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Original Article

Formulation and evaluation of tramadol HCl oral fast dissolving films

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ABSTRACT

Tramadol hydrochloride an opioid analgesic drug has been used for moderate to severe pain management in patients. The present work aimed at preparing oral fast dissolving films of Tramadol Hydrochloride with the purpose of developing a dosage form for a very quick onset of action, which is very convenient for administration, without the problem of swallowing and using water. Oral fast dissolving films of tramadol hydrochloride were prepared using Pullulan and HPMC (E3, E5 and E15) polymers as film forming agents and propylene glycol as plasticizer by solvent casting method. FTIR showed that there is no interaction between drug and excipients. Dissolution of prepared fast dissolving oral films of tramadol hydrochloride was performed using USP type II apparatus in pH 6.8 phosphate buffer medium at 50 rpm with temperature being maintained at 37±0.5ºC. The films prepared were evaluated for various parameters like thickness, percent elongation, drug content uniformity, weight variation, disintegration time, folding endurance and in vitro drug release and were showed satisfactory results. Formulation with 5% Pullulan has shown better in vitro dissolution profile compared with other formulations. In conclusion, development of fast dissolving oral films using Pullulan polymer gives rapid drug delivery and rapid onset of action.

Keywords: Oral fast dissolving films, Tramadol hydrochloride, Pullulan and HPMC.

INTRODUCTION

Conventional oral solid dosage forms like tablets, capsules are always preferred by patients over liquid dosage forms. Constantly changing lifestyle and interest demand more patient friendly dosage forms. Patient's disinterest in taking medicines which are difficult to swallow resulted in origination of the concept of orally disintegrating solid dosage forms in 1970. Orally fast-dissolving film is new drug delivery system for the oral delivery of the drugs. It was developed on the basis of technology of the transdermal patch. The delivery system consists of a very thin oral strip or film, which is simply placed on the patient's tongue or any oral mucosal tissue need not to take water, instantly wet by saliva the film rapidly hydrates in few seconds and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal and intra gastric absorption [1]. Orally dissolving systems like orally dissolving tablets (ODTs), orally dissolving films (ODFs) and wafers have carved niche amongst the oral drug delivery systems due to their high patient compliance. Most of the existing fast dissolving drug delivery systems are in the form of tablets and are designed to dissolve or disintegrate in the patient's mouth within a few seconds or minutes without the need of water [2]. Tramadol is a centrally acting synthetic analgesic that possesses two complementary mechanisms of action at therapeutic doses.

Tramadol binds weakly to μ- and δ- opioid receptors and inhibits the reuptake of serotonin and nor epinephrine. A major metabolite of tramadol, O-desmethyl tramadol, has an approximately 200-fold higher affinity for opioid receptors than the parent compound. Tramadol is indicated in the treatment of moderate to severe pain. It is suitable for those who are prone to constipation or respiratory depression. Tramadol is used to treat postoperative, dental, cancer and acute musculoskeletal pain and as an adjuvant to non-steroidal anti-inflammatory drug (NSAID) therapy in patients with osteoarthritis. Also, it is recommended in postsurgical pain when patient is hospitalized. In such conditions of pain, orally disintegrating dosage form will be preferred by patient over conventional solid dosage forms [8].

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The main objective of present research work is to formulate OFDF which will disintegrate within 30 seconds. Polymers like HPMC (E3, E5, and E15) and Pullulan were evaluated for film forming capacity. Effects of polymer and plasticizer concentrations on appearance of film, in vitro disintegration time, folding endurance were studied. The optimized formulations were further evaluated for drug content and in vitro dissolution.

MATERIALS

Tramadol hydrochloride, Tulsion335, Hydroxyl propyl β-cyclodextrin , Aspartame and Pullulan were obtained from Reddy's Laboratories, AP, India., Hydroxy propyl methyl cellulose and Hydroxyl propyl cellulose from Qualikems, Gujarath, India. Sodium carboxy methyl cellulose, Propylene glycol and Glycerin from S.d.fine chem. Ltd, Mumbai, India. All other chemicals and reagents were of analytical grade were purchased. Purified water was used for study.

METHODS

Preparation of oral fast dissolving film: The fast dissolving films of tramadol hydrochloride were prepared by solvent casting technique. The fast dissolving films were prepared using different polymers like HPMC (E3, E5 and E15), hydroxy propyl cellulose, Sodium carboxy methyl cellulose, sodium alginate and Pullulan. Propylene glycol and glycerin were used as plasticizer. The calculated amount of polymer was dispersed in the solvent with continuous stirring using magnetic stirrer and the homogenous solution is formed. The calculated amount of drug resin complex (1:2) was incorporated in the polymeric solutions after mixing with required volume of plasticizer. Then the sweetner and flavor was added to drug mixed polymeric solution. Then the solution was kept in sonicator for degassing. Then the bubble free solution was casted on to petriplate and was kept in hot air oven. Dried film is then cutted into the desired shape and size (2.5cm x 2.5cm) for the intended application. By carrying out the trial and error method different concentrations (2%, 2.5%, 3%, 4%, 5%) of film forming polymers were used for optimizing the formulation [3, 4].

EVALUATION OF FAST DISSOLVING FILMS

Thickness: As the thickness of film is directly concern with drug content uniformity so it is necessary to ascertain uniformity in the thickness of the film. It can be measured by micrometer screw gauge or calibrated digital Vernier Calipers at different strategic locations. The thickness was measured at three different spots of the films and average was taken [1].

Tensile strength: Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the applied load at rupture divided by the cross sectional area of the strip [1].

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 [1].

Folding endurance: Folding endurance is determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film is folded without breaking is computed as the folding endurance value [1].

Physical appearance and surface texture of patch: These parameters were checked simply with visual infection of films and by feel or touch.

Weight uniformity of films: Film (size of 2.5 cm^2) was taken from different areas of film. The weight variation of each film is calculated [5].

Drug Content uniformity or Assay of film: The films were tested for drug content uniformity by UV Spectrophotometrical method. Films of 2.5cm x 2.5cm square size were cut from three different places from the casted films. Each patch was placed in 100 ml volumetric flask and dissolved in 6.8 phosphate buffer. The absorbance of the solution was measured at 270nm using UV/visible spectrophotometer. The percentage drug content was determined using the standard graph and the same procedure was repeated for all the formulations [6].

In vitro Disintegration time: The in vitro disintegration time of fast dissolving films was determined visually in a glass dish of 25 ml 6.8 pH phosphate buffer with swirling action. The disintegration time is the time when a film starts to break or disintegrate. The in vitro disintegration time was calculated for different patches of the same film and average value was taken [7].

In vitro Dissolution Study: In vitro dissolution of tramadol hydrochloride oral dissolving films was studied in paddle type dissolution test apparatus. 900ml of 6.8 phosphate buffer solution was used as dissolution medium. The stirrer was adjusted to rotate at 50rpm. The temperature of dissolution medium was maintained at 37±0.5ºC throughout

the experiment. Samples of dissolution medium (5ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 270nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent of tramadol hydrochloride release was calculated and plotted against time.

RESULTS

Analytical Method Development for Tramadol Hydrochloride

λ Max Determination: Tramadol hydrochloride λ max was determined by spectrophotometer using pH 6.8 buffer medium. First dissolve 100mg of pure drug in 100ml of 6.8 buffer medium. From this 40µg/ml solution was prepared by using 6.8 buffers. 40µg/ml solution absorbance was scanned at 200 to 400nm range by spectrophotometrically using 6.8 buffers as reference solution and λ max was observed at 270nm.

Preparation of Drug-Resin Complex Mixture: Required amount of drug was mixed with different ratios of powdered ion exchange resin like 1:1, 1:1.5, 1:2, 1:3 ratios. The taste masked resinate (equivalent to 50mg of Tramadol Hydrochloride) was used for the further studies. On the basis of palatability the resinate is optimized for preparation of films.

Thickness: The thickness of each film was measured at three different locations (centre and corners) for all the formulations using screw gauge and the results are given in the table3. Thickness varies from 0.12 ± 0.01 to 0.31 ± 0.01mm. From the table it is concluded that as the polymer concentration increases, thickness also increased.

Percent Elongation: Percent elongation of the film is increase in length of the film divided by original length of the film. By using this formula percent elongation was calculated for each film of all the formulations and results were given in table3. Percent elongation varies from 23.98 ± 0.91 to 56.25 ± 0.82.

Folding Endurance: The folding endurance was measured manually. Folding endurance was determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film was folded without breaking known as the folding endurance value and this value for each film of formulation is given in the table 3. The folding endurance value varies from 109.33± 1.67 to 163.33 ± 1.33.

Physical Appearance and Surface Texture of Films: These parameters were checked simply with visual infection of films and by feel or touch. The observation suggests that the films are having smooth surface and they are elegant enough to see.

Weight Uniformity of Films: Three patches of the same film at different locations were weighed individually using digital balance and the average weights were calculated and same procedure was applied for all the formulations. Weight variation varies from 58.21 ± 0.56 to 77.10 ± 0.61mg. The results of weight variations were shown in the Table3. From the table it is concluded that as the concentration of the polymer increases, weight of the film also increases.

Drug Content Uniformity or Assay of Film: The films were tested for drug content uniformity by UV Spectrophotometric method. Films of 2.5cm x 2.5cm square size were cut from three different places from the casted films. Each patch was placed in 100 ml volumetric flask and dissolved in 6.8 phosphate buffer. The absorbance of the solution was measured at 270nm using UV/visible spectrophotometer. The percentage drug content was determined using the standard graph and the same procedure was repeated for all the formulations and the results were given in table 3.

Invitro Disintegration Time: This in vitro disintegration time in a glass bowl of 25 ml 6.8 pH phosphate buffer with swirling action will be determined for quick dissolving film. A film starts to break or disintegrate is known as disintegration time. The in vitro disintegration time was calculated for different patches of the same film of each formulation and the results were given in table-3.

Invitro Dissolution Studies: In vitro dissolution of tramadol hydrochloride oral dissolving films was studied in paddle type dissolution test apparatus. 900ml of 6.8 phosphate buffer solution was used as dissolution medium. Samples of dissolution medium (5ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 270nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent of tramadol hydrochloride release was calculated and plotted against time.

Comparison of Dissolution Profile for F1, F2, F3 and F4 Batches: In vitro dissolution study of formulations F1, F2, F3, F4 shown drug release of 79.92±1.45, 73.78±1.32, 72.31±1.76 and 70.91±1.29% respectively within 2min. Among

the formulations F1 showed good dissolution property. F1 batch contain 2% of HPMC E3 as film forming polymer.

Comparison of Dissolution Profile for F5, F6, F7 and F8 Batches: In vitro dissolution study of formulation F5, F6, F7 and F8 showed drug release of 74.65±1.44, 82.61±0.76, 73.98±2.23 and 71.51±0.88% within 2min respectively. Among formulations F6 showed good dissolution property. F6 batch contain 2.5% of HPMC E5 as film forming polymer.

Comparison of Dissolution Profile for F9, F10, F11 and F12 Batches: In vitro dissolution study of formulation F9, F10, F11 and F12 showed drug release of 76.93±1.32, 72.43±0.63, 67.14±1.35 and 57.34±1.31% respectively within 2min. Among the formulations F9 showed good dissolution property. F9 batch contain 2% of HPMC E15 as film forming polymer.

Comparison of Dissolution Profile for F13, F14 and F15 Batches: In vitro dissolution study of formulations F13, F14 and F15 showed drug release of 78.73±1.26, 81.93±1.35 and 83.76±2.66% respectively within 2min. Among the formulations F15 showed good dissolution property. F15 batch contain 5% of Pullulan as film forming polymer.

Comparison of Dissolution Profile for F1, F6, F9 and F15 Batches: In vitro dissolution study of formulations F1, F6, F9 and F15 showed drug release of 79.92±1.45, 82.61±0.76, 76.93±1.32 and 82.76±1.66% respectively within 2min. Among the formulations F15 showed good dissolution property. F15 batch contain 5% of Pullulan as film forming polymer.

DISCUSSIONS

The different film formulations were evaluated for mechanical properties like thickness, percent elongation folding endurance. The thickness of the films prepared with HPMC E3 of concentrations 2, 2.5, 3 and 5% were ranged from 0.12 ± 0.01 to 0.22 ± 0.02mm. The thickness of the films prepared with HPMC E5 of concentrations 2, 2.5, 3 and 5% were ranged from 0.16 ± 0.02 to 0.29 ± 0.01mm. The thickness of the films prepared with HPMC E15 of concentrations 2, 2.5, 3 and 5% were ranged from 0.17 ± 0.01 to 0.31 ± 0.01mm. The thickness of the films prepared with Pullulan of concentrations 3, 4 and 5% were ranged from 0.16 ± 0.02 to 0.23 ± 0.01mm. F12 formulation had the maximum thickness and F1 formulation had the lowest thickness values in all the formulations. From the thickness values it is concluded that as the polymer concentration increases, thickness also increased. The percent elongation of the films prepared with HPMC E3 of concentrations 2, 2.5, 3 and 5% were ranged from 56.25 ± 0.82 to 36.24 ± 0.57. The percent elongation of the films prepared with HPMC E5 of concentrations 2, 2.5, 3 and 5% were ranged from 48.74 ± 0.69 to 31.70 ± 0.81. The percent elongation of the films prepared with HPMC E15 of concentrations 2, 2.5, 3 and 5% were ranged from 39.09 ± 0.93 to 28.31 ± 0.88. The percent elongation of the films prepared with Pullulan of concentrations 3, 4 and 5% were ranged from 35.35 ± 0.66 to 23.98 ± 0.91. F1 formulation had the maximum percent elongation and F15 formulation had the lowest values in all the formulations. The folding endurance value of the films prepared with HPMC E3 of concentrations 2, 2.5, 3 and 5% were ranged from 109.33 ± 1.67 to 139.66 ± 2.12. The folding endurance value of the films prepared with HPMC E5 of concentrations 2, 2.5, 3 and 5% were ranged from 133.33 ± 1.87 to 150.66 ± 1.29. The folding endurance value of the films prepared with HPMC E15 of concentrations 2, 2.5, 3 and 5% were ranged from 126.66 ± 1.87 to 143 ± 1.45. The folding endurance value of the films prepared with Pullulan of concentrations 3, 4 and 5% were ranged from 163.33 ± 1.33 to 144.33 ± 1.23. In HPMC containing formulations as polymer concentration increases folding endurance values were also increased, where as in Pullulan containing formulations this value was decreased. Weight uniformity of films was carried out for all the formulations and weight variation varies from 58.21 ± 0.44 to 77.10 ± 0.67mg. Tramadol hydrochloride fast dissolving films prepared with HPMC E3, HPMC E5, HPMC E15 and Pullulan polymers were subjected to the uniform dispersion of drug throughout the film and the results were shown in Table 8. The drug was dispersed in the range of 93.22 ± 0.94 to 99.51 ± 0.73% which suggests that drug was uniformly dispersed throughout all films. The SD value calculated for such formulation is very less which suggest that the results are reproducible and accuracy in the method used to prepare the films. The time where a film starts to break or disintegrate is known as disintegration time. The in vitro disintegration time was calculated for all the formulations and it ranges from 44 ± 0.97 to 54 ± 1.98sec. Disintegration time of the films was increased with increase in concentration of the polymer, as more fluid is required to wet the film in the mouth. F13 formulation was quickly disintegrated that is in 44 ± 0.97sec. Finally selection of the best formulation from all the formulations was carried by using in vitro dissolution studies and release kinetics. In vitro dissolution study formulations of F1, F2, F3 and F4 contain HPMC E3 (2, 2.5, 3 and 5%) were showed different drug release of 79.92±1.45,

73.78±1.32, 72.31±1.76 and 70.91±1.29% respectively within 2min. Among the formulations F1 showed good dissolution property hence it is optimized and it contain 2% of HPMC E3 (300mg) as film forming polymer. In vitro dissolution study formulations of F5, F6, F7 and F8, contain HPMC E5 (2, 2.5, 3 and 5%) were showed different drug release of 74.65±1.44, 82.61±0.76, 73.98±2.23 and 71.51±0.88% respectively within 2min. Among the formulations F6 showed good dissolution property hence it is optimized and it contain 2.5% of HPMC E5 (375mg) as film forming polymer. In vitro dissolution study formulations of F9, F10, F11 & F12, contain HPMC E15 (2, 2.5, 3 and 5%) were showed different drug release of 76.93±1.32, 72.43±0.63, 67.14±2.35 and 57.34±2.31% respectively within 2min. Among the formulations F9 showed good dissolution property hence it is optimized and it contain 2% of HPMC E15 (300mg) as film forming polymer. In vitro dissolution study of formulations F13, F14 and F15, contains Pullulan polymer (2, 2.5, 3 and 5%) were showed different drug release of 78.73±1.26, 81.93±1.35 and 83.76±1.66% respectively within 2min. Among the formulations F15 showed good dissolution property hence it is optimized and it contains 5% of Pullulan as film forming polymer.

Small differences were observed in dissolution of drug from the different formulations of the film. From all formulations F15 formulation showed better thickness of 0.23±0.01mm, better percent elongation of 23.98±0.91, uniform dispersion of drug of 99.51±0.73%, better drug release of 83.76±1.66% (2min) and F13 formulation showed better disintegration time 44 ± 0.97sec. From all formulations F15 formulation showed satisfactory film parameters and it contains 5% of Pullulan polymer as film forming agent. Compared with HPMC E3, E5 and E15, Pullulan has good disintegration property which enables good dissolution of the formulations. So, it is assumed that 5% Pullulan containing oral fast dissolving film was optimized in which it showed a drug release of 83.76±1.66% compared with other batch formulations.

Fourier Transform Infrared (FTIR) Spectroscopy Studies: The FTIR samples (pure drug tramadol hydrochloride, placebo and placebo fast dissolving oral film formulation) were obtained, using Perkin Elmer FT-IR system Spectrum BX series (Beaconsfield, Buckinghamshire, UK), in the frequency range of 4000–550 cm^{-1} at 4 cm^{-1} resolution. The technique used very small amount of each sample which directly loaded into the system. Spectrum BX series software version 2.19 was used to determine peak positions. The IR spectra of pure tramadol hydrochloride drug showed the characteristic absorption bands and drug-polymer interaction was not observed in the FTIR spectra of the powder mixture of optimized formulation since the absorption peaks of the drug still could be detected in the mixture.

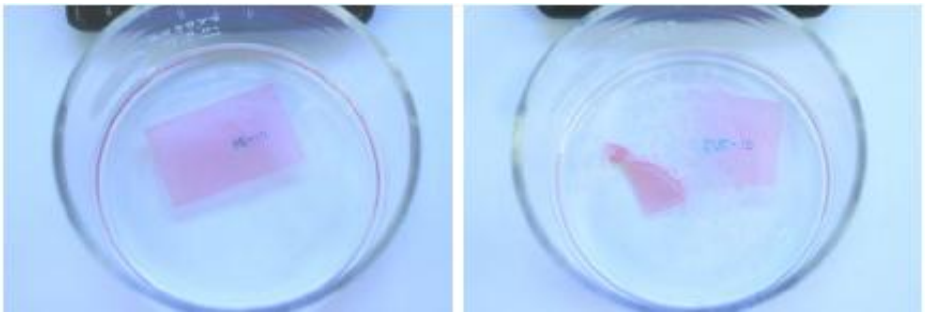
Table: 1 Formulation of Tramadol hydrochloride oral dissolving films

CODE	DRUG (mg)	TULSION 335 (mg)	HPMC E3 (mg)	HPMC E5 (mg)	HPMC E15 (mg)	PULLULAN (mg)	PG (mg)	GLYCERIN (mg)	ASPARTAME (mg)	BANANA FLAVOR (mg)
F1	384	768	300	-	-	-	375	-	75	300
F2	384	768	375	-	-	-	375	-	75	300
F3	384	768	450	-	-	-	375	-	75	300
F4	384	768	750	-	-	-	375	-	75	300
F5	384	768	-	300	-	-	375	-	75	300
F6	384	768	-	375	-	-	375	-	75	300
F7	384	768	-	450	-	-	375	-	75	300
F8	384	768	-	750	-	-	375	-	75	300
F9	384	768	-	-	300	-	-	395	75	300
F10	384	768	-	-	375	-	-	395	75	300
F11	384	768	-	-	450	-	-	395	75	300
F12	384	768	-	-	750	-	-	395	75	300
F13	384	768	-	-	-	300	375	-	75	300
F14	384	768	-	-	-	400	375	-	75	300
F15	384	768	-	-	-	500	375	-	75	300

Drug = Tramadol hydrochloride, PG = Propylene glycol

Table: 2 Absorption Data for Tramadol Hydrochloride in Ph 6.8 Phosphate Buffer

Concentration (µg/ml)	Absorbance(nm)
20	0.1116
30	0.1654
40	0.2329
50	0.3054
60	0.3510
70	0.4098
80	0.4680
90	0.5254



Initial Time Disintegrated Film

Figure 1: Disintegration of the film

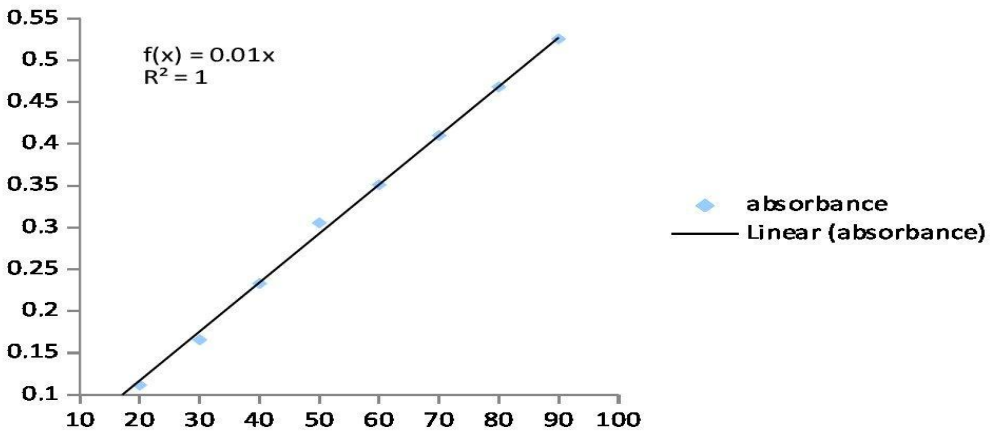
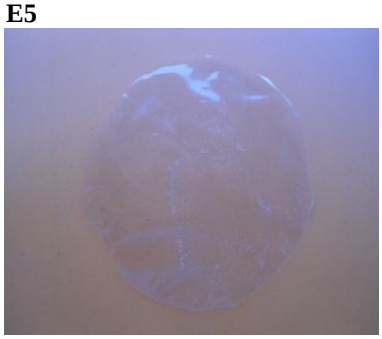


Fig: 2 Standard plot of Tramadol hydrochloride in pH 6.8 phosphate buffer

HPMC E3

HPMC E5

PULLULAN



HPMC E15

Fig: 3 Oral Fast Dissolving Films

Table: 3 Comparative Evaluation Of Thickness, Percent Elongation, Folding Endurance, Weight Uniformity, Drug Content Uniformity, Disintegration Time Of Oral Fast Dissolving Films

Formulation Code	Mean Thickness (mm) ± S.D	Mean Percent elongation ± S.D	Mean Folding Endurance ± S.D	Mean weight(mg) ± S.D	Mean of % Drug Content ± S.D	Mean disintegration time(sec) ± S.D
F1	0.12 ± 0.01	56.25 ± 0.82	109.33 ± 1.67	58.21 ± 0.56	94.52 ± 0.92	47 ± 0.93
F2	0.14 ± 0.02	49.95 ± 0.67	124.00 ± 1.88	65.40 ± 0.67	98.03 ± 0.82	47 ± 1.26
F3	0.18 ± 0.01	41.29 ± 0.78	138.66 ± 2.23	69.33 ± 0.61	93.96 ± 0.43	50 ± 1.29
F4	0.22 ± 0.02	36.24 ± 0.57	139.66 ± 2.12	71.07 ± 0.49	94.22 ± 0.32	51 ± 0.78
F5	0.16 ± 0.02	48.74 ± 0.69	133.33 ± 1.87	59.86 ± 0.59	93.45 ± 0.87	47 ± 0.98
F6	0.22 ± 0.01	40.15 ± 0.59	138.00 ± 1.56	63.38 ± 0.51	95.78 ± 1.23	49 ± 1.98
F7	0.27 ± 0.01	34.95 ± 0.62	139.33 ± 1.45	68.33 ± 0.44	98.78 ± 1.78	50 ± 2.12
F8	0.29 ± 0.01	31.70 ± 0.81	150.66 ± 1.29	71.80 ± 0.59	93.22 ± 0.94	52 ± 0.87
F9	0.17 ± 0.01	39.09 ± 0.93	126.66 ± 1.87	65.41 ± 0.62	98.48 ± 0.76	46 ± 0.98
F10	0.23 ± 0.02	36.82 ± 0.87	134.66 ± 2.55	66.77 ± 0.53	94.41 ± 1.89	46 ± 1.78
F11	0.27 ± 0.02	32.75 ± 0.53	136.00 ± 1.55	71.41 ± 0.51	96.26 ± 0.75	50 ± 1.87
F12	0.31 ± 0.01	28.31 ± 0.88	143.00 ± 1.45	77.10 ± 0.61	96.78 ± 0.98	54 ± 1.98
F13	0.16 ± 0.02	35.35 ± 0.66	163.33 ± 1.33	60.67 ± 0.66	97.89 ± 0.79	44 ± 0.97
F14	0.17 ± 0.01	26.84 ± 0.67	154.33 ± 2.88	69.00 ± 0.48	96.25 ± 0.66	45 ± 0.81
F15	0.23 ± 0.01	23.98 ± 0.91	144.33 ± 1.23	70.72 ± 0.49	99.51 ± 0.73	47 ± 1.67

Table: 4 In-vitro Drug Release for F1 to F15 Formulations

Time (min)	Cumulative Percent Drug Release														
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
2	79.92 ±1.45	73.78 ±1.32	72.31 ±1.76	70.91 ±1.29	74.65 ±1.44	82.61 ±0.76	73.98 ±2.23	71.51 ±0.88	76.93 ±1.32	72.43 ±0.63	67.14 ±1.35	57.34 ±1.31	78.73 ±1.26	81.93 ±1.35	83.76 ±1.66
4	87.23 ±0.67	83.65 ±0.46	80.72 ±1.41	79.23 ±1.66	82.33 ±1.76	86.69 ±2.34	79.38 ±1.86	76.16 ±1.87	88.95 ±1.46	78.73 ±1.35	72.84 ±1.13	64.51 ±1.11	83.63 ±1.53	85.34 ±1.65	91.14 ±1.38
	96.65 ±1.36	92.37 ±1.66	90.22 ±1.25	88.46 ±0.43	93.03 ±1.24	97.91 ±1.13	89.15 ±1.31	86.67 ±2.21	93.59 ±0.65	84.24 ±1.19	80.87 ±1.35	69.38 ±0.76	91.31 ±1.21	92.37 ±1.37	98.91 ±0.76
8	98.71 ±0.66	96.68 ±0.76	95.95 ±1.61	95.05 ±0.71	95.39 ±1.18	99.67 ±1.97	94.28 ±0.95	91.69 ±0.54	96.29 ±1.27	93.01 ±1.27	84.31 ±1.98	76.81 ±1.88	94.35 ±0.98	96.33 ±1.66	100.39 ±0.61
10	102.83 ±1.2	97.70 ±1.12	96.50 ±2.17	95.49 ±1.99	96.64 ±1.38	102.33 ±1.77	95.66 ±1.12	92.80 ±1.26	99.15 ±1.09	95.33 ±1.56	87.15 ±1.75	81.54 ±1.12	98.51 ±1.63	99.63 ±1.17	103.53 ±1.2

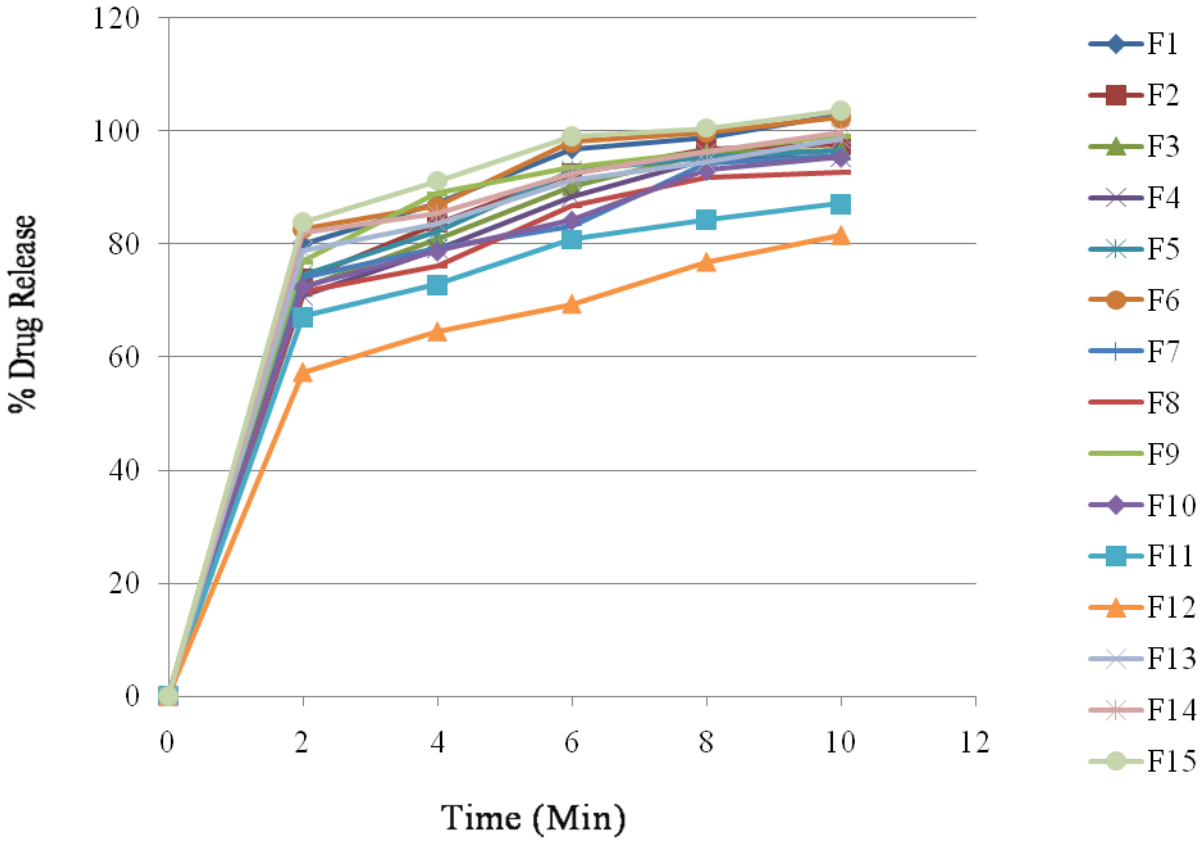


Fig: 4 Plot for in vitro drug release for F1 to F15 formulations

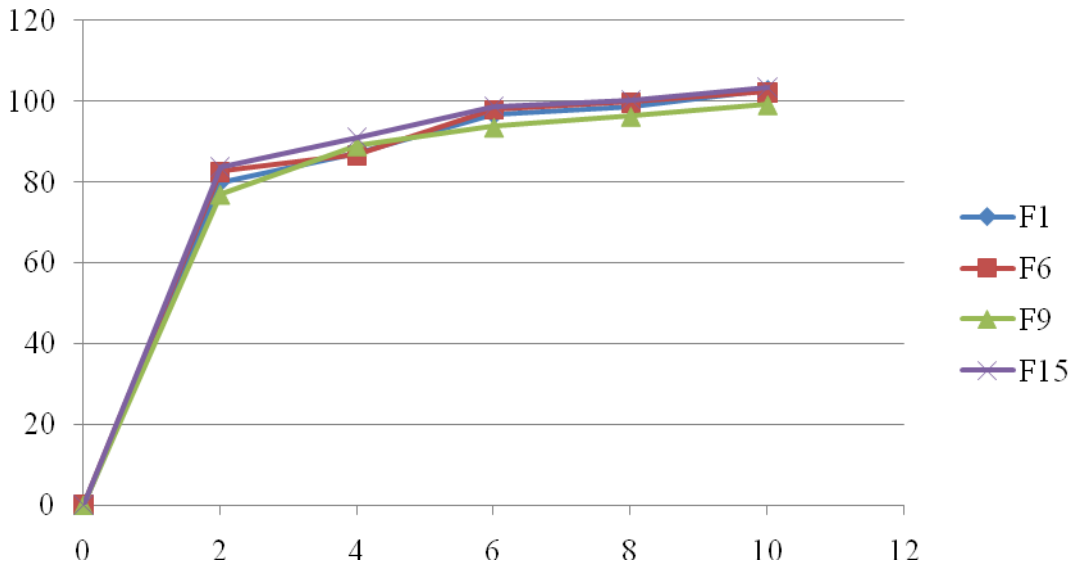
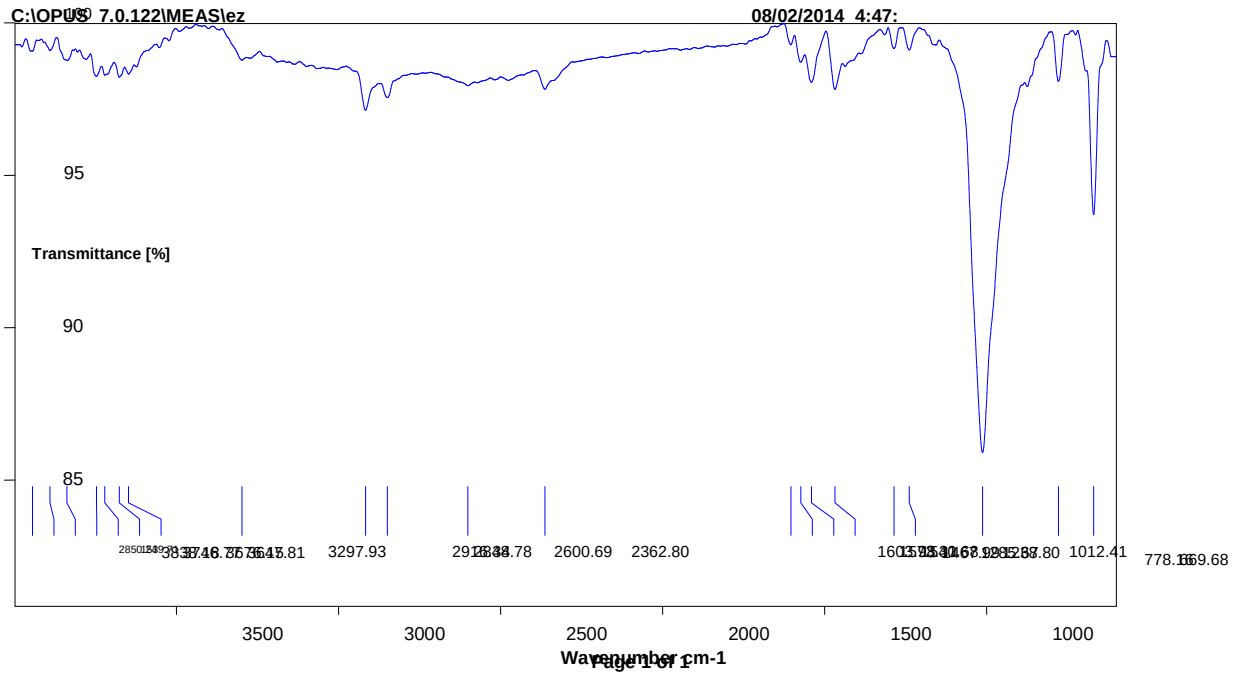


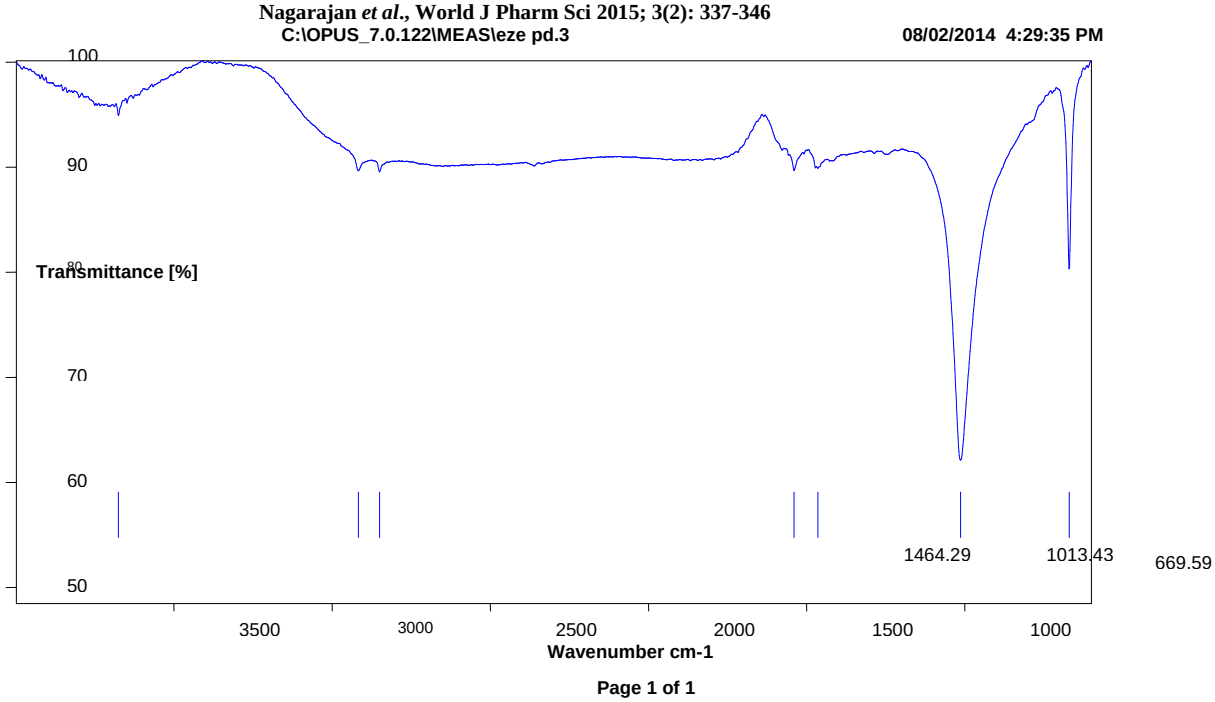
Fig 5 Plot for in vitro drug release for F1, F6, F9 and F15 formulations

Table: 5 FTIR Spectroscopy Studies

Characterization Bonds Of Tramadol Hydrochloride	Characteristic Wave Length Range (Cm^{-1})	Peaks Of Tramadol Hydrochloride Present In The Sample Cm^{-1}
O–H	3650-3600	3647.81
C–O–C (ether)	1275-1200	1238.80
	1075-1020	1012.41



Tramadol hydrochloride + placebo



Placebo

Fig: 8 FTIR Studies

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