Contents lists available at UGC-CARE

International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

Available online at www.ijpsdronline.com

Research Article

Development and Optimization of Wax Matrix Tablets of Levetiracetam for Zero-order Controlled Release

Ravi Parimi*, Rama Rao Vadapalli, K.E. Pravallika

University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur- 522510, Andhra Pradesh, India

ARTICLE INFO

Article history:

Received: 11 January, 2021

Revised: 29 March, 2021

Accepted: 07 April, 2021

Published: 30 May, 2021

Keywords:

Embedment,
Highlysoluble drugs,
Pore former,
Wax matrix,
Zero-order controlled release.

DOI:

10.25004/IJPSDR.2021.130302

ABSTRACT

The major objective of this work was to develop once-daily, extended-release tablets with zero-order drug release for levetiracetam using the wax matrix as the release retarding element. Extending drug release for highly water-soluble drugs is always a challenge. In this work, levetiracetam, a highly soluble drug, was chosen for which extended-release matrix tablets were developed using different waxes such as Compritol ATO 888, Imwitor 491, tristearin, and cetylpalmitateas rate controlling materials taken in different amounts. PEG 6000 was used to regulate water availability inside the wax matrix, and lactose was used as a pore-forming agent to aid the release of the drug from the wax matrix. Tablets were prepared by embedding the drug into the molten wax, followed by solidification, sieving, mixing with other excipients, and finally compression. The prepared tablets were tested for hardness, tensile strength, friability, drug content, and drug release studies. Type of wax, amount of wax, and PEG 6000 were optimized to achieve controlled drug release for about 24 hours. All the tablets showed good tensile strength in the range of 0.59–0.70 N/mm^2, packing fraction in the range of 0.85–0.92, and friability in the range of 0.42–55%, indicating their solid physical integrity. The drug release studies indicated that the tablets prepared with tristearin showed better control among the waxes taken. The tablets containing 150mg of tristearin, 50mg of PEG 6000, and 50 mg of lactose showed controlled drug release for 24 hours with the zero-order release.

Introduction

Controlling the drug release for longer times for highly water-soluble drugs is always challenging for a formulation development scientist. Besides, achieving constant (zero-order) drug release is further challenging as the drug accelerates to get out of the tablet after placing in a dissolution medium. Various technologies have been developed and still developing in this area, including matrix systems, reservoir systems, and osmotic systems using various synthetic high molecular weight water-insoluble and non-erodible polymers.[1-3] Formulation with these polymers necessitates the use of toxic organic solvents as either granulating solvents for matrix systems; or solvents for coating solutions for reservoir systems. Hence, the use of wax materials as release retard materials has significant advantages over synthetic polymers, including avoiding toxic organic solvents.

Levetiracetam (LVT) is an anti-epileptic drug that falls under BCS Class I drug i.e., having high solubility and permeability. The reported solubility of LVT is 1.04g/mL (freely soluble) and also is pH independent in the range of 0 to 14, which is a major requirement for developing oral controlled release formulations.[4] Hence, LVT was selected as a model drug in this research. Good amount of literature was published about the use of waxes for attaining controlled drug release, wherein the waxes employed are mostly carnauba wax,[5,6] shellac wax,[7] and hydrogenated castor oil.[8] In this research, we took novel lipids as matrix-forming wax materials such as Imwitor491 (glycerylmonostearate), Compritol ATO 888

*Corresponding Author: Dr. Ravi Parimi

Address: University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur- 522510, Andhra Pradesh, India

Email ✉: parimirv@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

(glyceryldibehenate) tristearin on which very limited work was published.

Better controlled release and maximum benefit from the lipids can be achieved if the drug is embedded into the lipid rather than just mixing physically.[9] The lipids selected are water-insoluble and non-erodible lipids. Hence, the drug embedded into them may not contact water and hence may not be released. So, water-soluble materials like lactose, PEG 6000 and swellable and removable materials like microcrystalline cellulose and gums may be used as pore formers and water regulating agents. Especially lactose in the wax matrix gets removed when the tablet is placed in dissolution medium, resulting in pore formation, thus enabling drug release.[10] The number, size, and degree of these pores and the wax matrix combinely regulate the drug release. Hence, in this research work, two different hydrophilic materials viz. lactose and PEG 6000 were used as pore former and water regulating agents to study their drug release influence.

Previous on LVT extended-release tablets were reported by some authors, including formulation of LVT tablets using Eudragit and ethyl cellulose by AirajMahajabeen*et al.*[11] the tablets developed by these authors had final weight of 900 mg for 500 mg of LVT and also the drug release was reported to be controlled only for 12 hours; another work by Sudarshan Singh *et al.*[12] reported that LVT extended release matrix tablets were developed using HPMC K4M, K15M and K100M that could control the drug release for 18 hours; another work by Himanshu Paliwal *et al.*[13] reported that the LVT tablets were developed using various grades of HPMC could control the drug release for 18 hours. from the extensive literature survey, it is observed that no work was reported on development of LVT extended release matrix tablets with lipophilic wax materials.

Towards the objective of controlling the release of LVT for about 24 hours and achieving zero-order release, various formulations were developed by taking three different lipids and two pore formers with variable amounts. Tablets were prepared by embedding the LVT into the molten wax, followed by mixing with other excipients and compression. The physical strength of the prepared tablets was studied through hardness, tensile strength and friability. Majorly the drug release studies and release kinetic studies were performed to analyze the influence of type of lipid and its concentration; and the type of pore former and its concentration on the drug release. Finally the formulation which provided constant drug release for about 24 hours was identified as an optimized formulation.

Materials and Methods

Materials

Levetiracetam was obtained as a gift sample from Hetero Drugs Pvt. Ltd., Hyderabad; Imwitor, Compritol ATO 888, tristearin, and PEG 6000 were procured from Sigma Aldrich, Mumbai; Lactose, magnesium stearate, and talc were procured from Loba Chemie Ltd, Hyderabad.

Drug-excipient Compatibility Studies

Compatibility between LVT and the selected lipids was studied by using fourier transform infrared (FTIR) spectroscopy.[14] Pure LVT and physical mixtures of LVT with the lipids at maximum weight ratios according to the formulae were made into pellets after admixing with KBr using hydraulic press. Each pellet was studied by FTIR spectroscopy in the wavelength range of 400 to 4000 cm^{-1}, and the spectrum was taken as an average of 16 scans. Later, the spectrum of pure drug was compared with those of its physical mixtures.

Preparation of Wax Matrix Tablets of LVT

Desired quantities of lipid and PEG 6000 according to the formulae (Table 1) were taken in a china dish and subjected to melting under controlled temperature just above their melting points. Pre-weighed quantity of LVT and was

Table 1: Compositions of various formulations of wax matrix tablets of LVT

	Quantity in mg per one tablet															
Ingredient	*CF1*	*CF2*	*CF3*	*CF4*	*IF1*	*IF2*	*IF3*	*IF4*	*TF1*	*TF2*	*TF3*	*TF4*	*CPF1*	*CPF2*	*CPF3*	*CPF4*
Levetiracetam	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500
Compritol ATO 888	125	125	125	175	-	-	-	-	-	-	-	-	-	-	-	-
Imwitor 491	-	-	-	-	125	125	125	175	-	-	-	-	-	-	-	-
Tristearin	-	-	-	-	-	-	-	-	125	125	125	175	-	-	-	-
Cetylpalmitate	-	-	-	-	-	-	-	-	-	-	-	-	125	125	125	175
PEG 6000	-	50	100	-	-	50	100	-	-	50	100	-	-	50	100	-
Lactose	100	50	-	50	100	50	-	50	100	50	-	50	100	50	-	50
Adsorbent	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Lubricant	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Glidant	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Total	765	765	765	765	765	765	765	765	765	765	765	765	765	765	765	765

embedded into the molten wax mixture maintained at the same temperature by uniform mixing followed by the dispersion of lactose. The china dish was removed from heating, and the dispersion was continuously mixed until it solidified completely. This LVT embedded wax dispersion was passed through sieve #20 to obtain wax matrix granules and then mixed with colloidal silica, magnesium stearate, and talc. Colloidal silica, an effective adsorbent, was taken to avoid the possible softening and sticking of waxy material because of the heat generated during compression. This blend was subjected to compression using 12 mm punch to obtain flat-faced round elegant tablets.

Characterization Studies for Pre-compression Mixture

The obtained wax matrix granules of all the formulations were evaluated for bulk density, tapped density, Carr's index, Hausner's ratio, and repose angle to assure their suitability for compression into tablets.

Characterization Studies for the Compressed Wax Matrix Tablets of LVT

Tensile Strength

It is the stress required to break a tablet and thus indicating the physical strength of tablets. Thickness (t) and diameter (D) were measured using Vernier caliper. Hardness or crushing strength (F_c) was determined using Monsanto hardness tester. Tensile strength was calculated using the following equation.[9,15]

Packing Fraction and Porosity

Packing fraction (P_f) indicates the degree of consolidation of tableting powder after compression. It can be calculated using the equation[15]

W is the weight of tablet; *r* and *t* are the radius and thickness of tablet, and ρ is the true density of the tableting powder. The true density of the tableting powder was determined by the liquid displacement method using liquid paraffin. Subtracting the packing fraction form 1 gives porosity which indicates the degree of water penetration into the tablet.

Friability

Friability was determined by taking 10 tablets into Roche friabilator, which was then rotated at a speed of 25 rpm for 4 minutes. to complete 100 revolutions. Then, the tablets were removed and dedusted to remove any adhered powder and weighed. From the weights of 10 tablets before (w_1) and after friabilation (w_2), % friability was calculated using the equation

Drug Content

Tablets were powdered, and 100mg drug equivalent powder was taken and added into water (as the LVT is freely water-soluble) and subjected to intense mixing, ensuring dissolution of LVT. Then the mixture was filtered, and the volume of the obtained filtrate was made 100 mL in a volumetric flask. The filtrate, after suitable dilutions, was analyzed using UV-Visible spectrophotometer at its maximum wavelength of 194 nm. From the obtained absorbance, the amount of drug content was measured from standard curve of LVT.

Drug Release Studies

The prepared wax matrix tablets of LVT were subjected to drug release studies according to the USFDA specified dissolution conditions. 900 mL of 0.05 M phosphate buffer pH 6.0 was taken as the dissolution medium in basket (USP type I) apparatus rotated at 100 rpm. 5 mL of samples were taken and replaced with fresh buffer at various time intervals. The collected samples, after suitable dilutions, were analyzed using UV-Visible spectrophotometer at its maximum wavelength of 194 nm.

Drug Release Kinetic Studies

The data obtained from the drug release studies were fitted to various kinetic models to determine the order of drug release kinetics and mechanism of drug release from the developed wax matrix tablets of LVT. The kinetic models employed to fit the data were zero-order, first-order, Higuchi's and Korsemeyer-Peppas models.[16]

Results and Discussion

Drug-excipient Compatibility Studies

The IR spectrum of pure LVT was compared with the spectra of its physical mixtures with the selected wax materials (Fig. 1). The characteristic peaks corresponding

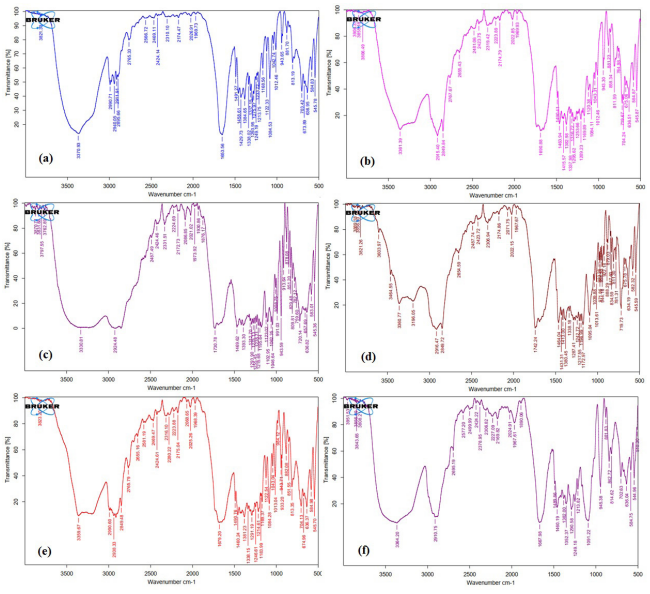

Fig. 1: FTIR spectra of pure LVT and physical mixtures of LVT with different waxes. (a) Pure LVT; (b) LVT + Compritol ATO 888; (c) LVT + Imwitor 491; (d) LVT + Tristearin; (e) LVT + Cetylpalmitate; and (f) LVT + PEG 6000

to the characteristic functional groups of LVT observed in the spectrum of the pure drug were N-H stretching at 3370.93 cm^{-1}; C-H stretching at 2895.66 cm^{-1}; C=O bending at 1653.56 cm^{-1}; C-H bending at 1429.73 cm^{-1}; C-N stretching at 1084.53 cm^{-1} [17] The same peaks at and close to these wave numbers were also observed in the spectra of physical mixtures. This indicated the absence of any incompatibility between LVT and the selected wax materials, thus allowing their use in LVT wax matrix tablets.

Characterization Studies for Pre-compression Mixture

The bulk density of all formulations before tapping was found in the range of 0.51–0.54 g/mL; after tapping, the values were found to be in the range of 0.59–0.62 g/mL. Before and after tapping, the difference in bulk densities before and after tapping suggested that the wax matrix granules had good compressibility and packageability for tableting. Hausner's ratio and Carr's index were found to be in the range of 1.16–1.13 and 13.56–11.48, respectively. Angle of repose values were found to be in the range of 12.51–14.76°. These values indicated that the wax matrix granules had good to excellent flow properties and thus be effectively compressed into tablets.

Preparation of Wax Matrix Tablets of LVT

The wax matrix tablets were prepared by embedding the drug into the heat-activated wax mixture of PEG 6000 and Imwitor/Compritol ATO 888/Tristearin, followed by mixing with lactose and other excipients finally compressed into flat-faced tablets of 12 mm diameter. Instead of physically mixing the drug with waxy materials, embedding it into the heat-activated max would be more effective as it would allow the wax to coat over the drug particles and thus effectively control the release of even highly water-soluble drugs.[9] This embedment of the drug into heat-activated (for waxes) or solvent activated (for polymers) matrix would make a relatively less amount of rate retardant material sufficient to achieve desired control release so that the weight of the final tablet would be reduced, which is a significant advantage especially for high dose drugs like LVT.

The prepared tablets had a continuous smooth textured surface and glazy in appearance because of the waxes present. The tablets did not show any sticking during compression, which might be because of Aerosil (colloidal silica) as adsorbent, which could avoid any possible sticking of tablets to punches upon softening the wax material due to the heat generated during compression.

Physical Characterization Studies

Tensile Strength

Wax matrix tablets of all the formulations were compressed using punches of 12 mm diameter and with an adjusted thickness of 5.5mm. The compressed tablets were found to have hardness in the range of 6.2–7.4 kilogram-force (kgf) or 60.80–72.57 N, and hence the tensile strength values were found in the range of 0.59–0.70 N/mm^2 as shown in the Table 2. These high hardness and tensile strength values indicated good physical strength of tablets which further designated suitability of the selected waxes and their mode of use for development of matrix tablets.

Packing Fraction

It indicates the degree of packaging of the pre-compression blend that is measured after compression into tablet

Table 2: The results of different physical characterization studies of LVT wax matrix tablets

S. No.	*Formulation*	*Tensile strength (N/mm^2)*	*Packing fraction (P_f)*	*Porosity fraction ($1–P_f$)*	*Friability (%)*
1	CF1	0.65 ± 0.02	0.85 ± 0.02	0.15 ± 0.02	0.48 ± 0.04
2	CF2	0.67 ± 0.02	0.87 ± 0.03	0.13 ± 0.03	0.49 ± 0.03
3	CF3	0.69 ± 0.01	0.90 ± 0.01	0.10 ± 0.01	0.53 ± 0.03
4	CF4	0.68 ± 0.03	0.90 ± 0.03	0.10 ± 0.03	0.55 ± 0.05
5	IF1	0.62 ± 0.02	0.86 ± 0.04	0.14 ± 0.04	0.51 ± 0.02
6	IF2	0.65 ± 0.01	0.87 ± 0.02	0.13 ± 0.02	0.50 ± 0.04
7	IF3	0.67 ± 0.01	0.90 ± 0.03	0.10 ± 0.03	0.47 ± 0.03
8	IF4	0.70 ± 0.02	0.89 ± 0.01	0.11 ± 0.01	0.45 ± 0.05
9	TF1	0.65 ± 0.03	0.87 ± 0.01	0.13 ± 0.01	0.43 ± 0.06
10	TF2	0.63 ± 0.03	0.90 ± 0.02	0.10 ± 0.02	0.42 ± 0.04
11	TF3	0.62 ± 0.02	0.91 ± 0.02	0.09 ± 0.02	0.47 ± 0.03
12	TF4	0.60 ± 0.01	0.91 ± 0.04	0.09 ± 0.04	0.45 ± 0.02
13	CPF1	0.59 ± 0.02	0.88 ± 0.03	0.12 ± 0.03	0.45 ± 0.05
14	CPF2	0.61 ± 0.01	0.90 ± 0.03	0.10 ± 0.03	0.42 ± 0.04
15	CPF3	0.64 ± 0.03	0.92 ± 0.02	0.08 ± 0.02	0.44 ± 0.04
16	CPF4	0.60 ± 0.02	0.91 ± 0.01	0.09 ± 0.01	0.47 ± 0.03

based on the weight, radius and thickness of the tablet, and true density of the pre-compression blend. It depends on the nature of the material to be compressed besides particle size. The higher packing fraction indicates greater tableting efficiency and hence greater strength of the tablet.[15] The values of this packing fraction for all formulations of wax matrix tablets of LVT were found in range of 0.92–0.85. These values indicated that all the formulations contained a significant amount of wax materials and had good tableting efficiency, thus suitable for compression into tablets. And these values further designated that the mode of incorporation of wax through adsorbing the molten wax onto the solid drug particles, followed by solidification and admixing with adsorbent, was effective for preparing tablets with good strength. Subtracting the packing fraction from 1 gave the residual porosity of the tablets after compression, and these values range from 0.08–0.15 (Table 2). This little porosity is necessary for water penetration into the wax matrix tablets to enable drug release.

Friability

The strength of wax matrix tablets was further evidenced by friability. The % friability values for all the formulations varied from 0.42–0.55% (Table 2). These values indicated that the developed tablets were strong enough to overcome the forces that might be applied during handling, packing, and transportation.

Drug Release Studies

The prepared wax matrix tablets of LVT were subjected to drug release studies according to USFDA dissolution specifications. The dissolution profiles in the form of zero-order plots for tablets of all lipids were shown in Figs. 2 to 5.

Majorly three materials in the formulation of wax matrix tablets are responsible for drug release: wax, PEG 6000, and lactose. Because of theirlong aliphatic straight chain that produces high lipophilicity, Waxy materials are the prime rate retarding materials. PEG 6000 is a hydrophilic and slowly soluble polymer that effectively regulates water availability inside the wax matrix. Lactose is a highly and readily water-soluble material and was incorporated in the tablets as an extra-granular material. When the wax matrix tablets are added into the dissolution medium, lactose readily dissolves and produces pores in the tablet, favoring the release of the drug from the wax matrix tablet.

After many trials in case of each waxy material, four formulations were developed to study the effect of amounts of wax, PEG 6000 and lactose. The first three formulations containing 125 mg and the fourth formulation contained 175 mg of lipid with varying PEG 6000 and lactose

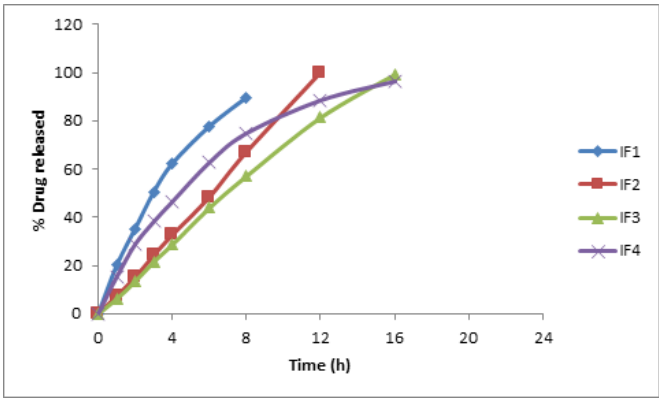

Fig. 3: Zero-order plots of drug release of tablets prepared with Imwitor 491

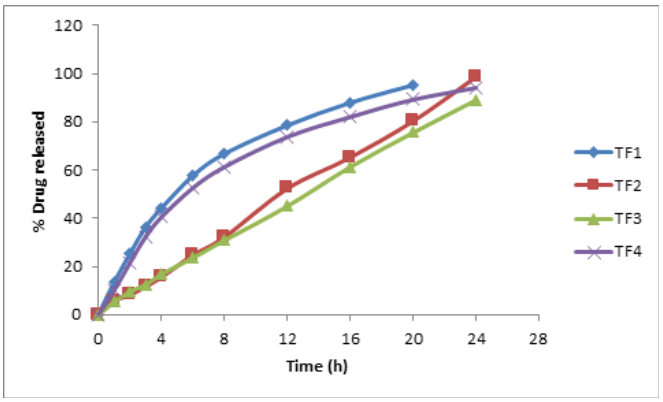

Fig. 4: Zero-order plots of drug release of tablets prepared with Tristearin

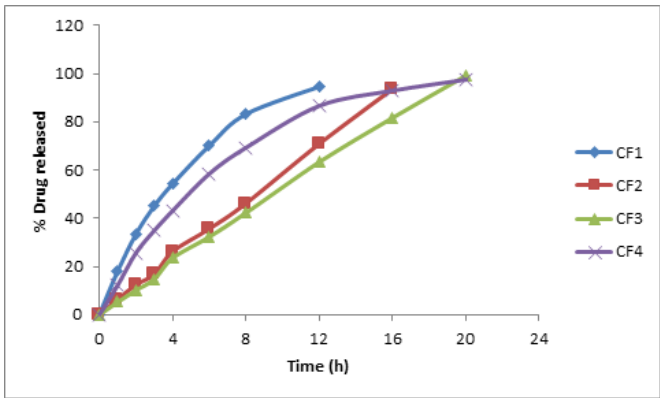

Fig. 2: Zero-order plots of drug release of tablets prepared with Compritol ATO 888

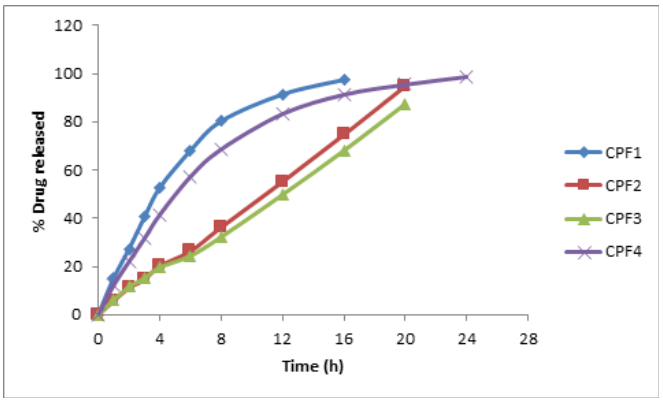

Fig. 5: Zero-order plots of drug release of tablets prepared with Cetylpalmitate

Table 3: The results of drug release studies of LVT wax matrix tablets

S. No.	Formulation	Regression (R^2) values			Zero-order rate constant (%/h)	First-order rate constant (h^{-1})	Peppas 'n' values
		Zero-order	First-order	Higuchi's			
1	CF1	0.807	0.986	0.978	-	0.229	0.672
2	CF2	0.999	0.847	0.842	5.871	-	0.968
3	CF3	0.997	0.746	0.859	5.092	-	0.989
4	CF4	0.76	0.99	0.972	-	0.169	0.681
5	IF1	0.904	0.986	0.968	-	0.262	0.727
6	IF2	0.999	0.669	0.823	8.247	-	1.049
7	IF3	0.99	0.762	0.869	6.598	-	1.007
8	IF4	0.784	0.985	0.978	-	0.189	0.663
9	TF1	0.732	0.989	0.983	-	0.141	0.638
10	TF2	0.998	0.714	0.845	4.103	-	0.942
11	TF3	0.998	0.909	0.864	3.783	-	0.896
12	TF4	0.735	0.996	0.979	-	0.115	0.667
13	CPF1	0.767	0.989	0.965	-	0.213	0.684
14	CPF2	0.997	0.819	0.838	4.522	-	0.923
15	CPF3	0.995	0.884	0.845	4.295	-	0.86
16	CPF4	0.748	0.981	0.967	-	0.164	0.661

amounts. For every wax taken, formulations F1 and F4 can be compared to understand the effect of the amounts of wax and lactose without the influence of PEG 6000. Formulations F2 and F3 can be compared to understand the effect of PEG 6000.

Effect of type of Wax

The efficiency of waxes taken in controlling the drug release was found to be highest for tristearin and lowest for Imwitor 491 in the order of tristearin >cetylpalmitate>Compritol ATO 888 >Imwitor 491. The constant rate values were showed in the Table 3. This could be attributed to the aliphatic straight-chain lengths and their molecular weights. Tristearin, a triglyceride with three stearic acid chains connecting to three hydroxyl groups of glycerol, has a molecular weight of 891.5 Daltons. The molecular weight of cetylpalmitate is 480.8; Compritol ATO 888 is chemically glyceryldibehenate with a molecular weight of 432.7; Imwitor 491 contains more than 90% of glycerylmonostearate, whose molecular weight is 358.6. All the selected wax materials are aliphatic straight-chain compounds whose lipophilicity increases with the length of straight-chain in aliphatic compounds.[18] This might be the reason behind their efficiency in controlling the drug release from the developed wax matrix tablets of LVT.

Effect of Amount of Wax Material

When comparing the formulations F1 and F4 in each wax, it was evident that drug release was found to be decreased upon increasing the amount of wax. The obtained results were correlated with those reported by Quing-Ri Cao *et al.*[5] This could be attributed to the increased lipophilicity and increased density of wax in the matrix at higher amounts. This could also be attributed to the presence of more lactose in F1 than in F4, which formed more pores in the matrix tablet, and hence the drug release rate was more[19] in formulation F1.

Effect of Amount of PEG 6000

Effect of PEG was found to be very significant as it affected the rate and the kinetics of drug release (results shown in Table 3). In the case of every wax, formulations F1 and F4 without PEG 6000 showed first-order kinetics of drug release; and F2 & F3 containing PEG 6000 showed zero-order kinetics of drug release. This could be attributed to PEG 6000 that could maintain the constant availability of water inside the matrix, which could modify the drug release[20,21] and the insoluble and non-erodible wax matrix, and hence drug was released constantly in zero-order. Further, the drug release was more in the case of F2 than in the case of F3, which might be because of the presence of lactose in F2 that could form pores in the matrix, allowing the release of the drug from the matrix.[19]

The mechanism of drug release was studied by Higuchi's and Korsemeyer-Peppas plots and the results were shown in Table 3. In case of each wax, formulations, F1 and F4 showed more Higuchi's regression values and lesser Korsemeyer-Peppas coefficients than those of their corresponding F2 and F3 formulations. This indicated that the drug release from F1 and F4 formulations was more by diffusion. But, in case of F2 and F3 formulations, lesser Higuchi's regression values (below 0.9) indicated less possibility of membrane diffusion and higher Korsemeyer-Peppas coefficients (above 0.9) indicated drug release by anomalous transport that is diffusion by boundary effect and pores. As the boundary effect and pores were constant

during drug release, zero-order release from these F2 and F3 formulations resulted.

Conclusion

This work was undertaken to develop once daily controlled release tablet of LVT with constant zero-order drug release and with minimum possible final weight. The tablets were developed as wax matrix tablets containing variable amounts of PEG 6000 as water content regulator and lactose as pore former in the matrix. Four different waxes viz. tristearin, cetylpalmitate, Compritol ATO 888 and Imwitor 491 were taken at various amounts. Four different formulations in case of each wax and hence a total of 16 formulations were developed. The tablets were prepared by embedding the LVT into molten mixture of lipid and PEG 6000. The prepared tablets were checked for different physical characterization studies such as tensile strength, packing fraction and friability. Results of these studies indicated that tablets were sufficiently strong enough which further designated that the selected waxes and their mode of incorporation were effective for developing matrix tablets. The drug release studies indicated that zero-order release was obtained with matrix tablets containing PEG 6000 i.e. formulations F2 and F3 in case of each wax. Further, the tristearin containing TF2 formulation was the best among the others as it exactly controlled the drug release for 24 hours with zero-order release kinetics. And also the weight of the tablet was only 765 mg for 500 mg of LVT so that it can be easily administered. Hence, the set objectives of this research work achieved successfully.

Acknowledgement

The authors are acknowledged to the authority of Acharya Nagarjuna University for providing the necessary facilities and support to carry out this research work.

References

1. Patel R, Patel J. Novel technologies of oral controlled release drug delivery system. Sys Rev Pharm. 2010;1(2):128-132.
2. Kushal M, Monali M, DurgavathiM, Mittal P, Umesh S, Pragna S. oral controlled release drug delivery systems: An overview. Int Res J Pharm. 2013;4(3):70-76.
3. Nokhodchi A, Raja S, Patel P, Asare-Addo K. The role of oral controlled release matrix tablets in drug delivery systems. BioImpacts. 2012;2(4):175-187.
4. Petrusevska M, Berglez S, Krisch I, Legen I, Megusar K, Peternel L *et al.*Biowaiver monographs for immediate release solid oral dosageforms: Levetiracetam. J Pharm Sci.2015;104:2676–2687.
5. Cao QR, Kim TW, Lee BJ. Photoimages and the release characteristics of lipophilic matrix tablets containing highly water-soluble potassium citrate with high drug loadings. IntJPharm. 2007;339(1-2):19-24.
6. Nart V, Beringhs AO, França MT, de Espíndola B, Pezzini BR, Stulzer HK. Carnauba wax as a promising excipient in melt granulation targeting the preparation of mini-tablets for sustained release of highly soluble drugs. Mater SciEng C. 2017;70:250-257.
7. Phaechamud T, Choncheewa C. Single and dual drug release patterns from shellac wax-lutrol matrix tablets fabricated with fusion and molding techniques. Indian JPharm Sci. 2015;77(1):62-74.
8. Yonezawa Y, Ishida S, Sunada H. Release from or through a wax matrix system. I. Basic release properties of the wax matrix system. Chem Pharm Bull. 2001;49(11):1448-1451.
9. Srikar G, Avula P, Koreddi S. Embedment technique: An alternative to wet granulation for bettercontrol of release of highly water soluble drugs–A case study with diltiazemHCl. Int J Pharm Pharm Sci. 2015;7(12):270-276.
10. Huang HP, Mehta SC, Radebaugh GW, Fawzi MB. Mechanism of drug release from an acrylic polymer-wax matrix tablet. JPharmSci. 1994;83(6):795-797.
11. Mahajabeen A, Krishna EH, Surya RS. Formulation and evaluation of levetiracetamextended release tablets. World J Pharm Pharm Sci. 2015;4(4):1446-1461.
12. Singh S, Bhavesh S, Sanjaykumar N, SunilB. Formulation and evaluation of levetiracetam extendedrelease tablets. Int J Pharm Sci Nanotech. 2013;6(1):1958-1965.
13. Paliwal H, Goyal S, Rathore KS, Singla S, Daksh S. Formulation and evaluation of levetiracetam extended release tablets. Int J Pharm Sci Rev Res. 2016;41(1):260-266.
14. Srikar G, Gouthamib KS, Manasac B, Sirishad AS. Formulation optimization and characterization of amlodipine oral disintegrating tablets prepared by co-grinding technique. Der Pharm Lett. 2013;5(4):335-343.
15. Uhumwangho MU, Ogedebe JO, Osazuwa EQ. Effect of surfactants on the mechanical properties of acetaminophen-wax matrix tablets and its implication on dissolution profile. Ife J Sci. 2012;14(1):31-36.
16. Srikar G, Avula P, Annapurna S, Boola M. Development of extended release matrix tablets of felodipine through solid dispersions for better drug release profile by a 3^2 factorial design. Indian J PharmEdu Res. 2016;50(2S):S89-99.
17. Sivaneswari S, Karthikeyan E, Chandana PJ. Novel expandable gastro retentive system by unfolding mechanism of levetiracetam using simple lattice design–Formulation optimization and in vitro evaluation. Bull Fac Pharm Cairo Univ. 2017;55(1):63-72.
18. Sinko PJ. Martin's physical pharmacy and pharmaceutical sciences. Wolter Kluwer and Lippincott Williams and Wilkins, 2011.
19. Yonezawa Y,Ishida S, Suzuki S,Sunada H. Release from or through a wax matrix System. IVgeneralized expression of the release process for a reservoir device tablet. Chem. Pharm. Bull. 2002;50(9):1219-1222.
20. D'souza AA. Shegokar R.Polyethylene glycol (PEG): A versatile polymer forpharmaceutical applications. Expert Opin Drug Deliv. 2016;13(9):1257-1275.
21. Robinson JR, Lee VHL. Controlled drug delivery – Fundamentals and Applications. Informa Healthcare, 2011.

HOW TO CITE THIS ARTICLE: Parimi R, Vadapalli RR, Pravallika KE. Development and Optimization of Wax Matrix Tablets of Levetiracetam for Zero-order Controlled Release. Int. J. Pharm. Sci. Drug Res. 2021;13(3):246-252. **DOI:** 10.25004/IJPSDR.2021.130302