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Original Article

Preparation And Release Study Of Levetiracetam 500 Mg Extended Release Tablet By Using Combination Of Hydrophilic And Hydrophobic Polymers

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Abstract

Levetiracetam, as an Anti-epileptic drug with an exclusive mechanism of action, has been approved by the USA Food and Drug Administration as an adjunctive therapy for treating epilepsy in young adults.
The purpose of this project was designing and formulating prolonged release form of levetiracetam using two types of a retarding agent including Hydroxyl Propyl Methylcellulose (HPMC K4M) and Xanthan Gum, as well as a fatty matrix of cetyl alcohol. In addition, by manufacturing this product, it is possible to make a domestic production of this form of medicine, importing this form of medicine into the list of generic drugs of Iran. Pre-formulation studies such as compaction of granules, compressibility and the ability of the powder to flow were observed prior to formulation. The percentage of excipients in the formulation such as HPMC K4M, PVP k30, Mg-st, were considered as variables to examine the rate of release and physical properties in Factorial design method. In the optimization process, xanthan gum is added alone to formulation abc obtaining formulation X, in addition, xanthan gum in combination with cetyl alcohol is used to obtain formulation F, then release studies were evaluated. According to data obtained from release profiles, prepared tablets with both hydrophilic and hydrophobic retard agent (HPMC K4M 30%, xanthan gum 2%, cetyl alcohol 2%) have revealed a similar profile of release to the active agent according to USP limited range. Furthermore, the release studies have shown that swelling, swelling/erosion, and dissolution were the most important mechanisms that could affect the release profile. It also suggested that the percentage release of formulation F was followed Higuchi model.

Keywords: Levetiracetam, Hydroxyl Propyl Methylcellulose, Drug Release, Factorial Design

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Introduction

Levetiracetam is used to treat patients with partial onset seizure who have not responded to initial pharmacotherapy. It is also used as a treatment for myoclonic and first-generalized seizure (Ulloa CM., 2009).

The Bioavailability of levetiracetam is almost 95%. The absorption is fast and not affected by food. The maximum plasma concentration is obtained in about 1.3 hours and the kinetic is linear. The protein binding is less than 10%. The half-life of the plasma is 6-8 hours and dose-dependent and may increase in the elderly patient. Levetiracetam metabolism is independent of the liver cytochrome P450 system. 66% of the dose is excreted unchanged in the urine and 27% is excreted as an inactive metabolite. The main route of metabolism is the enzymatic hydrolysis of the acetamide group which results in an inactive metabolite of carboxylic acid (Sweetman, et al., 2011).

In general, 10% of the world population experiences seizures during a period of their life. About 30% of these people are affected by CNS disorders and about 1% has epilepsy. It is one of the most common neurological disorders and is seen all over the world, mostly in developing countries. The annual incidence in developing countries is 7-40 per 100,000 and in developed countries is estimated to be 90-100 per 100,000. The highest incidence of age is seen in children and the elderly. The incidence in men is slightly higher than for women. 20% of people, despite the administration of multiple medications, remain uncontrolled, so it is suggested that there could be a genetic predisposition to anti-epileptic drug resistance cases. The most common reason for the failure of treatment with anti¬-epileptic drugs is the patient's refusal of medication and more than 60% of the patients do not have adequate compliance, which is due to the complexity of the therapeutic regimen, administration 3 to 4 times a day and the miss doses (Cramer, et al., 2000).

In conventional drug therapy, some drugs intrinsically remain in the body for a long period of time. These drugs will be taken once daily to remain in the bloodstream steady and have a therapeutic effect properly. For most drugs, the conventional method of drug administration requires periodic doses, so the patient's desire for consumption reduced or maybe missed taking the drug happened. On the other hand, some active agents are unstable or toxic and have narrow therapeutic ranges.

Controlled drug delivery systems have numerous advantages over traditional systems such as improved efficiency, less fluctuation of plasma levels, reduced toxicity, and improved patient compliance. In fact, this delivery system has the potential for extended release in the site of absorption. As a result, the main purpose of the controlled drug delivery system is providing a proper amount of drug release at regular intervals (Gupta, et al., 2012).

Extended-release (ER) drugs are products that are used to maintain the blood and tissue levels of the drug at the therapeutic level in long periods of time. This controlled drug delivery system has some advantages including better patient compliance, reducing the possibility of forgetting doses by the patient, better effects and less toxicity, better uniformity concentration in the blood, appropriate biological half-life and reduction of treatment costs as well as side effects of the drug (Joyce, et al., 2000).

Bphopate et al. studied the different matrix tablets using the various degree of viscosity of HPMC and cetyl alcohol. The quality control and release tests have been done and results have shown that HPMC K4M had a significant effect on controlling of drug release compared to other types of HPMC polymer and cetyl alcohol (Bhopale, et al., 2008).

Nath, B.S et al., investigated aliphatic alcohol and cetyl alcohol in extended release matrix tablets. Theophylline was used as a model for evaluating the matrix system. Cetyl alcohol and methyl Cellulose with different ratio of 20%, 25%, and 30% were used. In vitro drug

release studies demonstrated that the matrix system with 30% of total weight of formula had the best release and extended it to 8 hours (Nath, et al., 2000).

The relation between HPMC and the rate of release have been investigated by Ravi et al., and it was concluded that by increasing the amount of HPMC, the releasing rate decreased. It was also found that Avicel helped the compressibility and complete releasing of the active agent in the remaining time in the digestive system (Ravi, et al., 2007).

Conti et al., have studied the release rate of drugs in matrix tablets composed by the HPMC. It was found out that HPMC controls the rate of release by the formation of gel-like structure (Conti, et al., 2007).

In the present study extended release matrix tablet of levetiracetam was formulated using Hydroxyl Propyl Methyl Cellulose 4000 cps (HPMC K4M), xanthan gum and cetyl alcohol. The Sustained release matrix formulations have some swelling polymers, waxes or both which control the release rate. The tablets were prepared by wet granulation. The factorial design study was performed in order to investigate variables such as the percentage of HPMC K4M, PVP k30 and Mg-st and the effect of these three components in the release profile of levetiracetam extended-release tablets.

Material and Methods

Material and Equipment

Drugs and chemicals:

Levetiracetam was obtained from Ramofarmin Pharmaceutical Company, Tehran. Excipients such as Polyvinyl Pyrrolidone (PVP K30), Magnesium Stearate (Mg-st), Avicel PH102 were provided as a gift from Kosar Pharmaceutical Company, Iran. HPMC K4M(Hydroxyl Propyl Methyl Cellulose 4000cps), xanthan gum and cetyl alcohol were provided as a gift by Hakim Pharmaceutical Company, Iran.

Apparatus:

The High-Performance Liquid Chromatography (HPLC) Younglin Acme 9000 HPLC was used for assay studies that were equipped with a 254 nm detector and a 4.6 mm x 15 cm; 5-μm packing L7 column. Peak identity was confirmed by comparison of spectra and retention time against the standard (Rockville, et al., 2015).

Tablet hardness tester 5Y (Dr. Schleuniger Pharmaton-USA) was used to measure the hardness of tablets. Tablet friability tester FR1000 (Dr. Schleuniger Pharmaton-USA) was used to determine the friability of the tablets.

Tablet dissolution tester USP DT60 (Erweka-Germany) was used to do the release test and finally tablet compressing machine (Korsch-Germany) was used to press the tablets.

Chromatographic conditions:

The mobile phase including water and anhydrous dibasic sodium phosphate with the following ratios (3:5) and acetonitrile with above mixture following ratio (10:90) was prepared. Standard and sample solutions were prepared according to assay method in the USP39 monograph and injected to HPLC and the percentage of levetiracetam, based on the label claim, were calculated in the portion of tablets (Rockville, et al., 2015).

Methods

Pre-formulation study:

Prior to the preparation of a retard release tablet, it is necessary to carry out a prospective study for the Carr's index, the Hausner's Ratio, and the powder compaction test.

Formulation of the tablet:

After the pre-formulation studies, the ingredients and variables were selected in two levels: low

and high, and the evaluation of the tablets was carried out using the factorial design method.
Wet granulation technique was performed in order to prepare levetiracetam extended-release oral matrix tablets with three variable concentrations of HPMC K4M, PVP K30, and Mg-st. The amount of active ingredient was kept constant at 500mg. Ingredients, except for Magnesium Stearate and PVP, were weighted and blended uniformly. PVP, as a binder, was added to the dry powder and finally was stirred for two to five minutes. Based on to the amount of water required for granulation, for this purpose, add 5 to 10 ml of water to obtain a wet mass. Pass the wet granules from the sieve with mesh number 12 and then transfer on oil paper to dry. After drying, the granules passed through the No. 14 sieve and then the magnesium stearate was added and finally, granules were mixed for one to two minutes. The lubricated granules were compressed with the machine using 17.5mm*8mm, oval-shaped punch and the total weights were considered as 800-900 mg. The compositions of different formulations are given in Tables 2-4.

In factorial design procedure, the concentration of HPMC K4M (X1), the concentration of PVP (X2) and the concentration of Mg-st (X3) were selected as independent variables. They are also divided into two levels of high and low level (Table 1). The impact of these variables on drug release was investigated, too.

Table 1: factors used in the factorial design experiment

Factor	Low level	High level
HPMC4000cps (%) (X1)	20	25
PVP (%) (X2)	2.5	5
Mg-st (%) (X3)	1	5

Table 2: The compositions of the series 1 formulations

Formulation Ingredient	1 mg/tab	a mg/tab	b mg/tab	c mg/tab	Function of Each ingredient
Levetiracetam	496	496	496	496	active ingredient
HPMC4000cps	160	200	160	retarding agent	tr
PVP k-30	20	20	40	retarding agent	binder
Mg-st	8	8	8	40	lubricant
Avicel PH102	116	76	96	84	filler

Evaluation of granules:

In this study some properties like apparent bulk density, tapped bulk density, compressibility index and Hausner's ratio were determined and compared with the flow properties of levetiracetam powder.

• Bulk density:

The bulk density of a powder depends on variables such as particle size distribution, particle shape and the tendency of the particle to adhere together.10g of powder was sieved and transferred into a dry cylinder. The level

Table 3: The compositions of the series 2 formulations

Formulation Ingredient	ab mg/tab	ac mg/tab	bc mg/tab	abc mg/tab	Function of Each ingredient
Levetiracetam	496	496	496	496	active ingredient
HPMC4000cps	200	200	160	retarding agent	tr
PVP k-30	40	20	40	40	binder
Mg-st	8	40	40	40	lubricant
Avicel-PH102	56	44	64	24	filler

Table 4: The compositions of the series 3 formulations

Formulation Ingredient	X mg/tab	F mg/tab	Function of Each ingredient
Levetiracetam	495	495	active ingredient
HPMC4000cps	270	270	retarding agent
PVP k-30	45	45	binder
Mg-st	4/5	4/5	lubricant
Xanthan gum	18	18	retarding agent
Cetyl alcohol	-	18	retarding agent
Avicel-PH102	67/5	49/5	filler

of powder was carefully measured without compacting and the (Vo) was marked as apparent volume.
The bulk density was calculated using the formula:

$$\textbf{Bulk density}=M/V_o$$

Where,
M=weight of sample
Vo=apparent volume of powder

• Tapped density

The cylinder containing the sample was tapped after measuring the bulk density. The tapped density was calculated in g/ml using the below formula:

$$\textbf{Tapped density}=M/V$$

Where,
M=weight of sample
V=tapped volume of powder

• Measures of powder compressibility:

If limited quantities of the drug are available, the flowability of the powder can be determined by the Carr's Index. It is calculated from the tapped and bulk densities.

$$\textbf{Carr's Index}= [(\text{tap-bulk})/\text{tap}]*100$$

Table 5: Carr's Index value

Carr's Index	properties
5-15	Excellent
12-16	Good
18-21	Fair to passable
20-35	Poor
33-38	Very poor
>40	Very very poor

• Hausner's Ratio

The Hausner's ratio is used to determine and measure the flowability of the powder. The calculation method is based on the following equation:

Hausner ratio=tapped density/bulk density

Table 6: evaluation of powder API

Carr's Index	Tapped density	Bulk density	Hausner's ratio
17.97±0.22	0.57±0.35	0.48±0.30	1.18±0.007
17.65±0.22	0.66±0.35	0.56±0.30	1.17±0.007
17.81±0.22	0.615±0.35	0.52±0.30	1.175±0.007

Physical evaluation of levetiracetam XR tablet:

The prepared extended-release tablets were evaluated for the following official parameters: weight variation, hardness, thickness, friability and drug content were measured.

In vitro dissolution study:

The in vitro drug release studies of the matrix tablets was performed according to united state pharmacopoeia 39th using apparatus 1(100 rpm) at 37 ° C ± 0.5 in potassium phosphate monobasic medium (pH =6.0).The release study were carried out for 8 hours. Samples were collected at time intervals of 1,2,4, and 8 and replaced with an equal volume of buffer to keep the volume constant.The sample solution was diluted and analyzed at 210 nm by spectrophotometer. The percentage of the labeled amount of levetiracetam in each time point was calculated based on the below formula:

Ci= (Au/As)*Cs
Result1 (%) =C1*V*(1/L)*100
Result2 (%) = [(C2*V) + (C1*Vs)]*1/L*100
Result3 (%) = {(C3*V) +
[(C2+C1)*Vs}*(1/L)*100
Result4 (%) = {(C4*V) +
[(C3+C2+C1)*Vs]}*(1/L)*100

C_i= concentration of levetiracetam in the portion of sample withdrawn at the specified time point (mg/ml)
V=volume of the medium, 900ml

V_s=volume of sample solution withdrawn at each time point and replaced with medium (ml)
L=label claim (mg/tablet)

Assay studies:

The percentages of the levetiracetam, in the best formulation, were analyzed by HPLC method. In order to prepare an assay stock solution, 5 tablets were transferred to a suitable volumetric flask, containing tetrahydrofuran to fill about 5% of flask volume. 80% of the final volume was filled by mobile phase. The rest of the volume was filled with methanol. Finally, sample solution was prepared as 0.08mg/ml solution of levetiracetam from above solution in mobile phase.

Result and discussion

Pre-formulation study:

The drug is an odorless white crystalline powder found to be bitter in taste. The data obtained from the Carr's index experiment and the Hausner's ratio, shown in Table 6, indicates that the levetiracetam has the appropriate flowability to an acceptable level. The results obtained from the compressibility test show that levetiracetam does not have desirable hardening condition. As a result, it was decided to use a wet granulation to improve the compressibility. As expected, a powder that has a poor flowability is also difficult to compress.

Physicochemical characteristics:

The result of physicochemical tests has been summarized in Table 7-9. All formulations passed weight variation of 500±10% test. The obtained hardness was within the range of 5-15 kp. The thickness was within the range of 6.50-7.20mm. Friability in all formula, except c and a, were less than 0.9%.

Table 7: Physicochemical properties of series 1 formulations

Parameters	Weight Variation(mg)	Thickness(mm)	Hardness(kp)	Friability (%)
1	801.14±0.81	7.043±1.79	13.3±0.86	1.40
a	799.41±0.93	6.91±0.082	9.7±0.72	0.13
b	802.79±0.75	7.04±0.75	13.5±2.21	0.20
c	802.79±0.89	6.94±0.59	4.6±0.7	1.98

Table 8: Physicochemical properties of series 2 formulations

Parameters	Weight Variation(mg)	Thickness(mm)	Hardness(kp)	Friability (%)
ab	801.57±0.92	7.09±0.99	11.3±1.16	0.21
ac	804.30±0.79	6.95±1.05	4.7±1.23	1.20
bc	802.54±0.67	7.28±1.03	10.5±0.69	0.21
abc	805.00±0.71	6.72±1.15	4.5±0.78	0.77

Table 9: Physicochemical properties of the series 3 formulations

Parameters	Weight Variation(mg)	Thickness(mm)	Hardness(kp)	Friability (%)
X	899.78±0.84	7.56±1.50	12.40±1.29	0.11
F	902.22±0.66	7.52±1.26	9.40±1.00	1.20

In vitro Dissolution studies:

The result of the release profile is shown in Tables 10-12. Figures 1 and 2 illustrate the release profiles of all formulations and considering Table 13, the best formulation that fit within USP39 limits were selected.

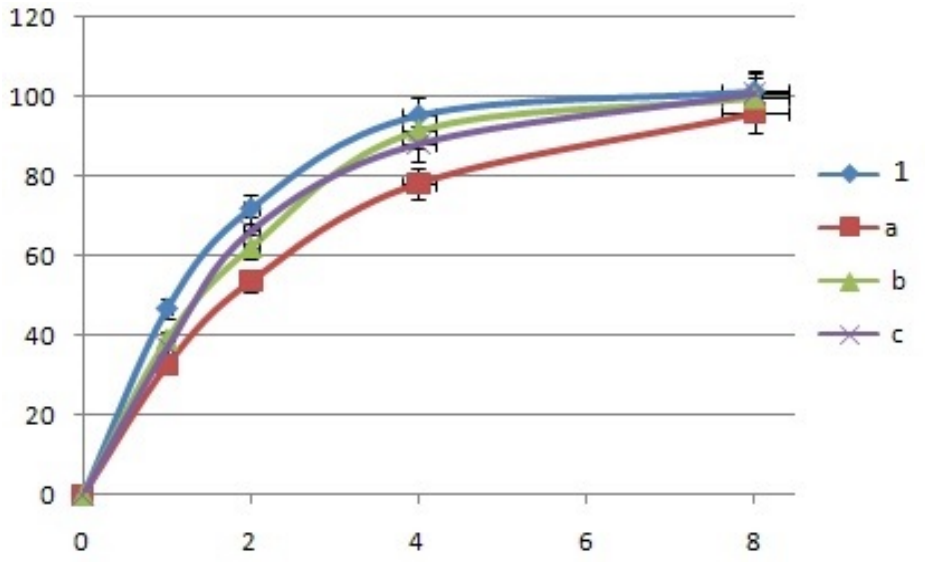

Figure1: release profile of levetiracetam in series 1 formulations versus time at wavelength 210nm

Table 10: Percentage of drug release versus time in series 1 formulations

Time(hour) Release (%)	1	2	4	8
1	46.8±2.55	71.9±1.46	95.3±1.45	101.3±1.46
a	32.6±1.89	53.7±1.08	78.3±0.91	95.8±1.47
b	37.0±1.75	66.4±1.97	88.3±2.15	100.9±1.80
c	39.1±2.10	63.2±1.51	91.5±2.91	99.7±1.72

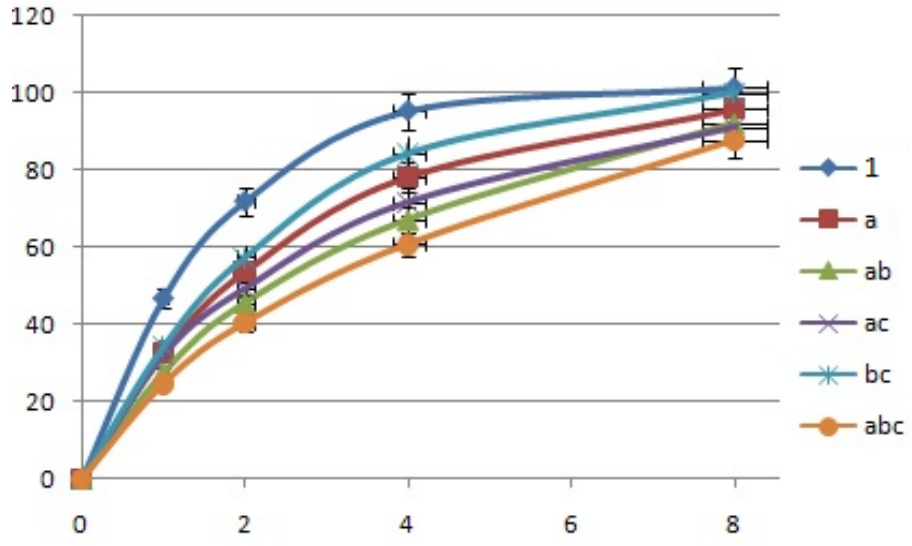

Figure2: Release profile of levetiracetam in series 2 formulations versus time at wavelength 210nm

Table 11: Percentage of drug release versus time in series 2 formulations

Time(hour) **Release (%)**	**1**	**2**	**4**	**8**
ab	27.6±1.99	45.6±0.99	67.1±1.69	92.1±1.11
ac	32.1±2.27	49.3±0.95	71.6±2.03	91.0±2.65
bc	34.3±1.40	57.4±1.29	84.3±1.13	100.0±2.19
abc	24.7±0.56	60.8±2.10	84.8±2.79	87.7±2.75

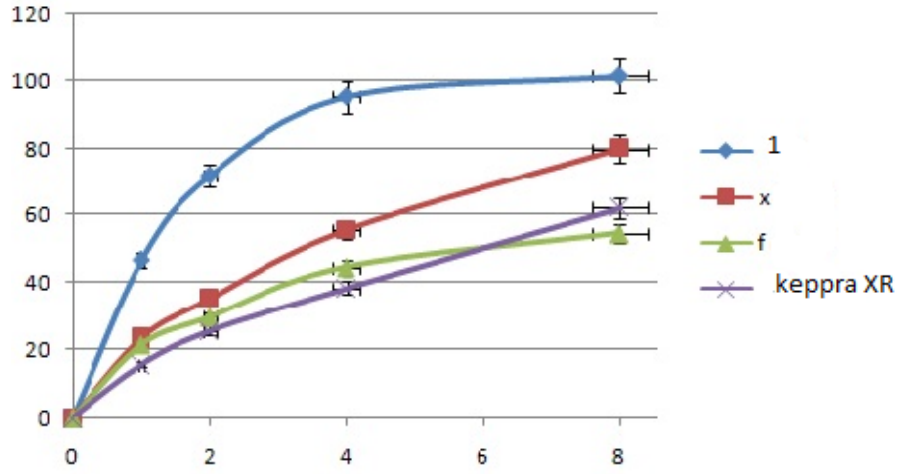

Figure3: release profile of levetiracetam in series 3 formulations and brand versus time at wavelength 210nm.

Table12: Percentage of drug release versus time in series 3 formulations

Time (hour) Release (%)	1	2	4	8
X	23.6±1.62	55.6±1.65	83.8±2.59	79.9±3.08
F	21.6±1.66	29.8±1.91	44.7±1.80	54.7±0.75

Table 13: Percentage of drug release versus time at test 4 of levetiracetam extended-release monograph in USP 39.

Time(h)	Release(%)
1	22-42
2	39-59
4	62-82
8	NLT 80

The context of Test 4 has described in the method section. According to the dissolution results formulation F successfully passed test 4 criteria, hence chosen for Assay study.

Assay study:

Assay studies for levetiracetam extended-release tablet were carried out according to USP 39 (not less than 90% and not more than 110). According to this test for X formulation, the results showed acceptable drug content (96.58%).

Mechanism of drug release:

Diffusion is one of the factors in the transfer mechanism that might control the drug release in drug delivery systems. Furthermore, in monolithic systems, the release depends on parameters such as device geometry and under the specific condition, the drug release might be followed by Higuchi model. Some hydrophilic polymers such as HPMC K4M show swelling characteristics once they contact with the aqueous medium. Regarding swelling of polymer, the length of the diffusion pathway will increase leading to a significant decrease in drug release rate. Considering the type of polymer that could affect the diffusion pathway and increase in drug mobility, as well as the solubility of the drug, it seems to have either decreasing or increasing effect on the rate of release comparing to non-relaxation polymers such as a waxy matrix. The drug release through waxy matrix depends on the solubility of active agent and erosion mechanism. Generally, in this system, it seems that multiple mechanisms might be involved in drug release through matrix levetiracetam tablets (Siepmann, et al.,1999).

In order to find the kinetic behavior of the extended-release levetiracetam tablet, the release data of the optimized formulation F was fitted to the zero-order, first-order, and Higuchi models. The regression values of each model are shown in Table 14.

Table 14: The regression value of formulation F

Formulation F	Higuchi model	First-order	Zero-order
Regression value	0.9873	0.8335	0.9723

It may be concluded that the drug release for levetiracetam tablet is the best fit in the Higuchi model.

Conclusion

This study demonstrated that HPMC K4M itself wasn't able to extend the release of levetiracetam up to 12 hours according to USP monograph. The possible reason for getting this type of result is due to insufficient amount of retarding agent or percentage of polymer that is not able to sustain the release of the active ingredient. Thus, in contrast to another experiment, we evaluate the interaction of both hydrophilic and hydrophobic matrix in order to achieve optimized formulation.

Considering that the ultimate goal of this study to achieve the formulation with release over 8 hours by the formulation abc did not occur and in order to achieve extended release formulation, a certain amount of xanthan gum alone, and in combination with cetyl alcohol were added to formulation abc. Then, the formulations x and f were obtained respectively (Table 4). In these formulations, in order to optimize the final formula, rely on the knowledge of sustained release polymers, the percent of the HPMC increased from 25% to 30%, and the overall weight of the tablet also modified. According to the results and obtained data in physiochemical tests such as hardness, friability, weight variation, assay and drug release, formulation F contains 30% HPMC K4M, 5% PVP, 2% xanthan gum and 2% cetyl alcohol was selected as modified and superior formulation. As a result, it could be concluded that adding cetyl alcohol to formulation X to modify drug release and achieve release pattern close to Keppra XR as the brand might successfully authorize.

Xanthan gum, a high molecular weight polysaccharide, plays a role as a hydrophilic polymer, which makes release time-dependent and retards the drug release. However, cetyl alcohol as a waxy matrix presents significant changes to the F formulation and has a tremendous effect on reducing drug release.

Cetyl alcohol was possibly a significant effect on prevents the rapid release of active ingredient in the early hours of intake (Gali 2006). In addition, it could expand the length of the diffusion pathway due to matrix swelling (HPMC) in controlling drug release. It is also effective as a hydrophobic matrix and can amplify the viscosity of the matrix system. Using a combination of the hydrophilic and hydrophobic matrix, providing modification of polymer-polymer and polymer-solvent interaction would be the result of drug release from the matrix.

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