withdrawn to make physical observations and analyzed after the exposure of the drug and excipient. Physical observation no significant color changes were observed after exposure of drug and excipient to 25°C/60% relative humidity (RH) and 40°C/75% RH for 4weeks. FTIR Spectra of the drug-excipient study revealed no interaction.

Method of preparation of tablets

The API (Gabapentin), Polymers and diluent were passed through sieve no 60. The API, polymers and diluent were mixed in a V-blender, and then the other excipients sifted through sieve no 60. Were added and mixed in geometric proportions, except the lubricant. The mixture was blended well for 10minutes. Then the lubricant which was previously sifted through sieve no.60 was added and mixed thoroughly for 5minutes. Compaction behavior was evaluated by compressing the blends into 9mm capsular tablets with an instrumented single punch tabletting machine (Compression Machine- GMI) at a compression speed of 10rpm. Compression force and upper and lower punch displacement were recorded during the compaction process (MGC plus, catman, HBM, Darmstadt, Germany). The blend formula as given in Table 1 was then directly compressed to produce tablets with 9mm capsular punch.

Characteristics of tablet formulations

The tablets were characterized by weight variation, hardness, disintegration, friability, content uniformity of dose and dissolution profile (Table 2). The average weight was measured over 20units, as recommended by the United State Pharmacopoeia (U.S.P), 2006. The hardness was determined in a Schleuniger Hardness Tester over 10 tablets. For each formulation, the friability was tested in a Roche Friabilator over a sample of 20 tablets and the acceptance criterion was a maximum loss of 2% of initial weight (U.S.P. 2006). Dissolution profile was determined by analyzing samples by UV Spectrophotometer, Shimadzu Corporation, Japan. Gabapentin controlled release tablets were evaluated as per the specified limit of USP to meet the quality of formulation.[2] Tablets were evaluated for individual and average weight variations, thickness, hardness, assay and *in vitro* drug release. Individual and average weight variations were measured in the Single Pan electronic balance- Sartorius BT 223S. The friability was tested using 6.0gm of tablets for 100RPM in Roche Friabilator and the limit was kept NMT 2% as per USP. Dissolution was performed by using Dissolution Apparatus by Electrolab.

Table 1 Composition (mg) of Gabapentin 600 mg tablet formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Gabapentin API	600	600	600	600	600	600	600	600	600	600
MCC PH 101	100	100	100	-	-	-	-	-	-	-
HPMC K15MCR	75	90	110	-	-	-	-	-	20	-
Eudragit RSPO	75	60	40	-	-	-	-	-	-	-
SLS	50	50	50	50	50	50	50	50	50	50
Talc	50	50	50	50	50	50	50	50	20	10
Magnesium Stearate	50	50	50	50	50	50	50	50	10	10
Dibasic Calcium Phosphate	-	-	-	200	150	100	40	50	130	100
HPMC K100 MCR	-	-	-	50	100	150	210	175	150	230
Aerosil	-	-	-	-	-	-	-	25	20	20

Each quantity mentioned in mg

Total weight of the tablet=1000mg

Each tablet contains=600mg of the API.

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Table 2 Evaluation of blend batches

Batch number	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Bulk Density (g/ml)	0.46	0.48	0.4	0.65	0.5	0.72	0.54	0.55	0.53	0.48
Tapped Density (g/ml)	0.59	0.61	0.52	0.81	0.62	0.89	0.67	0.64	0.62	0.57
Hausner's Ratio	1.28	1.27	1.28	1.25	1.24	1.23	1.23	1.15	1.16	1.17
Compressibility Index (%)	22.0	21.31	23.07	20.02	19.35	19.1	21.31	14.06	13.92	14.71
Angle of Repose (°)	44	42	41	41	40	41	40	38	35	35

Dissolution

Tablet dissolution was assessed in a standard USP 24 apparatus II in 900mL of Deionised water. The stirring speed was 100rpm. A total of 6 tablets were used in the test. Temperature was maintained at 37°C±0.5°C throughout the experiment. Dissolution was monitored for 12h, samples being taken at 1, 2, 4, 6, 8, 10, 12h. After the collection of each sample, the dissolution medium was replenished with the same volume of fresh medium. The samples were diluted to 100mL with dilution medium and analyzed for drug content by 198.1 nm. A calibration curve was generated from a Shimadzu Corporation, Japan at 198.1nm.[3,4]

Kinetics of the *in vitro* drug release

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted Hixon Crowell kinetic models. The kinetic parameters for the *in vitro* release of gabapentin were determined and then analyzed in order to find the drug release.

Stability studies

Optimized formula F10 was subjected to stability studies as per ICH guidelines to evaluate the shelf Life. F10 were exposed to 40°C/75% RH and 60°C for 15days and 1Month in a suitable packed condition. These subjected samples were further analyzed for appearance, hardness, friability, drug content and *in vitro* drug release.

Results & discussion

Direct compression into tablets requires good flowability and compatibility of the excipients to guarantee reproducibility of the process and product quality. The flowability of a powder depends on material properties like the particle surface, size and shape. Particles were found with average particle size of 28.8µm for almost all the excipients after Sieving. All the excipients and API were found stable. Study revealed that drug has compatibility with all the selected excipients (Figure 1-7).

Blend evaluation

According to the USP specifications, the flow properties of the powder blend is ''good'' if the angle of repose is between 31 and 35. Values between 25 and 30 indicate excellent flow characteristics and values of 36 or above indicate fair to poor flow properties. Accordingly, a formulation was adopted for modifications in the trials. Blend uniformity studies suggested poor flowability with the batches F1- F8 so increased quantity of Lubricant and glidant were used in the formulation. This improved flowability significantly while the flow was good for the formulation F9-F10 as shown in Table 3.

Evaluation of tablet formulations

The early indication showed that the Formulation F1-F4 had low hardness and other parameters meet the USP Specified limit. Table 4 summarizes the results obtained from the tests conducted on all batches. All batches met the requirement for weight variation test according to USP 32. The disintegration time for the tablets correlated well with their hardness (the greater the hardness of the tablet the longer was the time needed to achieve disintegration) F4, F6, F7 and F10 batches passed the test for Drug Content in Tablets which should not be less than 98.0 percent and not more than 102.0 percent.

For formulations F1-F4 it was found that the release was retarded compared to the marketed formulation. In formulation F5, it was found faster in earlier time points. Formulation F6-F9 found that release was satisfactory in early time points and faster in the later time points. Adequate results were obtained only for F10, while its difference factor was well within the specified limit of reference limit Pharmacopeia forum, 2006 (Table 4) (Figure 8).

Kinetics of the *in vitro* drug release

The kinetic parameters for the *in vitro* release of gabapentin CR tablets were analyzed in order to find the drug release. Hixson Crowell Kinetic model were investigated and found F 10 follow the Hixson Crowell model of kinetics. The value of intercept for Hixson Crowell Kinetic model was 0.932 (Figure 9). Zero-order release from swellable hydrophilic matrices occurs as an outcome of continuous diffusional path lengths. When the thickness of the gelled layer and diffusional path lengths are constant, zero-order release can be expected, as seen for formulations F10. In contrast, the majority of formulations that showed non-Fickian release must have had an increasingly thickening gel layer due to slower erosion. This led to a decrease in the drug release rate with time as previously reported. At higher concentrations, the viscosity enhancing polymers contributed by keeping the hydrated layers intact, thus maintaining the integrity of the matrix and slowing the erosion process.

Stability studies

Controlled release tablets of Gabapentin formulated in the present study were subjected to accelerated stability studies. Stability studies of the prepared formulations were performed at ambient humidity conditions, at room temperature, at 25^0C±2^0C & 60% RH, 40^oC±2^0C & 75% RH and 60^0C for a period up to 30days. The samples were withdrawn after periods of 15days, and 30days and were analyzed for their appearance, hardness, friability, drug content and *in vitro* drug release.[7–9] The results revealed that no significant changes in appearance, drug content, hardness, friability, and *in vitro* release were observed for F10 formulation (Table 5).

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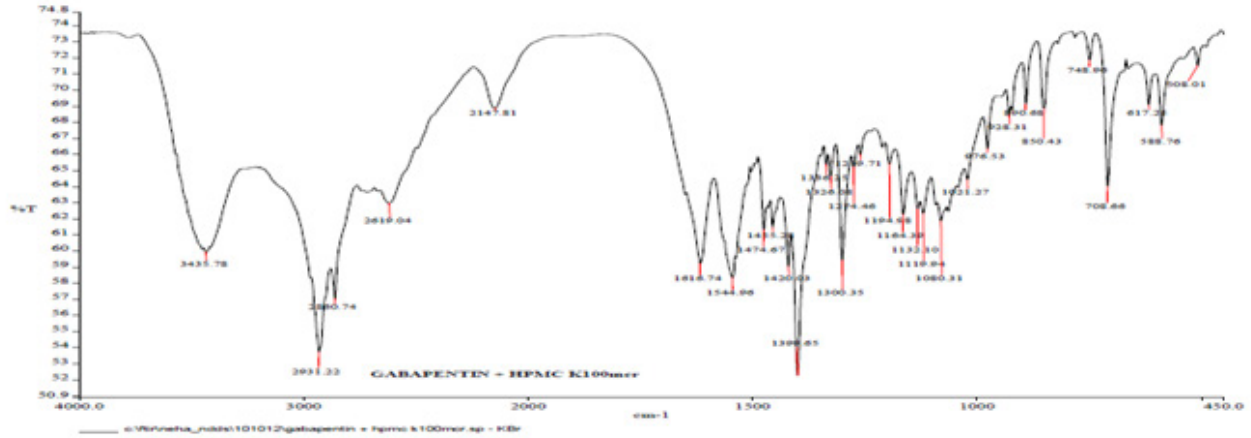

Figure 1 FTIR spectrum curve of Gabapentin + HPMCK100mcr.

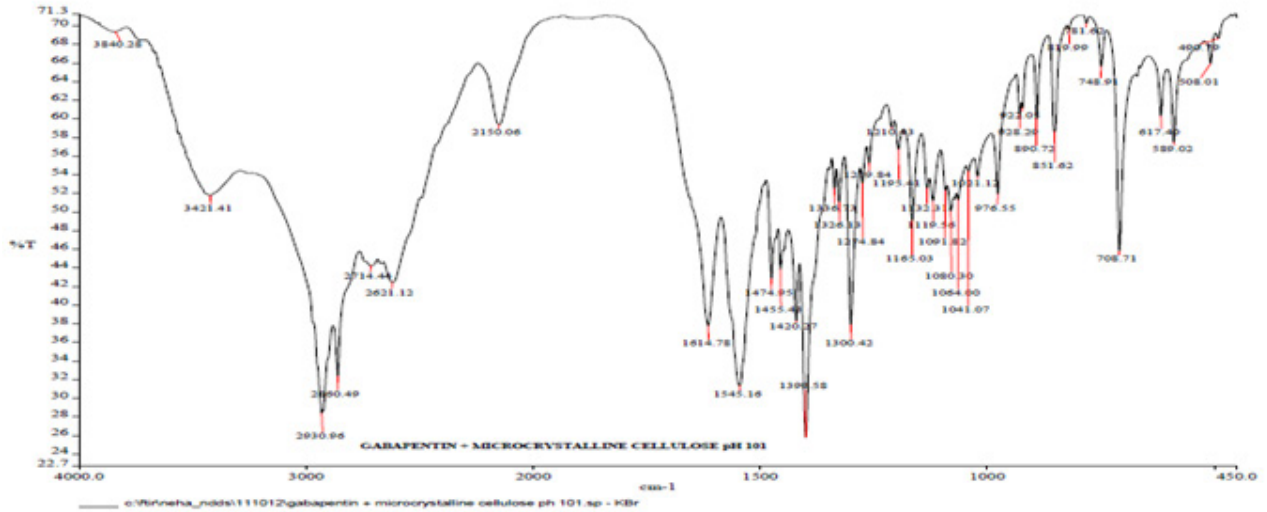

Figure 2 FTIR spectrum curve of Gabapentin + Micro crystalline cellulose.

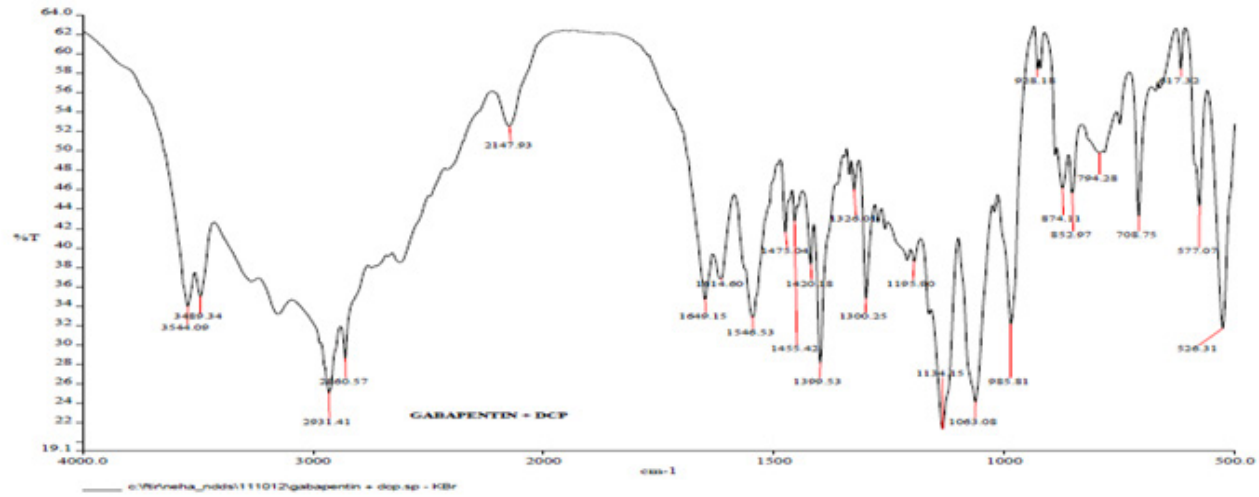

Figure 3 FTIR spectrum curve of gabapentin + dibasic calcium phosphate.

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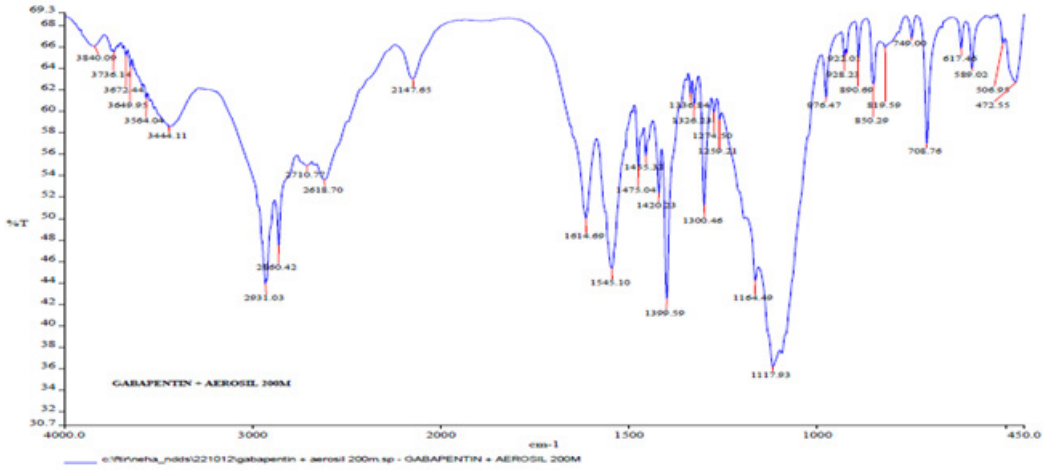

Figure 4 FTIR spectrum curve of gabapentin + aerosil 200M.

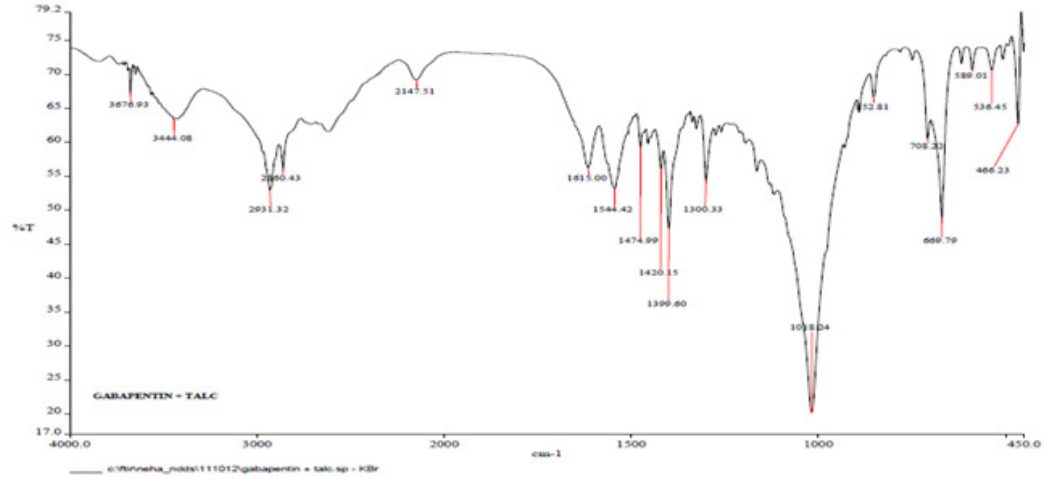

Figure 5 FTIR spectrum curve of gabapentin + talc.

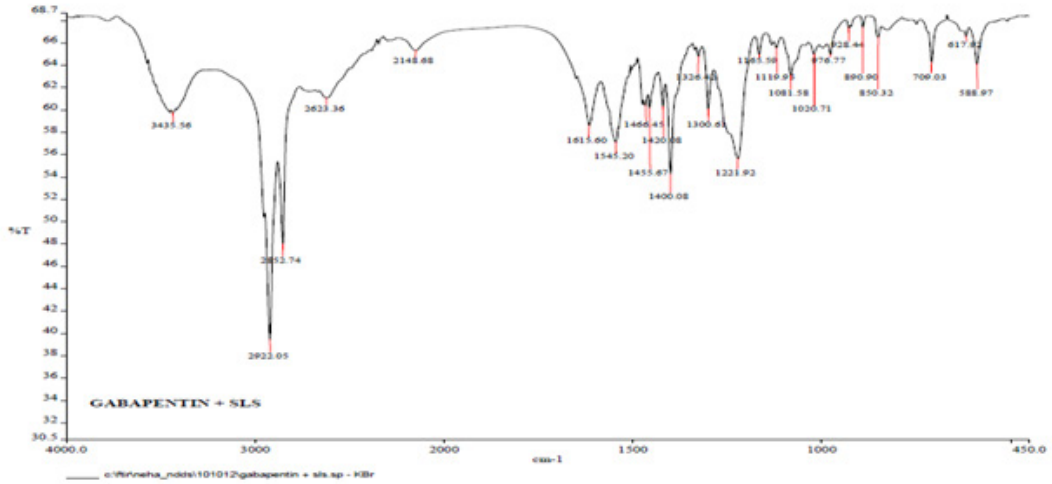

Figure 6 FTIR spectrum curve of gabapentin + sodium lauryl sulphate.

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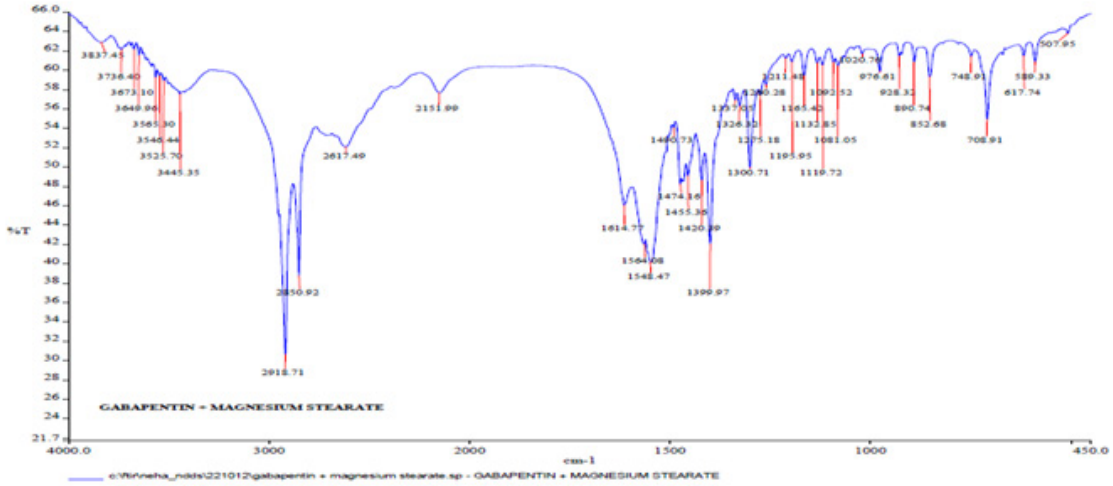

Figure 7 FTIR spectrum curve of gabapentin + magnesium stearate.

Table 3 Characteristics of tablet formulations

Batch Number	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Thickness (mm)	7.88	7.85	7.91	7.79	7.78	7.71	7.77	7.89	7.83	7.7
Weight Variation (%)	±2.0	±2.55	±3	±4	±3.6	±3	±2.4	±3.5	±4.2	±2
Hardness (kg/cm^2) Kp	2-4	2-4	2-4	2-4	3-5	2-4	2-4	2-3	2-5	4-5
Friability (%)	1	0.98	0.96	0.78	0.56	0.67	0.37	0.41	0.29	0.15
Drug Content (%)	97	97.26	96.2	98.93	97	99.89	98.53	97	96	99

Table 4 Dissolution profile of various formulations

Time (hrs)	MKTD SR Tablet	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0	0
1	18.83	2.33	3.33	8.33	12.50	47.17	21.67	19.83	18.67	19.50	19.17
2	28.35	13.46	15.17	43.51	49.01	53.05	36.36	24.86	23.35	28.36	30.02
4	45.22	20.21	20.52	48.22	57.57	59.44	59.40	55.05	35.05	42.72	45.22
6	66.44	41.55	43.88	78.28	66.30	64.68	64.63	84.78	47.25	67.93	66.60
8	78.18	45.45	54.59	82.53	79.21	82.08	82.04	82.54	53.64	76.01	78.18
10	85.10	57.12	66.65	89.29	93.96	97.34	97.29	99.46	68.86	87.59	83.43
12	100.52	69.53	71.56	100.22	99.40	98.78	98.73	100.91	99.27	100.69	98.69

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Table 5 Stability study results for F10

Temperature and humidity condition	Tested after time (days)	Hardness (Kp)	Friability (%)	Drug content (%)	Cum % drug released
25°C±2°C & 60% RH	15	4-5	0.14	99	98.67
	30	4-5	0.13	99.22	98.65
40°C±2°C & 75% RH	15	4-5	0.12	99.36	98.76
	30	4-5	0.14	99.23	98.66
60°C	15	4-5	0.15	99.26	98.06
	30	4-5	0.13	99.19	98.18

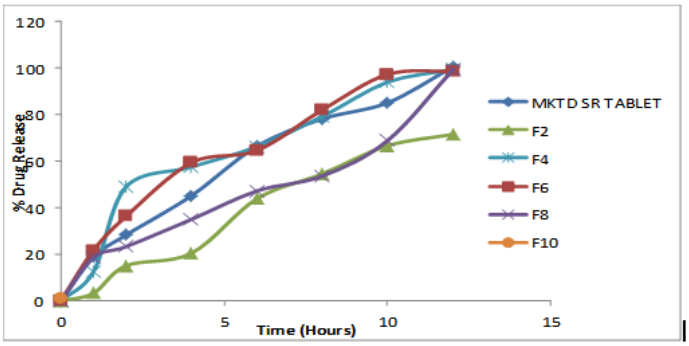

Figure 8 Comparative dissolution profile of various formulations.

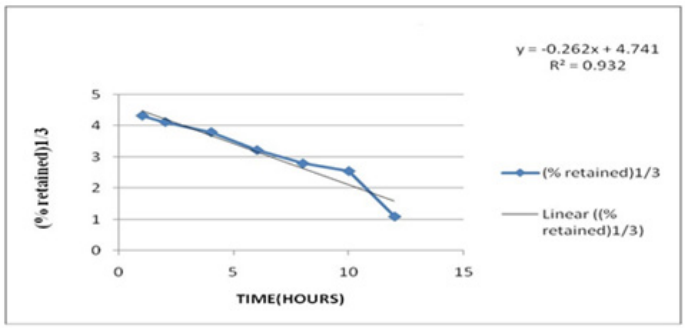

Figure 9 Hixon crowell plot for the optimized formulation.

Stability studies were conducted on tablets of Batch F10 stored at 25°C & 60% RH, 40°C & 75% RH and 60°C for one month. Tablets were evaluated for hardness, friability, *in vitro* release profile and drug content. After one month no significant changes were observed in any of the studied parameters during the study period. Thus it could be concluded that the formulation was stable.

Conclusion

Controlled release tablets of Gabapentin were studied using the different ratios and grades of rate controlling polymers. The Formula using 23% HPMC K100MCR and 10% of DCP fulfilled all the specified requirements of the USP. Stability studies were conducted on tablets of F10 stored at 25°C & 60% RH, 40°C & 75% RH and 60°C for one month. Tablets were evaluated for hardness, friability, *in vitro* release profile and drug content. After one month, no significant changes were observed in any of the studied parameters during the study period. Thus, it could be concluded that the formulation was stable. Percentage drug release in 12h was 98.69%. It was observed that tablets of F10 followed the Hixson Crowell model under Non-Fickian diffusion. From the above results, it was concluded that formulation of controlled release tablets of Gabapentin containing F10 ratios of excipients with the direct blending method was taken as an ideal or optimized formulation.

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Conflict of interest

The author declares no conflict of interest.

References

1. Narasimharao R, Anusha Reddy M, Swetha Reddy N, et al. Design and Evaluation of Metformin Hydrochloride Extended Release Tablets by Direct Compression. *International Journal of Research in Pharmaceutical and Biomedical Sciences*. 2011;2(3):1118–1133.
2. Berner B, Dinh SM. *"Fundamental Concepts in Controlled Release" in "Treatise on Controlled Drug Delivery"*. New York, USA: Marcel Dekker Publication; 1992. p. 1–4.
3. Ropper AH, Samuels MA. Chapter 33. Viral Infections of the Nervous System, Chronic Meningitis, and Prion Diseases. In: Ropper AH, et al. editors. *Adams and Victor's Principles of Neurology*. New York, USA: McGraw–Hill Medical; 2009.
4. Rappaport BA, Hertz S, Roca R, et al. *Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)*. FDA & Center for drug evaluation and research, USA; 2011.
5. Rowbotham M, Harden N, Stacey B, et al. Gabapentin for the treatment of postherpetic neuralgia:a randomized controlled trial. *JAMA*. 1998;280(21):1837–182.
6. Sang CN, Sathyanarayana R, Carter FJ, et al. *Gabapentin Extended Release (G–ER) For The Once Daily Treatment Of Post Herpetic Neuralgia (PHN)*. Pain week conference, USA: Aventine Health Sciences; 2010.
7. Amaral MH. The effect of the concentration of hydrophilic (hydroxypropyl methylcellulose [HPMC]) and hydrophobic (hydrogenated castor oil [HCO]) products, fillers and buffers". *Science Citation Index Expanded, Journal Citation Reports/Science Edition, and Web of Science*. 2006;68(1):53–58.
8. Efentakis M, Vlachou M, Choulis NH. Effect of excipients on swelling and drug release from compressed matrices. *Drug Development and Industrial Pharmacy*. 1997;23(1):107–112.
9. Efentakis MD. The influence of surfactant on drug release from a hydrophobic matrix". *Indian Journal of Pharmaceutical Science*. 1999;70(1–2):153–158.