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Research Article

PREPARATION AND EVALUATION OF SAFINAMIDE ORAL THIN FILMS

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ABSTRACT:

A fast-dissolving medicine delivery system provides a solution for people who experience trouble swallowing pills or capsules. This research aims to generate oral thin films of Safinamide via the solvent casting process. Oral thin films were made utilizing several super disintegrants, such as lycoat and crospovidone, in varying ratios alongside gelatin and polyvinyl alcohol as film-forming agents. The formulated films were assessed for film thickness, folding endurance, in-vitro disintegration time, and in-vitro drug release profile in pH 6.8 phosphate buffer. Investigation of drug content and drug-polymer interactions using infrared spectroscopy. Among all formulations, formulation F12, made with 450 mg of crospovidone, exhibited favorable drug release (99.34±1.25%).

Keywords: Safinamide, PVA, Crospovidone, Oral Thin Films and FT-IR.

INTRODUCTION

The oral delivery sector constitutes around 52 percent of the total drug delivery business, with considerable interest in the development of modified release oral dosage forms. However, there are other prevalent issues connected with oral medication delivery, such as the potential for partial active pharmaceutical ingredient (API) loss owing to tablet or capsule crushing, or inaccuracies in liquid administration, which can lead to dose errors and either overdosing or ineffectiveness of drug therapy.[1,2,3]. To address these challenges, quick dissolving drug delivery devices are receiving significant interest. These coatings rapidly disintegrate in the oral cavity, imparting the flavor [4,5,6]. Numerous pharmaceutical firms have been redirected by recent technological advancements to investigate new prospects in this domain, aiming to provide rapid and precise dosage that is anticipated to enhance compliance, especially among pediatric patients, while also improving the solubility of poorly soluble drugs [7,8,9].

No water or measurement is necessary, as the medication is ingested directly. The absorption of drugs through the oral mucosa into systemic circulation is a compelling method due to its high vascularization and permeability. Consequently, fast dissolving films have emerged as a favored oral dose form for several drugs, since their extensive surface area facilitates swift breakdown, thereby enhancing patient adherence.

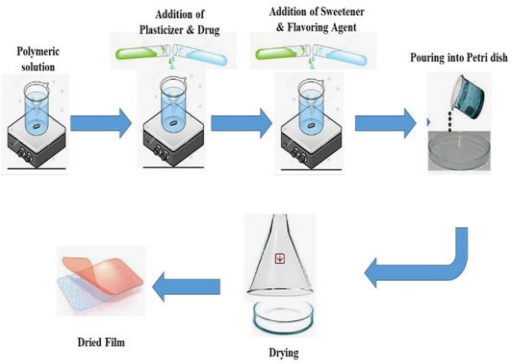

Figure No.1 Solvent casting technique

Oral Thin Films, an innovative medication delivery device for oral administration, was created utilizing transdermal patch technology. The delivery method comprises a thin oral strip that is applied on the patient's tongue or any oral mucosal tissue; upon contact with saliva, the film swiftly hydrates and sticks to the application site. It subsequently disintegrates and dissolves swiftly to release the drug for oromucosal absorption, or, with formula adjustments, will preserve the rapid-dissolving

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properties to facilitate gastrointestinal absorption upon ingestion.

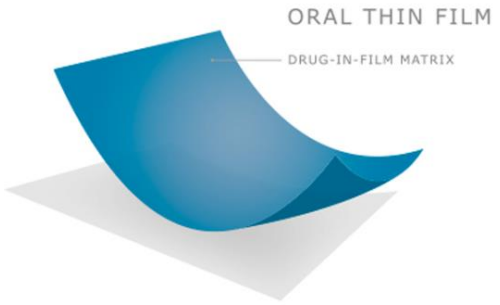

Figure No.2 Oral Thin Film

Despite significant advancements in various drug delivery systems developed for administration through multiple routes such as oral, parenteral, transdermal, and nasal, the oral route remains the preferred method due to its painless nature, ease of administration, and patient-friendliness. Several novel methods have been developed for oral administration to enhance patient compliance. The fast dissolving drug delivery system (FDDS) is increasingly favored by pharmaceutical firms as an innovative approach that facilitates the administration of medication without swallowing difficulties for patients.

The clinical syndrome, delineated by James Parkinson in his 1817 ‘Essay on the Shaking Palsy’ and commonly known as ‘Parkinson’s disease’ (PD), is characterized by the principal features of resting tremor, bradykinesia, rigidity, and postural instability, along with a range of additional motor and non-motor symptoms.[10,11,12] As the world population ages and life expectancy rises, age-related disorders such as Parkinson's Disease are garnering heightened focus from the scientific community. Neurological illnesses currently represent the primary cause of disability globally, with Parkinson's disease being the most rapidly increasing among them. [13] The Global Burden of Disease Study projects that the incidence of Parkinson's disease would increase from around 7 million cases in 2015 to over 13 million by 2040, indicating a possible 'PD Pandemic'.[14] This projection, predicated on anticipated population increase, serves just as an estimate, although it underscores the significant cost that Parkinson's disease and other neurodegenerative disorders may impose on society.

The term 'idiopathic' PD has often been employed to denote the predominant etiology of parkinsonism in clinical practice. Nonetheless, the identification of monogenic variants of Parkinson's disease (which may be clinically indistinguishable from the 'idiopathic' variant), the clinical heterogeneity of the condition, and the clinical overlap among Parkinson's disease dementia, dementia with Lewy bodies, and other parkinsonian disorders necessitate ongoing re-evaluation of the nosology of Parkinson's disease classification. [15,16,17]

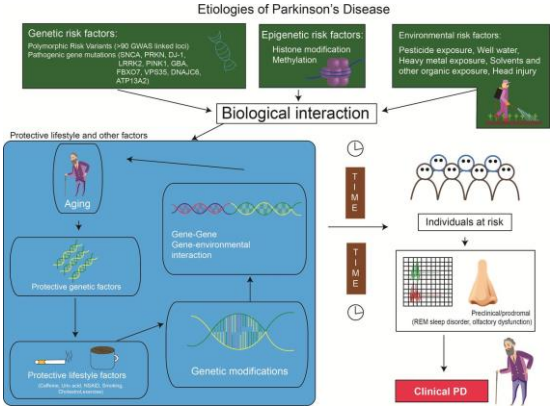

Figure No.3 Etiology of Parkinson’s Disease

Safinamide is a specific and reversible inhibitor of monoamine oxidase B. It also suppresses glutamate release and the reuptake of dopamine and serotonin. It has a high affinity for the σ1 receptor. Furthermore, it obstructs sodium and calcium channels. Safinamide pills serve as an adjunctive therapy for individuals with Parkinson's disease who are presently on levodopa/carbidopa and are encountering "off" periods. Patients contraindicated for safinamide include individuals with severe hepatic impairment and those concurrently using dextromethorphan, a medication for cough or cold treatment. Patients on a monoamine oxidase inhibitor should also avoid this medication, since it may induce a rapid and severe elevation in blood pressure. Patients using opioid medications, certain antidepressants (including serotonin–noradrenaline reuptake inhibitors, tricyclics, tetracyclics, and triazolopyridines), or cyclobenzaprine should avoid this, since it may induce a potentially fatal condition known as serotonin syndrome. The predominant adverse responses noted were uncontrollable involuntary movements, falls, nausea, and sleeplessness. Significant, but less prevalent, concerns encompass: hallucinations and psychotic behavior; issues with impulse control and compulsive behaviors; withdrawal-induced hyperpyrexia and disorientation; and retinal disease.[18]

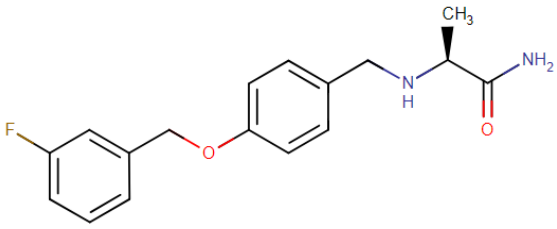

Figure No.4 Structure of safinamide

MATERIALS & METHODS USED:

Safinamide API was procured from Kekule Pharma Limited, and Gelatin, Propylene Glycol, Citric acid, Lycoat were procured from S.d.fine chemicals Mumbai, P.V.A was procured from INR chem. Mumbai, Trusil mixed flavor R.S.V was procured from International flavours of fragnance India Ltd.

Preparation Method:

Formulation of Oral Thin Films of Safinamide :

The oral thin films of Safinamide was prepared by solvent casting technique. The Oral Thin Films were prepared using polymers like Gelatin, PVA. Propylene glycol is used as a plasticizer and super disintegrants like Crospovidone and Lycoat. The calculated amount of polymer was dispersed in the three-fourth volume of with continuous stirring using magnetic stirrer and the final volume was adjusted with distilled water. The calculated amount of Safinamide was incorporated in the polymeric solutions after levitation with required volume of Propylene Glycol and Sodium saccharin and Flavor. The solution was cast onto Glass Plate then kept in hot air oven at 40^0c. The films were punched into size of 4cm^2 containing 50mg of Safinamide . By carrying out the trial and error method different concentrations for a film forming polymers were used like Gelatin, PVA. It has been found that 500mg of gelatin, 500 mg of PVA shows better films. Which these concentrations of films were prepared by dissolving different quantities of film forming polymers in required amount of water.

Table 1: Formulation details of Safinamide Oral thin films

Formulation Code / Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Safinamide	450	450	450	450	450	450	450	450	450	450	450	450
Gelatin	500	500	500	500	500	500	-	-	-	-	-	-
PVA	-	-	-	-	-	-	500	500	500	500	500	500
Lycoat	200	250	300	350	400	450	-	-	-	-	-	-
Crospovidone	-	-	-	-	-	-	200	250	300	350	400	450
Aspartame	20	20	20	20	20	20	20	20	20	20	20	20
Valina Flavor(mg)	20	20	20	20	20	20	20	20	20	20	20	20
Propylene Glycol(ml)	30	30	30	30	30	30	30	30	30	30	30	30
Distilled	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Calculation of dose for Safinamide :

The dose of Safinamide is 450 mg. Therefore, amount of Safinamide required in 4 cm2 film is 50 mg.

- Length of glass plate =6 cm.
- Width of glass plate =6 cm.
- Area of the plate =36 cm2.
- No. of 4 cm^2 films present whole plate =36/4 =9 films.
- Therefore, Each films contains 50 mg of drug
- 9 films contain 450 mg drug (9*50).
- So, the Labelled claim of drug = 50 mg

RESULTS AND DISCUSSIONS

Preformulation Studies:

Solubility: The solubility of Safinamide was carried out at 250C using 0.1 N HCL, 6.8 pH phosphate buffer, and purified water.

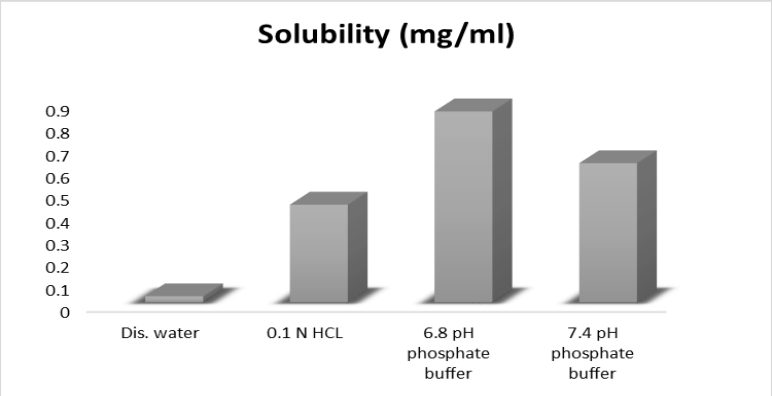

Figure No.5 Solubility studies of Safinamide

Discussion: From the conducted solubility studies in various solutions, we can say that 6.8pH Buffer solutions have more solubility when compared to other buffer solutions.

Flow properties of the pure drug

Table 2 Flow properties of the pure drug

Angle of repose	25.02±0.92
Bulk density	0.48±0.24
Tapped density	0.53±0.28
Carr's index	14.28±0.37
Hausner's ratio	1.15±0.08

Discussion: From the above flow properties of the pure drug, it was concluded that the all the parameters are within the limits indicating the free flow of drug. Total 12 formulations were prepared with 2 different film forming polymers with 2 different disintegrants. The films were then characterized by various physicochemical parameters.

UV spectrum of Safinamide

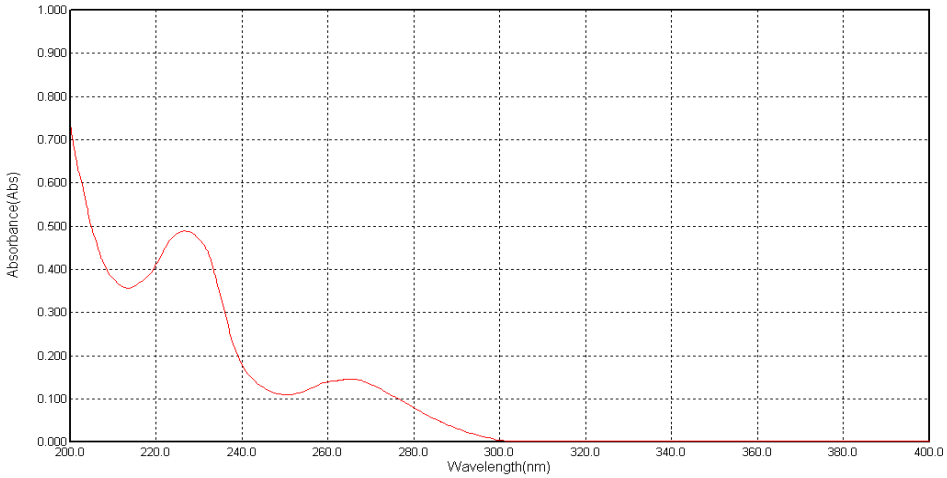

Figure No.6 UV spectra of Carbamazepine at 285.0 nm

Discussion: The λ-max of Safinamide of 100% solution i.e 20 ppm (µg/ml) by using Single Beam Spectrophotometer (YIS-294) was found to be at 228.0 nm by using 0.1 N HCL Buffer.

Calibration curve of pure Drug:

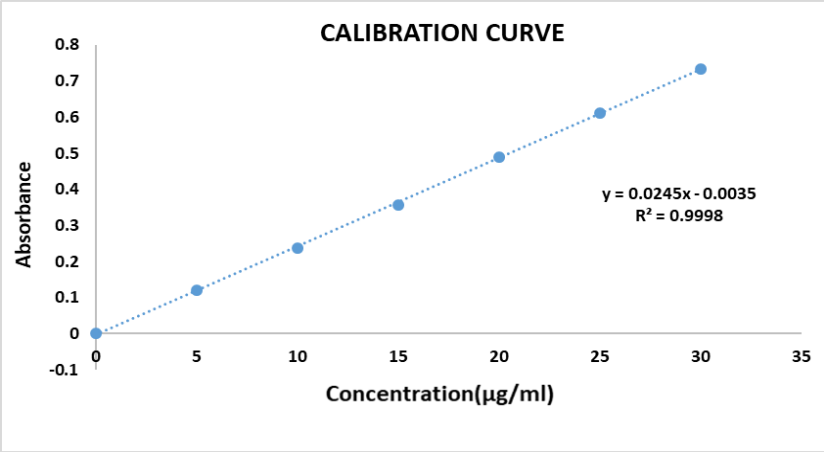

Figure No.7 Calibration curve graph

Discussion: The linearity was found to be in the range of 5-30µg/ml buffer. The regression value was closer to 1 indicating the method obeyed Beer-lamberts' law.

FT-IR SPECTROSCOPY STUDY.

Compatibility studies were performed using FT-IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied by making a KBr disc. The characteristic absorption peaks of Safinamide were obtained at different wave numbers in different samples.The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug is compatible with the formulation components. The spectra for pure drug and optimized formulation are shown below.

Pure Drug

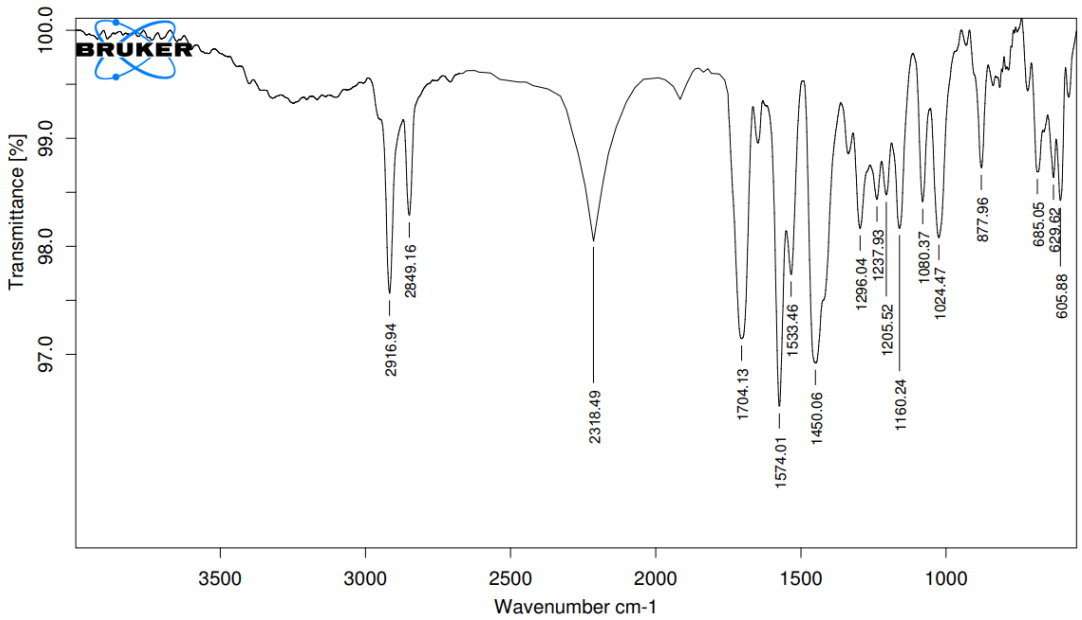

Figure No.8 I.R. Spectra of pure drug

Optimized Dosage form

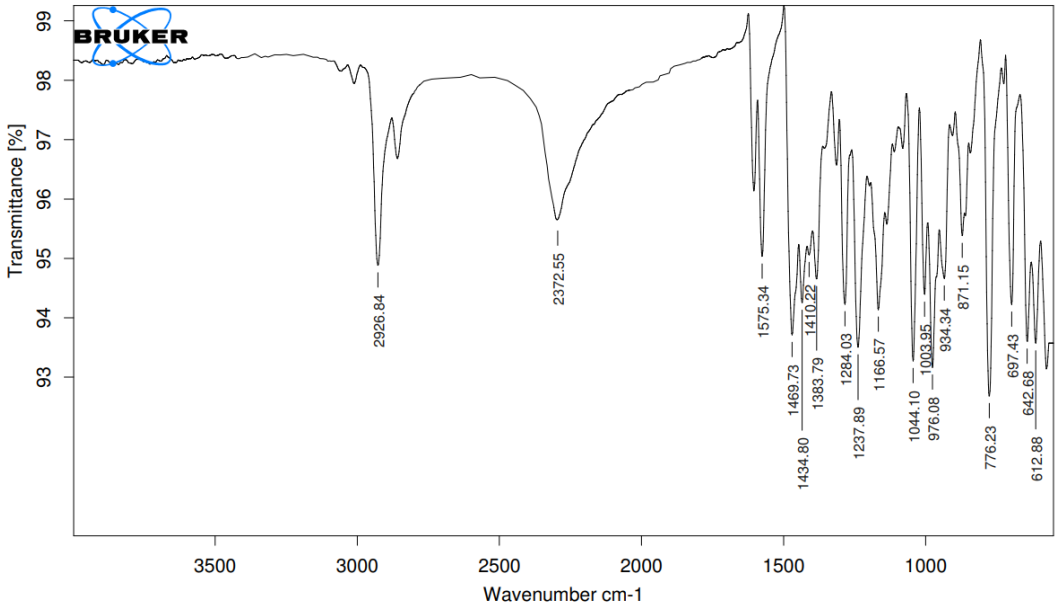

Figure No.9 I.R. Spectra of optimized formulation

Discussion: The FTIR spectrum of pure Safinamide are shown in Figure respectively. The units are represented as cm−1. The FTIR spectrum of pure Safinamide is displayed in Figure. No. Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Safinamide) and optimized formulation (Safinamide + Excipients) which indicates there are no physical changes.

Evaluation of Oral Thin Films Formulations:

Physical appearance and surface texture of films:

These parameters were checked simply with visual inspection of films and by feel or touch. The observation suggests that the films are having the smooth surface and they are elegant enough to see.

Table 3: Evaluation of Oral Thin Films of Safinamide

Formulation Code	Avg. Weight (mg)	Avg. Thickness (mm)	Average Folding Endurance
F1	198.74±1.12	0.53±0.05	143±1
F2	249.45±1.34	0.59±0.03	145±2
F3	302.18±1.42	0.62±0.06	156±4
F4	351.48±1.56	0.67±0.04	161±1
F5	401.25±1.19	0.71±0.02	167±3
F6	451.37±1.24	0.75±0.05	171±1
F7	201.24±1.15	0.58±0.03	146±2
F8	250.46±0.24	0.60±0.04	150±2
F9	303.49±0.15	0.63±0.05	158±3
F10	352.45±0.45	0.68±0.03	163±4
F11	402.34±0.25	0.73±0.04	169±2
F12	450.85±0.16	0.76±0.06	174±1

Discussion:

The average weight the films was found in between 198.74±1.12- 450.85±0.16. The average thickness of the films was found in between the range of 0.53±0.05-0.76±0.06.The average folding endurance of the films was been found in between the ranges of 143±1-174±1.

Table 4: Evaluation of Oral films of Safinamide

Formulation Code	Avg. Drug Content Uniformity (%)	Avg. In Vitro Disintegration (sec)	Avg. Surface pH
F1	90.45±0.42	19	6.7±0.08
F2	92.75±0.36	17	6.6±0.05
F3	93.37±0.48	16	6.5±0.04
F4	94.29±0.65	15	6.7±0.09
F5	96.82±0.29	13	6.6±0.07
F6	97.15±0.47	12	6.5±0.06
F7	92.19±0.65	17	6.4±0.05
F8	94.18±0.48	15	6.2±0.03
F9	95.26±0.25	14	6.6±0.04
F10	96.85±0.29	13	6.8±0.05
F11	97.45±0.42	12	6.7±0.08
F12	98.98±0.26	10	6.8±0.07

Discussion: The average content uniformity of the formulations from F1 to F12 was found in between 90.45±0.42% - 98.98±0.26.The Disintegration time of the films from F1 to F12 was in between the range of 19-10seconds.The average surface pH of the films was in the range of pH 6.2±0.03-6.8±0.07.

In-Vitro Dissolution Study:

The in-vitro drug release study of oral thin films from each batch (F1 to F12) was carried out in 6.8 pH phosphate buffer solution for 30 mins and the values are shown in Table. The plot of % Cumulative drug release V/s time (mins) were plotted and depicted as shown in Fig & Table

Table 5 In vitro dissolution studies

Time(min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	37.47 ±1.25	40.44 ±1.52	44.47 ±1.48	48.37 ±1.54	52.76 ±1.45	65.42 ±1.21
10	48.47 ±1.37	51.32 ±1.63	54.52 ±1.54	57.18 ±1.37	58.38 ±1.20	77.47 ±1.23
15	60.54 ±1.78	68.32 ±1.84	68.41 ±1.69	65.45 ±1.28	69.45 ±1.35	86.45 ±1.20
20	68.39 ±1.58	70.35 ±1.28	76.26 ±1.78	78.37 ±1.48	80.27 ±1.18	93.46 ±1.37
25	77.32 ±1.87	86.76 ±1.15	87.42 ±1.27	88.45 ±1.26	89.46 ±1.25	98.54 ±1.20
30	93.85 ±1.68	95.48 ±1.36	96.34 ±1.24	97.41 ±1.23	98.56 ±1.37	

Table 6: In vitro dissolution studies

Time(min)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
5	40.12 ±1.48	45.17 ±1.47	47.57 ±1.58	57.91 ±1.42	65.93 ±1.68	76.24 ±1.65
10	52.45 ±1.54	55.65 ±1.45	58.45 ±1.45	68.43 ±1.64	79.86 ±1.26	80.15 ±1.84
15	60.18 ±1.46	67.38 ±1.47	69.47 ±1.57	75.48 ±1.69	85.47 ±1.48	88.42 ±1.69
20	75.57 ±1.45	76.45 ±1.28	79.36 ±1.65	87.49 ±1.68	90.26 ±1.84	95.26 ±1.37
25	88.65 ±1.37	91.34 ±1.45	86.14 ±1.84	94.97 ±1.26	94.45 ±1.97	99.34 ±1.25
30	94.41 ±1.12	95.67 ±1.12	96.27 ±1.64	98.83 ±1.45	98.45 ±1.84	

Discussion: This shows that effectiveness of super disintegrants is in the order of Crospovidone>Lycoat. The concentration of super disintegrant's in the formulations also increased the dissolution rates. In all the formulations up to 500mg concentration of PVA and 450 mg of Crospovidone, there was linearly increase in dissolution rate. At higher concentration, all the formulations showed increase in dissolution rate.

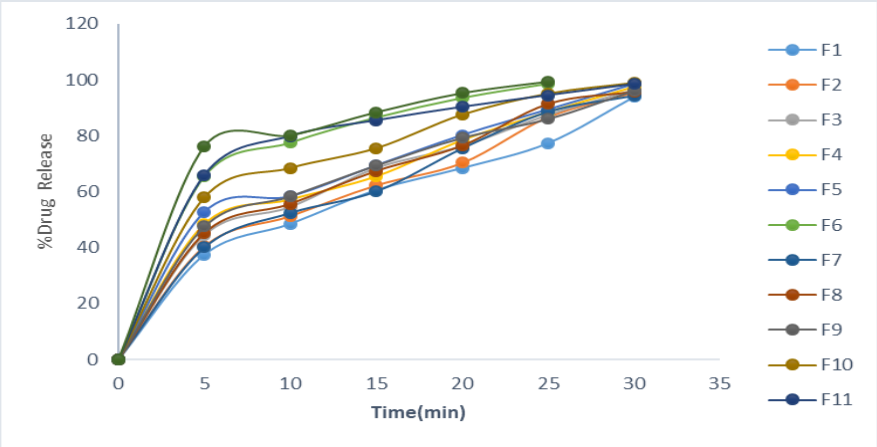

Figure No.10 In-vitro drug release of formulations (F1-F12)

Drug Release Kinetics of Safinamide

Zero Order Release Kinetics

Figure No.11 Zero order release profile of Safinamide Best formulation (F12)

First Order Release Kinetics Data

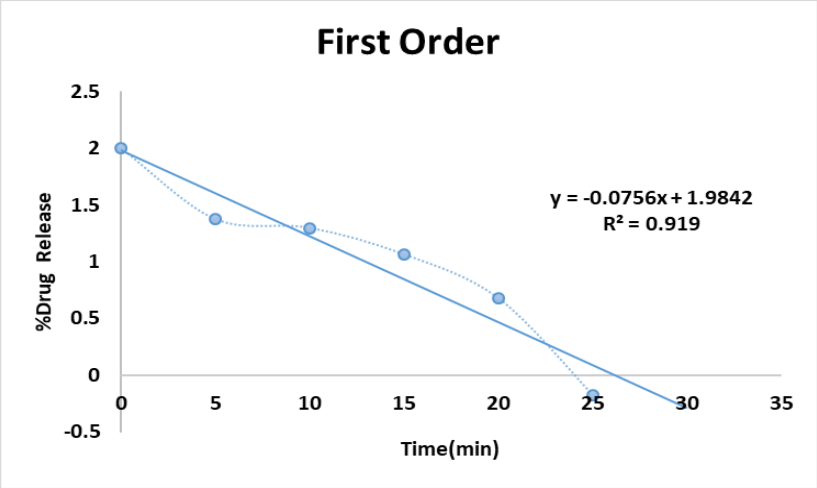

Figure No.12 First order release profile of Safinamide Best formulation (F12)

Table 7. Regression coefficients fit to different drug release kinetics models of Safinamide Best formulation (F12).

Formulation code	Zero order	First order
	r^2	r^2
F12	0.661	0.919

Discussion: The in vitro dissolution data for best formulation F12 were fitted in different kinetic models i.e, zero order, first order. Optimized formulation F12 follows first order.

SUMMARY:

In the present study Oral drug delivery system of Safinamide were successfully developed in the form of oral thin films which offers a suitable and practical approach in serving the desired objective of faster disintegration and dissolution characteristics with increase bioavailability. Oral thin films of Safinamide were prepared by using crospovidone and lycoat as super disintegrants. Under the pre-formulation studies, API characterization and drug-excipient compatibility studies were carried out. The API characterization showed compliance with the drug characteristics. The disintegrants and other excipients were selected based on the satisfying results produced during drug- excipient compatibility studies to develop the final formulation.

The final suitable formulation (F12) was achieved fruitfully by the solvent casting method using polyvinyl alcohol and Crospovidone as disintegrant which exhibited a rapid disintegration time (10sec) and in vitro drug release (99.34±1.25%) ate the end of 25minutes. Considering the results of batches containing lycoat and crospovidone as disintegrant it can be concluded that the formulation F12 was meeting the higher in-vitro correlation limits and in less instance of time when subjected to the comparison with other formulation with crospovidone as the disintegrating agent. It was also observed that solvent casting method was the best suitable method used for immediate drug release. Based on all the above considerations these formulas will be subjected to bioavailability studies and if it complies with all the requirement of those studies the same formula will be commercialized.

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