International Journal of Drug Development and Research

Pooja and Sayyad, Int J Drug Dev & Res 2018, 10:3

Research Article

Design, Development and Evaluation of Oxcarbazepine Loaded Fast Dissolving Oral Film

Pooja RD[1]* and Sayyad FJ[2]

[1]*Department of Biopharmaceutics, Government College of Pharmacy, Karad, Maharashtra, India*

[2]*Government College of Pharmacy, Karad, Maharashtra, India*

***Corresponding author:** Pooja RD, Department of Biopharmaceutics, Government College of Pharmacy, Karad, Maharashtra, India, Tel: 02164271196; E-mail: poojadoshi2193@gmail.com

Received July 22, 2018; **Accepted** July 28, 2018; **Published** July 31, 2018

Abstract

The present study was aimed to develop a novel fast dissolving drug delivery system for an antiepileptic drug such as Oxcarbazepine. The fast dissolving films were prepared by solvent casting technique using water-soluble polymers such as hydroxyl propyl methylcellulose HPMC E-5 LV, E-50 LV. In this study PEG 400 was used as plasticizer and Mannitol was used as a sweetener. Concentration of water soluble polymers were optimized during preliminary studies. The prepared films were evaluated for thickness, weight uniformity, drug content, surface pH, folding endurance, tensile strength, percent elongation, *in-vitro* disintegration time, swelling index and *in-vitro* drug release studies. The results obtained showed no physical chemical incompatibility between the drug and the polymers. The prepared films were clear, transparent and smooth surface. D4 formulation showed maximum *in-vitro* drug release 94.35%, following first order kinetics (r^2=0.9791).

Keywords: Fast dissolving films; Oxcarbazepine; Solvent casting technique; Water-soluble polymers

Introduction

Recently Fast dissolving technology have been emerges out as a new drug delivery system that provides a very convenient means of taking medications and supplements [1]. These systems either dissolve or disintegrate within a minute. This delivery system consists of a thin film, which is simply placed on the patient's tongue or mucosal tissue, instantly wet by saliva; the film rapidly dissolves. Then it rapidly disintegrates and dissolves to release the medication for oral mucosal absorption [2,3]. They undergo disintegration in the salivary fluids of the oral cavity, where they release the active ingredient. The major portion of the active ingredient is swallowed orally along the saliva and absorption takes place in the gastrointestinal tract subsequently making them particularly suitable for pediatrics and geriatric patients.

The fast dissolving films (FDF) were introduced in 1970's as an alternative to the conventional tablet and capsule which require swallowing of the dosage form. These dosage forms offer specific advantages including accurate dosing, ease of transport, handling, acceptable taste, rapid onset of action and patient compliance [4]. Solvent casting was proved to be reliable technique for the manufacturing of FDFs. The film strips prepared by this method undergo instantaneous disintegration upon placing in buccal/oral cavity. The plasticizers present in FDF formulation reduce the glass transition temperature and thereby enabling desired film qualities [5]. Oxcarbazepine, an antiepileptic drug and being a BCS Class II moiety has high permeability and low solubility. It is known that the pharmacological activity of oxcarbazepine occurs primarily through its 10-monohydroxy metabolite (MHD). *In vitro* studies indicate an MHD-induced blockade of voltage-sensitive sodium channels. Resulting in stabilization of hyper excited neuronal membranes, inhibition of repetitive neuronal discharges and diminution of propagation of synaptic impulses. The half-life of parent drug is 2 hours, while half-life of MHD is about 9 hours, so the MHD is responsible for most antiepileptic activity. Oxcarbazepine is well absorbed and its bioavailability is about 75%. In view of these facts this drug can be considered as a suitable candidate for fast dissolving oral film [6]. In order to enhance the solubility of Oxcarbazepine and subsequently dissolution and absorption, this research work is undertaken. Solid dispersions of OXC with PVP K30, PEG 6000 and HPMC E5 carriers were prepared. Solid dispersions were prepared by solvent evaporation technique at different drug: carrier weight ratios such as Oxcarbazepine: PVP K30 (1:1, 1:2, 1:3), Oxcarbazepine: PEG 6000 (1:1, 1:2, 1:3) and Oxcarbazepine: HPMC E5 (1:1, 1:2, 1:3) and were evaluated. The optimized formulation of solid dispersions, OXC: PVP K30 at 1:3 weight ratio was selected and used for further study. The optimized solid dispersion was used in preparation of OXC films by solvent casting method, which offers superiority over other practicing methods. In this study, an attempt is made to investigate the feasibility of fast dissolving oral films as a medium for the fast delivery of Oxcarbazepine with better bioavailability and enhanced patient compliance.

Materials and Methods

Oxcarbazepine was procured from Aarati Pharmaceuticals, Mumbai, India. HPMC E5 LV, HPMC E50 LV were purchased from Loba Chemicals, Mumbai, India. All other chemicals used were of analytical grade.

Characterization of drug and polymers

Characterization study has been performed to know drug and polymers were in stable and pure form so as to formulate into dosage form (Tables 1-16).

Physical properties

The sample of Oxcarbazepine and polymer were studied for physical properties such as colour and appearance by visual observation. The results are given in Table 7.

Melting point

The melting point of Oxcarbazepine and polymer were determined by open capillary tube method. Drug filled capillary attached to thermometer and placed in the thieles tube containing liquid paraffin as heating medium. Neck of thieles tube was heated using burner and the observed melting point was noted and matched with reported

Formulation code	Drug (ml)	3% HPMC E-50 (ml)	Mannitol (mg)	Citric acid (mg)	PEG 400 (ml)	Menthol (mg)	q.s
A1	1	8	15	20	0.2	0.03	10
A2	1	7	15	20	0.2	0.03	10
A3	1	6	15	20	0.2	0.03	10
A4	1	5	15	20	0.2	0.03	10

Table 1: Composition of fast dissolving film (A1-A4), 1% drug solution+3% HPMC E-50 solution.

Formulation code	Drug (ml)	4% HPMC E-50(ml)	Mannitol (mg)	Citric acid(mg)	PEG 400(ml)	Menthol (mg)	q.s
B1	1	8	15	20	0.2	0.03	10
B2	1	7	15	20	0.2	0.03	10
B3	1	6	15	20	0.2	0.03	10
B4	1	5	15	20	0.2	0.03	10

Table 2: Composition of fast dissolving film (B1-B 4), 1% drug solution+4% HPMC E-50 solution.

Formulation code	Drug (ml)	5% HPMC E-50(ml)	Mannitol (mg)	Citric acid(mg)	PEG 400(ml)	Menthol (mg)	q.s
C1	1	8	15	20	0.2	0.03	10
C2	1	7	15	20	0.2	0.03	10
C3	1	6	15	20	0.2	0.03	10
C4	1	5	15	20	0.2	0.03	10

Table 3: Composition of fast dissolving film (C1-C4), 1% drug solution+5% HPMC E-50 solution.

Formulation code	Drug (ml)	7% HPMC E-50(ml)	Mannitol (mg)	Citric acid(mg)	PEG 400(ml)	Menthol (mg)	q.s
D1	1	8	15	20	0.2	0.03	10
D2	1	7	15	20	0.2	0.03	10
D3	1	6	15	20	0.2	0.03	10
D4	1	5	15	20	0.2	0.03	10

Table 4: Composition of fast dissolving film (D1-D4), 1% drug solution+7% HPMC E-5 solution.

Formulation code	Drug (ml)	8% HPMC E-50(ml)	Mannitol (mg)	Citric acid(mg)	PEG 400(ml)	Menthol (mg)	q.s
E1	1	8	15	20	0.2	0.03	10
E2	1	7	15	20	0.2	0.03	10
E3	1	6	15	20	0.2	0.03	10
E4	1	5	15	20	0.2	0.03	10

Table 5: Composition of fast dissolving film (E1-E4), 1% drug solution 8%HPMC E-5 solution.

Formulation code	Drug (ml)	9% HPMC E-50(ml)	Mannitol (mg)	Citric acid(mg)	PEG 400(ml)	Menthol (mg)	q.s
F1	1	8	15	20	0.2	0.03	10
F2	1	7	15	20	0.2	0.03	10
F3	1	6	15	20	0.2	0.03	10
F4	1	5	15	20	0.2	0.03	10

Table 6: Composition of fast dissolving film (F1-F4), 1% drug solution+9%HPMC E-5 solution.

Identification Tests		Observed Result	Reported Standard
Colour	Oxcarbazepine	Off-White to Faintly Orange	Off-White to Faintly Orange
	HPMC	White	White
Melting	Oxcarbazepine	215°C	215°C-216°C
point	HPMC	192°C	190°C- 200°C

Table 7: Physical Properties and Melting point of drug and polymer.

value. Observed value of melting point are reported in Table 7.

UV spectroscopy

Accurately weighed quantity (5 mg) of drug was dissolved in acetone (50 ml). This was further diluted suitably with solvents phosphate buffer pH 6.8 to make concentrations of 100 (µg/ml). The λ max of drug was determined by scanning 100 µg/ml solution in phosphate buffer pH 6.8 over the wavelength range of 200-400 nm by using UV/VIS Spectrophotometer (Lab India 3000).

Calibration curve of oxcarbazepine in phosphate buffer pH 6.8

Oxcarbazepine (5 mg) was accurately weighed and transferred to 50 ml volumetric flask. It was then dissolved in 10 ml acetone. The volume was made up to 50 ml with phosphate buffer pH 6.8 to obtain stock solution (100 µg/ml). The UV spectrum was recorded in the range of 200-400 nm by using UV double beam spectrophotometer (Lab India 3000). The wavelength of maximum absorption (λ max) was determined. From the stock solution (100 µg/ml), standard solutions in the range 10-60 µg/ml were prepared by appropriate dilution with phosphate buffer pH 6.8. The absorbance of each standard solution was determined spectrophotometrically at λ max 306 nm. Using absorbance-concentration data, Beer-Lambert's plot was constructed. The absorbance-concentration data is given in Table 8.

Fourier Transform Infra-Red (FTIR) analysis

Infrared spectrophotometry is a useful analytical technique utilized to check the chemical interaction between the drug and other excipients used in the formulation. The sample (1 mg) was powdered and placed on sampler. The spectrum was recorded by scanning in the wavelength region of 4000-400 cm^{-1} using FTIR spectrophotometer. The interpretation of FTIR of drug and polymer are given in Tables 9-11 and Figures 1-4.

Differential Scanning Calorimetric (DSC) studies

The DSC thermogram of Oxcarbazepine and polymer were recorded by using a Perkin Elmer system with a differential scanning calorimeter equipped with a computerized data station. All samples were weighed and heated in a closed pierced aluminium pan at a scanning rate of 10°C/min between 30°C and 300°C and 60 ml/min of nitrogen flow. The DSC of Oxcarbazepine and polymer are given in Figures 5 and 6.

Solid dispersions

Solid dispersions of OXC with PVP K30 in the weight ratio of 1:3 were prepared using solvent evaporation technique. The appropriate weighed amounts of OXC and PVP K30 were moistened with methanol to get clear drug solution Methanol was removed by evaporation technique. The mass obtained was further dried at 50°C for 24 hrs in an Hot air oven. The product was crushed, pulverized and passed through a sieve number # 80. The sample prior to be used for the study were stored in a desiccator (Figures 7-10).

Preparation of fast dissolving films

Preparation of stock solution of drug: Solid dispersion of oxcarbazepine equivalent to 1 g was accurately weighed and dissolved in 100 ml of methanol to prepare 1% drug solution. The stock solution concentration become 10 mg/ml solution (Figures 11 and 12).

Preparation of stock solution of polymer

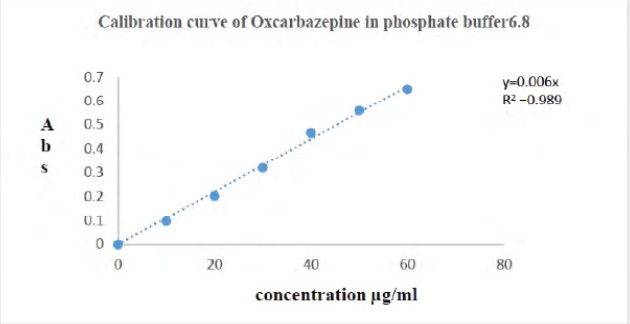

Figure 1: Calibration curve of OXC in pH 6.8 phosphate buffer.

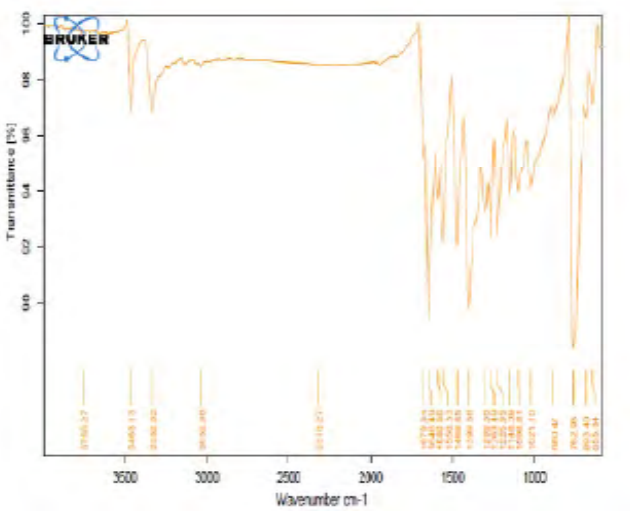

Figure 2: FTIR of Oxcarbazepine.

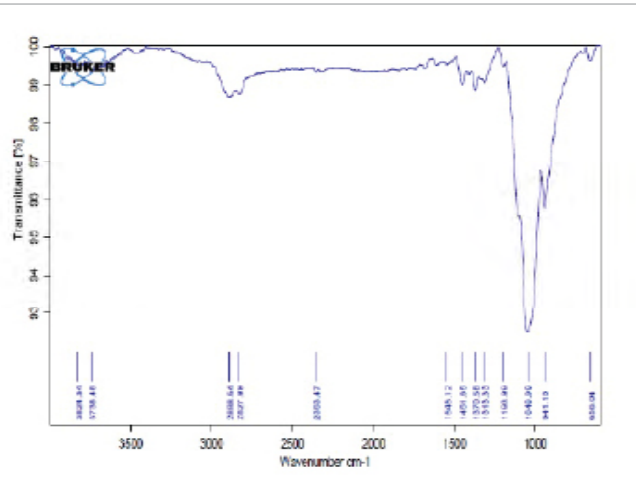

Figure 3: FTIR of HPMC.

HPMC E 50 solution: (3%, 4% and 5% w/v) was prepared by adding 3, 4, 5 gm of polymer in distilled water, and the final volume was made up to 100 ml by adding distilled water.

HPMC E 5 solution: (7%, 8% and 9% w/v) was prepared by adding 7, 8, 9 gm of polymer in distilled water, and the final volume was made up to 100 ml by adding distilled water.

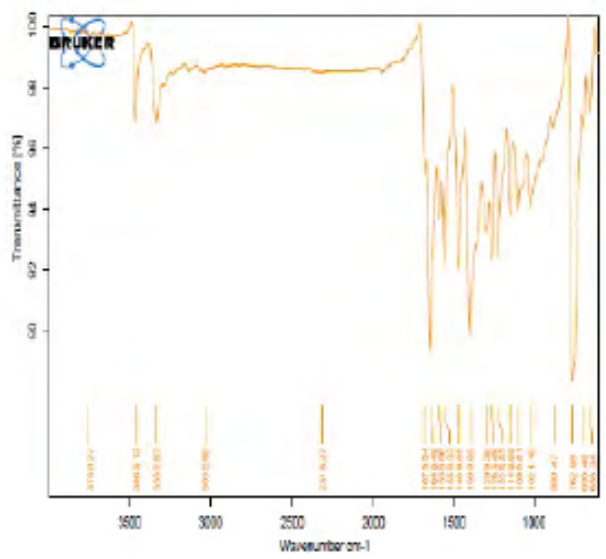

Figure 4: FTIR of Oxcarbazepine+HPMC.

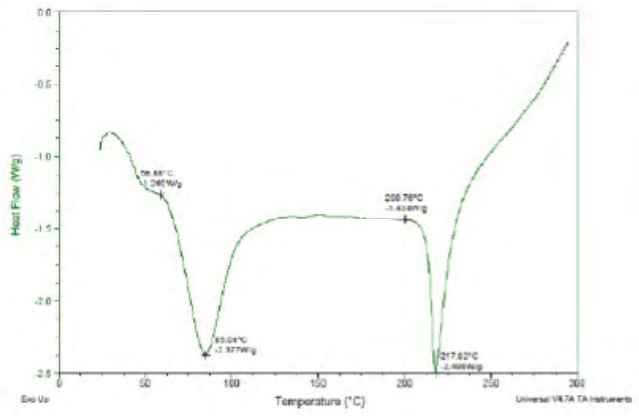

Figure 5: DSC of Oxcarbazepine.

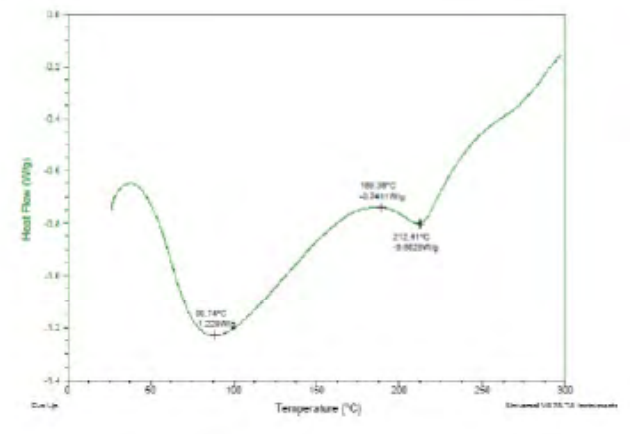

Figure 6: DSC of HPMC.

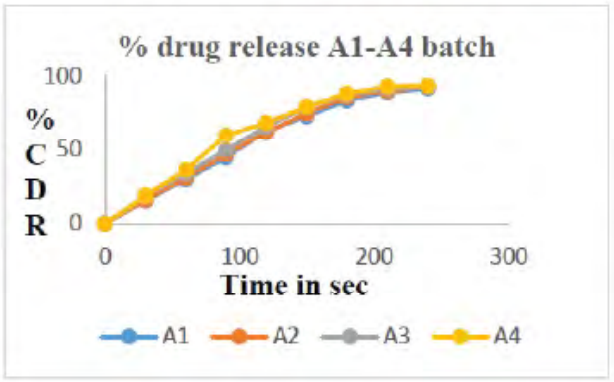

Figure 7: *In-vitro* drug release from A1-A4 batch.

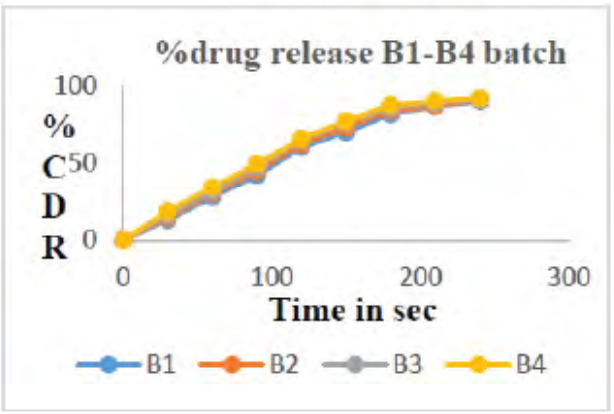

Figure 8: *In-vitro* drug release from B1-B4 batch.

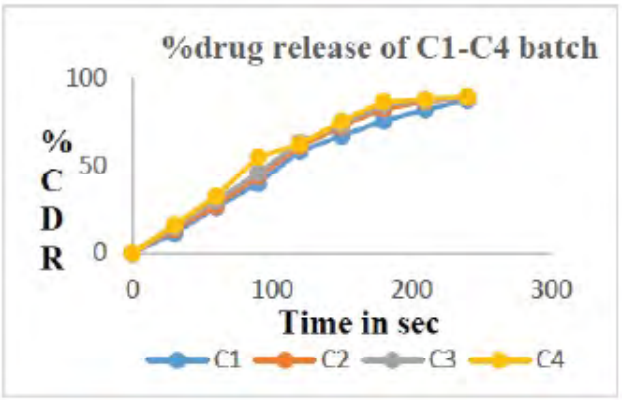

Figure 9: *In-vitro* drug release from C1-C4 batch.

For the preparation of FDF:

- FDF were prepared by taking 1 ml of drug solution in the beaker to this HPMC E50 LV and HPMC E 5 LV in different conc. i.e., 3%, 4%, 5% and 7%, 8%, 9% respectively were added.
- The above solution was mixed together with continuous stirring. Then excipients such as sweeting agent, saliva stimulating agent, flavoring agent were added to it.
- Plasticizer PEG 400 was added, followed by the addition of

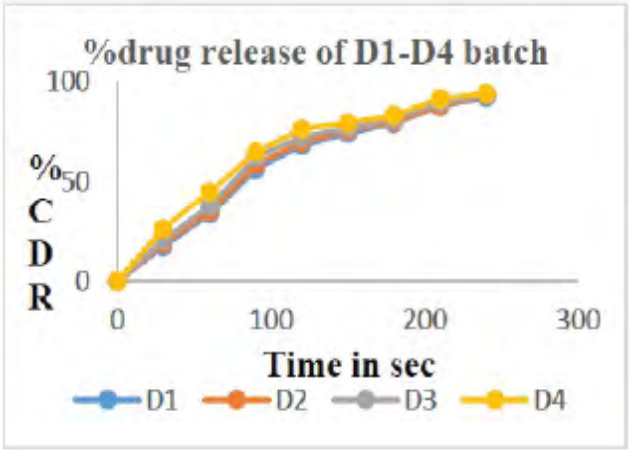

Figure 10: *In-vitro* drug release from D1-D4 batch.

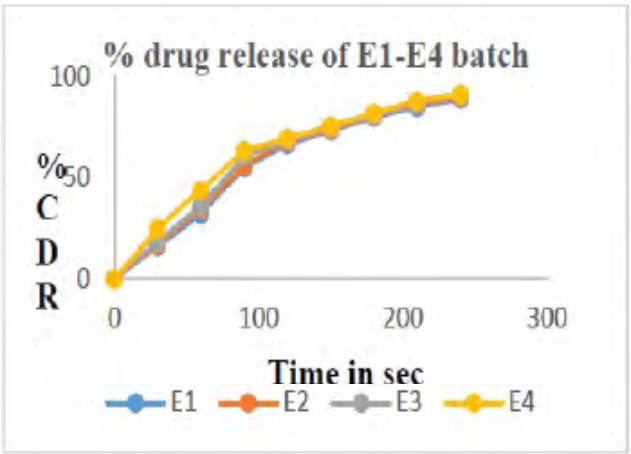

Figure 11: *In-vitro* drug release from E1-E4 batch.

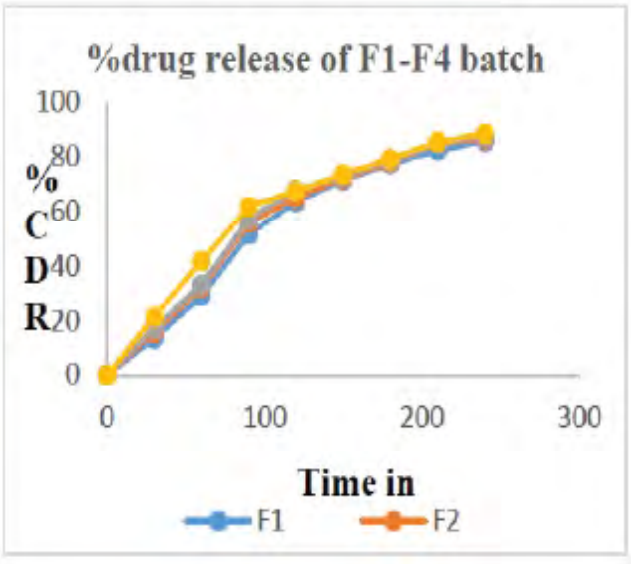

Figure 12: *In-vitro* drug release from F1-F4 batch.

distilled water to make up volume up to 10 ml and then sonicated at room temperature to ensure clear, bubble free solution.

- This solution was mixed thoroughly to obtain homogenous solution.
- The homogenous solution (10 ml) was spread in petridish (area 13 cm^2) and dried at 50°C temp in hot air oven for 24 hrs.
- After drying, the film was properly removed, packed in aluminum foil and stored in glass container for further evaluation. Composition of fast dissolving film is as shown in Tables 1-6.

Evaluation of fast dissolving film

The prepared films are evaluated for following properties these are given below [7-10]:

- Physical properties;
- Mechanical properties;
- Performance properties.

Physical properties of films

Thickness: The thickness of the drug loaded films was measured with the help of micrometer screw gauge at different strategic locations like four corners and center of each film. Mean SD is calculated. The standard range of film thickness should not be less than 5%. This is essential to assure uniformity in the thickness of the film as this was directly related to the accuracy of dose. The thickness of film should be in the range of the 5-200 micrometer. The thickness of all batches are given in Table 12.

Weight uniformity: Weight variation was studied by individually weighing 10 randomly selected films and calculating the average weight. According to specifications given in I.P. 2007 for 45 mg film standard deviation should not more than 10%. The weight uniformity of all batches are given in Table 12.

Surface pH: The film formulation has to be kept in the oral cavity, pH of saliva ranging from 5.5-7.5 So, to dissolve and solubilize the drug in saliva present in the oral cavity the pH of film should keep near to neutral. Since acidic or alkaline pH may leads to irritation to the buccal mucosa. Surface pH of film was determined to check whether the film causes irritation to the mucosa. The surface pH study was carried out by selecting 3 films randomly. The films were left to swell for 1 hrs on surface of agar plate, surface pH was measured by pH paper and mean SD calculated. The Surface pH of all batches are given in Table 12.

Mechanical properties of film

Folding endurance: Number of times a film can be folded at the same place without breaking or cracking gives the value of folding endurance. This was determined by repeatedly folding films at the same place until it broke. This test was performed on 3 films of each formulation and mean SD was calculated. The folding endurance of all batches are given in Table 13.

Tensile strength: Tensile strength is the maximum stress applies to a point at which strip specimen breaks. Tensile testing of film was determined with digital tensile tester, which consist of 2 load cell grips. The lower one is fixed and upper one is movable. The test film of specific size was fixed between cell grips and force was gradually applied till the film breaks. Tensile strength is calculated by formula;

Tensile strength=force at break/ initial cross-sectional area of film in mm^2

Concentration µg/ml	I	II	III	Absorbance
10	0.095	0.094	0.093	0.095 ± 0.001
20	0.192	0.192	0.193	0.194 ± 0.001
30	0.348	0.346	0.346	0.346 ± 0.001
40	0.466	0.464	0.465	0.465 ± 0.001
50	0.575	0.577	0.576	0.575 ± 0.001
60	0.68	0.681	0.681	0.681 ± 0.001

Table 8: Calibration data of OXC in pH 6.8 phosphate buffer.

Peak reported (cm^{-1})	Peak observed (cm^{-1})	Interpretation
3500-3000	3463.82	NH_2 group of amides
1725-1705	1679.34	C=O ketonic group
1800-1600	1588.86	C=C in Ar ring
1680-1630	1646.49	C=O of amide group

Table 9: Interpretation of FTIR of Oxcarbazepine.

Peak reported (cm^{-1})	Peak observed (cm^{-1})	Interpretation
1150-1050	1046.99	C-O
3000-2850	2888.64	C-H
1800-1600	1545.12	C=C in Ar ring

Table 10: Interpretation of FTIR of HPMC.

Peak reported (cm^{-1})	Peak observed (cm^{-1})	Interpretation
3500-3000	3463.82	NH_2 group of amide
1725-1705	1679.34	C=O ketonic group
1800-1600	1588.86	C=C in Ar ring
1500-1400	1399.88	NH group(B)
1680-1630	1646.49	C=O of amide group
1150-1050	1098.81	C-O
3000-2850	3032.99	C-H

Table 11: Interpretation of FTIR of OXC+HPMC.

Code	Thickness* (mm)	Average weight* (mg)	Surface pH	Folding endurance	Tensile strength
A1	0.029 ± 0.120	36.37 ± .421	6.72 ± 0.282	105.9 ± 1.23	7.38 ± 0.256
A2	0.028 ± 0.073	36.30 ± 0.562	6.76 ± 0.777	104.3 ± 1.53	7.56 ± 0.254
A3	0.027 ± 0.083	35.25 ± 0.320	6.35 ± 0.356	103.9 ± 0.895	7.84 ± 0.275
A4	0.026 ± 0.053	35.12 ± 0.456	6.41 ± 0.494	101.2 ± 0.962	7.95 ± 0.321
B1	0.035 ± 0.025	39.56 ± 0.852	6.25 ± 0.141	121.8 ± 0.758	6.81 ± 0.245
B2	0.033 ± 0.064	38.35 ± 1.023	6.75 ± 0.124	120.2 ± 0.952	6.9 ± 0.215
B3	0.031 ± 0.046	37.30 ± 0.259	6.62 ± 0.707	119.5 ± 0.230	7.1 ± 0.256
B4	0.030 ± 0.096	37.16 ± 0.506	6.45 ± 0.671	117.5 ± 0.752	7.2 ± 0.321
C1	0.041 ± 0.045	40.2 ± 0.652	6.32 ± 0.374	149.5 ± 0.466	5.1 ± 0.214
C2	0.039 ± 0.051	39.98 ± 0.352	6.45 ± 0.346	145.2 ± 0.236	5.4 ± 0.218
C3	0.038 ± 0.071	39.01 ± 0.754	6.52 ± 0.612	140.6 ± 0.245	5.6 ± 0.219
C4	0.037 ± 0.093	38.55 ± 0.684	6.69 ± 0.230	135.2 ± 0.158	5.95 ± 0.220
D1	0.038 ± 0.113	36.86 ± 0.751	6.56 ± 0.633	172.2 ± 1.252	6.5 ± 0.221
D2	0.036 ± 0.043	36.25 ± 0.421	6.65 ± 0.254	170.3 ± 1.36	6.6 ± 0256
D3	0.034 ± 0.016	36.02 ± 1.023	6.75 ± 0.850	169.8 ± 1.689	6.7 ± 0.254
D4	0.033 ± 0.025	35.19 ± 0.856	6.73 ± 0.325	167.2 ± 0.636	6.9 ± 0.278
E1	0.043 ± 0.133	38.26 ± .952	6.28 ± 0.652	187.5 ± 0.558	3.25 ± 0.245
E2	0.042 ± 0.014	37.75 ± 0.452	6.42 ± 0.452	185.2 ± 0.895	3.3 ± 0.236
E3	0.041 ± 0.15	37.19 ± 0.125	6.72 ± 1.268	181.5 ± 0.825	3.4 ± 0.3211
E4	0.039 ± 0.263	36.95 ± 0.895	6.41 ± 0.555	179.5 ± 0.982	3.5 ± 0.224
F1	0.047 ± 0.285	41.8 ± 0.752	6.24 ± 0.895	190.2 ± 0.723	2.34 ± 0.289
F2	0.046 ± 0.295	41.40 ± 0.852	6.72 ± 0.562	187.6 ± 0.236	2.46 ± 0.275
F3	0.045 ± 0.014	40.1 ± 0.954	6.42 ± 0.862	181.2 ± 0.452	2.57 ± 0.233
F4	0.044 ± 0.012	39.60 ± 0.562	6.23 ± 0.552	177.6 ± 0.952	2.64 ± 0.286

Table 12: Evaluation of fast dissolving film.

Code	Percent Elongation	D.T (SEC)	Drug content (%)	Swelling Index
A1	21.75 ± 0.231	30.12 ± .0.63	90.23 ± 0.134	0.191 ± 0.023
A2	21.85 ± 0.245	30.10 ± 0.085	92.6 ± 0.565	0.195 ± 0.021
A3	22.62 ± 0.256	29.85 ± 0.052	91.55 ± 0.558	0.200 ± 0.015
A4	22.90 ± 0.263	28.50 ± 0.12	89.25 ± 0.160	0.202 ± 0.036
B1	18.75 ± 0.324	34.15 ± 0.32	91.6 ± 0.301	0.171 ± 0.045
B2	19.2 ± 0.321	33.05 ± 0.40	92.46 ± 0.268	0.175 ± 0.062
B3	20.2 ± 0.328	32.56 ± 0.650	90.52 ± 0.374	0.180 ± 0.075
B4	20.9 ± 0.324	30.52 ± 0.298	88.52 ± 0.895	0.182 ± 0.095
C1	9.0 ± 0.245	38.25 ± 0.615	91.53 ± 0.671	0.152 ± 0.045
C2	9.2 ± 0.278	37.25 ± 0.895	87.66 ± 0.456	0.156 ± 0.095
C3	10.75 ± 0.259	36.5 ± 0.452	89.67 ± 0.895	0.160 ± 0.087
C4	10.95 ± 0.256	35.6 ± 0.652	90.68 ± 0.597	0.168 ± 0.125
D1	20.69 ± 0.564	29.15 ± 0.62	91.76 ± 0.684	0.251 ± 0.056
D2	20.75 ± 0.468	28.91 ± 0.258	88.56 ± 0.466	0.259 ± 0.089
D3	21.05 ± 0.562	28.10 ± 0.65	89.45 ± 0.258	0.261 ± 0.023
D4	21.50 ± 0.456	27.58 ± 0.722	93.45 ± 0.698	0.265 ± 0.145
E1	19.32 ± 0.356	32.34 ± 0.952	91.56 ± 0.752	0.232 ± 0.232
E2	19.65 ± 0.378	31.56 ± 0.10	91.65 ± 0.459	0.235 ± 0.532
E3	20.1 ± 0.368	30.56 ± 1.25	90.89 ± 0.687	0.243 ± 0.692
E4	20.3 ± 0.319	29.88 ± 1.65	92.45 ± 0.698	0.246 ± 0.085
F1	10.5 ± 0.345	40.23 ± 0.895	90.79 ± 0.756	0.201 ± 0.466
F2	11.8 ± 0.398	39.15 ± 0.892	92.56 ± 0.895	0.202 ± 0.655
F3	12.5 ± 0.371	38.6 ± 0.522	91.31 ± 0.466	0.212 ± 0.566
F4	12.89 ± 0.366	35.7 ± .0988	90.27 ± 0.789	0.223 ± 0.456

Table 13: Evaluation of fast dissolving film.

Time (sec)->	30	60	90	120	150	180	210	240
A1	15.8 ± 0.57	29.68 ± 0.23	44.9 ± 0.78	62.6 ± 0.85	72.9 ± 0.78	83.5 ± 0.23	88.9 ± 0.56	92.25 ± 1.02
A2	16.1 ± 0.78	30.78 ± 0.56	46.8 ± 0.18	61.9 ± 0.75	74.8 ± 0.55	85.8 ± 0.89	89.8 ± 0.96	92.86 ± 1.1
A3	18.5 ± 0.45	33.89 ± 0.89	49.8 ± 0.32	65.8 ± 0.38	78.8 ± 0.89	87.6 ± 0.96	91.5 ± 1.02	93.25 ± 1.3
A4	19.13 ± 0.35	36.25 ± 0.18	59.93 ± 0.89	68.37 ± 0.12	79.25 ± 0.77	88.26 ± 0.12	92.9 ± 0.98	93.50 ± 1.2
B1	13.10 ± 1.23	27.9 ± 1.02	41.8 ± 0.85	60.8 ± 0.56	70.50 ± 0.23	81.89 ± 0.52	86.8 ± 0.52	90.23 ± 0.89
B2	14.5 ± 0.78	29.8 ± 1.01	44.9 ± 0.89	62.5 ± 0.53	73.4 ± 0.85	83.8 ± 0.52	87.2 ± 0.63	91.89 ± 0.12
B3	16.1 ± 0.85	31.5 ± 1.10	47.8 ± 0.77	64.8 ± 0.23	76.8 ± 0.77	85.8 ± 0.12	89.2 ± 0.25	92.0 ± 0.89
B4	18.5 ± 0.89	34.15 ± 1.2	49.5 ± 0.85	66.2 ± 0.89	77.6 ± 0.63	87.89 ± 0.25	90.56 ± 0.42	92.18 ± 0.12
C1	11.1 ± 1.02	25.9 ± 0.89	39.5 ± 0.78	58.6 ± 0.56	67.2 ± 0.895	75.6 ± 0.294	81.9 ± 0.58	87.5 ± 0.258
C2	13.4 ± 0.235	26.9 ± 0.56	43.8 ± 0.85	61.3 ± 0.258	72.5 ± 0.69	82.2 ± 0.185	86.5 ± 0.963	88.89 ± 0.11
C3	15.05 ± 0.61	29.8 ± 0.66	45.8 ± 0.62	63.5 ± 0.25	73.6 ± 0.96	84.4 ± 0.874	87.6 ± 0.58	89.1 ± 0.258
C4	16.1 ± 0.235	32.5 ± 0.895	55.2 ± 0.28	65.5 ± 0.45	75.8 ± 0.125	86.2 ± 0.258	88.7 ± 0.360	89.37 ± 0.698

Table 14: *In-vitro* drug release data.

The tensile strength of all batches are given in Table 13.

Percent elongation: It is calculated by the distance travelled by pointer before the break of the film on the graph paper. When the stress is applied, a film strip sample stretches, and this is referred to as strain. Strain is basically the deformation of film strip is divided by original dimension of the sample. Generally, elongation of strip increases as the plasticizer content increases [11-13]. It is calculated as:

% Elongation=Increase in length/Original length × 100

The percent elongation of all batches are given in Table 13.

Performance properties of film

***In vitro* disintegration time:** A film was placed onto 2 ml distilled water taken in petri dish. Time taken by the film to dissolve completely is considered as the disintegrating time. The disintegration time is the time when the film starts to break or disintegrates completely, normally disintegration time for oral films is within 2 min. The disintegration time of all batches are given in Table 14.

Determination of drug content uniformity in the film: Drug content of oral fast dissolving films were determined by standard assay

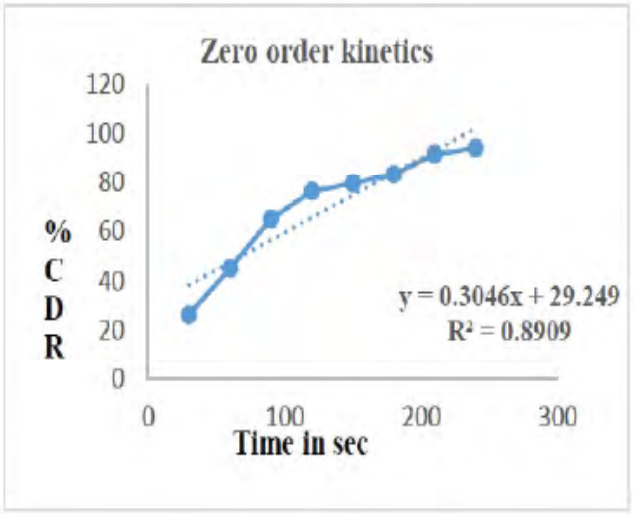

Figure 13: Graph of zero order kinetics

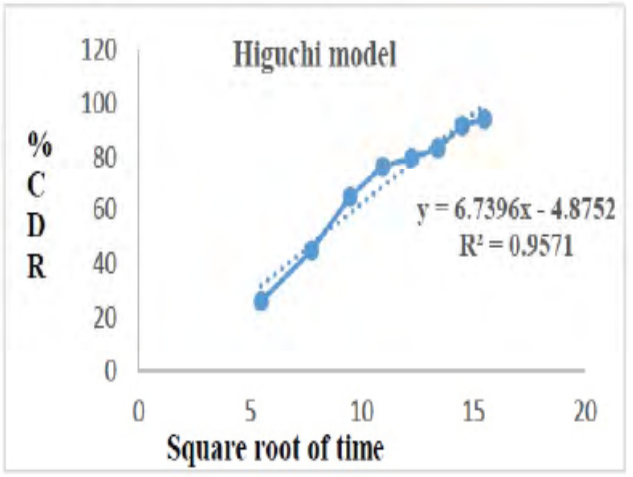

Figure 14: Graph of Higuchi model.

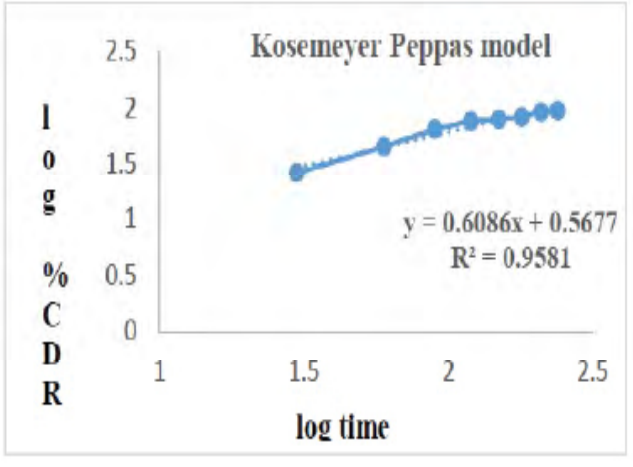

Figure 15: Graph of Kosemeyer Peppas.

method taken for three individual samples as per the test procedures. The acceptance value of the test is less than 15 in accordance with all pharmacopoeia. A film of size 1 cm^2 was cut and kept in 100 ml of volumetric flask containing distilled water. This was then shaken in a mechanical shaker till it was dissolved to get a homogeneous solution and then filtered. The drug was determined spectroscopically after appropriate dilution and dilutions were measured at 256 nm to get absorbance. The acceptance value (AV) of the preparation 85-115%. The drug content uniformity of all batches are given in Table 15.

Hydration study: Hydration study (water uptake/swelling study). The film sample was weighed and placed on a pre-weighed stainless-steel wire mesh. The wire mesh was then submerged in a petridish containing 20 ml distilled water. Increase in weight of the film is determined at regular time intervals until a constant weight is obtained the hydration ratio of the film is calculated using following formula:

Hydration ratio=W_t-W_0/W_t

Where, W_t=Weight of film at time t and W_0=Weight of film at zero time.

The Hydration study (water uptake/swelling study) of all batches are given in from Table 15.

***In vitro* dissolution studies:** The release rate of film was performed using a dissolution apparatus (Disso test, Lab India). The dissolution medium comprised 900 ml of phosphate buffer pH 6.8 maintained at a temperature of 37 ± 0.5°C and rotation speed of 50 rpm was kept. 5 ml of sample were collected at predetermined time interval for 4 min. The drug concentration was measured by a UV Spectrophotometer (UV-1800, Shimadzu) at 306 nm. The drug content uniformity of all batches are given from Tables 15-20.

Study of release kinetics: a. zero-order kinetic: $Q_t=Q_0+k_0t$

Where, Q_t is amount of drug release at time t; K_0 is zero order release rate constant; Q_0 is amount of drug present initially at t=0.

First-order kinetic: In (100-Q)=InQ_0-K_1t

Where, Q=amount of drug present initially; K_1=first order release rate constant.

Higuchi equation: $Q=kH\ t_{1/2}$

Where, $t_{1/2}$=amount of drug release at time t; k_H=Higuchi dissolution constant.

Korsmeyer-Peppas model: $Q=Kpt^n$

Where, Kp is a constant incorporating the structural and geometric characteristics of the drug dosage form.

Hence to study the drug release kinetics data obtained from *in-vitro* dissolution study. The data obtained is plotted against:

- Time *vs.*% CDR for Zero order kinetics;
- Square root of time *vs.*% CDR for Higuchi model;
- Log time *vs.*% Log% CDR for Kosemeyer Peppas model;
- Time *vs.* Log% drug remaining for First order kinetics.

The result of release kinetics are reported in Tables 16-19 and Figures 13-16. Table 20 shows value of slope and regression coefficient [14-17].

Stability study: In any rational design and evaluation of dosage forms of drugs, the stability of the active component is the major

criteria in determining their acceptance or rejection. During the stability studies, the product is exposed to normal conditions of temperature and humidity. The optimized Oxcarbazepine formulation were subjected for stability studies. The desiccators was kept at room temperature condition 25°C ± 2°C for a period of one month and the optimized formulation was analyzed for organoleptic characteristics, thickness, folding endurance, drug content and dissolution [18-20].

Stability protocol

Packaging material: The films were wrapped in aluminum foils.

Storage condition: The films were subjected to stability as per ICH guidelines at the following conditions. Samples were kept in a desiccators was kept at room temperature condition 25°C ± 2°C.

Sampling points: The optimized formulations were subjected to stability for a period of one month. The samples were withdrawn at the end of 1 month for all conditions and subjected to following tests.

Appearance: The Oxcarbazepine formulations were inspected for any change in color and integrity [21].

Thickness: The Oxcarbazepine formulations were inspected for any change in thickness of film.

Folding endurance: The Oxcarbazepine formulations were inspected for any change in folding endurance of film.

Disintegration time: The Oxcarbazepine formulations were inspected for any change in disintegration time of film.

Drug content: Drug content of Oxcarbazepine formulations at sampling point were determined as per procedure given as above.

Dissolution profile: Dissolution study was carried out for optimized formulation (0 week and 4 week) stored as per stability condition.

Results and Discussion

Characterization of drug and polymer

Physical properties: The sample of Oxcarbazepine and polymer HPMC were studied by visual observation for its physical characters such as colour and appearance. The results are presented in Table 7.

Melting point: The melting point of Oxcarbazepine and polymer HPMC were found to be similar to that mentioned in literature. The results are given in Table 7.

UV-spectroscopy and Beer-Lambert's plot: Calibration curve data of OXC in phosphate buffer 6.8 is given in Table 8.

FTIR spectroscopy: The functional groups shown by IR spectra correctly matches with functional group of in the structure Oxcarbazepine and HPMC. From this result it was concluded that sample Oxcarbazepine and HPMC were pure [22].

FTIR of oxcarbazepine: The spectrum of oxcarbazepine was characterized by the presence of strong absorption band at 3463.82 cm^{-1}, which is indicative of amines (-NH- group). The carbonyl-stretching mode appeared as a very strong doublet at 1679.34 cm^{-1} (C=O stretching) and 1646.49 cm^{-1}. Other characteristic band was found at 1588.86 cm^{-1} which was indicative of presence of aromatic rings. From the above interpretation it was concluded that observed peaks compiles with standard ranges of functional group of Oxcarbazepine. The interpretation of FTIR of drug is as shown in Table 9 and Figure 2.

FTIR of HPMC

The spectrum of HPMC was characterized by the presence of strong absorption band at 1046.99 cm^{-1}, which is indicative of ether (-C-O- group). Other characteristic band was found at 1545.12 cm^{-1} which was indicative of presence of aromatic rings and other characteristic band was found at 2888.64 cm^{-1} which was indicative of presence of aliphatic chain. From the above interpretation it was concluded that observed peaks compiles with standard ranges of functional group of HPMC. The interpretation of FTIR of HPMC is as shown in Table 10 and Figure 3.

FTIR Study of oxcarbazepine+HPMC

In this there was no any extra peaks observed and from this confirm that the drug is compatible with polymer. There is no any interaction between drug and HPMC. The spectrum of drug+HPMC showed different peak which are described in Table 11 and Figure 4.

Differential Scanning Calorimetry (DSC)

Thermal analysis of drug and polymer were carried out by using DSC analysis. The DSC study showed sharp endothermic peak of Oxcarbazepine at 217.82°C at which corresponds to its melting point. This sharp endothermic peak indicates its crystalline nature and purity of sample. The DSC thermogram are shown in Figure 5. DSC of HPMC shows broad endothermic peak at 189.38°C. Thermal analysis of HPMC was carried out by using DSC analysis. The DSC study showed broad endothermic peak and melting at 189.38°C which corresponds to its melting point. This reveals its amorphous nature and purity of sample. The DSC thermogram is shown in Figure 6.

Evaluation of fast dissolving film

Thickness: The thickness of the drug loaded films was measured with the help of digital thickness gauze at different strategic locations like four corners and center of each film. Mean SD is calculated. Physical evaluation of film containing HPMC E50 LV and HPMC E5 LV in different concentrations was evaluated and they were found to be uniform thickness in the range of 0.026-0.047 mm. Among which A4 formulation is thinnest and F1 formulation being thick. It reveals that as concentration of film forming polymer increases, there is increase in thickness. In all the cases the calculated standard deviation values are very low which suggest that, the prepared films were uniform in thickness. The thickness of all batches are given in Table 12.

Weight uniformity: The weight of each film was taken on Electronic analytical balance and the weight variation is calculated as mean SD. Physical evaluation of film containing HPMC E50 LV and HPMC E5 LV in different concentrations was evaluated and they were found be uniform weight in the range of 35.12 ± 0.456 to 41.8 ± 0.752 mg. Among which A4 formulation contains the lowest weight and F1 formulation contains the highest weight. It reveals that as concentration of film forming polymer increases, there is increase in weight of film. In all the cases the calculated standard deviation values are very low which suggest that, the prepared films were uniform in weight. The weight uniformity of all batches are given in Table 12.

Surface pH: The surface pH of the films was ranging from 6.23 ± 0.552 to 6.76 ± 0.777. The surface pH of the films was found to be neutral. There will not be any kind of irritation to the mucosal lining of the oral. The surface pH of all batches are given in Table 12.

Folding endurance: Folding endurance evaluation was done for film containing HPMC E50 LV and HPMC E5 LV in different concentrations and they were found in the range of 101.2 ± 0.962 to

Time (sec)->	30	60	90	120	150	180	210	240
D1	17.4 ± 1.02	33.7 ± 1.23	56.5 ± 1.05	68.5 ± 1.25	74.5 ± 0.98	79.5 ± 0.55	87.9 ± 0.78	92.5 ± 0.58
D2	18.9 ± 0.96	35.1 ± 0.25	58.8 ± 0.39	70.1 ± 0.59	75.8 ± 0.39	80.3 ± 0.25	88.2 ± 0.69	93.78 ± 1.02
D3	20.6 ± 0.652	37.8 ± 0.895	62.5 ± 0.588	72.8 ± 0.257	76.8 ± 0.569	81.5 ± 0.589	89.7 ± 0.587	94.2 ± 0.558
D4	26.3 ± 0.284	45.3 ± 0.694	65.2 ± 0.288	76.56 ± 0.25	79.81 ± 0.89	83.5 ± 0.785	91.9 ± 0.99	94.35 ± 0.895
E1	15.9 ± 0.185	31.5 ± 0.595	54.8 ± 0.891	66.5 ± 0.789	73.1 ± 0.79	79.8 ± 0.125	84.7 ± 0.89	88.78 ± 0.569
E2	16.8 ± 0.235	33.9 ± 0.589	56.1 ± 0.898	67.9 ± 0.698	73.8 ± 0.77	80.6 ± 0.59	85.9 ± 0.69	89.56 ± 0.36
E3	18.1 ± 0.28	35.5 ± 0.39	60.5 ± 0.98	68.5 ± 0.58	74.8 ± 0.69	80.9 ± 0.99	86.8 ± 0.684	90.56 ± 0.25
E4	24.5 ± 0.698	43.8 ± 0.25	63.4 ± 0.547	69.5 ± 0.657	75.5 ± 0.651	81.9 ± 0.39	87.89 ± 0.58	91.25 ± 0.954
F1	13.55 ± 0.23	29.02 ± 0.32	51.7 ± 0.41	63.5 ± 0.58	71.5 ± 0.59	77.5 ± 0.63	82.3 ± 0.89	85.78 ± 0.96
F2	15.78 ± 0.32	31.9 ± 0.45	55.7 ± 0.53	65.2 ± 0.58	72.1 ± 0.69	78.1 ± 0.72	84.9 ± 0.88	86.8 ± 0.99
F3	17.10 ± 0.45	33.1 ± 0.78	57.5 ± 0.79	67.9 ± 0.86	72.9 ± 0..877	78.7 ± 0.858	85.1 ± 0.966	87.59 ± 1.01
F4	21.24 ± 0.56	41.7 ± 0.65	61.89 ± 0.71	67.5 ± 0.89	73.8 ± 0.96	79.4 ± 1.02	85.5 ± 1.1	88.57 ± 1.2

Table 15: *In-vitro* drug release data.

Time (Sec)	%CDR
30	26.3
60	45.3
90	65.2
120	76.56
150	79.81
180	83.5
210	91.9
240	94.35

Table 16: Zero order kinetics.

Square root of time	%CDR
5.477226	26.3
7.745967	45.3
9.486833	65.2
10.95445	76.56
12.24745	79.81
13.41641	83.5
14.49138	91.9
15.49193	94.35

Table 17: Higuchi model.

Log Time	Log %CDR
1.477121	1.419956
1.778151	1.656098
1.954243	1.814248
2.079181	1.884002
2.176091	1.902057
2.255273	1.921686
2.322219	1.963316
2.380211	1.974742

Table 18: Kosemeyer Peppas model.

190.2 ± 0.723 which is optimum ensures that films exhibited good physical and mechanical properties. It reveals that as concentration of film forming polymer increases, there is increases in folding endurance. In all the cases the calculated standard deviation values are very low which suggest that, the prepared films were uniform in folding endurance. The folding endurance of all batches are given in Table 12.

Tensile strength: Tensile strength evaluation was done for film containing HPMC E50 LV and HPMC E5 LV in different concentrations and they were found in the range of 2.34 to 7.95 N/mm^2 which is optimum ensures that films exhibited good physical and mechanical properties. It reveals that as concentration of film forming polymer increases, there is decrease in tensile strength**.** In all the cases the calculated standard deviation values are very low which suggest that, the prepared films were uniform in tensile strength. The tensile strength of all batches given in Table 12.

Percent elongation: Percent Elongation evaluation was done for film containing HPMC E50 LV and HPMC E5 LV in different concentrations and they were found in the range of 9.0 to 22.90 which is optimum ensures that films exhibited good physical and mechanical properties. It reveals that as concentration of film forming polymer increases, there is decrease in percent elongation. In all the cases the calculated standard deviation values are very low which suggest that, the prepared films were uniform in percent elongation. The percent elongation of all batches given in Table 13.

***In-vitro* disintegration time:** The disintegration time of the films was found to be in the range 27.58 ± 1.65 sec to 40.23 ± 0.895 sec. It reveals that as concentration of film forming polymer increases, there is increase *in-vitro* disintegration time. The *in-vitro* disintegration time of all batches given in Table 13.

Determination of drug content: Drug content of all batches was found in between 87.66 ± 0.456 to 93.45 ± 0.698. The drug content of all batches given in Table 13.

Hydration study (Swelling index): The swelling index of all batches was calculated in the range 0.152 ± 0.045 to 0.265 ± 0.14. It reveals that as concentration of film forming polymer increases, there is decrease in swelling index. The observations are given in Table 13.

***In-vitro* drug release of study:** The dissolution rate studies were performed to evaluate the dissolution character of Oxcarbazepine from the rapidly dissolving film. Figures 17-19 shows release profiles of all the batches. The drug release of all batches given in Tables 14 and 15. The graphs of *in-vitro* drug release are as shown in Figures 7-12.

Stability studies: Stability of a drug has been defined as the ability

Time in sec	Log % cumulative drug remaining
30	1.867467
60	1.737987
90	1.541579
120	1.369958
150	1.305136
180	1.217484
210	0.908485
240	0.752048

Table 19: First order kinetics.

S. No.	Kinetics Model	Slope	Regression Coefficient
1	Zero order kinetics	0.3046	0.8909
2	First order kinetics	-0.0052	0.9791
3	Kosemeyer Peppas model	0.6086	0.9581
4	Higuchi model	6.73	0.9571

Table 20: Regression coefficient value of release kinetics model.

Parameter	After one month
Appearance	Colourless
Thickness(mm)	0.035
Folding endurance	181.5
Film weight(mg)	37.65
Disintegration(sec)	29.19
Drug content (%)	92.35

Table 21: Evaluation of optimized formulation subjected to stability study.

Time (sec)	% Release
0	0
30	27.8
60	49.3
90	64.3
120	71.2
150	79.2
180	81.57
210	87.56
240	93.56

Table 22: % release of the optimized formulation batch subjected to stability study.

of a particular formulation, in specific container, to remain within its physical, chemical, therapeutic and toxicological specification. Rapidly dissolving films of batch D4 was kept for stability study for 1 month in the desiccator. After a period of one month, the samples were observed for change in physical parameters. It was observed that surface was devoid of any change in color or appearance of any kind of spots on it. It was also noted that surface was free of any kind of microbial or fungal growth or bad odor. No change in the smoothness of the film were noted. At the end film were analyzed for physical appearance, percentage drug content, thickness, *in vitro* disintegration time, and *in vitro* drug release studies. From Table 21, Thickness was found to be 0.035 mm, Folding endurance was found to be 181.5, Film weight was found to be 37.65 mg, Disintegration was found to be 29.19 sec, Drug content was found to be 92.35%. Short term stability testing was carried out for the optimized formulation (D4). *In vitro* drug release study of optimized formulation (D4) kept for stability at 25°C. Table 22 and Figure 17 shows dissolution data of formulation which was subjected to stability [23-25].

FTIR of optimized batch

The infrared spectra of drug and polymers are matching peak with the drug spectra. The characteristics peaks of drug were also present in the spectra of all polymer combination. It reveals that no interaction occurred between drug and polymer, so drug and polymers are compatible with each other. The spectrum of FTIR is as shown in Figure 18.

DSC study of fast dissolving film

The pure Oxcarbazepine showed sharp endothermic peak at 217.82°C which represents melting point. But this sharp endothermic peak was shifted to the left side i.e., 213.27°C in fast dissolving film formulation batch D4. This might be indicating the decrease in crystallinity of drug. This could be attributed to higher polymer concentration and uniform distribution of drug in the crust of polymer, resulting in complete miscibility of drug in the polymer. Thus, it might confirm the enhancement of solubility and dissolution rate of drug from the formulations. Moreover, the data also indicate there seems to be no interaction between the drug and polymer. The graph of DSC is as shown in Figure 19.

Conclusion

The fast dissolving films of oxcarbazepine were prepared using the easily accessible component such as HPMC of different grades (E5, E50) by solvent casting technique. The method of formulation was found to be modest and economic. Oxcarbazepine, a poorly water-soluble drug could be magnificently assimilated in the fast dissolving films with the help of PVP K30 which serves as carrier in increasing the solubility of valsartan and HPMC E5, E 50 as film forming polymer. Amongst the all formulations, D4 was found as best formulation which contains HPMC E 5 and oxcarbazepine solid dispersion with PVP K30 at weight ratio of 1:3 and showed excellent film forming characteristics such as disintegration time of 27 sec and percentage drug release 94.35% within 4 minutes.

Acknowledgements

Every step towards goal needs appreciable extent of self-motivation, inspiration, blessings and support of complimentary factors along with our efforts. Words may be failed to portrait gratefulness of all those, who have been lifted me up to this stage. I take this opportunity to express my heartfelt gratitude to my revered guide. I consider myself most lucky to work under the excellent guidance of Dr. FJ Sayyad, Assistant Professor of Govt. college of Pharmacy, Karad for

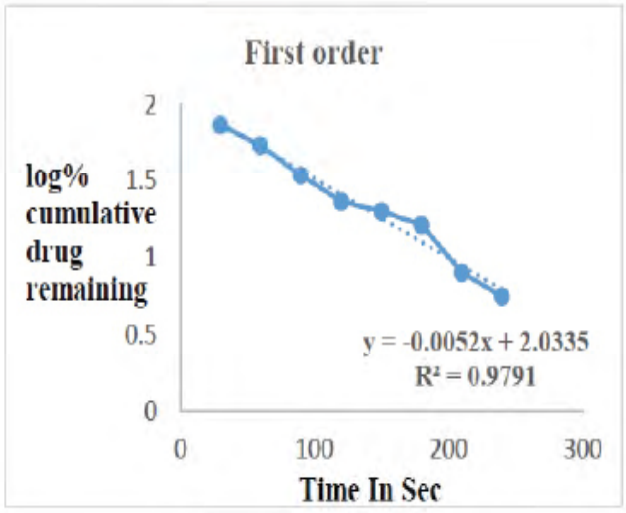

Figure 16: Graph of first order kinetics.

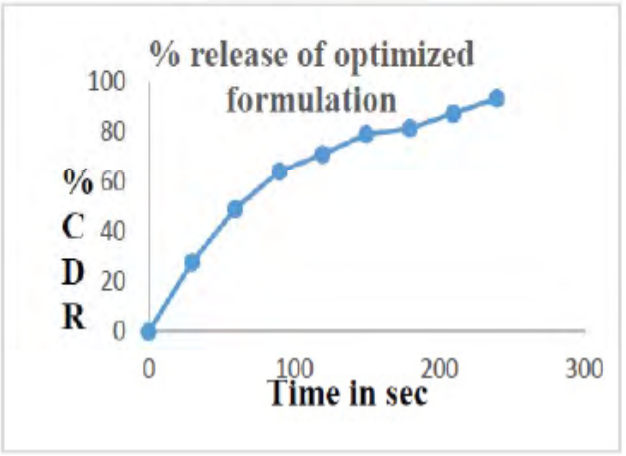

Figure 17: Graph of % drug release of optimized formulation batch subjected to stability study.

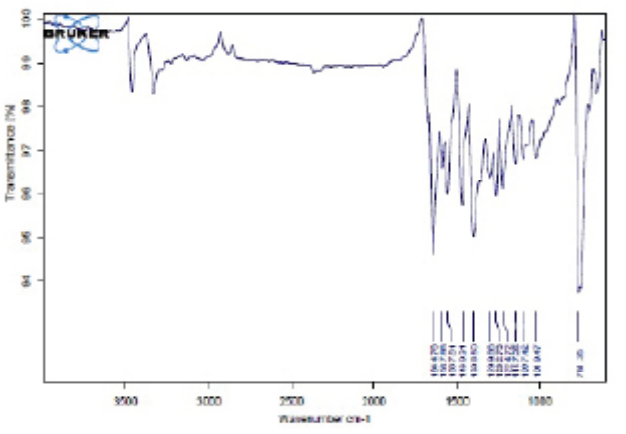

Figure 18: FTIR Spectra of optimized formulation.

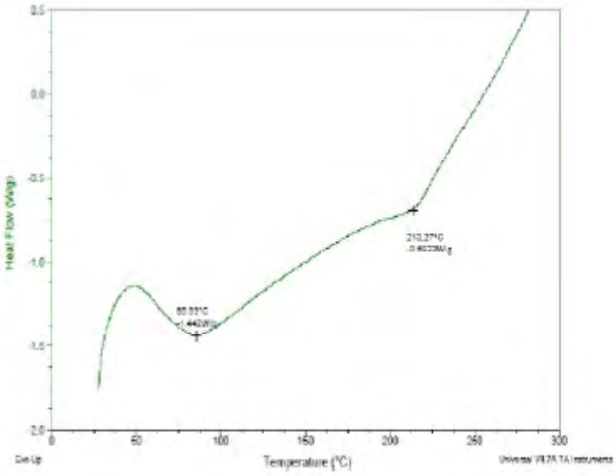

Figure 19: DSC of optimized formulation.

her active guidance, innovative ideas, constant inspiration, continuous supervision, valuable suggestions, and support to complete the project work effectively and successfully. I am very much grateful to her for invaluable guidance.

References

1. Biradar SS, Bhagvati ST, Kuppasad IJ (2006) Fast dissolving drug delivery systems: a brief review. Internet J Pharmcol, p: 4.
2. Dixit RP, Puthli SP (2009) Oral strip technology: Overview and future potential. J Cont Rel 139: 94-107.
3. Vollmer U, Galfetti P (2006) Rapid film: Oral thin films as an innovative drug delivery system and dosage form. Drug Dev Report, pp: 64-67.
4. Kunte S, Tandale P (2010) Fast dissolving strips: a novel approach for the delivery of verapamil. J Pharm Bioallied Sci 2: 325-328.
5. Prabhu P, Malli R, Koland M, Vijaynarayana K, D'Souza U, et al. (2011) Formulation and evaluation of fast dissolving films of levocitirizine dihydrochloride. Int J Pharm Inv 1: 99-104.
6. Tripathi KD (2003) Essentials of Medical Pharmacology. 6th edn. Jaypee Medical Publications, New Delhi, India, pp: 213-215.
7. Desai P (2012) Evaluation of fast dissolving film of domperidone. International Research Journal of Science.
8. Kaza R (2012) Design and Characterization of fast dissolving film of Valsartan. Turk J Pharm Sci 11: 175-184.
9. Shaik MR (2013) Formulation and Characterization of domperidone oral thin films. International Journal of Pharma Science 3: 126-128.
10. Upreti K (2011) Formulation and Evaluation of mouth dissolving films of paracetamol. International Journal of Pharmacy and Pharmaceutical Science 6: 201.
11. James B (2016) An overview on Epilepsy. Encyclopaedia of Life Sciences, pp: 1-8.
12. Simon S (2016) A review on Treatment of Epilepsy. John Wiley & Sons, pp: 1-11.
13. Nandy BC (2011) An overview on fast dissolving drug delivery system. Asian Journal of Pharmaceutical Sciences and Research 1: 1-30.
14. Thomas RH (2012) A Review on Seizures and Epilepsy: Pathophysiology and Principles of Diagnosis. Turner White Communications 1: 1-26.
15. Shweta K (2012) Recent Trends in the development of Oral dissolving film. International Journal of Pharmatech Research 4: 725-733.
16. Patel JC (2013) A review on fast dissolving film. International Journal of Advanced Pharmaceutics 3: 44-50.

17. Bhupinder B (2011) Orally fast dissolving films: Innovations in formulation and technology. International Journal of Advanced Pharmaceutics 9: 009.

18. Rathod S (2014) A review on Mouth Dissolving Film Technology. International Journal for Pharmaceutical Research Scholars, p: 3.

19. Sameer S (2011) A review on solid dispersion. International Journal of Pharmacy and Life Science 2: 1078-1095.

20. Ladan AN (2012) A review on "Solid dispersion: methods and polymers to increase the solubility of poorly soluble drugs". Journal of Applied Pharmaceutical Science 2: 17-170.

21. Ishwarya S (2013) A review on Solid dispersion: an approach to enhance solubility of poorly water-soluble drugs. Journal of Scientific and Innovative Research 2: 685-694.

22. Jaskirat J (2013) Solubility Enhancement by solid dispersion method. Journal of Drug Delivery and Therapeutics 3: 148-155.

23. Tagalpallelwar VR (2015) Enhancement of solubility of poorly water-soluble drug by solid dispersion technique. International Journal of Pharma Sciences and Research, p: 6.

24. Raju PN (2013) Formulation and Evaluation of fast dissolving film of Loratidine by solvent casting method. p: 2.

25. Qadir KA (2012) Formulation and Evaluation of fast dissolving films of Loratidine for sublingual use. p: 7.