Available online on 15.06.2024 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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Research Article

Formulation and evaluation of sustained release floating tablets of venlafaxine using natural polymers

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Article Info:

Article History:

Received 11 March 2024
Reviewed 23 April 2024
Accepted 18 May 2024
Published 15 June 2024

Cite this article as:

Yadav NK, Gupta N, Jain UK, Formulation and evaluation of sustained release floating tablets of venlafaxine using natural polymers, Journal of Drug Delivery and Therapeutics. 2024; 14(6):125-130

DOI: http://dx.doi.org/10.22270/jddt.v14i6.6611

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Abstract

Over the past three decades, oral controlled-release dosage forms have been developed due to their therapeutic advantages, such as ease of administration, patient compliance, and flexibility in formulation. However, this approach has faced physiological difficulties, such as the inability to contain and position the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying and motility. Venlafaxine is an antidepressant and a serotonin and norepinephrine reuptake inhibitor (SNRI). Its active metabolite, desvenlafaxine, works by blocking the reuptake of serotonin and norepinephrine, which are key neurotransmitters in mood regulation. Gastroretentive dosage forms can stay in the gastric region for several hours and significantly prolong the gastric residence time of drugs. Natural materials have been extensively used in drug delivery because they are readily available, cost-effective, eco-friendly, capable of many chemical modifications, potentially degradable, and compatible due to their natural origin.

Keywords: Sustained Release Floating Tablets, Venlafaxine,

INTRODUCTION:

The oral route of drug administration is the most convenient and commonly used method of drug delivery. These difficulties have prompted researchers to design a drug delivery system that can stay in the stomach for prolonged and predictable periods. Attempts are being made to develop a drug delivery system that can provide therapeutically effective plasma drug concentration for a longer period[1], thereby reducing the dosing frequency and minimizing fluctuation in plasma drug concentration at a steady state by delivering the drug in a controlled and reproducible manner[2]. Dosage forms that can be retained in the stomach are called GRDDs. GRDDSs can improve the controlled delivery of drugs with an absorption window by continuously releasing the drug for a prolonged period before it reaches its absorption site. Prolonging the gastric retention of the drugs is sometimes desirable for achieving therapeutic benefits of a drug that are absorbed from the proximal part of the GIT (gastrointestinal tract) or those are less soluble in or are degraded by alkaline pH or encounter at the lower part of the GIT. GRDDS are beneficial for such drugs by improving their[3]. A floating dosage form is a feasible approach, especially for drugs that have limited absorption sites in the upper small intestine. The controlled, slow delivery of the drug to the stomach provides sufficient local therapeutic levels and limits systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site-directed delivery system may also reduce the dosing frequency. Multiple unit floating delivery systems, like floating microspheres or microcapsules, can be distributed widely throughout the GI tract, providing the possibility of achieving a longer-lasting and more reliable release of drugs[4]. A floating drug delivery system is also called a hydrodynamically balanced system (HBS). Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. This delivery system is divided into no effervescent and effervescent (gas-generating system). Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery[5]. Venlafaxine is a selective serotonin and norepinephrine reuptake inhibitor (SNRI) used for the treatment of major depression, generalized or social anxiety disorder, and panic disorder. Venlafaxine is an antidepressant and a serotonin and norepinephrine reuptake inhibitor (SNRI). Venlafaxine has been used as a first-line treatment for MDD, GAD, social anxiety disorder, and panic disorder in Canada for many years. It was also considered a second-line treatment for obsessive-compulsive disorder (OCD). Venlafaxine was also investigated in off-label uses for the prophylaxis of migraine headaches, for the reduction of vasomotor symptoms associated with menopause, and for the management of neuropathic pain

(although there is only minimal evidence of efficacy for this condition). The exact mechanism of action of venlafaxine in the treatment of various psychiatric conditions has not been fully elucidated; however, it is understood that venlafaxine and its active metabolite O-desmethyl venlafaxine (ODV) potently and selectively inhibits the reuptake of both serotonin and norepinephrine at the presynaptic terminal. Venlafaxine is well absorbed after oral administration and is used to treat depression. Venlafaxine extended-release (long-acting) capsules are also used to treat generalized anxiety disorder (GAD; excessive worrying that is difficult to control), social anxiety disorder (extreme fear of interacting with others or performing in front of others that interferes with normal life), and panic disorder (sudden, unexpected attacks of extreme fear and worry about these attacks). Venlafaxine is in a class of medications called selective serotonin and norepinephrine reuptake inhibitors (SNRIs). It works by increasing the amounts of serotonin and norepinephrine, natural substances in the brain that help maintain mental balance. This investigation aims to focus on the development and evaluation of floating gastro retentive tablets of venlafaxine using natural polymers[6-7].

MATERIAL AND METHODS

Determination of maximum wavelength (λmax): The drug's maximum wavelength (λmax) is determined by a 20 µg/ml standard solution of venlafaxine. The prepared drug solution was scanned at 200 – 400 nm by using a UV spectrophotometer (Shimadzu 1800). Accurately weighed 50 mg of drug sample was soluble in 50 ml of simulated gastric fluid containing 0.1 N Hcl as simulated gastric fluid pH1.2 buffer in 50 ml volumetric flask. The mixture was sonicated with the help of sonication in a bath sonicator for 20 min to get 1000 µg/ml of drug solution as stock-I solution. Withdrawn 1 ml of prepared solution was again diluted up to 100 ml with the same solvent separately with sonication for 20 min to obtain 10 µg / ml solution. The spectrum of these solutions was run in the 200 – 400 nm range in double beam UV spectrophotometer[8].

Determination of calibration curve: The standard solution of venlafaxine was subsequently diluted with 0.1 N HCl as simulated gastric fluid pH1.2 buffer to give 1000 µg/ml of solution. The dilutions were analyzed at 279 nm using the 0.1 N Hcl as blank Accurately weighed 50 mg of drug sample was soluble in 50 ml of simulated gastric fluid containing 0.1 N Hcl as simulated gastric fluid pH1.2 buffer in 50 ml volumetric flask. The mixture was sonicated with the help of sonication in a bath sonicator for 20 min to get 1000 µg/ml of drug solution as stock-I solution. From the above stock solution, 10 ml was again diluted with 100 ml of dissolution medium to obtain 100 µg / ml solution. The above-prepared solution was withdrawn as 0.2 ml, 0.4 ml, 0.6 ml up to 2.0 ml and diluted up to 10 ml with respective solvents in 10 ml volumetric flasks to get the concentration of 2 µg / ml, 4 µg / ml, 6 µg / ml, upto 20 µg / ml respectively. The absorbance of each solution was measured separately at 279 nm for 0.1 N Hcl as simulated gastric fluid pH1.2 buffer.

Preformulation studies for venlafaxine: The objective of the pre-formulation study is to develop an elegant, stable, safe, and effective dosage form by establishing compatibility with the other ingredients and establishing the physicochemical parameters of the new drug substance. The parameters are organoleptic identification, physical characteristics, particle size, micrometric properties, melting point determination, solubility determination, partition coefficient identification, and drug and excipient compatibility studies[9].

Formulation of Floating tablets: The tablets are prepared by direct compression method. The drug, guar gum, citric acid, sodium bicarbonate, HPMC, Magnesium stearate, and MCC are used for formulation. The tablets were prepared by direct compression method. All ingredients are sieved through #30 sieves. Magnesium stearate and MCC were sieved through #60 sieves before the use. All the materials were accurately weighed and blended using a hand blender and directly compressed on a manual single punch tablet compression machine into 90 mg tablets using flat-faced, round punches 4 mm in diameter[10].

Table 1: Various compositions of floating GRDDS tablets

F. Code	Drug (mg)	Guar gum (mg)	Citric acid (mg)	Sodium bicarbonate (mg)	HPMC (mg)	Magnesium stearate (mg)	Microcrystalline cellulose (mg)
VFT1	5	35	20	10	5	5	10
VFT2	5	30	25	10	5	5	10
VFT3	5	20	35	10	5	5	10
VFT4	5	35	20	7.5	7.5	5	10
VFT5	5	30	25	7.5	7.5	5	10
VFT6	5	20	35	7.5	7.5	5	10
VFT7	5	35	20	5	10	5	10
VFT8	5	30	25	5	10	5	10
VFT9	5	20	35	5	10	5	10

Characterization of floating tablets:

Flow properties: Flow properties depend on particle size, shape, porosity, and density of the bulk powder. The angle of repose, Carr's index, and Hausner's ratio were identified.

Weight variation: The average weight by more than the percent shown below and none deviates by more than twice that percent.

Hardness: The hardness of a tablet is defined as the force required to break a tablet in a diametric direction. A tablet was placed between two anvils. Hardness is thus the tablet crushing strength. Monsanto tester is used for hardness testing.

Friability: Weigh 10 tablets and place them in a friability chamber rotated at 25 rpm they are dropped at a distance of 6 inches and allowed to rotate for 100 revolutions. The difference in the weight is calculated and the weight loss should not be

more than 1%.

Thickness: The thickness of tablets was performed on 20 tablets from each formulation by using a Vernier caliper.

in-vitro buoyancy lag time: The Buoyancy lag time and total floating time were determined by immersion of tablets of different formulations in 0.1 N HCL at 37±.5°C.

Drug content estimation: Crushed 10 tablets from all batches were in pestle-mortar and weighed equivalent to 150 mg as the drug dose used for the single tablet was taken in a volumetric flask (100ml) and dissolved in 0.1 N HCL and filtered. This solution was analyzed in a UV spectrophotometer at λmax 263 nm.

***in-vitro* Dissolution study:** In vitro dissolution study was carried out using USP type II (basket type) apparatus with 0.1N HCl as a dissolution medium. The temperature was maintained at 37±0.5^{0}C with 50 rotations per minute. 1ml of aliquots were withdrawn at different time intervals and the same amount of fresh dissolution medium was replaced to maintain sink condition. The aliquots were analyzed for drug content at λ max 263 nm wavelength using a UV-spectrophotometer. The cumulative percentage of drug release was calculated and reported.

***in-vitro* drug release kinetic study:** The drug release and mechanism it follows to release can be determined by matching the data with various release models like Higuchi, Korsmeyer-Peppas, zero order, and first-order plots. The kinetics of drug release were studied in various kinetic models by plotting the data obtained from the in vitro drug release study. The zero-order kinetics was studied by plotting the cumulative amount of drug released versus time. Whereas first-order kinetics was studied by plotting the log cumulative percentage of the drug remain versus time. Higuchi's model of kinetics was studied by plotting the cumulative percentage of drugs released versus the square root of time. The mechanism of drug release from the formulation was confirmed by fitting the in vitro drug release data with the Korsmeyer–Peppas model by plotting log cumulative percentages of drug release versus log time. The release exponent 'n' and 'k' values were calculated from the Y-intercept and slope of a straight line respectively[11].

RESULTS AND DISCUSSION

Analytical method: It was scanned on a double-beam UV-visible spectrophotometer (Shimadzu 1800) between wavelength 200-400 nm and the UV spectrum was recorded. Venlafaxine's maximum Absorbance was found at 229 nm.

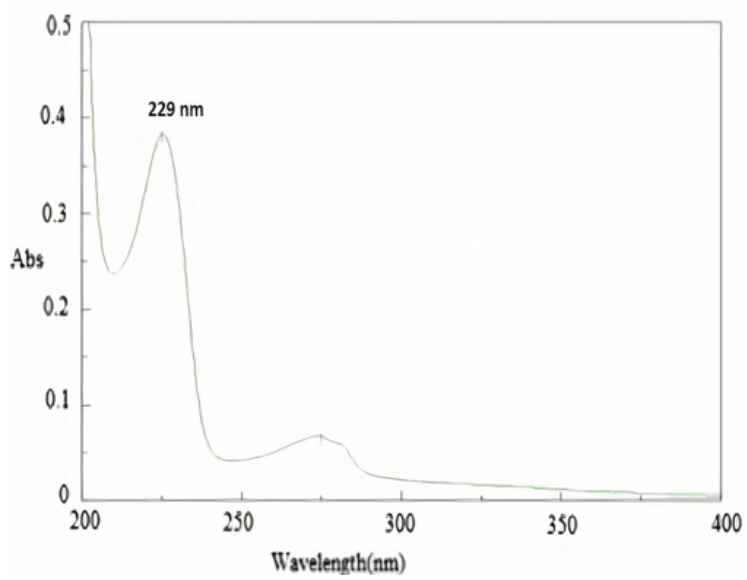

Figure 1: Maximum absorbance using UV-Spectrophotometer

Calibration Curve: The stock solution was made in the concentration range of 10-100 µg/ml. The standard graph of venlafaxine was plotted by standard samples absorbencies on the y-axis and their concentrations on the x-axis. The regression coefficient value was found to be 0.999

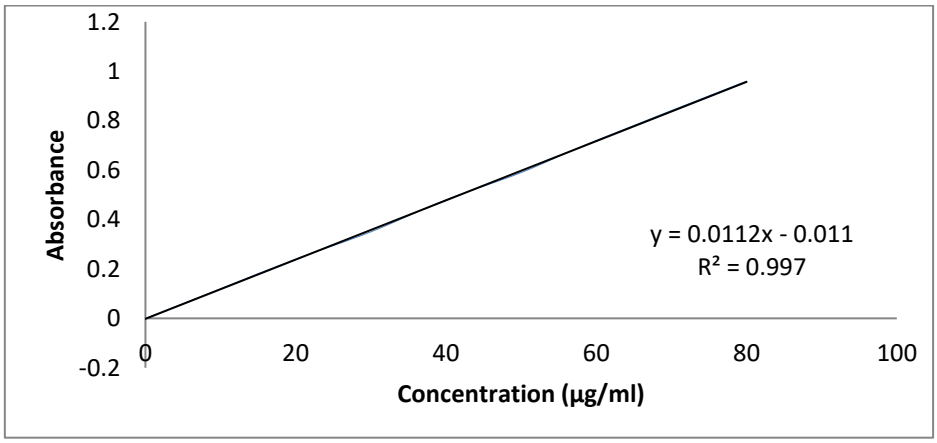

Figure 2: Standard curve of venlafaxine in 0.1 N HCl simulated gastric fluid

Preformulation studies: The objective of a pre-formulation study is to develop an elegant, stable, safe, and effective dosage form by establishing compatibility with the other ingredients and establishing physicochemical parameters of the new drug substance. Organoleptic parameters of the drug were checked by visual inspection and it was yellowish in color, bitter taste with odorless. The bulk density of drug powder was 0.264 gm/cm3 and tapped density was 0.292 gm/cm3. The drug particle size was 93 µm. The tap density of pure drug venlafaxine was determined using a tap density tester, carr's index was 12.53%, Hausner's ratio was 1.12 and the angle of repose was 23.01º assessed to know the flowability of microspheres exhibited with good flowability. The melting range of the drug was 221.05ºC. The venlafaxine solubility in water is very poor; have been reported 0.167 mg/ml as an increased concentration of co-solvent to increase the solubility of the drug. This study observed that venlafaxine solubility was increased at 0.1 N Hcl upon the addition of various co-solvents in different strengths. The maximum solubility of the drug in various solvents were 1.21±0.82, 1.08±0.79 and 1.12±0.96 mg/ml respectively. Based on these results 0.1 N Hcl pH 1.2 simulated gastric fluids were preferred as diffusion medium for maintaining better sink condition over the drug release studies. The partition coefficient of the drug examined in n-octanol: 0.1 N Hcl pH buffer system by shake flask method, was found to be 2.45. Drug- An excipients compatibility study was performed to determine any physical change in the drug when kept in contact with various formulation excipients. FTIR peaks were found at 1072 cm-1 C-O Stretching, 774 cm-1 C-F Stretching, 1210 cm-1C-N Stretching, and 1434 cm-1 C-H Bending 3186 cm-1N-H Stretching. The spectrum showed there is no change in the characteristic peaks of a drug. So that indicated the compatibility of drug and polymer.

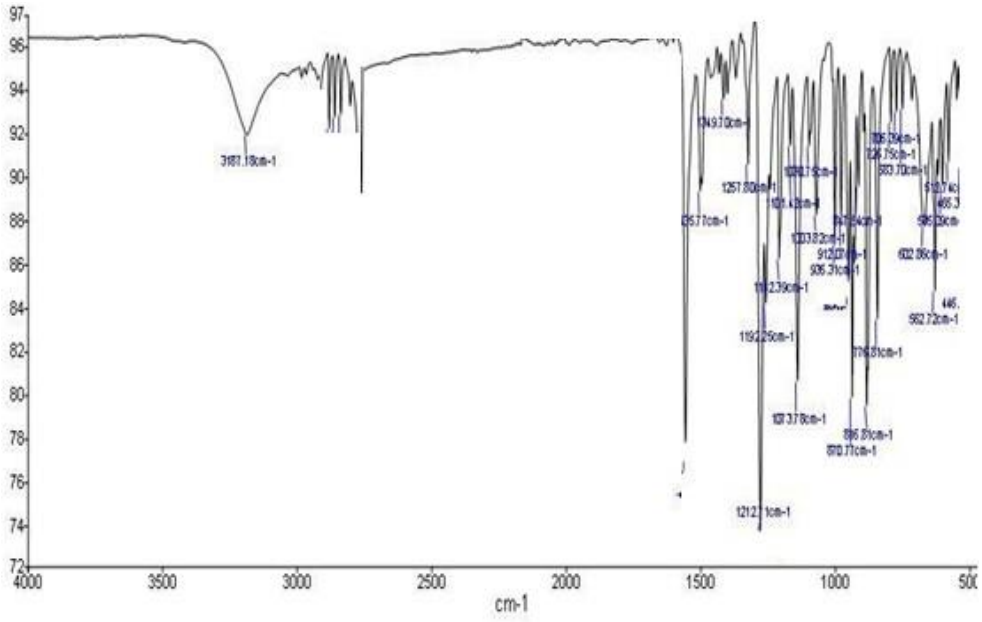

Figure 3: FTIR study of pure drug and excipients

Formulation of floating tablets: The tablets are prepared by direct compression method. The drugs, Guargum, citric acid, sodium bicarbonate HPMC, Magnesium stearate, and MCC are used for formulation. Pre-compression parameters such as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio were evaluated for powder blends. Swellable mucoadhesive tablets were prepared by the direct compression method, using HPMC, and Guargum as natural polymers. The effect of the nature of polymers was studied by preparing various formulations of swelling adhesive tablets. In all these formulations, a constant amount of drug (5 mg) was maintained and the prepared granules were initially characterized for flow properties and all other parameters. The different characterization as the angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio include angle of repose (26.02), bulk density (0.174 g/cm^3), tapped density (0.173 g/cm^3), Carr's index (23.31 %) and Hausner's ratio was found to be (1.18). The oral sustained release dosage form with prolonged residence time in the stomach helps in the absorption of the drugs that are less soluble or unstable in the alkaline pH and those that are absorbed from the upper gastrointestinal tract. GRDDSs help in the maintenance of constant therapeutic levels for prolonged periods and produce therapeutic efficacy thereby reducing the total dose of administration. In the present study, an attempt was made to develop a floating properties tablet of venlafaxine with variation gas generating agents and polysaccharide polymeric combination with different ratios to increase floated behaviors with adhesion properties at gastric mucosa. Such type of proposed formulations increase the gastric residence time, thus increasing the bioavailability. The other characterization includes thickness, hardness, friability, weight variation, drug content, and in-vitro drug release. The thickness of all the tablets was in the range of 4.01 to 4.09 mm. The average weights of the entire prepared tablet were 89.17 mg to 91.73 mg which was within the specified limit. The hardness of all the formulated tablets was found to be in the range of 5.04 to 5.36 kg/cm^2. Friability was found to be 0.31 to 0.38 %. The preliminary and screening studies were performed using different polymers and the polymers citric acid, sodium bicarbonate, and HPMC, promising excellent properties for controlled release and muco-adhesion. Using selected polymers, the final batches were prepared by direct compression method and were evaluated for buoyancy lag time and total buoyant time, swelling index, drug content, ex-vivo mucoadhesive strength, and in-vitro dissolution study. The formulation VFT4 was found to be the best formulation in terms of sustained drug release. Drug release kinetics was performed by using various kinetic models such as Zero order, First order, Korsmeyer- Peppas, and Higuchi's equation. The regression coefficient (r^2) value of various models was found to be non-fiction drug release diffusion mechanism and followed super case II transport mechanism respectively.

Table 3: The various characterizations of venlafaxine floating tablets

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Percent Drug content (%)
VFT1	91.21±.49	4.09±.01	5.51±.11	0.36±.13	99.52±0.26
VFT2	89.17±.01	4.01±.02	5.54±.12	0.31±.16	99.08±0.18
VFT3	91.12±.02	4.06±.01	5.31±.13	0.38±.11	99.29±0.98
VFT4	90.19±.04	4.04±.01	5.04±.18	0.32±19	99.15±0.15
VFT5	91.21±.01	4.03±.03	5.14±.11	0.34±.17	98.65±0.14
VFT6	90.15±.05	4.01±.02	5.36±.10	0.38±.16	99.91±0.32
VFT7	91.11±.01	4.06±.03	5.25±.44	0.35±.17	99.16±0.44
VFT8	91.73±.03	4.09±.03	5.11±.27	0.32±.13	99.14±0.08
VFT9	90.21±.06	4.06±.02	5.10±.21	0.34±.13	101.32±0.16

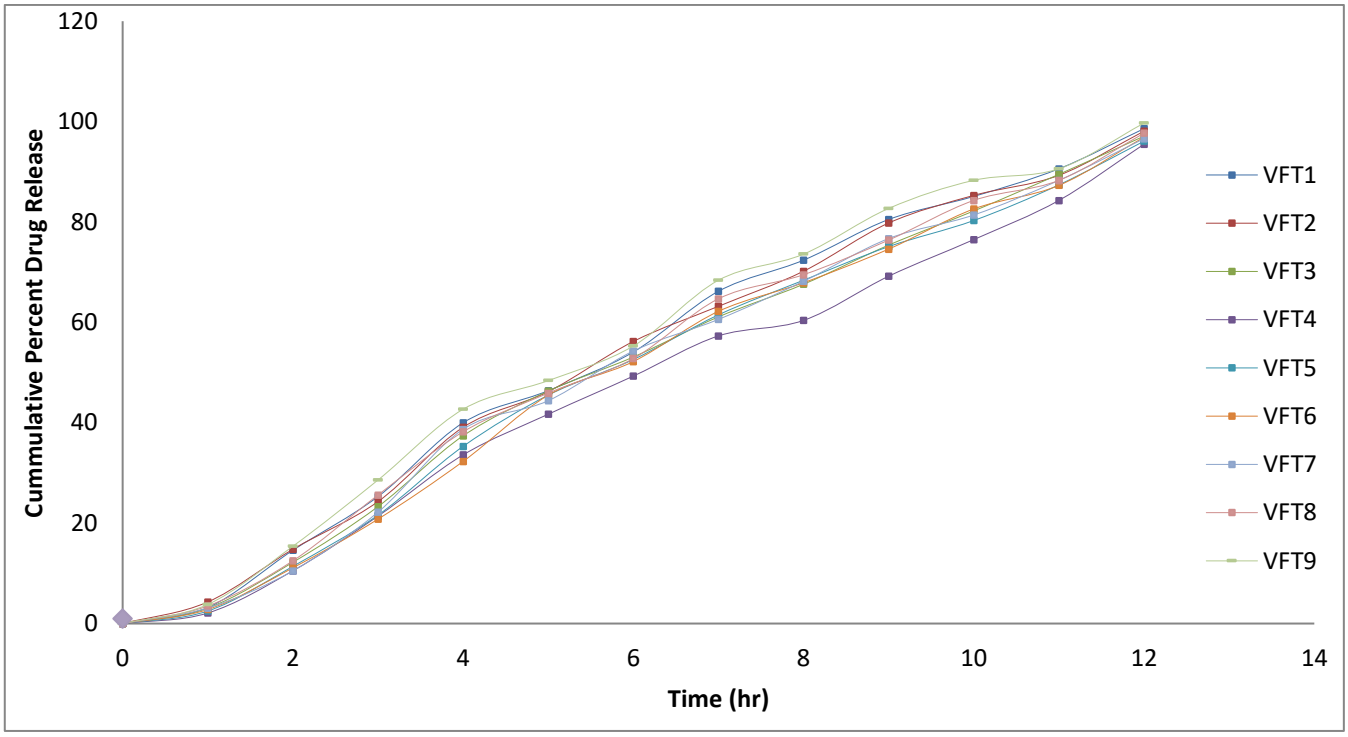

Figure 4: Zero-order kinetic plot of the prepared venlafaxine floating tablets (VFT1 - VFT9)

SUMMARY AND CONCLUSION:

The present investigation aimed at the formulation and evaluation of gastroretentive tablets based on a combination of natural polymers. Oral floating GRDDS release dosage form with prolonged residence time in the stomach helps in the absorption of the drugs that are less soluble or unstable in the alkaline pH and those that are absorbed from the upper gastrointestinal tract. GRDDSs help in the maintenance of constant therapeutic levels for prolonged periods and produce therapeutic efficacy thereby reducing the total dose of administration. In the present study, an attempt was made to develop a mucoadhesive buoyant tablet of venlafaxine with variation in polysaccharide polymeric combination with different ratios to increase floatation behavior at gastric mucosa. The preliminary and screening studies were performed using different polymers and the polymers citric acid, sodium bicarbonate, HPMC, and guar gum promised excellent properties for controlled release and muco-adhesion. Using selected polymers, the final batches were prepared by direct compression method and were evaluated for buoyancy lag time and total buoyant time, swelling index, drug content, ex-vivo mucoadhesive strength, and in-vitro dissolution study. Drug release kinetics was performed by using various kinetic models such as Zero order, First order, Korsmeyer- Peppas, and Higuchi's equation. The regression coefficient (r2) value of various models was found to be non-fiction drug release diffusion mechanism and followed super case II transport mechanism respectively.

REFERENCES:

1. Singh B.N. and Kim K.H., Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release, 2000; 63: 235-259. https://doi.org/10.1016/S0168-3659(99)00204-7 PMid:10601721

2. Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery system. Expert Opin Drug Deliv. 2006; 3 (2): 217-233. https://doi.org/10.1517/17425247.3.2.217 PMid:16506949

3. Dhakar RC, Maurya SD, Aggarwal S, Kumar G, Tilak VK, Design and evaluation of SRM microspheres of metformin hydrochloride, Pharmacie Globale (IJCP), 2010;1(07);

4. Kawashima, Y., Niwa, T., Takeuchi, H., Hino, T., and Ito, Y. Preparation of multiple unit hollow microspheres (micro ballons) with acrylic resin containing tranilast and their drug release characteristics (in vitro) and floating behavior (in vivo). J. Control. Rel. 1991;16: 279-290. https://doi.org/10.1016/0168-3659(91)90004-W

5. Gharti KP, Budhathoki U, Thapa P, Bhargava A. Formulation in vitro evaluation of floating tablets of hydroxypropyl methylcellulose and polyethylene oxide using ranitidine hydrochloride as a model drug. Journal of Young Pharmacists. 2012 Oct 1;4(4):201-8. https://doi.org/10.4103/0975-1483.104363 PMid:23493037 PMCid:PMC3573371

6. Fu J, Yin H, Yu X, Xie C, Jiang H, Jin Y, Sheng F. Combination of 3D printing technologies and compressed tablets for preparation of riboflavin floating tablet-in-device (TiD) systems. International journal of pharmaceutics. 2018 Oct 5;549(1-2):370-9. https://doi.org/10.1016/j.ijpharm.2018.08.011 PMid:30107218

7. Patel VF, Patel NM, Yeole PG. Studies on formulation and evaluation of ranitidine floating tablets. Indian journal of pharmaceutical sciences. 2005;67(6):703.

8. Garg R, Gupta GD. Progress in controlled gastroretentive delivery systems.Trop. J Pharm Res 2008; 7(3): 1055-66. https://doi.org/10.4314/tjpr.v7i3.14691

9. Lin X, Fu H, Hou Z, Si Y, Shan W, Yang Y. Three-dimensional printing of gastro-floating tablets using polyethylene glycol diacrylate-based photocurable printing material. International Journal of Pharmaceutics. 2021; 15; 603:120674. https://doi.org/10.1016/j.ijpharm.2021.120674 PMid:33964341

10. Rouge N, Buri P, Voelker E. Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. Int J Pharma. 1996; 136:117-139. https://doi.org/10.1016/0378-5173(96)85200-8

11. Emara LH, Abdou AR, El-Ashmawy AA, Mursi NM. Preparation and evaluation of metronidazole sustained release floating tablets. Int J Pharm Pharm Sci. 2014;6(9):198-204.

12. Kumar PD, Rathnam G, Prakash CR, Saravanan G, Karthick V, Selvam TP. Formulation and characterization of bilayer floating tablets of ranitidine. Rasayan J. Chem. 2010;3(2):368-74.