INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Research Article

Formulation And Evaluation of Oral Disintegrating Film Containing Brivaracetam

Sheetal P.[1], Nagendra R.[1], Nanditha V. V.[1], Venkatesh[1], Hanumanthachar Joshi[2]

[1]*Department of Pharmaceutics, Sarada Vilas College of Pharmacy Mysuru, Karnataka, India*
[2]*Department of Pharmacognosy, Sarada Vilas College of Pharmacy Mysuru, Karnataka, India.*

ARTICLE INFO

Published: 12 Nov. 2024
Keywords:
Oral disintegrating film, Hydroxypropyl methylcellulose, Solvent casting, Brivaracetam.
DOI:
10.5281/zenodo.14106902

ABSTRACT

Oral disintegrating films (ODFs) are innovative drug delivery systems designed to dissolve rapidly in the oral cavity without the need for water. These films are particularly beneficial for patients who have difficulty swallowing traditional dosage forms, such as the elderly and paediatric populations. This study aims to develop ODF containing Brivaracetam were formulated using a different grade of HPMC E15 and HPMC E50 and plasticizers like polyethylene glycol and propylene glycol using solvent casting method. The formulated films were evaluated for thickness, folding endurance, weight variation, percentage elongation, drug content, in-vitro dissolution and in-vitro disintegration. The optimized formulation F4 containing HPMC E15 showed minimum disintegration time at 20 secs and highest in-vitro dissolution 98.9% within 10 mins. Stability data indicated no significant changes in parameters over time. Therefore, Formulation F4 is recognized as stable and effective. Hence oral disintegrating films represent a promising advancement in pharmaceutical formulations, offering a convenient and effective means of drug delivery. Their rapid dissolution and ease of use make them an attractive option for improving patient adherence to medication regimens.

INTRODUCTION

Oral disintegrating films offer a sophisticated and effective route for systemic drug delivery, that dissolves or disintegrates quickly in tongue or buccal cavity than conventional dosage form. Fast dissolving oral film is prepared using hydrophilic polymers, which dissolves rapidly in buccal cavity or on tongue. The film overcomes the drawbacks of conventional quick dissolving/ dispersing intraoral tablets like fear of choking. Study showed that 26% of 1576 patients experienced difficulty in swallowing tablets. ODF is easy to handle, alleviates unpleasant taste, easy to manufacture, ensure accurate dose administration, afford a simple and convenient packaging and making

***Corresponding Author:** Nagendra R.
Address: *Department of Pharmaceutics, Sarada Vilas College of Pharmacy Mysuru, Karnataka, India*
Email : nagendrar16@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.

them particularly suitable for paediatrics and geriatric patients.[1] Fast dissolving oral thin films is an ultra-thin film that are placed on top or floor of tongue instantly get wet by saliva. The film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oral mucosal absorption or with formula modifications Disintegrated film rapidly releases the drug from the polymer matrix which are absorbed directly and enter the systemic circulation without undergoing hepatic first pass metabolism and increases the bioavailability of the active ingredient, there by reduction in dose which can lead to reduced side effects.[2] The oral drug delivery system prolongs the residence time of dosage form at the site of action, improves the therapeutic performance of the drug and provides a better enzymatic flora for drug absorption. It provides direct entry of drug into the systemic circulation, therefore, avoid all the drawbacks of the per-oral administration of drugs as hepatic first pass metabolism, pre-systemic elimination of GIT by enzymatic degradation, that prohibit oral administration of certain types of drugs especially proteins and peptides. The mucosa is relatively permeable and rich with blood supply, it is firm, strong and it shows short recovery times after stress or damage. An important point is that the lack of Langerhans cells makes the buccal mucosa tolerant to potential allergies.[3]

Brivaracetam (BVR) a derivative of levetiracetam, exhibits a high affinity for synaptic vesicle protein 2A (SV2A), making it effective in managing epilepsy. Since epileptic patients have to strictly follow the dosage regimen for preventing subtherapeutic concentration, FDF will avoid missing out of a dose even during travelling or other situations, where there is no access to water; offers a suitable and practical approach in serving desired objective of faster disintegration and dissolution characteristics with increased bioavailability and maintaining effective drug levels in the body. [4]

MATERIALS AND METHODS:

Brivaracetam is a gift sample from Micro Labs Ltd, Bangalore. Hydroxy propyl methyl cellulose E5 and E15 are purchased from Otto Chemica-Biochemika reagent, Mumbai. PEG and Propylene glycols are from Karnataka fine chemicals, Bangalore. Citric acid and Saccharin sodium are from Sisco Research Laboratories Pvt Ltd, Mumbai for carrying out various experiments. All the chemicals used were of analytical grade.

FORMULATION DEVELOPMENT OF BRIVARACETAM:

Table-1: Formulation trials of oral disintegrating film with Brivaracetam

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Brivaracetam in (g)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
HPMC E50 (g)	1.0	1.25	1.5	-	-	-	1.25	-	1.25
HPMC E15 (g)	-	-	-	1.0	1.25	1.5	-	1.25	-
PEG 400 (g)	1.5	1.25	1.0	-	-	-	-	1.25	1.25
Propylene glycol (ml)	-	-	-	1.5	1.25	1.0	1.25	-	-
Citric acid (g)	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
Sodium saccharin (g)	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125
Water (ml)	10	10	10	10	10	10	10	10	10
Total (g)	12.775	12.775	12.775	12.775	12.775	12.775	12.775	12.775	12.775

Preparation of Oral Disintegrating Films:

The water-soluble polymers and plasticizers were dissolved in distilled water. The solution was stirred up for 2 hrs in the magnetic stirrer and kept aside to remove all air bubbles entrapped. Meanwhile, the excipients and drug were dissolved and stirred well for 30 min, after the completion of stirring both the solutions are mixed

together. Finally, the bubble free solution is casted on a suitable petri plate to form a film. The plates were kept in a hot air oven at 60° C for 1 hour. The dried film was gently separated from glass plate and cut into a desired size.[5]

Preformulation studies:

i. Determination of melting point:

The melting point of a drug was determined by the capillary method. The drug was filled to capillary which was sealed at one end. The filled capillary was placed in melting point apparatus and temperature at which drug melted was noted.

ii. Determination of solubility of drug:

Solubility of Brivaracetam was checked in various solvents like Ethanol, Methanol and Glacial acetic acid, Acetone and water.[6]

iii. FTIR studies:

FTIR study was carried out to check the chemical interaction of drug and polymer. The samples comprised physical combinations of the drug and polymers as well as pure drug, which were combined with an appropriate amount of potassium bromide to create dry pellets. Then, using an FTIR spectrophotometer, pellets were scanned between 4000 and 400 cm^{-1}. A comparison was made between the pure drug spectrum and the FTIR spectra of physical mixtures to find out any variations in peak presence or disappearance.[7]

EVALUATION OF ORAL FILM

a. Thickness:

A micrometre screw gauge was used to measure the film thickness. In order to obtain uniformity of film, thickness will be measured at 5 different locations of the whole intact film. Three films were used in this test. [8]

b. Folding endurance:

The number of folds (the number of times a film is folded at the same plain) needed to break the specimen or cause visible fissures is the expression for folding endurance. This suggests that the film is fragile. The test involved folding the film at the same plane multiple times on a small strip of 4^2 cm until a visible crack was noticeable. [9]

c. Weight variation:

Ten films were randomly selected and their average weight was weighed. Individual films were weighed and compared with the average weight for the deviation.

$$\% \text{ Weight variation} = \frac{Difference\ in\ weight}{average\ weight} \times 100$$

d. Percent elongation:

When stress is applied, a strip sample stretches and this is referred to as strain. Strain is basically the deformation of strip divided by original dimension of the sample. Generally, elongation of strip increases as the plasticizer content increases. [10]

$$\% \text{ elongation} = \frac{Increase\ length\ of\ strip}{Initial\ length\ of\ strip} \times 100$$

e. Tensile strength:

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the formula: [11]

$$\text{Tensile strength} = \frac{Load\ at\ failure\ \times 100}{Strip\ thickness\ \times \text{strip width}}$$

f. *In-vitro* disintegration:

Disintegrating time is the time (sec) at which a film breaks when brought in contact with water or saliva. It's performed to ensure the disintegration of film in phosphate buffer pH 6.8. Film was placed in beaker containing 10 ml of phosphate buffer pH 6.8. Slight agitation was given at every 10s, the time at which film starts to disintegrate or break is the disintegration time. [12]

g. Drug content:

This test was performed by dissolving a 4 cm^2 area of film in 50 ml of 0.1 N HCL with stirring. This solution was filtered using a Whatman filter paper, and the filtrate was diluted to 100 ml with the same buffer in a volumetric flask. This solution was analysed using UV spectrometer.[13]

h. *In-vitro* dissolution:

In vitro dissolution study of fast dissolving films of Brivaracetam was performed using USP type I (Basket apparatus) in 300 ml simulated phosphate

buffer (pH 6.8). Dissolution media was kept at 37.5±0.5°C and at 50 rpm. Every 30 sec, 5 ml of samples were withdrawn, and replaced with the same amount of fresh medium. The filtered sample were analysed by UV spectroscopy at 272 nm and the percentage of drug released was plotted against time. [14]

i. Stability studies:

Stability studies were conducted for optimized formulations where the formulation is wrapped in aluminium foil and subjected to accelerated stability at 40±2º C/75±5% RH for 3 months according to ICH guidelines. Stability test evaluates the quality, safety and efficacy of drug products over time.[15]

RESULT AND DISCUSSION

Melting point determination:

The melting point was carried out by using capillary tube method. The result was found to be 131.97°C. Hence complies with USP standard, thus indicates the purity of the drug sample.

Solubility:

Solubility of the powder in different solvents like ethanol was determined at 20°C. The solubility studies of drug revealed that, Brivaracetam is highly soluble in various solvents. It is freely soluble in water, buffer (pH 1.2, 4.5, 7.4), Ethanol, Methanol and Glacial acetic acid, Soluble in Acetone, Toluene and slightly soluble in n-hexane. Brivaracetam has a solubility of 21.23 mg/ml in both DMSO and water. Hence Brivaracetam exhibits excellent solubility in water and common organic solvents, which facilitates its formulation and administration.

FTIR studies of Brivaracetam:

Studies on the compatibility of the drug polymer were carried out using the transformation of the FTIR- spectroscopy to determine any possible interaction between Brivaracetam with polymers used in the composition. FT-IR spectra were compared to the spectra of pure FT-IR drug. The results are shown in Fig:1,2,3, which show that the characteristic absorption peaks did not undergo any significant changes in their positions, and indicating the absence of chemical interactions between Brivaracetam and the polymer.

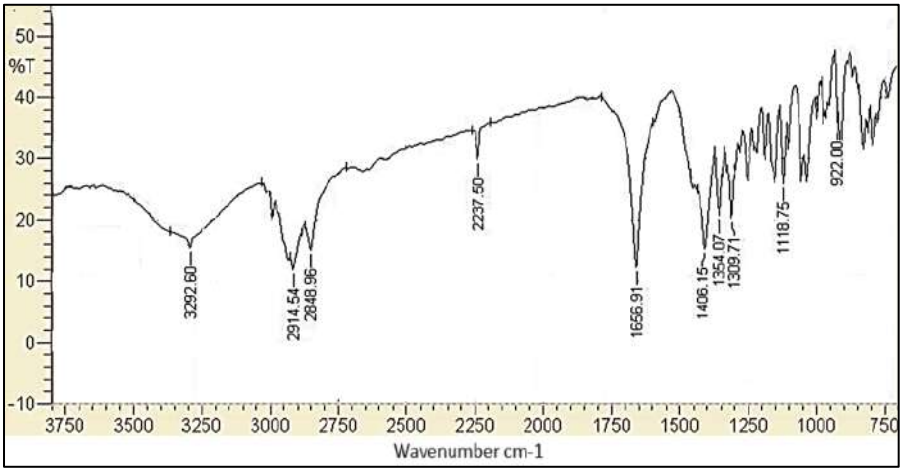

Figure 1: FTIR Spectra of Brivaracetam

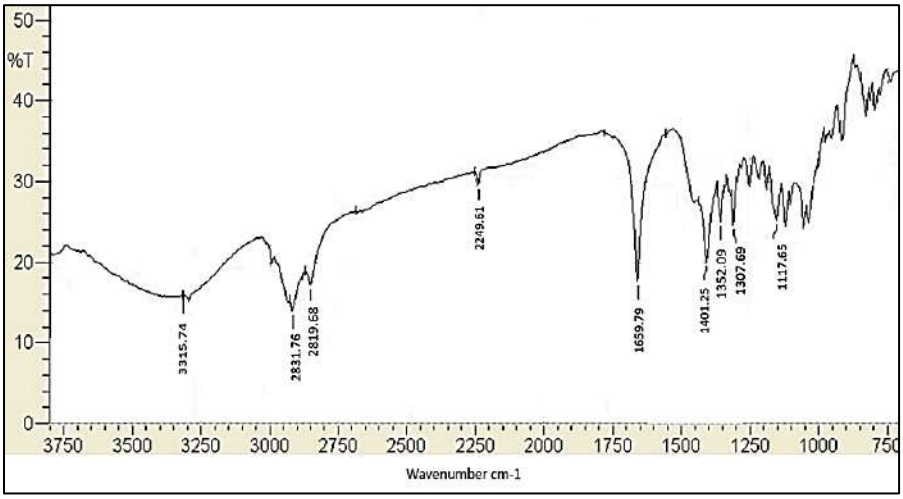

Figure 2: FTIR Spectra of Brivaracetam + HPMC E15

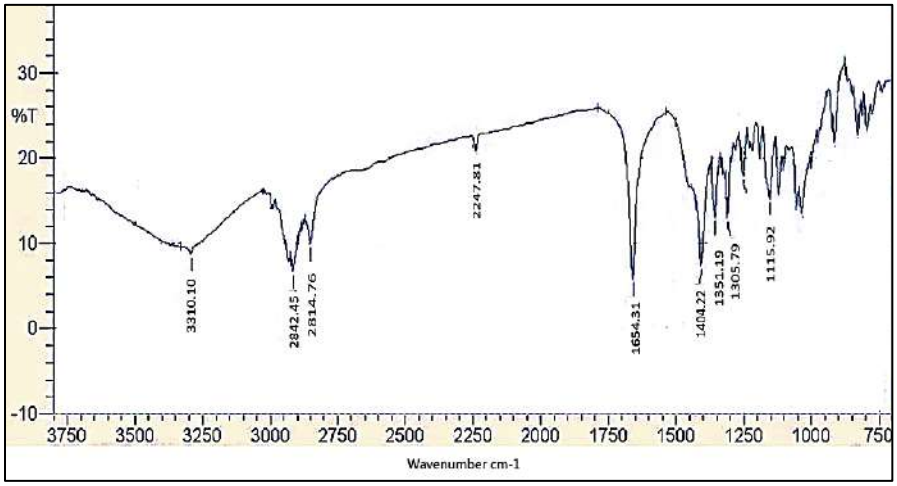

Figure 3: FTIR Spectra of Brivaracetam + HPMC E50

Table 2: Comparison peak of functional groups of Brivaracetam observed in FTIR spectra of compatibility studies.

Sl no	Types of vibrations	Drug (cm^{-1})	Physical mixture (Drug + Polymer)	
			Drug + HPMC E15	Drug + HPMC E50
1	O-H stretching	3292.60	3315.74	3310.10
2	N-H stretching	2914.54	2831.76	2842.45
3	C-H stretching	2848.96	2819.68	2814.76
4	C-N stretching	2237.50	2249.61	2247.81
5	C=O stretching	1656.91	1659.79	1654.31
6	C-C stretching	1406.15	1401.25	1404.22

EVALUATION PARAMETERS:

The prepared oral disintegrating film were evaluated for Thickness, Folding endurance, Weight variation, Percentage elongation, Tensile strength, Drug content %, *In-Vitro* Disintegration Time and all the studies were performed and results are shown in Table 3.

Table 3: Evaluation Parameters of Brivaracetam

Formulation code	Thickness	Folding endurance	Weight variation	% elongation	Tensile strength	% Drug content	*In-vitro* disintegration
F1	0.54± 0.1	120 ± 1.5	69.1±0.1	20.7±0.9	2.1±0.1	97.1±0.6	21±1.4
F2	0.57 ± 0.2	125 ± 3.6	69.1±0.1	24.5±0.5	2.31±0.4	98.3±0.8	25±1.0
F3	0.59 ± 0.1	132 ± 2.0	69.5±0.3	25.8±0.6	2.54±0.3	97.9±0.3	28±2.8
F4	0.55 ± 0.2	122 ± 1.0	70.3±0.1	27.0±0.5	2.25±0.1	98.9±0.5	20±2.1
F5	0.56 ± 0.0	124 ± 2.0	69.4±0.0	29.7±0.3	2.28±0.4	97.1±0.5	22±3.6
F6	0.56 ± 0.2	129 ± 2.1	69.6±0.2	31.7±0.2	2.39±0.4	97.1±0.7	29±2.5
F7	0.52 ± 0.2	123 ± 3.4	70.4±0.3	26.6±0.2	2.19±0.7	98.2±0.3	24±1.1
F8	0.53 ± 0.1	125 ± 3.2	69.6±0.1	26.5±0.3	2.32±0.2	97.4±0.4	27±1.2
F9	0.52 ± 0.3	122 ± 2.4	70.6±0.1	2.0±0.3	2.40±0.1	97.9±0.5	23±1.6

All values are represented by mean ± standard deviation n=3

Thickness:

The thickness of ODF formulation was in the range of 0.52 ± 0.2 to 0.59 ± 0.1mm. The results are given in Table 3 which shows a gradual increase in the thickness, by increase in the concentration of the polymer. Hence thickness is directly proportional to concentration of the polymer.

Folding Endurance:

Brittleness of the film was determined by the folding endurance. It measures the ability of the film to withstand rupture. The value of folding endurance of all the formulations was in the range of 120 ± 1.5 to 132 ± 2.0. It was observed that with increase in concentration of polymer and plasticizer, the folding endurance also increases. Higher the value of folding endurance, lower is the chance of film to rupture, and the results are given in Table 3.

Weight Variation:

Film weights ranged from 69.1 ± 0.1 to 70.6 ± 0.1in all formulations. The standard deviation was within 5% of the mean, for all batches which indicates uniformity in the weight, and the results are given in Table 3.

Percentage Elongation:

This test measures the ductility and stretchability of the film. Elongation values ranged from 20.73 ± 0.9% to 31.74 ± 0.2%. A higher elongation indicates a more ductile film, whereas a lower elongation indicates a more brittle film. All formulations were within the limits and the results are presented in Table 3.

Tensile Strength:

Tensile strength of film ranged from 2.1 ± 0.1 to 2.54 ± 0.3 kg/mm² revealing that the films had good mechanical strength and flexibility. Tensile strength of film increases with the increase in the polymeric concentration, and the results are revealed in Table 3.

% Drug content:

The percent of drug content of the film was obtained in the range of 97.1 ± 0.5to 98.9 ± 0.5 % . The results indicated in table 3 shows that the drug is distributed uniformly in all film formulations and will deliver the dose of drug accurately. The values were within the limits.

***In-Vitro* Disintegration:**

The disintegration time of oral film was in the range of 20 ± 2.1 to 29 ± 2.5sec. Disintegration time increases as the concentration of polymer and plasticizer increases. From the table 3 disintegration time indicates that how quickly the

film breaks down in oral cavity upon the contact with saliva. The values were within the limits.

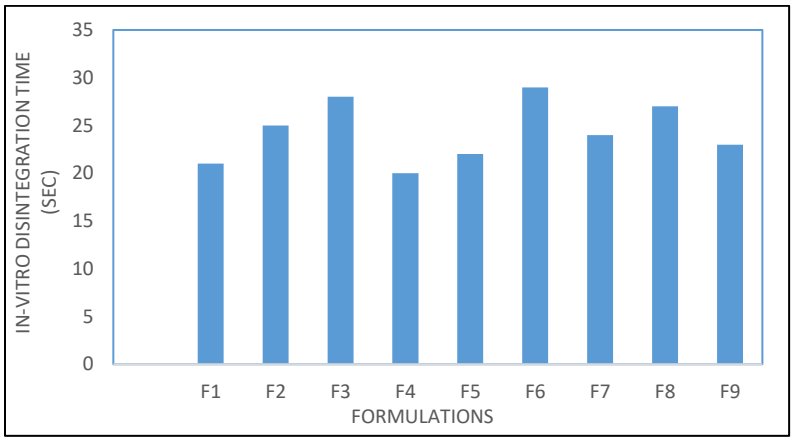

Figure 4: *In-Vitro* Disintegration profile

***In-vitro* Dissolution:**

The *in-vitro* drug release studies were carried out using USP dissolution apparatus at 50 rpm. The dissolution medium consisted of 300 ml of phosphate buffer of 6.8 pH, maintained at 37.5ºC. The drug release at different time intervals was measured using an UV spectrophotometer at 272 nm.

Table 4: *In-vitro* Dissolution Studies of Brivaracetam from F1-F9

Time (mins)	% Cumulative Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	00	00	00	00	00	00	00	00	00
2	34.5±0.1	27.2±0.3	29.6±0.4	32.8±0.3	29.3±0.4	31.4±0.3	25.8±0.2	29.9±0.3	32.3±0.2
4	53.6±0.1	59.4±0.3	65.2±0.4	47.2±0.4	49.5±0.2	58.6±0.2	43.4±0.3	41.6±0.2	50.7±0.4
6	62.2±0.2	67. ±0.2	77.4±0.5	68.3±0.4	60.4±0.3	69.4±0.3	60.8±0.4	62.9±0.1	65.1±0.4
8	79.6±0.3	85.4±0.4	88.3±0.1	81.4±0.3	76.2±0.2	82.2±0.3	83.9±0.3	78.2±0.2	76.1±0.3
10	94.4±0.4	93.3±0.2	91.1±0.4	98.9±0.3	97.9±0.2	95.3±0.1	98.7±0.6	95.9±0.1	93.1±0.2

All values are represented by mean ± standard deviation n=3

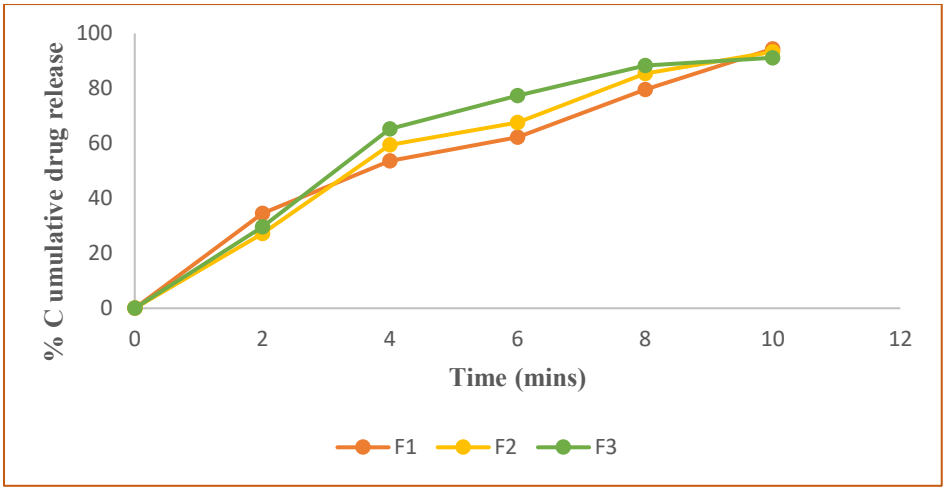

Figure 5: *In-Vitro* Dissolution profile of F1 to F3

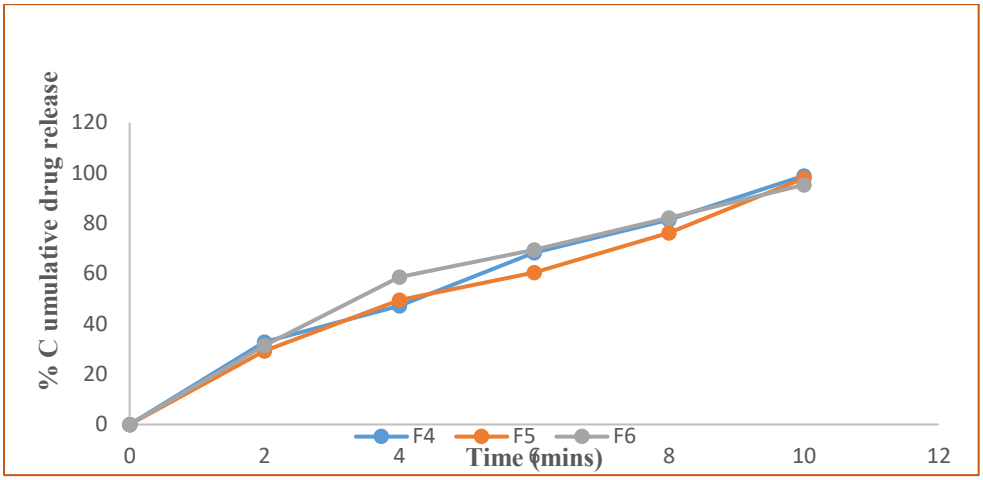

Figure 6: *In-Vitro* Dissolution profile of F4 to F6

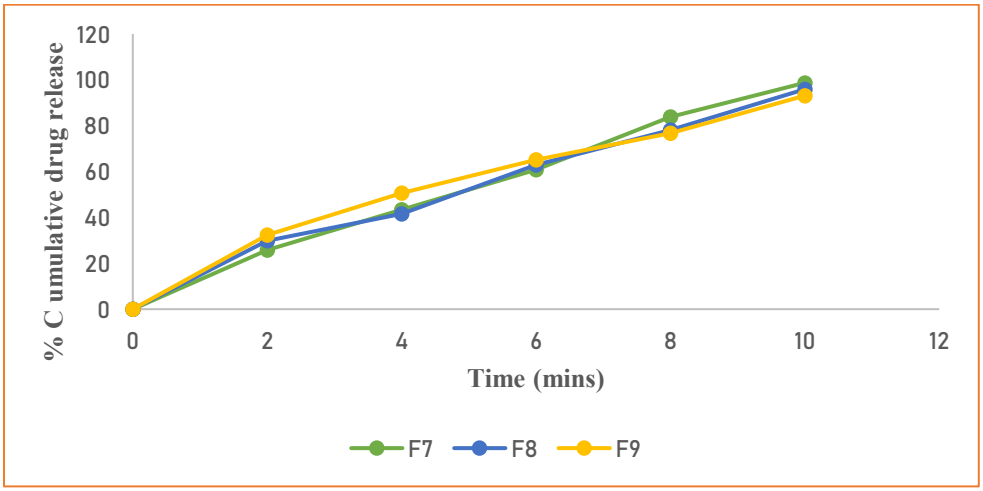

Figure 7: *In-Vitro* Dissolution profile of F7 to F9

The drug release from formulation F1 to F9 was found to be 91.1±0.4% to 98.9±0.3%. It was observed that increasing the concentration of polymer in ODFs typically results in a decreased dissolution rate of drug release due to formation of a gel-like barrier that impedes drug diffusion. Among the 9 formulations F4 was found to be the best and shows 98.9% of drug release within 10mins, So F4 was considered as an Optimized formulation and results are in table 4.

Stability Study:

Accelerated stability studies were carried out for optimized formulation (F4) with conditions of 40ºC/75% RH as per ICH guideline over 3 months and determine the % Drug content. From the result it was concluded that, formulation F4 is stable and retained their original properties with minor differences. The optimized formulation F4 values for the films indicates that there is no or minor alteration after storage.

Table 5: Stability studies with optimized formulation

Test	Initial	1 Month	2 Month	3 Month
% Drug Content	98.98 ± 0.05	98.86 ± 0.03	98.53 ± 0.06	98.21 ± 0.02

All values are represented by mean ± standard deviation n=3

CONCLUSION

ODFs are an innovative dosage form that enhances drug delivery efficiency and patient compliance. ODF containing Brivaracetam were formulated by solvent-casting method using different concentration of polymer. Compatibility of Brivaracetam with polymer was confirmed by FTIR studies. ODF were evaluated for thickness and weight variation that showed satisfactory result. Tensile strength Percentage elongation and folding endurance of the film were increased with increase in concentration of the polymer due to increase in elasticity nature of polymer. The rate of drug release and disintegration time of film were increased with increase in the concentration of the polymer. Among the prepared formulations F4 released 98.9% of drug within 10 min and showed minimum disintegration time at 20 sec when compared to the other formulations and F4 was finalized as optimized formulation. It can be concluded that ODF of Brivaracetam could be promising approach for treatment of epilepsy by overcoming the drawbacks associated with conventional dosage forms.

ACKNOWLEDGEMENTS

The authors are thankful to Micro labs, Bangalore, India for the gift sample of Brivaracetam and We sincerely acknowledge the Guide, Management, Principal, HOD, Teaching and Non-teaching staff of the principal, Sarada Vilas College of Pharmacy, Mysore for providing facilities to carry out this work.

REFERENCES

1. Kshirsagar T, Jaiswal N. Formulation & evaluation of fast dissolving oral film. World J. Pharm. Res. 2021 May;10(9):503-61.
2. Irfan M, Rabel S, Bukhtar Q. Orally disintegrating films: A modern expansion in drug delivery system. Saudi Pharm. J. 2016 Sep 1;24(5):537-46.
3. Mostafa DA. Fast dissolving oral film: overview. Eur. J. Biomed. 2018;5(8):86-101.
4. Shukla R. Formulation and evaluation of fast dissolving oral films of anti-epileptic drug. Int. J. Pharm. Sci. Drug Res. 2019;7(2):60-66.
5. Juber k, Usama K. Formulation development, optimization and evaluation of fast dissolving oral film of Verapamil Hydrochloride. Int. J. Pharm. Sci. Res. 2022 Oct;8(8):112-116.
6. Linku A, Sijimol J. Formulation and evaluation of fast dissolving oral film of anti-allergic drug. Asian J. Pharm. Res.Dev. 2018 Jul 10;6(3):5-16.
7. Dharmasthala S, Shabaraya AR. Fast dissolving oral film of piroxicam: Solubility enhancement by forming an inclusion complex with β-cyclodextrin, formulation and evaluation. J. Young Pharm. 2019;11(1):1-6.
8. Deepthi KS, Goutam K, Sharma A, Khushal S. Formulation and characterization of atenolol fast dissolving films. Indian J. Pharm. Sci. 2012;2(2):58-62
9. Deepthi A, Reddy BV, Navaneetha K. Formulation and evaluation of fast dissolving oral films of Zolmitriptan. Am. J. Adv. Drug Deliv. 2014;2(2):153-63.
10. Padamwar PA, Phasate PP. Formulation and evaluation of fast dissolving oral film of bisoprololfumarate. Int. J. Pharm. Sci. Res. 2015 Jan;6(01):135-42.
11. Karthikeyan D, Sri S, Kumar CS. Development of fast dissolving oral film containing of Rizatriptan benzoates an anti-migraine medication. Indo. Am. J. Pharma Res.2013;3(3):2642-53.
12. Bhikshapathi DV, Madhuri VD, Rajesham VV, Suthakaran R. Preparation and evaluation of Fast Dissolving Oral film containing Naratriptan HCl. Am. J. Pharm. Tech. Res. 2014 Mar;4(2):799-812.
13. Rao NR, Kistayya C, Kumar GV. Design and development of fast dissolving thin films of Losartan potassium. Int. J. Pharma. Sci. Drug. Res. 2016 Jan;8(1):01-6.

14. Zayed GM, Abd-El Rasoul S, Ibrahim MA, Saddik MS, Alshora DH. In vitro and in vivo characterization of domperidone-loaded fast dissolving buccal films. Saudi. Pharm. J. 2020 Mar 1;28(3):266-73.
15. Murthy AV, Ayalasomayajula LU, Earle RR, Jyotsna P. Formulation and evaluation of tramadol hydrochloride oral thin films. Int. J. Pharm. Sci. 2018 Apr 1;9(4):1692-98.

HOW TO CITE: Sheetal P., Nagendra R., Nanditha V. V., Venkatesh, Hanumanthachar Joshi, Formulation And Evaluation of Oral Disintegrating Film Containing Brivaracetam, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 11, 556-565. https://doi.org/10.5281/zenodo.14106902