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Development and Evaluation of Sustained Release Tablet Formulations of Venlafaxine Hydrochloride

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ABSTRACT

Aim: Depression is a mental disorder which affects more than 250 million people independently of their age. Venlafaxine is an antidepressant drug and used also for the treatment of panic attack and anxiety with fewer side effects than older antidepressant therapeutics. However, venlafaxine hydrochloride (VH) has a short half-life which requires three times dosing daily to maintain sufficient plasma drug concentration. The aim of this study is to develop sustained release VH tablets to be given once a day.

Material and Methods: Polyethylene oxide, sodium alginate, hydroxypropyl methyl cellulose, guar gum and polyacrylic acid were used as controlled release agent. Tablets were prepared by direct compression method. Powder (angle of repose, flow rate, Carr index and Hausner ratio) and tablet (weight uniformity, hardness, friability,) characterizations were evaluated. *In vitro* release studies were carried out for 24 h and drug release kinetics were evaluated using different models.

Results: All formulations showed suitable Carr index and Hausner ratio except the formulation prepared with guar gum. The tablets which had been manufactured via direct compression method were compared to the commercial tablet. Sustained release of VH was observed for all formulations. Based on the *in-vitro* dissolution studies, the drug release from F1 formulation which comprising HPMC and Carbopol polymers was found similar as compared to the commercial tablets.

Conclusion: Directly compressed VH tablets could be a preferable alternative to the commercial tablets on behalf of patient compliance and fewer manufacturing steps compared to other production methods.

Keywords: Oral tablet; venlafaxine hydrochloride; sustained release; direct compression; depression treatment

Venlafaksin Hidroklorürün Uzatılmış Salım Yapan Tablet Formülasyonlarının Geliştirilmesi ve Değerlendirilmesi

ÖZ

Amaç: Depresyon, 250 milyondan fazla insanı yaştan bağımsız olarak etkileyen mental bozukluktur. Venlafaksin, antidepresan bir ilaçtır ve eski antidepresan ilaçlara göre daha az yan etki ile panik atak ve anksiyete tedavisinde kullanılır. Bununla birlikte, venlafaksin hidroklorür (VH), yeterli plazma-ilaç konsantrasyonunu sağlamak için günde üç kez dozlama gerektiren kısa yarı ömre sahiptir. Bu çalışmanın amacı, günde bir kez verilecek uzun süreli salım yapan VH tabletleri geliştirmektir.

Gereç ve Yöntemler: Kontrollü salım ajanı olarak polietilen oksit, sodyum aljinat, hidroksipropil metil selüloz, guar zamkı ve poliakrilik asit kullanıldı. Tabletler doğrudan basım yöntemi ile hazırlandı. Toz (yığın açısı, akış hızı, Carr indeksi ve Hausner oranı) ve tablet (ağırlık homojenliği, sertlik, friabilite) karakterizasyonları değerlendirildi. 24 saat boyunca *in vitro* salım çalışmaları yapıldı ve ilaç salım kinetikleri farklı modeller kullanılarak değerlendirildi.

Bulgular: Guar zamkı ile hazırlanan formülasyon dışında tüm formülasyonlar uygun Carr indeksi ve Hausner oranı gösterdi. Doğrudan basım yöntemi ile üretilen tabletler, ticari tablet ile karşılaştırıldı. Tüm formülasyonlar için uzun süreli VH salımı gözlendi.

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In vitro salım hızı test sonuçlarına göre, HPMC ve Carbopol polimerlerini içeren F1 formülasyonundan ilaç salımı, ticari tabletlere kıyasla benzer bulunmuştur.
Sonuç: Doğrudan basılmış VH tabletler, hasta uyumu ve diğer üretim yöntemlerine kıyasla daha az üretim aşaması ile ticari tabletlere tercih edilebilir bir alternatif olabilir.
Anahtar Kelimeler: Oral tablet; venlafaksin hidroklorür; uzatılmış salım; doğrudan basım; depresyon tedavisi

INTRODUCTION

Depression, which affects approximately 250 million people worldwide, is one of the most common mental illness. While 20% of the patients recover completely, the remaining 80% suffer from depression that recurs at least once in their lifetime (1). Depression, which has prevalence of 1.5% to 19%, causes serious social problems with high treatment costs and high mortality and morbidity rates when not properly treated (2). Among the depressive disorders, the most researched disorder is major depressive disorder (MDD). Although major depression is seen in different populations with different frequencies, the frequency of its incidence varies between 3.5-6.5% (3). It has been suggested that the main reason for this difference is biological, hormonal differences and social roles (4). The most important cause of the MDD, which is not fully understood, is thought to be genetic and environmental factors.

Antidepressant drugs are used in the treatment of depression. Antidepressant drugs act as enzyme or receptor inhibitors and reuptake blockers. Serotonergic and noradrenaline reuptake inhibitors are frequently preferred for treatment among the groups. Venlafaxine hydrochloride (VH), which is a serotoninergic and noradrenergic reuptake inhibitor, has a more effective and less side effect than selective serotonin inhibitors. VH mechanism of action is by blocking presynaptic transporters of serotonin, noradrenaline. VH also acts as a dopamine reuptake inhibitor (5). Increasing the intracellular concentration of these monoamines caused to increase the neurotransmitter activity in the central nervous system. (6). VH is a highly water soluble drug with 313.87 molecular weight (7). VH is a Biopharmaceutical Classification System (BCS) Class 1 drug, and it shows good linear pharmacokinetics (8). The half-life of VH following immediate release tablets is around 5±2 h, and immediate release VH tablets must be given two or three times a day to maintain adequate plasma drug concentration (9). Modified drug formulations offers the advantage of the adjusting the release profile compared to conventional formulations. There are some types of modified release dosage forms such as prolonged (sustained or extended) release, delayed release and pulsatile release dosage forms (European Pharmacopeia 6.0). In the pharmaceutical market, VH is available in immediate release tablets, sustained release tablets, sustained release micropellet capsules and oral solution. Extended release formulations are often used for better therapeutic efficacy by reducing the number of doses in drug therapy, increasing patient compliance and reducing fluctuations in plasma levels (7). Different dosage forms (nanoparticles, pellets, alginate beads, hydrogels, dissolving tablets) have been developed for venlafaxine administration (8, 10–13).

Selection of different tablet fabrication methods are depending on the dosage and physical properties of the active substance. Direct compression is the most frequently used method in the pharmaceutical industry, in the fact that it is more economical, faster and easier to apply good manufacturing practices than wet granulation and dry granulation (14). For these reasons, this method was used in this study for preparing tablet formulations. Natural and semi-synthetic gums such as guar gum, xanthan gum, cellulose derivatives such as hydroxymethyl cellulose (HPMC), ethyl cellulose (EC), hydroxy propyl cellulose (HPC) are often used to prolong or delay the release of the active ingredient. Guar gum, a glycoside-linked polysaccharide derivative, is a hydrophilic polymer and has been used for controlled release of many drugs by gelling (15). HPMC provides drug release independent from pH due to its nonionic structure. Its high molecular weight form more viscous gel and cause slower drug release. Drug release is controlled by matrix swelling and polymer dissolution (16). Carbopol is a highly crosslinked and produces high viscosity gels. It has ability to absorb water quickly and form a gel which enables it to be used in controlled release systems**.** There are studies in which various tablet formulations are prepared with these substances for controlled release (17–20). There are different commercially available extended release formulations of venlafaxine such as osmotic-controlled release tablets (contains mainly mannitol, povidone, microcrystalline cellulose, polyethylene glycol), micropellet capsules (contains mainly microcrystalline cellulose, hydroxypropylmethylcellulose, ethylcellulose) and sustained release tablets (contains mainly contains microcrystalline cellulose, mannitol, povidone K-90 and macrogol 400) (21). The aim of present study was to develop VH sustained release tablets with various polymers to be given once a day which have dissolution profile similar to commercial VH sustained release tablets. HPMC K100M, Carbopol 974P, PEO, guar gum and alginate LF240 were used to modify the drug release and ensure that most of the drug is released in gastrointestinal residence time. Powder mixtures and tablets were examined for various parameters and *in vitro* release of VH from formulations was compared with a commercial tablet containing VH equivalent to 75 mg venlafaxine.

MATERIAL AND METHODS

Materials

VH was provided by Dr. Reddy's Laboratories, India. Avicel PH-102 and alginate (Protanal LF240) was purchased from FMC Biopolymer, Switzerland. Aerosil 200 was purchased from Evonik, Germany. Magnesium Stearate was obtained from Riedel-de Haen Company, Germany. Carbopol 974P was purchased from Noveon, Parkoteks Chemical, Turkey. Hydroxypropyl methylcellulose (HPMC K100M) and polyethylene oxide (PEO) were kindly donated by Colorcon, England. Guar gum (viscosity of 1% w/v aqueous dispersion, 4000 cPs) was obtained from Sigma (Germany). Commercial sustained release venlafaxine formulation was purchased from pharmaceutical market. All other chemicals were of analytical grade.

Preparation of Formulations

In this study, four different sustained release tablet formulations with same weighted tablets were developed to determine optimum formulation using different polymers which are Carbopol 974P, HPMC K100M, PEO (Polyox WSR303), guar gum (Supercol NF) and alginate (Protanal LF240). The polymer concentration was fixed to 40 % (w/w) according to previous studies (22). Because of the commercial tablet contains 75 mg venlafaxine, our tablet formulations contain 84.85 mg (VH) which is equivalent to 75 mg venlafaxine free base. The remaining 35% of formulation consists of filler (microcrystalline cellulose), glidant (Aerosil) and lubricant (magnesium stearate) (Table 1). Round shaped VH tablets were prepared by direct compression (Erweka, Germany). First, all ingredients were sieved separately and then geometrically mixed except Aerosil and magnesium stearate for 20 minutes. After that, Aerosil and magnesium stearate were added to the powder mixture, mixed 10 minutes more and then compressed into nearly 350 mg tablets, using 10 mm, rounded-flat punch and die set.

Table 1. Composition of tablet formulations

Formulation Code / Ingredients (mg)	**F1**	**F2**	**F3**	**F4**
VH	84.85	84.85	84.85	84.85
Avicel PH-102	115	115	115	115
Aerosil200	5	5	5	5
Magnesium Stearate	5	5	5	5
Carbopol 974P	20	-	-	-
HPMC K100M	120	-	-	-
PEO (PolyoxWSR303)	-	140	-	-
Guar Gum (Supercol NF)	-	-	140	-
Alginate (Protanal LF240)	-	-	-	140

Angle of repose

The angle of repose values of powder mixtures were determined by the funnel method (23). The funnel height was adjusted to be at approximately 2 cm above from the top of the powder. The sample was flowed through from the funnel to form symmetrical powder cone. The diameter and height of the powder cone were measured and the angle of repose was calculated. The experiment was repeated three times.

Flow rate

The sample of specified weight powder mixture was flowed through from the funnel in the same time flowing time is monitored. The flow rate is usually measured in mass per flowing time. The experiment was repeated three times.

Carr index and Hausner ratio

CI and HR are simple, fast, and popular methods of measuring powder flow characteristics. These two parameters are directly affected by powders' bulk density, size, shape, surface area, moisture content, and cohesiveness of materials. HR and CI are described as the flowability of a powder and the compressibility of a powder, respectively. The unsettled apparent volume (V_0) was determined by filling the known weights powder samples into a volumetric the cylinder for each powder. After the initial volume was noted, cylinder was tapped into a hard surface from a height of 2.5 cm. Tapping was continued until the fixed volume was observed and the final tapped volume (V_f) was noted. The CI and the HR are calculated as follows:

$$Carr's\ Index = 100 \times \frac{V_0 - V_f}{V_0} = 100 \times \frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}}$$

$$Hausner\ Ratio = \frac{V_0}{V_f} = \frac{\rho_{tapped}}{\rho_{bulk}}$$

ρbulk, ρtapped are bulk density and tapped density, respectively.

Weight uniformity

The tablets were randomly chosen and weighted individually using an electronic balance. The average weight and standard deviation were also calculated. Then weight variation was evaluated in accordance with United States Pharmacopeia 36.

Hardness

Tablet hardness which is the force required to break tablets in a specific plane was determined using tablet hardness tester (CGS HighSpeed Hardness Tester HDT, 1V-2, Germany). The tablets were chosen randomly from each formulation and then tested. The average value was recorded.

Friability

20 tablets were randomly taken from each formulation, accurately weighted and then tablets were placed in the friabilitor (PTF 20E Pharma Test, Germany). The speed was adjusted to 25 rpm for 4 min. At the end of the experiment, tablets were dedusted and reweighted. Then, the percentage weight loss was calculated. According to the pharmacopeia standards, friability of tablets are considered acceptable if the weight loss is not more than 1% (24). Friability as a percent of weight loss was calculated according to the equation:

$$\%\ \text{Weight loss} = \frac{W1 - W2}{W1} x100$$

Where, W1 = weight of tablets before testing, while W2 = weight of tablets after testing.

***In vitro* drug release study**

In vitro drug release studies were performed by using the basket method dissolution tester (Varian VK 7000 Dissolution Apparatus, USA). Six tablets were chosen randomly from each formulation and marketed product and then the tablets were placed inside the baskets. 0.1N HCl (pH 1.2) and phosphate (pH 6.8) buffers were used as dissolution media. The HCl and phosphate buffer mimic the stomach and small intestine conditions, respectively. The temperature was maintained at 37±0.5°C and stirring rate at 100 rpm. At time intervals of 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 h, sample (5 mL) of the solution was withdrawn by volumetric pipette and replaced with an equal volume of fresh dissolution media equilibrated at 37±0.5 °C. First, 0.1N HCl buffer was used as dissolution media for the first 2 h. After 2 h, dissolution media was changed with phosphate buffer. The samples which were collected at predetermined time intervals were analyzed by UV-Vis Spectrophotometer (Cary 60 UV-Vis, Agilent Technologies, US) at 225 nm

for determination of amount of VH. This method was developed and validated for pH 1.2 HCl and pH 6.8 phosphate buffers. All experiments were carried out in triplicate.

Kinetic Analysis of the Release Data

Dissolution data of reference product and formulations were evaluated by model-independent and also model-dependent methods with DDSolver®. Difference factor (f1) and similarity factor (f2) were used for evaluating model- independent method. f1 and f2 factor were calculated as follows:

$$f_1 = [\sum_{t=1}^{n}|R_t - T_t| / \sum_{t=1}^{n} R_t] \times 100$$

$$f_2 = 50 \cdot \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

Rt and, Tt are the percentage dissolved of the reference and test profile, respectively, t is the time point; n is the number of sampling points.

The model dependent method is used to determine drug release mechanisms using DDSolver®. Different mathematical models fitting the dissolution profiles are described. In this study, 6 different models were used from DDSolver®'s library. The adjusted coefficient of determination (r^2_{adj}), Akaike information criterion (AIC) and model selection criterion (MSC) were used to determine release model. The equations of these models were presented at Table 2. *In vitro* dissolution data of reference product and all formulations of VH were calculated and also modelled with using DDSolver® program. According to these criteria, as the r^2_{adj} approaches 1, as the AIC decreases and as the MSC increases, the fitness of the mathematical model with the release profiles increases (25). Different kinetic models were used to found the most suitable models for all formulations.

Table 2. Kinetic models used for analysis of drug release data from dosage forms

No	Model Name	Model
1	Zero Order	$F=k_0t$
2	First Order	$\ln (1-F) = - k_ft$
3	Higuchi	$F = k_h\sqrt{t}$
4	Korsmeyer-Peppas	$Mt/M = k_tn$
5	Hixson-Crowell	$1 - \sqrt[s]{1-F} = k_{1/2}t$
6	Weibull	$\ln[-\ln(1-F)]= - \beta\ln td + \beta\ln t$

RESULTS

Micromeritic properties of powders were evaluated through Pharmacopeial methods. All characterization parameters of powders before compression are shown in Table 3. The flow properties of powders were estimated by Hausner ratio (HR) and Carr index (CI). The CI values were found to be good flow ability for powders except for the F3 formulation. The HR shows the flow properties of the powder and is measured by the ratio of its tapped density to the bulk density. If HR is below 1.25, it is considered as good flow and if >1.25 it is considered as bad flow. Except F3 formulation, the values were all in range and have good flow properties. The angle of repose is defined as the maximum angle between the surface of the powder stack and the horizontal plane. For all formulation batches, angle of repose values were found in the range of 28.8±1.91°-56.75±7.96°. The angle of repose is considered as good flow up to 35°. The powder used only for F4 formulation using alginate showed extremely poor flow rate. Interestingly, there was no problem with tablet compressing.

Table 3. Different characteristics of powder mixtures

	F1	**F2**	**F3**	**F4**
Angle of Repose (°)	28.9±3.2	28.8±1.9	32.1±5.6	56.8±8.0
Flow Rate (g/s)	35.1±7.1	4.3±0.3	3.8±1.3	33.0±3.3
Carr Index (%)	17.5	13.2	21.4	16.7
Hausner Ratio	1.2	1.15	1.3	1.2

The thickness, hardness, friability, and weight variation of the tablet formulations are shown in Table 4. Weight variation of all formulations ranged from 0.4 to 1.9 % and the thickness of all formulations ranged from 4.1±0 to 4.407±0.216 mm. Tablet hardness values of formulations in the range of 4.38±0.37 to 14.57±2.57 kg/cm^2 were determined.

Table 4. Physical properties of formulations

Formulation Code	**Weight variation (%)**	**Thickness (mm)**	**Hardness (kg/cm^2)**	**Friability (%)**
F1	0.9	4.41±0.21	12.05±3.65	0.211
F2	1.7	4.21±0.08	14.57±2.57	0.077
F3	0.4	4.36±0.11	4.38±0.37	0.764
F4	1.9	4.10±0	5.59±0.99	0.664

The release profiles of formulations were shown in Fig 1. All formulations provided sustained release of VH for 24 hours as aimed. After the release study, f1 and f2 factors were calculated for all formulation with reference commercial tablets and the f1 and f2 factors were found as 15.0 and 54.4 for F1, 35.0 and 39.0 for F2, 44.0 and 32.0 for F3 and 45.0 and 33.0 for F4 formulations, respectively. For curves to be considered similar, f1 values should be close to 0, and f2 values should be close to 100. Therefore, f1 values between 0-15 and f2 between 50-100 are sufficient for similarity.

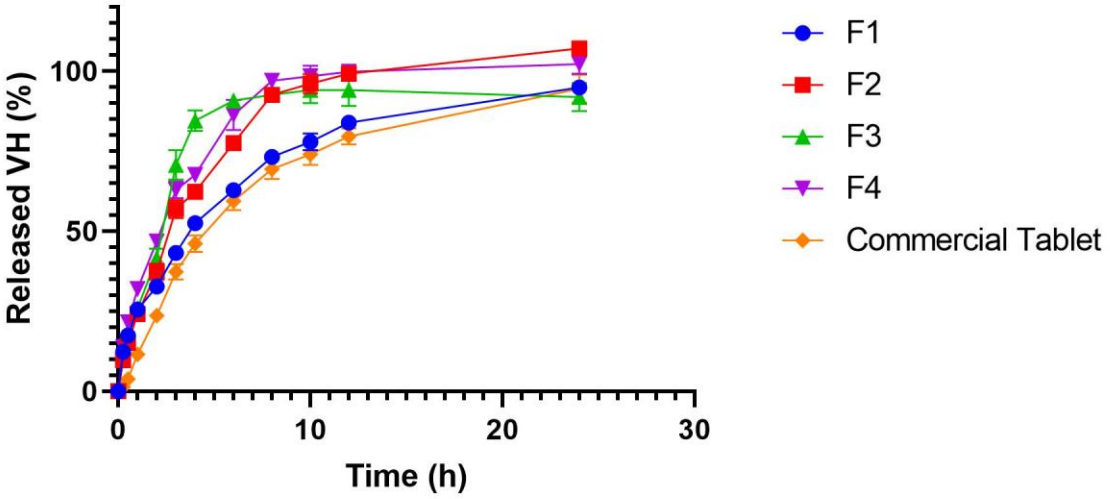

Figure 1. *In vitro* release study of VH tablet formulations and commercial tablet at 37 °C (vertical bars represent the SD, results are shown as mean ± S.D.; n=6)

After *in vitro* drug release studies, kinetic models were found for tablet formulations. For this purpose DDSolver Software was used and r^2_{adj}, AIC and MSC were chosen as criteria (Table 5). According to the values First-Order kinetic model was found to the most suitable model for F2, F3 and F4 formulations. Weibull kinetic model was found to the most suitable model for F1 formulation and commercial tablet.

Table 5. Kinetic models for formulations. Adjusted coefficient of determination (r^2_{adj}), Akaike information criterion (AIC) and model selection criteria (MSC) for different mathematical models obtained from experimental data via DDsolver®.

Mathematical Models	**Compliance Criteria**	**Formulations**				
		F1	**F2**	**F3**	**F4**	**Commercial Tablet**
Zero Order	**r^2_{adj}**	0.16	0.16	-0.49	0.30	0.57
	AIC	99.01	104.06	109.21	107.42	94.57
	MSC	-0.01	-0.01	-0.58	-0.45	0.66
First Order	**r^2_{adj}**	0.94	0.99	0.95	0.99	0.99
	AIC	69.85	57.71	72.07	57.74	56.25
	MSC	2.64	4.21	2.80	4.07	4.15
Higuchi	**r^2_{adj}**	0.93	0.89	0.65	0.79	0.94
	AIC	71.02	81.50	93.46	87.44	73.60
	MSC	2.53	2.05	0.85	1.37	2.57
Korsmeyer-Peppas	**r^2_{adj}**	0.94	0.80	0.70	0.84	0.33
	AIC	71.31	89.15	92.41	85.37	100.32
	MSC	2.51	1.35	0.95	1.56	0.14
Hixson-Crowell	**r^2_{adj}**	0.92	0.96	0.79	0.85	0.97
	AIC	72.58	70.06	87.43	83.31	65.05
	MSC	2.39	3.08	1.40	1.74	3.35
Weibull	**r^2_{adj}**	0.98	0.97	0.94	0.95	0.99
	AIC	59.38	69.37	76.22	72.56	56.23
	MSC	3.59	3.15	2.42	2.72	4.15

DISCUSSION

Suitable powder flow properties and compressibility index are essential for direct compressing, so excipients should have good flow characteristics and compressibility (26). Compressibility is used to measure the free flow of the powder (27). The type and amount of polymers in the formulation affect the flow and compressibility properties of the formulation. Therefore, the flow rate, angle of repose, CI and HI differed in formulations. The best flow rate was observed for F1 formulation, which contains HPMC and Carbopol (Table 3). Similar to our results, Anisuzzman et al. reported that the flow and compressibility values of the powders improved by increasing the amount of HPMC and Carbopol in the formulations. In addition, when the formulations containing the same amount of HPMC and Carbopol are compared, it was seen that the formulations containing Carbopol have better flow and compressibility compared to HPMC (28). The angle of repose values of the formulations (F1 and F2) prepared with HPMC/Carbopol and PEO were found to be similar and less than the other polymers. F4 formulation which contains alginate had the highest angle of repose value. Angle of repose value >40 indicates that the flow of powders is difficult. Yang et al reported that various physical properties of PEOs at different molecular weights. Powders showed similar angle of repose and good flow characteristics (29) HI and CI values were found to be high in formulations prepared with guar gum. The increase in the values of these parameters indicates that the flow properties of the powders become poor. The highest values were found in the formulation prepared with PEO. From these results, it was concluded that F1 formulation had better flow properties for compressing tablets compared to other formulations.

Thickness may vary depending on the compression forces, flowability or interaction between the polymers in the formulation and other ingredients. The thickness values of the formulations were very close to each other however thickness value of the F1 formulation using HPMC and Carbopol was found higher than other formulations. The hardness values of the tablets prepared with PEO and HPMC/Carbopol were found to be the higher compared to other formulations. As expected F1 and F2 formulations showed lower friability than F3 and F4 formulations. Formulations prepared with PEO were found to be more resistant to breakage and friability than other polymers. In a study, venlafaxine matrix tablets compressed by using 8 mm round punches using different polymers. The tablet formulations were developed by using HPMC K100M and microcrystalline cellulose, and the hardness (8 kg/cm^2) and thickness (~2 mm) values were found lower than our F1 formulation prepared with HPMC K100M and Carbopol974 (30). Tablet hardness can also be expressed by friability. In general, the tablets with low hardness values have higher friability compared to tablets with high hardness values. All formulations of friability values which were found it ranges from 0.077 to 0.764 were seen convenient because of, the tablet, which loses less than 1% of its weight is considered acceptable according to pharmacopeia limits.

In vitro release studies are essential studies to compare formulations prepared and commercial product. Sustained release of VH was observed for all hydrophilic matrix tablet formulations (Figure 1). When a hydrophilic matrix tablet comes into contact with water, a layer of viscous gel is formed consisting of polymer chains entangled physically, and the polymer chains are released into the release medium from this layer (31,32). The release rate and swelling properties of the tablets were shown to depend on the amount, chemical composition, molecular weight of the polymers (32). Based on the *in-vitro* dissolution studies, the drug release from F1 was found similar as compared to the commercial tablets. F1 formulation contains HPMC and Carbopol as matrix agent. Carbopol 974P is a suitable polymer of controlled release systems due to its easily water absorption and swelling properties. In tablet formulations, increased Carbopol amount reduces drug release rate. HPMC is a generally preferred polymer for sustained release, or sustained release tablet formulations with the advantage of to achieve drug release independently of the processing parameters (33). Some studies showed the effectiveness of HPMC and Carbopol for providing controlled drug release profile (34). When the drug release amount of two different formulations containing HPMC and Carbopol in the same amount was compared, it was observed that Carbopol decreased drug release compared to HPMC (28). In addition, it has been proven by the use of Carbopol and HPMC in formulations that it reduces the dose dumping effect and is suitable for ER formulations (35). Considering our results, both f1 and f2 values prove to similarity of the dissolution profile of F1 formulation to the commercial tablet formulation. PEO, which is often used to prepare for sustained release dosage forms, was used to prepare the F2 formulation, and drug release is accomplished by polymer swelling and erosion and diffusion of drug molecules (36). Using different molecular weight PEO, dissolution and water swelling rates, viscoelastic properties and biological adhesion of the gel can be adjusted (37-39). F2 formulation released VH faster than commercial tablet with a f2 value of less than 50. When exposed to cold or hot water, guar gum hydrates and forms a viscous gel layer. Therefore, it is used as an agent to release the active substance in tablet formulations (40). Tugcu-Demiroz et al. found that tablets prepared with high viscosity guar gum swell more than tablets prepared with low viscosity guar gum (18). When the guar gum-containing tablets come into contact with the dissolution medium, the polymer hydrates and swells, and a sudden release of active substance emerges from the tablet surface without forming gel (41). Similarly, F3 formulation containing guar gum, released complete VH in 8 hours. Therefore, f1 and f2 values of F3 formulation were not suitable for similarity. Hydration of alginate with media provide to the formation of gelatinous mass which act as retardant material for the drug to diffuse out (42,43). Directly compressed tablets containing alginates showed sustained release drug-delivery system owing to this property (44). F4 formulation released a rapid VH release compared to commercial tablet and other formulations. This may be due to the sodium alginate type or amount.

Although drug release from formulations F2, F3 and F4 occurred with the first-order release, the best fitting was obtained with the Weibull model for F1 formulation. Drug release profile of commercial tablet fitted both first order and Weibull model. In the Weibull model, ß constants (ß <0.75 Fickian release, 0.75 <ß <1 combined release mechanism and ß> 1 complex release mechanism) define the active substance release from the dosage forms. The ß constant of F1 formulation and commercial tablet were found as 0.632 and 1.072, respectively. According to the ß values, while the drug release from F1 formulation was through the Fickian release, the drug release from commercial tablet was through the complex release mechanism. These differences of release kinetics are thought to be due to the difference in the choice of excipients used for the formulations (45). k values of F2, F3, and F4 formulations were found as 0.257, 0.449, 0.345, respectively. According to k values, the release of the drug from the formulations was through at different speeds (46).

CONCLUSION

In this study, four different VH tablet formulations for sustained release of VH prepared and characterized. HPMC and Carbopol are generally preferred polymers for controlled release effect by forming a viscous gel layer on the matrix surface when in contact with aqueous media. F1 formulation containing HPMC and Carbopol as controlled release agent showed that VH sustained-release tablets which were similar to the commercial tablet can be manufactured easily by direct compression method owing to good characteristics of the powder properties. It can be concluded that F1 formulation could prevent the disadvantage of short half-life of venlafaxine for sustained release. Directly compressed VH tablets could be a preferable alternative to the commercial sustained release formulations on behalf of patient compliance and fewer manufacturing steps compared to other production methods.

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